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Innovative approaches to promote stroke recovery

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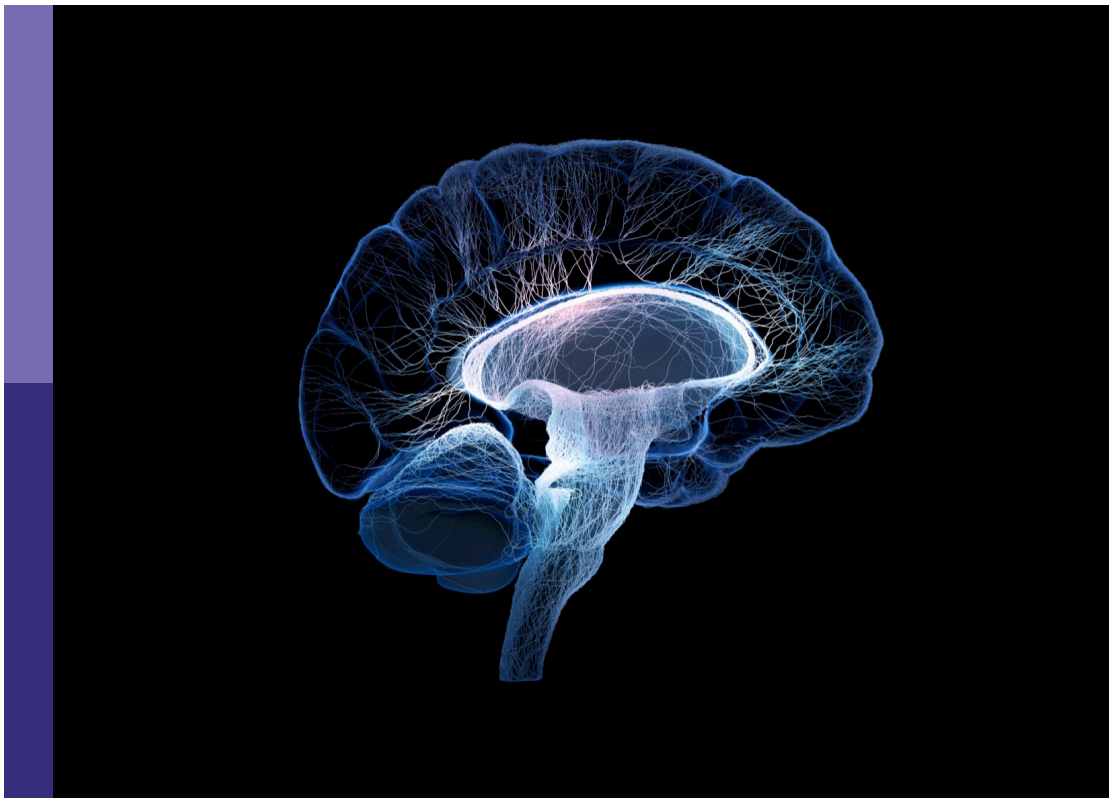

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Innovative approaches to promote stroke recovery

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Dr Rupert Ortner is full time employed by g.tec medical engineering, a company providing a stroke rehabilitation tool (recoveriX PRO).

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Resting-state electroencephalogram microstate to evaluate post-stroke rehabilitation and associate with clinical scales

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Introduction: Stroke is usually accompanied by a range of complications, like post-stroke motor disorders. So far, its evaluation of motor function is developed on clinical scales, such as Fugl-Meyer Assessment (FMA), Instrumental Activities of Daily Living (IADL), etc. These scale results from behavior and kinematic assessment are inevitably influenced by subjective factors, like the experience of patients and doctors, lacking neurological correlations and evidence.

Methods: This paper applied a microstate model based on modified k-means clustering to analyze 64-channel electroencephalogram (EEG) from 12 stroke patients and 12 healthy volunteers, respectively, to explore the feasibility of applying microstate analysis to stroke patients. We aimed at finding some possible differences between stroke and healthy individuals in resting-state EEG microstate features. We further explored the correlations between EEG microstate features and scales within the stroke group.

Results and discussion: By statistical analysis, we obtained significant differences in EEG microstate features between the stroke and healthy groups and significant correlations between microstate features and scales within the stroke group. These results might provide some neurological evidence and correlations in the perspective of EEG microstate analysis for post-stroke rehabilitation and evaluation of motor disorders. Our work suggests that microstate analysis of resting-state EEG is a promising method to assist clinical and assessment applications.

KEYWORDS

resting-state EEG, microstate analysis, post-stroke, rehabilitation assessment, clinical scales

Introduction

Stroke is usually accompanied by a range of complications, one of the recognized post-stroke complications is motor disorder (Handley et al., 2009). Although dyskinesia occurs uncommonly in adult stroke patients, about 1–4% of patients have dyskinesia after stroke severely affecting their life of patients (Bansil et al., 2012; Mehanna and Jankovic, 2013).

There are two clinical scales for motor function evaluation. The first one is the Fugl-Meyer Assessment (FMA), which assesses sensory-motor disorders in stroke patients. FMA has good consistency, responsiveness, and accuracy and is most widely used in clinical assessment (Gladstone et al., 2002). The other is the Instrumental Activities of Daily Living (IADL) assessment, which assess IADL functions in eight categories: shopping in the street, going out, food preparation, household maintenance, laundry, ability to use the telephone, taking medication, and ability to handle finances (Lawton and Brody, 1969). Both scales are based on behavioral scores, which are inevitably influenced by subjective factors, like the experience of patients and doctors, lacking neurological correlations and evidence.

Electroencephalogram (EEG) is an electrical field recording of the cerebral cortex (Nunez and Srinivasan, 2006), where the large-scale activity of cortical neurons creates a specific distribution of electrical fields in the cortex (Schmidt, 1983)and through volume conduction (Helmholtz, 1853), a potential distribution is created on the scalp surface through the skull and scalp (Michel and Murray, 2012). Placing electrodes on the scalp surface, changes in scalp surface potential distribution can be recorded and used to assess the spatial and temporal dynamics of brain electrophysiological activity (Rappelsberger, 1978). EEG is non-invasive, easy to use, and inexpensive, so it is a quite common tool for studying brain activity. EEG signals have a high temporal resolution (Michel and Brunet, 2019) compared to other neuroimaging tools, such as functional magnetic resonance imaging (fMRI). However, the presence of volume conduction affects the spatial resolution of EEG (Michel and Murray, 2012), and the high spatial dimension of EEG signals cannot be interpreted directly, so it is difficult to extract valuable information from EEG data.

There are many methods of EEG analysis used to extract feature information, and microstates analysis is one of them. A microstate is a sub-stable pattern of cortical potential distribution in space and time (Lehmann et al., 1987). In the temporal dimension of EEG, it can be observed that the temporal sequence of EEG topography consists of a set of discrete prototype topographies, each of which maintains a sub-stable state for approximately 60–120 ms before shifting to another prototype topography (Michel and Koenig, 2018). These prototypical topographies are called functional microstates, and in resting-state EEG, microstate topographies share a high similarity across individuals (Koenig et al., 1999), which ensures the feasibility of consistent microstate analysis among subjects. At present, microstate analysis is widely used, such as in the fields of Alzheimer's disease, schizophrenia, and depression research (Michel and Koenig, 2018), but it is rarely used for motor disorder analysis in stroke.

We applied this method to explore the feasibility of applying microstate analysis to stroke patients. Our work is to find some possible differences between stroke and healthy individuals in resting-state EEG microstate features, and furthermore, to find some correlations between EEG microstate features and scales within stroke patients. It expects to obtain some significant results which can provide some neurological evidence or correlations in the perspective of EEG microstate analysis for post-stroke rehabilitation and evaluation of motor disorders.

Materials and methods

Subjects

Our study included 12 patients (nine males and three females, with an average age of 59.8 $\pm$ 12.8) with different degrees of stroke motor disorder and 12 healthy subjects (eight males and four females, with an average age of 29.0 $\pm$ 7.1). All subjects gave signed informed consent. This study has been approved by the Ethics Committee of Tianjin University and Tianjin Hospital in Tianjin, China.

Experimental setup

For both groups, resting EEG was collected with eyes open, and additional FMA scale and IADL scale scores were collected in the patient group with stroke motor disorders. Clinical diagnosis was assessed by experienced doctors. The experiment was performed in a quiet room. Subjects were comfortably seated in a chair, and they were asked to rest for a period to meet the standard of resting state EEG. Subjects were asked to keep still to avoid artifacts such as myoelectricity. The EEG data were acquired while remaining resting in the open-eyed state, and record each subject's EEG for more than 200 s. For patients, the clinical diagnosis was evaluated by an experienced doctor after data collection, then FMA and IADL scores were given. FMA has three scores: total score, upper limb score, and lower limb score.

Data acquisition and preprocessing

Eye-opened resting-state EEG data were acquired from a 64-channel electrode cap with 64 scalp electrodes (Ag-AgCl) placed according to the 10–20 electrode system of the International Federation of Clinical Neurophysiology (Klem et al., 1999).

A 64-channel SynAmps2 system (NeuroScan Inc., USA) was used for EEG recording. The sampling rate was 1,000 Hz. The impedance for all electrodes was kept below 10 kΩ.

Electroencephalogram data were preprocessed offline on MATLAB (R2021b, MathWorks Inc., USA) with the EEGLAB (Delorme and Makeig, 2004) 2022.0 toolbox.

First, down-sampling was performed, and the sampling rate was reduced to 250 Hz, for decreasing the amount of data and the computational stress of data processing. The sampling rate satisfies Nyquist's sampling theorem (Landau, 1967), and 250 Hz is much larger than twice the 45 Hz.

Second, a Finite Impulse Response (FIR) filter with a filtering range of 1–45 Hz was applied to eliminate low-frequency signal shifts and high-frequency interference.

Third, an Independent Component Analysis (ICA) was performed. After the ICA decomposition of the components, the joint use of ICLabel (Han et al., 2019) and ADJUST (Mognon et al., 2011) algorithm assists in identifying artifactual components, such as blink, muscle movement, eye movement, and electrode loosening components. After that, use EEGLAB's clear raw data and Artifact Subspace Reconstruction (ASR) function to clean up bad channels and abnormal data segments, then do ICA on the data again, use ICLabel and ADJUST algorithm to assist in identifying artifact components, and visually remove most of the other artifact components.

After the last ICA processing, most of the components in the top ranking of ICA components are brain-active components, and their confidence level can reach more than 90%.

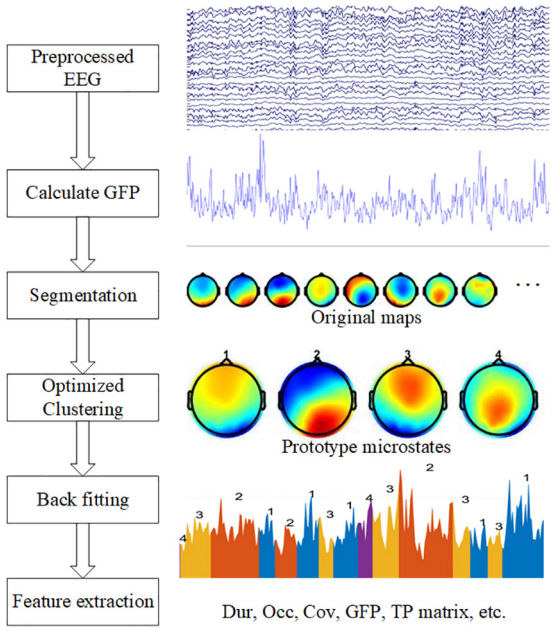

FIGURE 1
Graphical representation of the analysis method in the study. The left side shows five steps: calculate GFP, EEG segmentation, optimized clustering, back fitting, and feature extraction. On the right side are examples of each step.

Data analysis

We performed microstate analysis to extract features from data using the microstate toolbox (Poulsen et al., 2018), and then performed a statistical analysis of the features. The complete analysis graphical representation shows in **Figure 1**.

Microstate analysis

A common average reference (CAR) is helpful before microstate analysis (Ludwig et al., 2009). Then, the largest signal-to-noise ratio point is determined by calculating the Global Field Power (GFP) of each topography in time series, which is calculated as follows:

$$GFP = \sqrt{\frac{\sum_i^N (V_i(t) - V_{mean}(t))^2}{N}}$$

where $V_i(t)$ denotes the instantaneous potential value of the No. i electrode at time t; $V_{mean}(t)$ represents the average potential value of all electrodes at time t; N is the number of electrodes.

Second, the EEG data was segmented. Before segmentation, EEG data should be normalized. The time point where the GFP local maximum was located often indicated the presence of a stable microstate, so the brain topography map at the time point of the GFP local maximum was extracted, these maps were also called original maps. The extracted brain topographies were clustered and analyzed using a modified K-means clustering algorithm (Pascual-Marqui et al., 1995), and the prototype microstates formed by clustering were ranked based on the global explained variance. The clustering operation was repeated using the algorithm for clustering parameters 3–8, respectively.

Third, Optimization of clustering parameters. Usually, the optimization of the clustering parameters is based on the cross-validation criterion (CV), Global explained variance (GEV), Dispersion (W), and Krzanowski-Lai (KL) criterion to choose the suitable number of prototype microstates (Poulsen et al., 2018). However, according to the previous experience (Koenig et al., 1999), the number of resting-state microstates clustering is generally chosen to be 4, because the topography of four prototype microstates has high similarity among different studies, and the fixed microstate clustering number of 4 can ensure the consistency and comparability between individual studies (Michel and Koenig, 2018). These prototype microstate topographic maps are easily recognized, and therefore they are labeled as four classes A, B, C, and D, which are left-right direction (type A), left-right direction (type B), anterior-posterior direction (type C), and frontocentral maximum (type D).

When we got the four microstates, a back fitting was performed based on the number of microstates selected. After the four prototype microstates are obtained by clustering, the

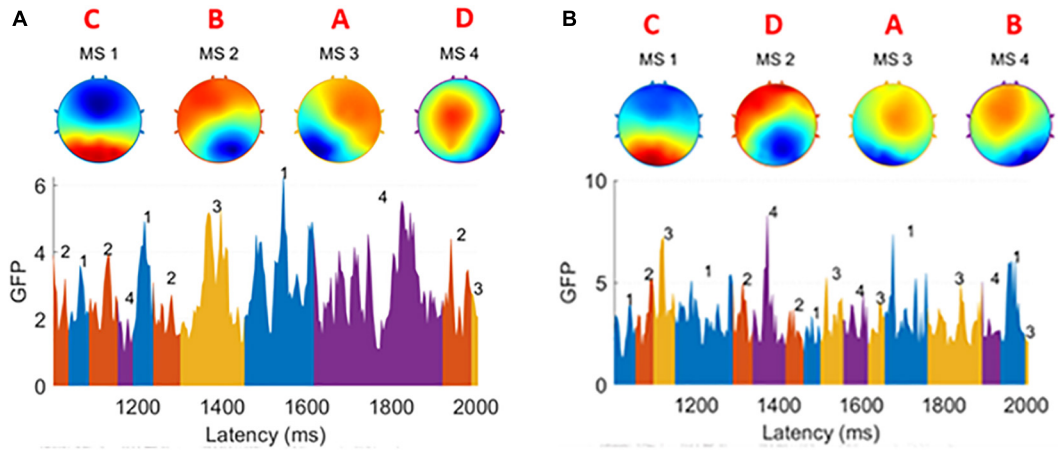

FIGURE 2
(A) Four prototype microstates extracted from one healthy subject. **(B)** Four prototype microstates extracted from one patient subject. The brain topographies are labeled as type A, B, C, and D. In both graphs GFP, the EEG data is divided into small segments. Each of them is corresponding to one of four microstates and a microstate sequence is formed. There are slight differences between the healthy group and the patient group.

TABLE 1 Microstate features GFP, Occ, Dur, and Cov for each prototype microstate.

Microstate features	A	B	C	D
GFP	2.5429	2.6814	2.9412	2.5121
Occ	3.0817	3.3100	3.7209	1.9061
Dur (ms)	79.1481	85.1345	92.6626	67.9401
Cov	0.2439	0.2818	0.3448	0.1295

whole data set is fitted to the prototype microstates, and each segment of EEG data is matched with a microstate label, which is one of the four prototype microstates. A winner-take-all method was used, i.e., the prototype microstate with the highest similarity is selected as the microstate label of the EEG data and a sequence of microstates is formed. However, the presence of interference and artifacts in the original data affects the quality of the microstate back fitting and may produce some microstates with short durations, which are not true microstates and do not meet the requirements of sub-stability. Therefore, these short microstates need to be rejected, temporal smoothing was performed by merging data segments with microstate durations of less than 30 ms.

In the last step, the microstate features are calculated. For each microstate, the duration (Dur) is defined as the average duration of the microstate per second. Occurrence (Occ) frequency was defined as the average frequency of the observed microstates. Coverage (Cov) was defined as the percentage of each microstate that occurred in each period. The average GFP is defined as the average amplitude of GFP during each microstate class dominance. The transition probability (TP) is defined as the probability of moving from one microstate to another different microstate.

Statistical analysis

Statistical analysis was performed on SPSS software (IBM Inc., USA). In this study, the significance level is 0.05. All statistical tests are two-tailed tests.

We conducted an independent sample *t*-test to find whether there are some differences between the features of resting-state patients' microstates and those of healthy subjects. Then we conducted a Pearson correlation analysis to analyze the correlation between EEG microstate features and scale scores within the stroke group. Considering that the features of microstates may be affected by factors such as age, further partial correlation analysis was performed with age as the control variable.

Results

Descriptive statistics

In both groups, the number of clusters was set to 4. The cluster maps obtained from each subject's EEG were highly consistent (Michel and Koenig, 2018), so we called them prototype microstates, yet slight differences could still be found when comparing patients and healthy subjects as **Figure 2** shows. We have marked the type of prototype microstates manually. In the EEG time series, the EEG signal is segmented corresponding to each prototype microstate, and each prototype microstate lasts for about 60–120 ms. The topography of the microstates was slightly different between patients and healthy subjects.

For each prototype microstate, we calculated the features corresponding to each prototype microstate and grouped them according to the label of the microstate. Each microstate corresponds to four features: average duration, average

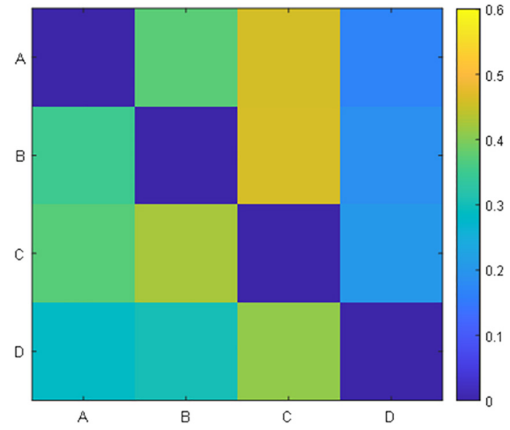

FIGURE 3
Transition probability matrix.

occurrence, coverage, and average GFP. The features between microstates are the transition probabilities, 12 values in total, they are A-B (A-B denotes the transfer from the prototype microstate A to the prototype microstate B unidirectionally, the same below), A-C, A-D, B-A, B-C, B-D, C-A, C-B, C-D, D-A, D-B, D-C, respectively. A TP matrix was formed with a zero diagonal because the prototype microstate transfer to itself is not meaningful. Table 1 and Figure 3 show the data on the microstate features of one of the patients.

Independent samples *t*-test

To find differences between the health and patient group, we did independent samples *t*-test. There are two group settings: the experimental group (healthy subjects) and the experimental group (patients), with a total of 28 test variables, i.e., 12 probabilities of transition and a total of 16 (4*4) microstate features corresponding to each prototype microstate. When performing the independent samples *t*-test, it was found that the two groups of data did not meet the requirement of homogeneity of variance, so Welch's method was used for correction. The following Table 2 was obtained, labeling the differences between the two groups for each microstate feature respectively, and the average duration of microstate C (Dur_C) was significantly different between the groups (t=2.268, p=0.038). The detailed information is shown in Figure 4. To examine the influence of age, we applied a two-factor ANOVA analysis to the data, then, we got the result that the factor age has no statistical significance (F = 0.782, p = 0.387) and the factor Dur_C has a statistical significance (F = 5.077, p = 0.036).

Scale correlations

Pearson correlation analysis was performed using SPSS 25 software to analyze the correlation between the microstate features and the clinical scales. The dependent variables are the scale scores: FMA, upper limb score, lower limb score, and IADL score. The independent variables are the microstate features corresponding to each prototype microstate: average GFP, average duration, average occurrence, coverage, and transition probabilities. Statistical analysis showed a significant correlation between the transition probability from C to D and the scale scores.

There was a significant correlation between C-D transition probability and FMA score within the confidence interval of

TABLE 2 Independent samples *t*-tests for 28 variables respectively with *t*-values and significance *p*-values.

Characters	A-B	A-C	A-D	B-A	B-C	B-D	C-A
t-value	−0.696	1.511	−0.552	−0.227	1.360	−1.009	0.530
Significance	0.499	0.146	0.587	0.823	0.189	0.325	0.602
Characters	**C-B**	**C-D**	**D-A**	**D-B**	**D-C**	**GFP_A**	**GFP_B**
t-value	0.546	−0.843	−0.390	−0.802	0.978	−0.312	−0.131
Significance	0.591	0.409	0.700	0.433	0.344	0.759	0.897
Characters	**GFP_C**	**GFP_D**	**Occ_A**	**Occ_B**	**Occ_C**	**Occ_D**	**Dur_A**
t-value	0.042	−0.444	−0.409	−0.414	1.439	−0.859	−0.362
Significance	0.967	0.663	0.687	0.684	0.168	0.401	0.722
Characters	**Dur_B**	**Dur_C**	**Dur_D**	**Cov_A**	**Cov_B**	**Cov_C**	**Cov_D**
t-value	−0.393	2.268	−0.018	−0.522	−0.564	1.907	−0.716
Significance	0.700	0.038*	0.986	0.607	0.582	0.075	0.482*

GFP_A represents the character GFP of microstate A, and similar definitions as the table show (*represents $p < 0.05$, **represents $p < 0.01$).

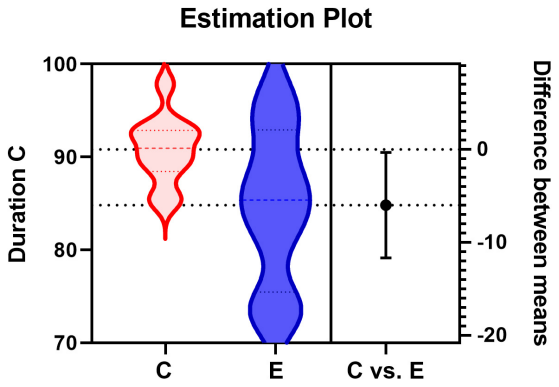

FIGURE 4
Estimation Plot for the average duration of microstate C. C represents the control group (healthy group) and E represents the experimental group (patient group).

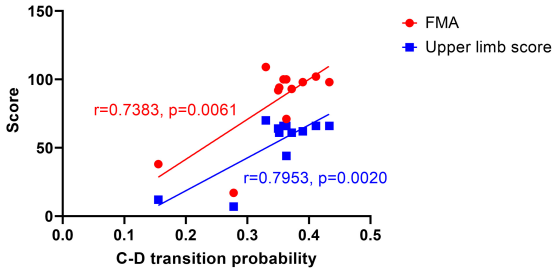

FIGURE 5
Linear regression graph between C-D transition probability and scores. The dots represent the FMA score, and the squares represent the upper limb score.

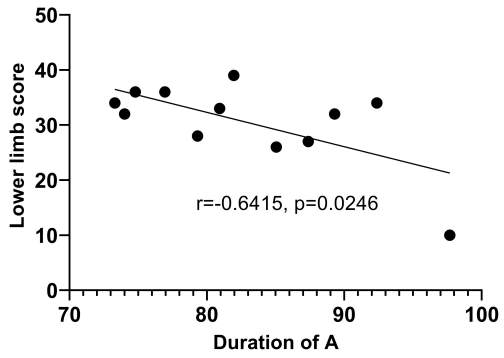

FIGURE 6
Linear regression graph between duration of microstate A and lower limb score.

95% (r = 0.7383, p = 0.0061, two-tailed test), which indicates that C-D transition probability influences the FMA score. Furthermore, the C-D transition probability was significantly correlated with the upper limb score (r = 0.7953, p = 0.0020, two-tailed test) within the confidence interval of 95%. It is noted that the r-value of the latter correlation test is higher, and the p-value is smaller, suggesting that the C-D transition probability reflects the upper limb score and implies the mobility of the upper limb. Since the microstate features are also influenced by age and gender (Hu and Zhang, 2019), we further implemented a partial correlation analysis, which was performed mainly on the age variable. By setting the control variable as age, there was a significant correlation between C-D and FMA (r = 0.742, p = 0.009), and C-D and upper limb score (r = 0.802, p = 0.003) also had a significant correlation. The comparison revealed that age had an insignificant effect on the correlation, which indicates that age is not a major factor affecting the scores and that there is a significant correlation between the transition probability C-D and the FMA score, as well as the upper limb score. For the other microstates, no significant correlation was found. Then we did a linear regression as **Figure 5** shows. For transition probability C-D vs. the FMA score, the R squared is 0.5451; for transition probability C-D vs. upper limb score, the R squared is 0.6325.

The resting state microstate feature average duration of microstate A(Dur_A) was significantly correlated with the lower limb score (r = −0.6415, p = 0.0246) as **Figure 6** shows. Furthermore, partial correlation analysis was performed with the control variable age, and there was statistically significant (r = −0.673, p = 0.023), suggesting that the correlation between Dur_A and the lower limb score was significant when influenced by the age variable. Linear regression was done, and the R squared is 0.4115.

Discussion

We used microstate analysis to assess the EEG differences between patients and healthy subjects, and further assessed the correlations between patient microstate features and clinical scales. Our study got statistically significant results. The transition probability from A to C was slightly decreased in patients with stroke motor disorders compared to healthy subjects and the variance was larger within the patient group compared to the healthy group. There was a significant correlation between transition probability from C to D and the FMA score, upper limb score. Particularly, a more significant correlation between transition probability from C to D and upper limb score was found. There was a significant correlation between the average duration of microstate A and the lower limb score. For other microstate features, no significant difference was found between groups, and no correlation was found between other features and other clinical scale scores.

Microstates provide information on the combinatorial activity of large-scale neural networks, and correlations between EEG microstates and fMRI resting states are found in previous studies (Britz et al., 2010; Musso et al., 2010; Yuan et al., 2012).

Microstate A correlates with negative Blood Oxygen on Level Depending (BOLD) activation in the bilateral superior temporal lobe and middle temporal lobe, microstate B correlates with negative BOLD activation in the bilateral occipital cortex. Microstate C correlates with positive BOLD activation in the dorsal anterior cingulate cortex, bilateral inferior frontal cortex, and right insula area. Microstate D is associated with negative activation of BOLD in frontal and parietal cortical righting dorsal and ventral areas. Britz et al. (2010) correlate microstate C with activity in cognitive control networks (mainly salience networks) and with activation of the anterior cingulate and insula (Seeley et al., 2007). According to (Britz et al., 2010), microstate D is associated with the focal attention network.

There is an antagonistic relationship between microstate C and microstate D, creating a dynamic equilibrium (Santarnecchi et al., 2017). When a stroke occurs, the equilibrium is disrupted, and the degree of this imbalance varies depending on the severity of the stroke motor disorder. As seen in the figure, the lower the patient score is, the lower the transition probability C-D is, representing a state transition from microstate C to microstate D is less likely to occur. This suggests that the connectivity of the microstate C salience network to the microstate D dorsal attention network is reduced. However, there is no evidence to determine the relationship between changes in network connectivity balance and stroke motor disorder. This may be related to impaired proprioception, which requires a more detailed study of the relationship between microstates and fMRI of patient brain function.

Our study involved a limited number of subjects, more healthy subjects and patients could be involved to get furthermore detailed analysis in the future. However, it suggests the feasibility of applying microstate analysis to stroke patients and that there are some correlations between microstate features and clinical scales. As a purely phenomenological concept, the association between microstates and brain activity remains vague, and more work needs to be done in the future to reveal the association between microstate features and brain activity and to find more neurological evidence.

Conclusion

In summary, we found some differences between stroke and healthy individuals in resting-state EEG microstate features, which is statistically significant by independent samples *t*-test. And we performed the Pearson correlation analysis between EEG microstate features and scales within the stroke group. We obtained significant differences in EEG microstate features between the stroke and healthy groups, and significant correlations between microstate features and scales within the stroke group. These results might provide some neurological evidence of EEG microstate analysis for stroke rehabilitation. Resting-state EEG microstate might assist clinical diagnosis and assessment application as a neurological marker.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Tianjin University and Tianjin Hospital in Tianjin, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZW, LC, and DM were involved in the conception and design of the study, data interpretation, and critically reviewed the manuscript. ZW, SL, MX, FH, and ZL participated in the experimental data collection of this manuscript. ZL and ZW were involved in the manuscript drafting and revision. ZW was involved in the data analysis for this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Bansil, S., Prakash, N., Kaye, J., Wrigley, S., Manata, C., Stevens-Haas, C., et al. (2012). Movement Disorders after Stroke in Adults: A Review. *Tremor Other Hyperkinetic Mov.* 2:tre–02–42–195–1. doi: 10.5334/tohm.110

Britz, J., Van De Ville, D., and Michel, C. M. (2010). Bold correlates of EEG topography reveal rapid resting-state network dynamics. *Neuroimage* 52, 1162–1170. doi: 10.1016/j.neuroimage.2010.02.052

Delorme, A., and Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Gladstone, D. J., Danells, C. J., and Black, S. E. (2002). The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. *Neurorehabil. Neural Repair* 16, 232–240. doi: 10.1177/154596802401105171

Han, K., Wen, H., Shi, J., Lu, K. H., Zhang, Y., Fu, D., et al. (2019). Variational autoencoder: An unsupervised model for encoding and decoding fMRI activity in visual cortex. *Neuroimage* 198, 125–136. doi: 10.1016/j.neuroimage.2019.05.039

Handley, A., Medcalf, P., Hellier, K., and Dutta, D. (2009). Movement disorders after stroke. *Age Ageing* 38, 260–266. doi: 10.1093/ageing/afp020

Helmholtz, H. (1853). Ueber einige Gesetze der Vertheilung elektrischer Ströme in körperlichen Leitern mit Anwendung auf die thierisch-elektrischen Versuche. *Ann. Phy.* 165, 211–233. doi: 10.1002/andp.18531650603

Hu, L., and Zhang, Z. (eds) (2019). *EEG Signal Processing and Feature Extraction*. Singapore: Springer Singapore, doi: 10.1007/978-981-13-9113-2

Klem, G. H., Lüders, H. O., Jasper, H. H., and Elger, C. (1999). The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr. Clin. Neurophysiol. Suppl.* 52, 3–6.

Koenig, T., Lehmann, D., Merlo, M. C., Kochi, K., Hell, D., and Koukkou, M. (1999). A deviant EEG brain microstate in acute, neuroleptic-naive schizophrenics at rest. *Eur. Arch. Psychiatry Clin. Neurosci.* 249, 205–211. doi: 10.1007/s004060050088

Landau, H. J. (1967). Sampling, data transmission, and the Nyquist rate. *Proc. IEEE* 55, 1701–1706. doi: 10.1109/PROC.1967.5962

Lawton, M. P., and Brody, E. M. (1969). Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. *Gerontologist* 9, 179–186.

Lehmann, D., Ozaki, H., and Pal, I. (1987). EEG alpha map series: Brain micro-states by space-oriented adaptive segmentation. *Electroencephalogr. Clin. Neurophysiol.* 67, 271–288. doi: 10.1016/0013-4694(87)90025-3

Ludwig, K. A., Miriani, R. M., Langhals, N. B., Joseph, M. D., Anderson, D. J., and Kipke, D. R. (2009). Using a Common Average Reference to Improve Cortical Neuron Recordings From Microelectrode Arrays. *J. Neurophysiol.* 101, 1679–1689. doi: 10.1152/jn.90989.2008

Mehanna, R., and Jankovic, J. (2013). Movement disorders in cerebrovascular disease. *Lancet Neurol.* 12, 597–608. doi: 10.1016/S1474-4422(13)70057-7

Michel, C. M., and Brunet, D. (2019). EEG Source Imaging: A Practical Review of the Analysis Steps. *Front. Neurol.* 10:325. doi: 10.3389/fneur.2019.00325

Michel, C. M., and Koenig, T. (2018). EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: A review. *Neuroimage* 180, 577–593. doi: 10.1016/j.neuroimage.2017.11.062

Michel, C. M., and Murray, M. M. (2012). Towards the utilization of EEG as a brain imaging tool. *Neuroimage* 61, 371–385. doi: 10.1016/j.neuroimage.2011.12.039

Mognon, A., Jovicich, J., Bruzzone, L., and Buiatti, M. (2011). ADJUST: An automatic EEG artifact detector based on the joint use of spatial and temporal features: Automatic spatio-temporal EEG artifact detection. *Psychophysiology* 48, 229–240. doi: 10.1111/j.1469-8986.2010.01061.x

Musso, F., Brinkmeyer, J., Mobascher, A., Warbrick, T., and Winterer, G. (2010). Spontaneous brain activity and EEG microstates. A novel EEG/fMRI analysis approach to explore resting-state networks. *NeuroImage* 52, 1149–1161. doi: 10.1016/j.neuroimage.2010.01.093

Nunez, P. L., and Srinivasan, R. (2006). *Electric Fields of the Brain: The Neurophysics of EEG*. Oxford: Oxford University Press.

Pascual-Marqui, R. D., Michel, C. M., and Lehmann, D. (1995). Segmentation of brain electrical activity into microstates: Model estimation and validation. *IEEE Trans. Biomed. Eng.* 42, 658–665. doi: 10.1109/10.391164

Poulsen, A. T., Pedroni, A., Langer, N., and Hansen, L. K. (2018). Microstate EEGlab toolbox: An introductory guide. *Neuroscience* [Preprint]. doi: 10.1101/289850

Rappelsberger, P. (1978). EEG informatics. A didactic review of methods and applications of EEG data processing: A. Rémond (Elsevier, Amsterdam, 1977, 425 p., US $ 36.75)'. *Electroencephalogr. Clin. Neurophysiol.* 45, 677–678. doi: 10.1016/0013-4694(78)90171-2

Santarnecchi, E., Khanna, A. R., Musaeus, C. S., Benwell, C. S. Y., Davila, P., Farzan, F., et al. (2017). EEG Microstate Correlates of Fluid Intelligence and Response to Cognitive Training. *Brain Topogr.* 30, 502–520. doi: 10.1007/s10548-017-0565-z

Schmidt, R. F. (1983). "Integrative Functions of the Nervous System," in *Human Physiology*, eds F. S. Robert and G. Thews (Berlin: Springer), 145–174. doi: 10.1007/978-3-642-96714-6_7

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J. Neurosci.* 27, 2349–2356. doi: 10.1523/JNEUROSCI.5587-06.2007

Yuan, H., Zotev, V., Phillips, R., Drevets, W. C., and Bodurka, J. (2012). Spatiotemporal dynamics of the brain at rest–Exploring EEG microstates as electrophysiological signatures of BOLD resting state networks. *NeuroImage* 60, 2062–2072. doi: 10.1016/j.neuroimage.2012.02.031

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Brain–computer interface treatment for gait rehabilitation in stroke patients

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The use of Brain–Computer Interfaces (BCI) as rehabilitation tools for chronically ill neurological patients has become more widespread. BCIs combined with other techniques allow the user to restore neurological function by inducing neuroplasticity through real-time detection of motor-imagery (MI) as patients perform therapy tasks. Twenty-five stroke patients with gait disability were recruited for this study. Participants performed 25 sessions with the MI-BCI and assessment visits to track functional changes during the therapy. The results of this study demonstrated a clinically significant increase in walking speed of 0.19 m/s, 95%CI [0.13–0.25], $p < 0.001$. Patients also reduced spasticity and improved their range of motion and muscle contraction. The BCI treatment was effective in promoting long-lasting functional improvements in the gait speed of chronic stroke survivors. Patients have more movements in the lower limb; therefore, they can walk better and safer. This functional improvement can be explained by improved neuroplasticity in the central nervous system.

KEYWORDS

brain–computer interfaces, BCI, stroke, neurorehabilitation, functional electrical stimulation, lower limb, 10 Meter Walking Test, gait

1. Introduction

Stroke is one of the main causes of mortality and long-term disability worldwide. Functional deficit of the lower limb is the most common paresis after a stroke. Stroke patients rarely fully recover after months or even years of therapy and other treatment, leaving them with permanent impairment. Many of these patients never regain the ability to walk well enough to perform all their daily activities (Hesse et al., 2008; Mehrholz et al., 2017). Gait recovery is one of the major therapy goals in rehabilitation programs for stroke patients and many methods for gait analysis and rehabilitation have been developed (Mehrholz et al., 2017). Weakened muscle tone is another common challenge in motor rehabilitation. Therapies such as active foot drop exercises, electromechanically assisted therapy and treadmill therapy are usually limited to patients with mild or moderate impairment (Mills et al., 2011; Mehrholz et al., 2017).

A 2018 study (Mehrholz et al., 2018) conducted a network meta-analysis based on 95 publications out of 44.567 that were considered. In this study, 4.458 patients were included, and the effectiveness of the most common interventions for gait rehabilitation after stroke was analyzed. The interventions where classified in five groups: (1) No walking training, (2) Conventional walking training (walking on the floor, preparatory exercises in a sitting position, balance training etc. without technical aids and without treadmill training or electromechanical-assisted training), (3) Treadmill training without or with body-weight support, (4) Treadmill training with or without a walking speed paradigm, (5) Electromechanical-assisted training with end-effector devices or exoskeletons. For the primary endpoint of walking speed, end-effector-assisted training (EGAIT_EE) achieved significantly greater improvements than conventional walking rehabilitation (mean difference [MD] = 0.16 m/s, 95% CI = [0.04, 0.28]). None of the other interventions improved walking speed significantly.

Functional electrical stimulation (FES) has also been used in motor rehabilitation therapy over the last few decades. Passive FES therapy can reduce muscle spasms and shorten the term of motor recovery (Hong et al., 2018). Passive therapies such as continuous passive motion or cycling therapy have been employed for patients and showed functional improvements in previous studies (Janssen et al., 2008; Yeh et al., 2010; Ambrosini et al., 2011). However, they do not include devices or systems to monitor the patient's active engagement in the therapy.

Today, Brain-Computer Interfaces (BCIs) can provide an objective tool for measuring Motor Imagery (MI), creating new possibilities for "closed-loop" feedback (Wolpaw and Wolpaw, 2012). Closed-loop feedback depends on sensing the desired mental activity and is possible with MI-based BCIs, which could significantly improve rehabilitation therapy outcomes (Ortner et al., 2012; Cho et al., 2016; Cantillo-Negrete et al., 2018; Irimia et al., 2018).

MI-based BCIs have been employed in rehabilitation training for stroke patients to fill the gap between patients' expectations and therapy outcomes. In conventional rehabilitation therapies, patients are often asked to try to move the paretic limb, or to imagine moving it, while a FES, physiotherapist and/or robotic device helps them to perform the desired movement. Their feedback is often provided when the users are not performing the required mental activity. There is no objective way to determine whether patients who cannot move are actively performing the desired motor imagery (MI) task and thus producing concordant neural activation. Its efficacy has been shown in multiple studies implementing exoskeleton, orthosis or robots which induce passive movement of their affected limbs (Ramos-Murguialday et al., 2013; Ono et al., 2014; Ang et al., 2015). During repetitive neurofeedback training sessions, even patients with severe impairment could complete the sensorimotor loop in their brains linking coherent sensory feedback with motor intention (Cho et al., 2016; Pichiorri et al., 2017; Irimia et al., 2018).

This concurrent sensory feedback with motor intention is an important factor for motor recovery (Ortner et al., 2012; Bolognini et al., 2016; Pichiorri et al., 2017; Cantillo-Negrete et al., 2018; Irimia et al., 2018). Concurrent feedback based on users' intention may help them learn mental strategies associated with movement and BCI use, which can affect results (Neuper et al., 2005; Neuper and Allison, 2014). Neural networks are strengthened when the presynaptic and postsynaptic neurons are both active. In conventional therapies, when patients receive feedback while they are not performing MI, these two neuronal networks are not simultaneously firing. This dissociation between motor commands and sensory feedback may explain why the therapy does not significantly induce the reorganization of the patients' brains around their lesioned area. Non-simultaneous, dissociated feedback cannot underlie the Hebbian learning between two neuronal populations that underlies the desired improvements from rehabilitation (Mayford et al., 2012; Wolpaw and Wolpaw, 2012). Thus, conventional therapies may sometimes fail because they rely on open-loop feedback.

This clinical trial investigated the impact of combining BCI technology with MI and FES feedback for motor recovery of the lower limbs. The patients' real-time sensory feedback depended on their movement intention. We explore the relationship between the proposed rehabilitation method and rehabilitation results, including changes in walking speed. Patients who use the training mode may have better motor outcomes, and these outcomes will be compared with those from patients who had EGAIT_EE therapy.

2. Methods

2.1. Participants and study design

The study was approved by the Ethikkommission des Landes Oberösterreich (Nr. 1,126/2020) and the Bundesamt für Sicherheit im Gesundheitswesen (clinical trial number 101210314) in Austria. Each participant provided written informed consent before the pre-assessment. No adverse events were reported during the entire study period.

Each participant received 3 months of BCI-supported MI training with 3 weekly sessions, 25 sessions in total. Two pre-assessments (Pre1 and Pre2) and three post-assessments (Post1, Post2, and Post3) were performed by two certified physiotherapists and were evaluated by the research team. Pre1 and Pre2 were scheduled 1 month and a few days before the intervention (respectively), while Post1, Post2, and Post3 were carried out a few days, 1 month, and 6 months after the intervention (respectively).

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used when recruiting patients: understand written and spoken instructions; at least 10 days after stroke onset; a restriction of the lower extremities that prevents activities of daily life; stable neurological status; willing to participate in the study and to understand and sign the informed consent; available to attend meetings; be able to provide their diagnosis in detail including brain images; can perform 10 Meter Walking Test.

The patients' recruitment used the following exclusion criteria: ossification; contraction or stiffness of the wrist or ankle joint; metal (e.g., jewelry, piercings, buckles, surgical surface staples) in the target stimulation area; strong visual or auditory deficits that could prevent them from following the tasks; had a brain stem stroke; unable to tolerate cutaneous electrical stimulation; implanted medical devices such as pacemakers; implanted metallic fragments in the extremities which can limit the use of FES; cerebellar lesions; multiple stroke history; elevated intracranial pressure; pronounced hemi-neglect; uncontrolled epilepsy or seizures; under the influence of anesthesia or similar medication; fractures or lesions in the stimulated extremities; severe lung diseases, infections, renal insufficiency, liver damage, heart

diseases: severe pusher syndrome; significant circulatory disturbances of the stimulated extremities; inability to independently maintain a seated position (without assistance) for about 60 min; sensory disorders which can significantly affect the patient's ability to feel pain and react to unsuitable proprioceptive stimuli; diseases of the peripheral nervous system affecting the upper or lower limbs; botulinum-toxin treatment of the paretic lower limb during this study; cognitive impairments that could limit understanding of task instructions (MOCA ≤22).

2.3. Subjects

Twenty-five stroke patients were enrolled in this study. Three of them withdrew from the study after the Pre2 assessment. This analysis is based on the 22 remaining patients. Thirteen were males and nine females. The mean age was 53.79 years (SD = 17.22). The median time since the stroke was 47.63 months, IQR = [26.7–99.66]. The time since the stroke ranged between 7 months and 397 months. Twenty-one patients were in the chronic phase, and only 1 was in the subacute phase.

The functional measures recorded in Pre1 and Pre2 assessment did not show any significant differences, indicating that the patients' functional baseline was stable before the BCI treatment.

2.4. Functional and behavioral assessment

The following personal data were recorded for each participant: date of birth; sex; contact information; profession; hobbies, medical history and diagnosis; and previous and current rehabilitation if available.

A series of functional and behavioral scales were administered in pre- and post-assessments. These scales were used to evaluate each patient's performance in the following five spheres: (1) Gait speed, (2) Balance and gait quality, (3) Range of motion and muscular balance, (4) Motor function, and (5) Cognition and daily living activities. The assessments were conducted by a qualified healthcare professional with expertise in stroke rehabilitation.

2.4.1. Gait speed

The primary measure of this study is the gait speed assessed by the 10 Meter Walking Test (10MWT). The 10MWT assesses walking speed in meters per second over a short duration and is one of the most common ways to evaluate the functional mobility, gait, and balance for lower limb therapy (Wade, 1992). In this test, the individual walks 10 meters without physical assistance. The first and last two meters are not considered to provide time for acceleration and deceleration, and the time to walk the intermediate six meters is measured. Assistive devices can be used but should be kept consistent and documented from test to test. This test is repeated 3 times for more robust measurements.

2.4.2. Balance and gait quality

Timed Up and Go (TUG) assesses the time that patients need to get out of a chair, walk 3 meters, turn around, walk back 3 meters, and sit down again. This measure is related with the coordination and balance (Bohannon, 2006).

The Berg Balance Scale (BBS) was designed to assess static balance and risk to fall. Scores on the BBS range from 0 to 56. 0 and 56 indicate low and high level of function and balance, respectively.

The Functional Ambulation Classification (FAC) categorizes patients according to basic motor skills necessary for functional ambulation. Patients are classified into six different classes: (1) Non-functional, (2) Dependent Level III, (3) Dependent Level II, (4) Dependent with supervision, (5) Independent, level surfaces only, and (6) Independent.

2.4.3. Range of motion and muscular balance

We used the Modified Ashworth Scale (MAS) to assess spasticity, in which low punctuations reflect less spasticity (Meseguer-Henarejos et al., 2018). The MASAnkle was used to test ankle spasticity and the MASKnee scale tested knee spasticity.

The passive and active range of motion (ROMp and ROMa respectively) of the ankle and the knee movements were analyzed using a digital goniometer. The same starting position was used through all measurements in order to keep consistent results and detect changes in mobility.

Muscle strength of the ankle and the knee was assessed by the Manual Muscle Test (MMT), where high values are related to high muscle strength and low values to muscle weakness.

2.4.4. Motor function

The Fugl Meyer Assessment for the Upper Extremity and Lower Extremity (FMA-UE and FMA-LE) was used to evaluate the motor impairment. FMA-UE ranges from 0 to 66 points, and FMA-LE from 0 to 34. The score reflects impairment in limb functions, with lower scores corresponding to greater impairment, and is often used to assess the damage resulting from stroke and progress during therapy (Woytowicz et al., 2017).

2.4.5. Cognition and daily living activities

The Barthel Index (BI) is a questionnaire designed to test the patient's ability to perform daily living activities (Quinn et al., 2011).

We used the Stroop Color-Word Test (SCWT) and the Montreal Cognitive Assessment (MOCA) for cognitive assessment (under academic license), both tests were in paper version. The SCWT entails three different cards, each with a 10×10 matrix of words of color names, and the patient is asked to read as many words as possible in 45 s (Stroop, 1935). The first card is printed in black, the second card contains words printed in the same color (such as the word "BLUE" printed in blue), and the third card has words printed in a different color (such as the word "BLUE" printed in red). People with some types of cognitive dysfunctions will be able to read fewer words than healthy persons. The MOCA scale is widely used to assess the cognitive state of neurologic patients (Koski, 2013). This scale has 8 parts, and the total score ranges from 0 points to 30 points. Higher scores indicate better cognitive function and a MOCA score above 25 points is considered normal.

2.5. BCI system description

Patients were seated in a comfortable chair in front of an LCD screen with the arm resting on a desk and the leg on a support chair. Patients wore EEG caps with 16 active electrodes (g.Nautilus PRO,

g.tec medical engineering GmbH, Austria). EEG electrode positions were FC3, FCz, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CP1, CPz, CP2, CP4 and Pz according to the international 10/20 system. A reference electrode was placed on the right earlobe and a ground electrode at AFz (see Figure 1).

One pair of FES pads were placed on the skin over both the ankle and wrist extensors. The two FES devices (g.Estim FES, g.tec medical engineering GmbH, Austria) were set to a frequency of 50 Hz and a rectangular pulse width of 300 μs for the wrist and 400 μs for the ankle. The stimulation amplitude (in mA) was adjusted to find the optimal movement produced by electrical stimulation in both the healthy and affected limbs without inducing pain or spasms.

All participants were instructed to imagine dorsiflexion of the paretic ankle vs. opposite wrist based on the system indications. This is a type of MI task. Each recording session was divided in 3 runs with 40 trials for each limb type (wrist or ankle). Hence, each session had 240 MI trials. Each session lasted about 1 h, including time for preparation and cleaning.

The MI tasks were presented in a pseudo-random order with inter-trial intervals of 1 s. Figure 2 depicts the timing of each trial. Patients were first cued to the start of a trial with an attention beep. Two seconds later, an animated arrow in the avatar window pointed either left or right to instruct patients to imagine moving the ankle or hand. At the same time, an auditory instruction cued the patient to imagine either ankle or hand movement during that trial. During the feedback phase, the FES and avatar were triggered when the system detected MI of the correct limb. If no MI was detected, feedback was deactivated. Feedback was updated five times per second.

2.6. Signal processing

EEG signals were sent from a biosignal amplifier and were bandpass filtered (4th order Butterworth filter) between 8 and 30 Hz. Then, common spatial patterns (CSP) were applied to transform the data to a new matrix with minimal variance of one class and maximal variance of the other class (Blankertz et al., 2008). Each class reflects the MI of the cued limb versus the MI of the other limb. The CSP method calculated a 16×16 projection matrix from 16 EEG channels for each left and right trial X. This matrix is a set of spatial patterns that may reflect regional cortical activation during hand MI. The decomposition of a trial is written as $Z = WX$. This transformation projects the variance of X onto the rows of Z and results in 16 new time series. The columns of $A = W^{-1}$ are a set of CSPs and are time-invariant EEG distributions. The variance for left trials is largest in the first row of Z and decreases with the subsequent rows. The opposite occurs in a trial with right trials. The variances were extracted as reliable features of the newly calculated 16 time series for the binary classification (left vs. right).

According to Mueller-Gerking's work, the optimal number of CSPs should be four (to reduce the dimensionality of EEG) (Muller-Gerking et al., 1999). Using an artifact corrected training set, XT, only the first and last two rows ($p = 1, 2, 15, and\ 16$) of W were used to process new input X. Then, the variance ($VARp$) of the time series was calculated for a time window T. After normalizing and log-transforming, four feature vectors were obtained via equation 1.

$$f_p = \log\left(\frac{VAR_p}{\sum_{p=1}^{4} VAR_p}\right) \quad (1)$$

A linear discriminant analysis (LDA) classified each trial as either left or right MI. When the input signals were correctly classified according to the assigned task, the feedback devices were triggered. This online classification and control of the FES and avatar were updated every 20 ms.

We estimated offline classification accuracy via a 10-fold cross validation. This refers to partitioning a sample of movements into 10 complementary subsets and validating the analysis on one subset (called the validation set or testing pool) and training the CSPs and classifier on the other subsets (called the training pool).

The accuracy was calculated (in steps of half a second) for all trials in the testing pool within a 4.5 s time window beginning 1.5 s after the attention beep and ending with the end of the trial. For each step and each single trial, the classification result is either 100% or 0%. The accuracy of all trials of the test pool is then averaged for each single step, resulting in accuracy levels ranging between 0 and 100%. After averaging all 10 repetitions of the cross validation, the maximum value during the feedback phase was noted as the session accuracy.

FIGURE 1
This photograph shows components of the BCI system used in this study, including a monitor with an avatar to instruct the patient and provide visual feedback. The EEG system measures the brain activity that the BCI analyzes in real-time. As soon as the BCI system detects foot or hand movement imagination, the avatar moves its foot or hand while the FES activates to produce the movement.

2.7. Statistical analysis methods

The software used for the statistical analysis was MATLAB R2020a and RStudio (R version 4.0.3 and RStudio version 2022.02.4). We designated the mean of Pre1 and Pre2 as the baseline value for each outcome measure [Baseline = (Pre1 + Pre2)/2]. Post-assessment was the outcome measure after completion of the 25 training sessions. The primary and secondary outcomes were statistically analyzed after a normal distribution was determined with the Shapiro–Wilk test. The significance threshold was set to $\alpha = 0.05$. The statistical test was chosen according to the normality of the sample, the homogeneity of

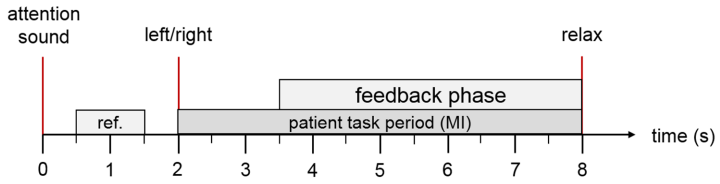

FIGURE 2
Trial description. The patient hears an attention sound at trial onset. At second 2, the system presents an arrow on the computer screen to instruct the patient to imagine ankle or hand movement (through the left/right cue) and a corresponding verbal instruction in the patient's native language. During the feedback period, the FES and the virtual avatar are activated if the MI was classified correctly. At second 8, the patient hears a relax command.

variance (Levene's or Brown-Forsythe test of equal variance) and sample size. Descriptive statistics will be shown as mean and the standard deviation (SD), or the median with the inter-quartile rate (IQR) of 0.25 and 0.75.

A two-tailed paired sample *t*-test or a Wilcoxon signed rank test was used to investigate the outcome of changes between two different assessments in the same group of patients.

For multiple comparisons, *p*-values were corrected using the False Discovery Rate (FDR) described by Benjamini and Hochberg (1995), which explains that adjusted *p*-values can be greater than 1. All *p*-values greater than 1 were converted to 1. The *p*-values below 0.05 that are shown in the results tables are marked in red color.

First, we analyzed the functional improvement after the BCI therapy using paired comparison (*t*-test or Wilcoxon signed rank test) between PRE values and Post1 values. The second step was to analyze the middle-term effects 1 month after therapy by comparing Post1 vs. Post2, and long-term effects 6 months after the therapy by comparing Post1 vs. Post3.

2.8. Ethics for re-use

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

3. Results

Twenty-seven patients were assessed for eligibility. Two of these patients were immediately excluded because their stroke location did not meet the inclusion criteria. The other twenty-five patients were assigned to the intervention group (BCI group). Three patients dropped-out from the study. One of those three patients decided to not continue in the study because of a loss of interest. The other two patients could not finish the study because they lacked transportation to attend the sessions. Hence, twenty-two patients finished the BCI sessions, and only results from these patients were analyzed further.

3.1. Functional improvement after BCI therapy

The results in this section summarize differences from the Baseline to Post1 assessments across different tests (please see Table 1). We used the Wilcoxon signed rank test or paired t-test for statistical analysis, depending on whether or not the data presented a normal distribution. The improvement of each scale is presented using the median and IQR, and the mean and SD are also provided if differences are significant.

Gait function was mainly assessed by 10MWT and the balance and coordination by TUG, all of which show some significant improvement after the therapy.

3.2. Gait speed

The primary measure of this study is the 10MWT. This test has two different parameters: Self-Selected Velocity (10MWT-SS) and Fast Velocity (10MWT-FV). The results can be presented based on the time (s) or speed (m/s).

3.2.1. Self-selected velocity (10MWT-SS)

The results at the baseline ($\bar{x}$ = 8.5 s IQR = [6.8 to 28.91]) and Post1 assessment ($\bar{x}$ = 6.81 s IQR = [6.03 to 18.54]) show a significant reduction in the test time, Δ10MWT-SS [t] = −1.58 s IQR = [−2.23 to −0.49], Z = 4.901, $p < 0.001$. The results also show an increase of the test speed from the baseline ($\bar{x}$ = 0.71 m/s IQR = [0.21 to 0.88]) and Post1 assessment ($\bar{x}$ = 0.88 m/s IQR = [0.32 to 1]), Δ10MWT-SS [v] = 0.08 m/s IQR = [0.02 to 0.16], $Z = 4.718$, $p < 0.001$. See Figure 3A.

A non-parametric Friedman test of differences among repeated measures was conducted and rendered a Chi-squared value of 33.379 with $p < 0.001$ Therefore, a post-hoc test was conducted using the Nemenyi multiple comparison test. Table 2 presents the results.

3.2.2. Fast velocity (10MWT-FV)

The results of the 10MWT-FV in the baseline ($\bar{x}$ = 5.78 s IQR = [5.15 to 26.08]) vs. Post1 assessment ($\bar{x}$ = 5.14 s IQR = [4.56 to 15.09]) show a significant reduction in the test time, Δ10MWT-FV [t] = −0.99 s IQR = [−3.9 to −0.46], Z = 3.442, $p = 0.012$. The results also show an increase of the test speed from the baseline ($\bar{x}$ = 1.09 m/s IQR = [0.25 to 1.2]) and Post1 assessment ($\bar{x}$ = 1.26 m/s IQR = [0.41 to 1.43]), Δ10MWT-FV [v] = 0.16 m/s IQR = [0.08 to 0.3], Z = 4.649, $p < 0.001$. The mean improvement with 95% CI: Δ10MWT-FV [v] = 0.19, 95% CI [0.13, 0.25]. See Figure 3B.

A non-parametric Friedman test of differences among repeated measures was conducted and rendered a Chi-squared value of 43.12 with $p < 0.001$ Therefore, a *post hoc* test was conducted using the Nemenyi multiple comparison test.

TABLE 1 Summary of the functional improvement after BCI treatment.

Scale	*n*	Baseline Median [IQR]	Post1 Median [IQR]	Δ Median [IQR]	Δ Mean (SD)	*p*
BI	22	90 [80 to 90]	90 [81.25 to 95]	1.25 [0 to 5]	2.73 (SD = 3.26)	0.021
FMA-UE m	22	22.75 [16.25 to 32.75]	24 [18 to 37]	0.75 [−0.38 to 5.62]	2.43 (SD = 4.5)	0.103
FMA-LE m	21	24 [20.5 to 25.5]	25 [22 to 27]	1 [0 to 2.5]	1.1 (SD = 2.68)	0.166
MOCA	20	26 [22.88 to 28.25]	27 [24 to 30]	0.5 [−0.5 to 1.62]	0.82 (SD = 1.58)	0.126
SCWT Word	21	73 [46 to 96]	80 [47 to 98]	3 [−1 to 6]	4.67 (SD = 7.64)	0.044
SCWT Color	21	68 [48 to 93]	65 [50 to 92]	1 [−2 to 6]	1.74 (SD = 6.8)	0.383
SCWT ColorWord	21	24 [15.5 to 30]	26 [18 to 34]	1.5 [0 to 6]	2.9 (SD = 4.06)	0.024
MAS knee	22	0 [0 to 1]	0 [0 to 1]	0 [0 to 0]	−0.2 (SD = 0.47)	0.195
MAS ankle	22	3 [1 to 3]	2.5 [1 to 3]	0 [−1 to 0]	−0.42 (SD = 0.55)	0.038
ROM passive Ankle DF	22	24.75 [19.35 to 31.26]	30.05 [21.33 to 37.25]	4.32 [1.16 to 10.09]	5.67 (SD = 7.89)	0.023
ROM passive Ankle_FL	22	15.05 [8.59 to 21.1]	19.15 [12.92 to 22.73]	2.25 [−0.94 to 5.88]	2.01 (SD = 6.53)	0.281
ROM passive Knee FL	21	128.9 [124.1 to 133.95]	135.3 [126.6 to 139.7]	2.95 [−1 to 9.25]	7.35 (SD = 15.2)	0.043
ROM active Ankle DF	22	7.7 [1.63 to 18.41]	17.7 [2.08 to 30.6]	5.95 [0.45 to 8.64]	7.02 (SD = 7.27)	0.008
ROM active Ankle FL	22	5.55 [3 to 9.18]	10 [3.7 to 15.6]	2.13 [0 to 5.82]	3.7 (SD = 5.84)	0.031
ROM active Knee FL	21	114.6 [109.2 to 118.1]	117.1 [112 to 124.6]	2.5 [−1.1 to 9.5]	6.21 (SD = 12.96)	0.126
MMT Ankle DF	22	6 [4 to 7]	7 [4.5 to 9]	0 [0 to 1]	0.73 (SD = 1.03)	0.031
MMT Ankle FL	22	6 [4 to 7.75]	7.5 [4.25 to 9]	0.25 [0 to 1]	0.84 (SD = 1.18)	0.024
MMT Knee EX	22	8.25 [6.25 to 9]	9 [8 to 10]	0 [0 to 1]	0.68 (SD = 0.91)	0.031
MMT Knee FL	22	9 [8 to 10]	10 [9 to 10]	0 [0 to 1]	0.34 (SD = 0.56)	0.068
TUG	21	14.09 [13.5 to 28.97]	11.69 [11 to 27]	−2.59 [−3.62 to −1.97]	−5.73 (SD = 8)	< 0.001
10MWT SS	22	8.5 [6.8 to 28.91]	6.81 [6.03 to 18.54]	−1.58 [−2.23 to −0.49]	−3.89 (SD = 6.45)	< 0.001
10MWT FV	22	5.78 [5.15 to 26.08]	5.14 [4.56 to 15.09]	−0.99 [−3.9 to −0.46]	−4.75 (SD = 9.09)	0.010
BBS	22	51.25 [28.25 to 54.75]	52.5 [31.75 to 55]	0 [0 to 1.75]	0.61 (SD = 2.18)	0.294
FAC	22	5 [4.12 to 6]	6 [5 to 6]	0 [0 to 0.88]	0.3 (SD = 0.45)	0.053

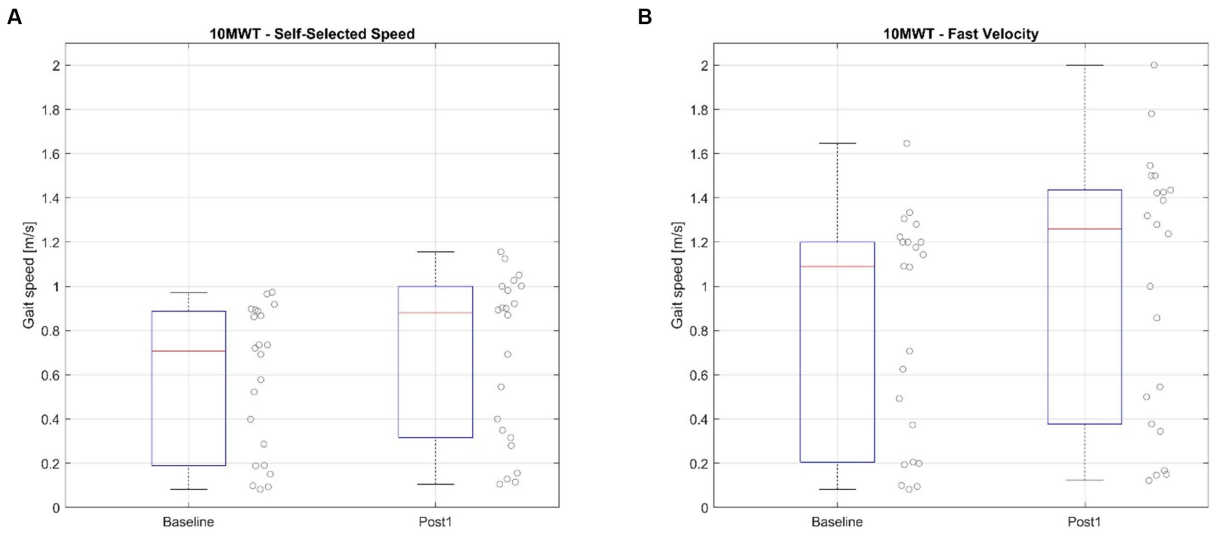

FIGURE 3
Ten Meter Walking Test before and after the BCI treatment. **(A)** Shows the values of the Self-selected speed mode, **(B)** shows the values of the Fast Velocity mode.

TABLE 2 Repeated measures analysis for the 10MWT.

10MWT						
	Baseline	S6	S11	S16	S21	Post1
S6	0.8564	–	–	–	–	–
S11	0.3994	0.9906	–	–	–	–
S16	0.0580	0.6791	0.9767	–	–	–
S21	0.0027	0.1547	0.5620	0.9716	–	–
Post1	0.0001	0.0112	0.1015	0.5382	0.9716	–
Post2	0.0024	0.1427	0.5382	0.9657	1.000	0.9767

Post hoc Nemenyi test.

3.3. Balance and gait quality

3.3.1. Timed up and go

Timed Up and Go test (TUG) was also evaluated for this study. This scale asks people to stand up, walk 3 m, turn around, walk back 3 m and sit down. Patient #9 was not able to perform the TUG test before the therapy, but he could do it in 92.0 s during the Post1 assessment. This patient has been excluded from the time analysis (ΔTUG [t]). However, this patient has been included in the TUG-speed based analysis (ΔTUG [v]). The Shapiro–Wilk test was significant, so a non-parametric test was used for this comparison.

The results in the TUG before the therapy ($\bar{x}$ = 14.09 s IQR = [13.5 to 28.97]) and Post1 assessment ($\bar{x}$ = 11.69 s IQR = [11–27]) show a significant reduction in the test time, ΔTUG [t] = −2.59 s IQR = [−3.62 to −1.97], Z = 4.681, $p < 0.001$. The results also show an increase of the test speed from the baseline ($\bar{x}$ = 0.39 m/s IQR = [0.15 to 0.44]) to Post1 assessment ($\bar{x}$ = 0.51 m/s IQR = [0.22 to 0.55]), ΔTUG [v] = 0.08 m/s IQR = [0.02 to 0.1], Z = 4.718, $p < 0.001$. See Figure 4.

A non-parametric Friedman test of differences among repeated measures was conducted and rendered a Chi-squared value of 44.415 with $p < 0.001$. Therefore, a post-hoc test was conducted using the Nemenyi multiple comparison test shown in Table 3.

3.3.2. Functional ambulation classification

The Functional Ambulation Classification (FAC) categorizes the ambulation on different degrees of dependency. This scale ranges from 0 to 6, where 6 reflects totally independent ambulation and 0 represents the inability to walk. Scores from 0–3 indicate dependence, while 4–5 show reflect independent walking on level ground (4) or uneven surfaces (5). Only two patients' scores on this scale changed. Subject #3 increased one point (FAC_Baseline = 5, FAC_Post1 = 6), and subject #10 increased one point (FAC_Baseline = 5, FAC_Post1 = 6). The median improvement on this scale was ΔFAC = 0 points, and IQR = [0–0.88], Z = 2.439, $p = 0.053$.

3.3.3. Berg balance test

The Berg Balance Test (BBS) assess the balance on different conditions. This scale ranges from 0 to 56, where higher scores reflect better balance. The median score on this scale at the baseline was $\bar{x}$ = 51.25 points, IQR = [28.25 to 54.75], where 2 patients achieve the maximum score on this scale before the therapy. These high scores during the pre-assessment suggest that this scale has an important ceiling effect limitation and that the room for improvement is relatively low. The median score on the Post1 assessment was $\bar{x}$ = 52.5 points, IQR = [31.75 to 55]. The median improvement after the treatment is ΔBBS = 0 points, and IQR = [0–1.75], Z = 1.341, $p = 0.294$.

3.4. Range of motion and muscular balance

3.4.1. Range of motion

3.4.1.1. Ankle

3.4.1.1.1. Flexion

The active ROM of the ankle flexion (ROMa_A_FL) at the baseline was $\bar{x}$ = 5.55°, IQR = [3 to 9.18], and the median ROMa_A_FL after the therapy was $\bar{x}$ = 10°, IQR = [3.7 to 15.6]. This improvement was significant, ΔROMa_A_FL = 2.13°, and IQR = [0–5.82], Z = 2.746, $p = 0.031$.

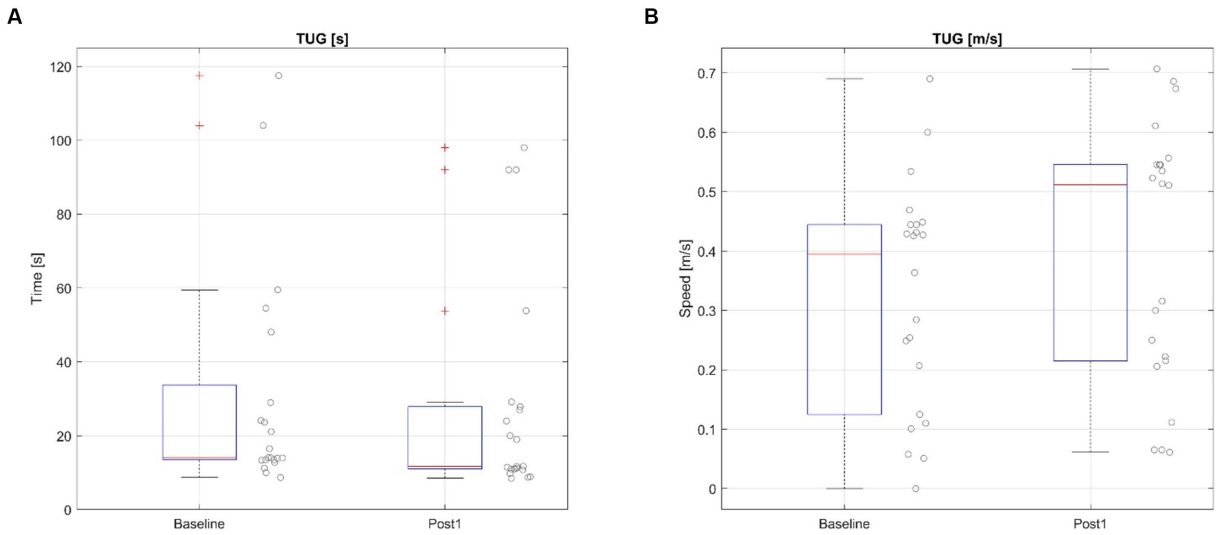

FIGURE 4
Timed Up and Go test before and after the BCI treatment based on time **(A)** and speed **(B)**.

TABLE 3 **Repeated measures analysis for the TUG.**

	Baseline	S6	S11	S16	S21	Post1
S6	0.88616	-	-	-	-	-
S11	0.02809	0.46745	-	-	-	-
S16	0.16744	0.87176	0.99452	-	-	-
S21	0.00016	0.02012	0.83997	0.42167	-	-
Post1	< 0.00001	0.00238	0.46745	0.13137	0.99703	-
Post2	0.00007	0.01120	0.74477	0.31565	1.00000	0.99959

Post hoc Nemenyi test.

However, the passive ROM of the ankle flexion (ROMp_A_FL) at the baseline was $\bar{x} = 15.05°$, IQR = [8.59 to 21.1], and the median ROMp_A_FL after the therapy was $\bar{x} = 19.15°$, IQR = [12.92 to 22.73]. This improvement was not significant, ΔROMp_A_FL = 11.3°, and IQR = [−0.94 to 5.88], Z = −1.442, $p = 0.281$.

3.4.1.1.2. Dorsiflexion

The active ROM of the ankle dorsiflexion (ROMa_A_DF) at the baseline was $\bar{x} = 7.7°$, IQR = [1.63 to 18.41], while the median ROMa_A_DF after the therapy was $\bar{x} = 17.7°$, IQR = [2.08 to 30.6]. This improvement was significant, ΔROMa_A_DF = 5.95°, and IQR = [0.45–8.64], Z = 3.598, $p = 0.008$.

The passive ROM of the ankle dorsiflexion (ROMp_A_DF) at the baseline was $\bar{x} = 24.75°$, IQR = [19.35 to 31.26], and the median ROMp_A_DF after the therapy was $\bar{x} = 30.05°$, IQR = [21.33 to 37.25]. This improvement was significant, ΔROMp_A_DF = 4.32°, and IQR = [1.16–10.09], Z = −3.368, $p = 0.023$.

3.4.1.2. Knee

3.4.1.2.1. Flexion

The active ROM of the knee flexion (ROMa_K_FL) at the baseline was $\bar{x} = 114.6°$, IQR = [109.2 to 118.1], and the median ROMa_K_FL after the therapy was $\bar{x} = 117.1°$, IQR = [112 to 124.6]. This improvement was not significant, ΔROMa_K_FL = 2.5°, and IQR = [−1.1 to 9.5], Z = 1.929, $p = 0.126$.

The passive ROM of the knee flexion (ROMp_K_FL) at the baseline was $\bar{x} = 128.9°$, IQR = [124.1 to 133.95]. The median ROMp_K_FL after the therapy was $\bar{x} = 135.3°$, IQR = [126.6 to 139.7]. This improvement was not significant, ΔROMp_K_FL = 2.95°, and IQR = [−1 to 9.25], Z = 2.572, $p = 0.043$.

3.4.2. Modified Ashworth scale

The spasticity in the ankle at the baseline was $\bar{x} = 3$ points, IQR = [1 to 3], which changed to $\bar{x} = 2.5$ points, IQR = [1–3] in the Post1. This improvement was significant, ΔMAS_ankle = 0 points, and IQR = [−1 to 0], Z = 2.656, $p = 0.038$.

3.4.3. Manual muscle test

3.4.3.1. Ankle

The Manual Muscle Test (MMT) of the ankle flexion (MMT_A_FL) at the baseline was $\bar{x} = 6$ points, IQR = [4.12 to 8.38]. In the Post1, it was $\bar{x} = 8.5$ points, IQR = [5–9]. This improvement was significant, ΔMMT_A_FL = 0.25 points and IQR = [0–1], Z = 2.907, $p = 0.024$.

The MMT of the ankle dorsiflexion (MMT_A_DF) at the baseline was $\bar{x} = 6$ points, IQR = [4–7], and in the Post1 was $\bar{x} = 7$ points,

IQR = [4.5 to 9]. This improvement was significant, ΔMMT_A_DF = 0.73 points and IQR = [0–1], Z = 2.763, $p = 0.031$.

3.4.3.2. Knee

The Manual Muscle Test (MMT) of the knee flexion (MMT_K_FL) at the baseline was $\bar{x} = 9$ points, IQR = [8–10], and was $\bar{x} = 10$ points, IQR = [9–10] in the Post1. This improvement was not significant, ΔMMT_K_FL = 0.34 points and IQR = [0–1], Z = 2.33, $p = 0.068$.

The MMT of the knee extension (MMT_K_EX) at the baseline was $\bar{x} = 8.25$ points, IQR = [6.25 to 9]. In the Post1, it was $\bar{x} = 9$ points, IQR = [8–10]. This improvement was significant, ΔMMT_K_EX = 0.68 points and IQR = [0–1], $Z = 2.777$, $p = 0.031$.

3.5. Motor function of upper and lower limbs

The motor function of the upper and lower extremities was assessed using the motor section of the Fugl-Meyer Assessment (FMA). The FMA for the upper extremities (FMA-UE) ranges from 0 to 66 points, while the FMA for the lower extremities (FMA-LE) ranges from 0 to 36 points.

The FMA-UE of the upper extremity at the baseline was $\bar{x} = 22.75$ points, IQR = [16.25 to 32.75]. It was $\bar{x} = 24$ points, IQR = [18–37] in the Post1. This improvement was not significant, ΔFMAue_m = 0.75 points and IQR = [−0.38 to 5.62], Z = 2.115, $p = 0.103$.

The FMA-LE of the upper extremity at the baseline was $\bar{x} = 24$ points, IQR = [20.5 to 25.5]. In the Post1, it was $\bar{x} = 25$ points, IQR = [22–27]. This improvement was not significant, ΔFMAle_m = 1 points and IQR = [0–2.5], Z = −1.872, $p = 0.166$.

3.6. Cognition and daily living activities

3.6.1. Barthel index

The score for daily living activities assessed by the Barthel Index (BI) at the baseline was $\bar{x} = 90$ points, IQR = [80–90]. In the Post1, the BI was $\bar{x} = 90$ points, IQR = [81.25 to 95]. This improvement was significant, ΔBI = 1.25 points and IQR = [0–5], Z = 3.078, $p = 0.021$.

3.6.2. Montreal cognitive assessment

Cognitive abilities were assessed by the Montreal Cognitive Assessment. This test contains 7 sections: Visual-execution (Vis-Exe), Abstraction (Abst), Attention (Att), Delayed recall (DRec), Language (Lang), Naming (Nam) and Orientation (Ori). The total score of the MOCA scale (MOCA_total) at the baseline was $\bar{x} = 26$ points, IQR = [22.88 to 28.25], and changed to $\bar{x} = 27$ points, IQR = [24–30] in the Post1. This improvement was not significant, ΔMOCA = 0.5 points and IQR = [−0.5 to 1.62], Z = 1.959, $p = 0.126$.

3.6.3. Stroop color word test

Cognitive state was also assessed by the Stroop Color Word test (SCWT). This test contains three different sub-test or cards: the Word card, the Color card and the Color-Word card.

The Word card score at the baseline was $\bar{x} = 73$ points, IQR = [46–96], and in the Post1 was $\bar{x} = 80$ points, IQR = [47–98]. This improvement was not significant, ΔSCWT_Word = 3 words and IQR = [−1 to 6], $Z = -2.798$, $p = 0.044$.

The Color card score at the baseline was $\bar{x} = 68$ points, IQR = [48–93]. In the Post1, it was $\bar{x} = 65$ points, IQR = [50–92]. This improvement was not significant, ΔSCWT_Color = 1 word and IQR = [−2 to 6], Z = −1.171, $p = 0.383$.

The Color-Word card score at the baseline was $\bar{x} = 24$ points, IQR = [15.5 to 30], and was $\bar{x} = 26$ points, IQR = [18–34] in the Post1. This improvement was significant, ΔSCWT_ColorWord = 1.5 words and IQR = [0–6], $Z = -3.28$, $p = 0.024$.

3.7. Functional outcomes in the long term

The analysis of the long-term effects is based on comparisons between the Post1 vs. Post2 and Post1 vs. Post3 assessments. Table 4 shows the scales that shown a significant results in the statistical analysis.

3.7.1. Middle-term effects

The only significant change seen in the middle-term was in the functionality of the upper limb assessed by the Fugl Meyer Assessment, ΔFMAue_m = 1.5 points and IQR = [0–3], Z = 2.115, $p = 0.021$. This change shows that the therapy can help the patients improve the motor ability of the hand during the first month after the therapy.

3.7.2. Long-term effects

Seven patients did not complete the Post3 assessment. Five of them did not come to the Post3 assessment due to lack of motivation, and two of them had personal and logistical issues that prevented

TABLE 4 Summary of the changes in tests of long-term functional outcomes that showed statistical significance.

Scale	*N*	Post1 vs. Post2 Median [IQR]	*p*	*n*	Post1 vs. Post3 Median [IQR]	*p*
FMA-UE m	22	1.5 [0 to 3]	0.021	15	4 [3 to 7]	0.021
MMT Ankle FL	22	0 [0 to 0]	0.245	15	1 [0 to 1]	0.046
TUG	22	0.03 [−0.61 to 0.97]	0.704	14	1.61 [0.68 to 3.34]	0.021
10MWT SS	22	0.06 [−0.29 to 0.91]	0.5	15	0.64 [0.05 to 1.19]	0.038

them from coming to the therapy center. Therefore, the analysis of the long-term effects (Post3) is presented using the data from 15 patients.

The functional evaluation 6-months after the therapy shows an increase of the FMAue scale, ΔFMAue_m = 4 points and IQR = [3–7], $Z = 2.115$, $p = 0.021$.

The comfortable gait speed also increased significantly 6 months after the therapy, Δ10MWT-SS = 0.64 m/s and IQR = [0.05–1.19], Z = 4.901, $p = 0.038$.

3.8. BCI performance

The BCI performance was evaluated using the motor imagery accuracy provided by the system after each session. Figure 5 shows the evolution of the motor imagery accuracy during the treatment for each patient (gray lines). The mean MI accuracy for all participants was 82.68% (SD = 10.05).

3.9. Adverse events

No adverse events have been reported during the study.

4. Discussion

This study shows that 22 chronic stroke patients with a median time since stroke onset of 4 years improved their walking speed by 0.19 m/s 95% CI [0.13, 0.25] on average. All of these patients performed 18.75 h of BCI based treatment for the lower limb in a sitting down position.

The results show that patients significantly improved their gait speed assessed by the 10MWT. This improvement is above the substantial meaningful change, 0.14 m/s (Perera et al., 2006). Results also showed that treatment increase patients' performance of daily living activities, improved their cognitive skills, reduced spasticity in the ankle and increased the ankle range of motion and muscular strength of the main joints involved into the gait patterns.

The functional improvement achieved after the BCI training was maintained 1 month after the end of the therapy. Middle-term effects were assessed in the Post2 assessment, 1 month after the last BCI session. Patients reported an increase of the upper extremity function assessed by the FMA-UE scale. This improvement contributed to the increased participation of the subjects in the daily living activities. The upper extremity functionality increases continued at least until the long-term assessment, 6 months after the end of the therapy (Post3). Patients also reported an increase of the comfortable gait speed assessed by the 10MWT-SS.

Based on the repeated measures analysis of the 10MWT, patients started showing a significant improvement of gait speed after session 21. Therefore, the protocol based on 25 sessions distributed in 3 times per week seems to be a viable treatment schedule, although further exploration of different treatment schedules could identify more effective approaches.

On one hand, a large meta-analysis done by Mehrholz et al. (2018) shows that treatment based on electromechanical gait devices with end

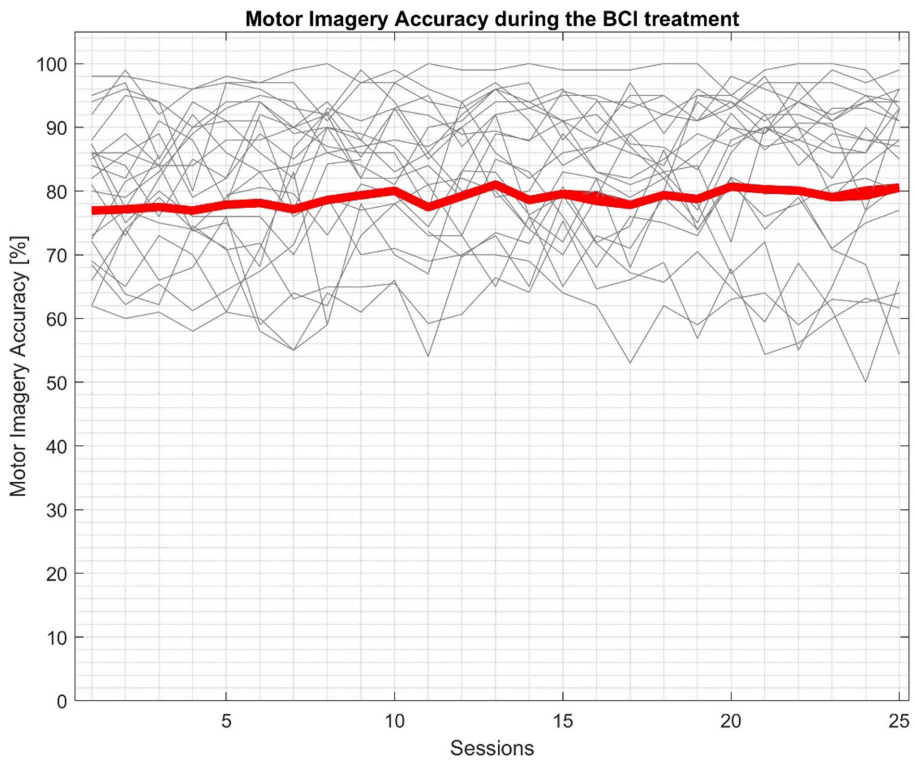

FIGURE 5
BCI performance during the BCI therapy. Gray lines represent the participants accuracy during the BCI treatment of each session, while the red line shows the mean accuracy of all participants.

effector (EGAIT_EE) seems to be one of the most powerful approaches for the gait rehabilitation after stroke. Those devices are able to reproduce walking patterns with high accuracy, and patients can train their gait with different levels of body weight support. Pohl et al. (2007) conducted a randomized clinical trial including 170 patients in the acute state (less than 60 days since the stroke onset). This study reported that patients in the EGAIT_EE group ($n = 77$) increased gait speed 0.31 m/s (SD = 0.40), while patients in the control group improved only 0.18 m/s (SD = 0.28). This big improvement occurred because the treatment was given in a very early stroke stage and the baseline gait velocity was substantially lower than the mean gait speed of this study. The same reasoning can explain the results from other clinical trials like Werner et al. (2002), Tong et al. (2006), Chua et al. (2016), Aprile et al. (2019), and Kim et al. (2019). Nevertheless, other studies such as Peurala et al. (2005) included patients in the chronic stage and obtained results similar to our study; the change in the gait speed was 0.11 m/s (SD = 0.05) in the EGAIT_EE group.

On the other hand, other BCI devices reported similar improvements in gait speed with the same target population. Chung et al. (2020) carried out a clinical trial with both arms to compare the BCI-based treatment to the functional electrical stimulation (FES) treatment alone. Results show that patients in the BCI group improved by 0.13 m/s (SD = 0.03) while the improvement in the control group was about 0.05 m/s (SD = 0.04). Mihara et al. (2021) had a similar approach with a two-arm clinical randomized trial. Fifty-four patients were recruited for this study, with 28 in a real feedback group and 26 in the sham feedback group. The results demonstrated that patients in the experimental group significantly increased their gait speed by 0.10 m/s (SD = 0.08), and patients in the sham group 0.07 m/s (SD = 0.06). Finally, Mrachacz-Kersting et al. (2016) reported the highest improvement in gait speed in the control 0.32 m/s (SD = 0.33) and experimental groups 0.49 m/s (SD = 0.55). This big improvement could be explained because 12 out of 24 participants were not able to perform the gait test before the treatment, but 8 of them could perform it after the last session. This fact also explains the high SD in both groups.

Most of the gait rehabilitation techniques assumed that patients should be standing when retraining their gait patterns. Usually, those techniques require a system for supporting the user's weight, especially in moderate or severely impaired patients. Other systems that use functional electrical stimulation also recommend the stimulation during walk. The BCI device used in this study (recoveriX, g.tec medical engineering GmbH) does not need a body weight support system because patients are seated during the BCI training. This is a safer approach because it reduces the risk of falling, but patients can still train gait patterns and thereby increase functionality, gait speed and coordination and balance. The role of neurofeedback provided through BCI technology seems to be key in the rehabilitation process.

Another discussion point is the low sensitivity of the FMA-LE to detect functional changes in the lower extremity. The FMA-LE functional scale is oriented to evaluate specific movements of the lower extremity and not the walking ability. From the functionality point of view, the main task of the lower extremity is walking, this fact leads researchers to question the sensitivity of the FMA-LE scale for the detection of changes in gait ability in stroke patients. All the gait scales used in this protocol showed significant changes, but this contrasts with the lack of significant results obtained on the FMA-LE scale.

There were no significant changes in the MOCA scale. This result may be explained in part by the exclusion criteria. All participants had a MOCA score of 22 or higher, and they did not have major cognitive deficits.

The results involving the spasticity in the knee (MAS_Knee) and balance (BBS) were not significant. This is because most of the study participants did not show spasticity in the knee before the study or the values in the BBS at the baseline were high. Finally, the FAC assessment was not sensitive enough to detect changes in the gait for this population.

The long-term results shown in Table 4 are also clinically relevant to understand the progression of rehabilitation at a later stage. Our results show that stroke patients continued to improve their functional abilities even 6 months after therapy. Patients improved their gait, gained more independence for other complex tasks, and increased their participation in society – all of which probably contributed to this ongoing improvement. It is also important to note the positive long-term effect on the upper limb. Patients showed significant improvement in upper extremity function 1 month after therapy and continued to improve 6 months after therapy. This is a clear example of how the positive effect of gait rehabilitation has a positive impact on whole-body rehabilitation.

The BCI performance plot indicates that participants were able to control the system well, which fits well to the work of Ang et al. (2011). The MI accuracy reflects the degree of stimulation that the system delivered to the user. Therefore, given the mean MI accuracy across all participants (82.68%), the therapy was highly successful in terms of the FES and VR dosage.

This study has some limitations. First, the patients involved in this study were in the chronic stage of stroke recovery, which may limit the generalizability of the results to the subacute phase. Previous research has shown that the time since stroke onset is a crucial factor for functional rehabilitation, and that patients in the subacute phase tend to improve gait functionality more than patients in the chronic stage. Second, this study did not have a control group, which prevented a direct comparison to a sham condition using the same methods. A control group would have allowed us to rule out the effects of spontaneous recovery, motivation, attention, and placebo on the outcomes of the BCI therapy.

No adverse events were reported during the investigation. This is also consistent with the studies mentioned above that use BCI devices for stroke rehabilitation. The customization of the FES settings for each individual, the patient's safe (seated) position during the therapy, the short session time and the easy set-up of this BCI system help explain that patients did not have side effects.

The clinical investigation has been conducted in accordance with the GCP.

Data availability statement

The datasets presented in this article are not readily available because patients' data need to be treated according to current data protection laws and ethical guidelines. Requests to access the datasets should be directed to CG, guger@gtec.at.

Ethics statement

The studies involving humans were approved by Ethikkommission des Landes Oberösterreich (Nr. 1,126/2020). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed

consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MS-R: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. WC: Investigation, Writing – review & editing. RO: Supervision, Writing – review & editing. SS: Data curation, Writing – review & editing. TO: Writing – review & editing. KK: Writing – review & editing. SL: Writing – review & editing. BA: Writing – review & editing. CG: Supervision, Writing – review & editing.

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Conflict of interest

MS-R, WC, RO, and SS were employed at g.tec medical engineering. CG was CEO of g.tec medical engineering, who developed and sells the BCI system used in this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Ambrosini, E., Ferrante, S., Pedrocchi, A., Ferrigno, G., and Molteni, F. (2011). Cycling induced by electrical stimulation improves motor recovery in postacute hemiparetic patients: a randomized controlled trial. *Stroke.* 42, 1068–1073. doi: 10.1161/STROKEAHA.110.599068

Ang, K. K., Chua, K. S. G., Phua, K. S., Wang, C., Chin, Z. Y., Kuah, C. W. K., et al. (2015). A randomized controlled trial of EEG-based motor imagery brain-computer Interface robotic rehabilitation for stroke. *Clin. EEG Neurosci.* 46, 310–320. doi: 10.1177/1550059414522229

Ang, K. K., Guan, C., Chua, K. S. G., Ang, B. T., Kuah, C. W. K., Wang, C., et al. (2011). A large clinical study on the ability of stroke patients to use an EEG-based motor imagery brain-computer interface. *Clin. EEG Neurosci.* 42, 253–258. doi: 10.1177/155005941104200411

Aprile, I., Iacovelli, C., Goffredo, M., Cruciani, A., Galli, M., Simbolotti, C., et al. (2019). Efficacy of end-effector robot-assisted gait training in subacute stroke patients: clinical and gait outcomes from a pilot bi-centre study. *Neuro Rehabil.* 45, 201–212. doi: 10.3233/NRE-192778

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser.* 57, 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Blankertz, B., Tomioka, R., Lemm, S., Kawanabe, M., and Muller, K. R. (2008). Optimizing spatial filters for robust EEG single-trial analysis. *IEEE Signal Process. Mag.* 25, 41–56. doi: 10.1109/MSP.2008.4408441

Bohannon, R. W. (2006). Reference values for the timed up and go test: a descriptive meta-analysis. *J. Geriatr. Phys. Ther.* 29, 64–68. doi: 10.1519/00139143-200608000-00004

Bolognini, N., Russo, C., and Edwards, D. J. (2016). The sensory side of post-stroke motor rehabilitation. *Restor. Neurol. Neurosci.* 34, 571–586. doi: 10.3233/RNN-150606

Cantillo-Negrete, J., Carino-Escobar, R. I., Carrillo-Mora, P., Elias-Vinas, D., and Gutierrez-Martinez, J. (2018). Motor imagery-based brain-computer Interface coupled to a robotic hand orthosis aimed for neurorehabilitation of stroke patients. *J Healthc Eng* 2018, 1–10. doi: 10.1155/2018/1624637

Cho, W., Sabathiel, N., Ortner, R., Lechner, A., Irimia, D. C., Allison, B. Z., et al. (2016). Paired associative stimulation using brain-computer interfaces for stroke rehabilitation: a pilot study. *Eur J Transl Myol.* 26, 219–222. doi: 10.4081/ejtm.2016.6132

Chua, J., Culpan, J., and Menon, E. (2016). Efficacy of an electromechanical gait trainer Poststroke in Singapore: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* 97, 683–690. doi: 10.1016/j.apmr.2015.12.025

Chung, E., Lee, B.-H., and Hwang, S. (2020). Therapeutic effects of brain-computer interface-controlled functional electrical stimulation training on balance and gait performance for stroke: a pilot randomized controlled trial. *Medicine* 99:e22612. doi: 10.1097/MD.0000000000022612

Ferrante, S., Pedrocchi, A., Ferrigno, G., and Molteni, F. (2008). Cycling induced by functional electrical stimulation improves the muscular strength and the motor control of individuals with post-acute stroke. Europa Medicophysica-SIMFER 2007 award winner. *Eur. J. Phys. Rehabil. Med.* 44, 159–167.

Hesse, S., Mehrholz, J., and Werner, C. (2008). Robot-assisted upper and lower limb rehabilitation after stroke. *Deutsches Ärzteblatt* 105, 330–336. doi: 10.3238/arztebl.2008.0330

Hong, Z., Sui, M., Zhuang, Z., Liu, H., Zheng, X., Cai, C., et al. (2018). Effectiveness of neuromuscular electrical stimulation on lower limbs of patients with hemiplegia after chronic stroke: a systematic review. *Arch. Phys. Med. Rehabil.* 99, 1011–1022.e1. doi: 10.1016/j.apmr.2017.12.019

Irimia, D. C., Ortner, R., Poboroniuc, M. S., Ignat, B. E., and Guger, C. (2018). High classification accuracy of a motor imagery based brain-computer Interface for stroke rehabilitation training. *Front Robot AI* 5:130. doi: 10.3389/frobt.2018.00130

Janssen, T. W., Beltman, J. M., Elich, P., Koppe, P. A., Konijnenbelt, H., de Haan, A., et al. (2008). Effects of electric stimulation–assisted cycling training in people with chronic stroke. *Arch. Phys. Med. Rehabil.* 89, 463–469. doi: 10.1016/j.apmr.2007.09.028

Kim, J., Kim, D. Y., Chun, M. H., Kim, S. W., Jeon, H. R., Hwang, C. H., et al. (2019). Effects of robot-(morning walk ®) assisted gait training for patients after stroke: a randomized controlled trial. *Clin. Rehabil.* 33, 516–523. doi: 10.1177/0269215518806563

Koski, L. (2013). Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. *Cerebrovasc. Dis.* 36, 6–18. doi: 10.1159/000352051

Mayford, M., Siegelbaum, S. A., and Kandel, E. R. (2012). Synapses and memory storage. *Cold Spring Harb. Perspect. Biol.* 4:a005751. doi: 10.1101/cshperspect.a005751

Mehrholz, J., Pohl, M., Kugler, J., and Elsner, B. (2018). The improvement of walking ability following stroke. *Deutsches Ärzteblatt* 115, 639–645. doi: 10.3238/arztebl.2018.0639

Mehrholz, J., Thomas, S., Werner, C., Kugler, J., Pohl, M., and Elsner, B. (2017). Electromechanical-assisted training for walking after stroke. *Cochrane Database Syst. Rev.* 5:CD006185. doi: 10.1002/14651858.CD006185.pub4

Meseguer-Henarejos, A. B., Sáchez-Meca, J., López-Pina, J. A., and Carles-Hernández, R. (2018). Inter-and intra-rater reliability of the modified Ashworth scale: a systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.* 54, 576–590. doi: 10.23736/S1973-9087.17.04796-7

Mihara, M., Fujimoto, H., Hattori, N., Otomune, H., Kajiyama, Y., Konaka, K., et al. (2021). Effect of neurofeedback facilitation on Poststroke gait and balance recovery: a randomized controlled trial. *Neurology* 96, e2587–e2598. doi: 10.1212/WNL.0000000000011989

Mills, E., Bansback, N., Ghement, T., Tholund, K., Kelly, S., Puhan, et al. (2011). Multiple treatment comparison meta-analyses: a step forward into complexity. *Clin. Epidemiol.* 3, 193–202. doi: 10.2147/CLEP.S16526

Mrachacz-Kersting, N., Jiang, N., Stevenson, A. J. T., Niazi, I. K., Kostic, V., Pavlovic, A., et al. (2016). Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface. *J. Neurophysiol.* 115, 1410–1421. doi: 10.1152/jn.00918.2015

Muller-Gerking, J., Pfurtscheller, G., and Flyvbjerg, H. (1999). Designing optimal spatial filters for single-trial EEG classification in a movement task. *Clin. Neurophysiol.* 110, 787–798. doi: 10.1016/S1388-2457(98)00038-8

Neuper, C., and Allison, B. Z. (2014). The B of BCIs: Neurofeedback principles and how they can yield clearer brain signals. in *Different psychological perspectives on cognitive processes: current research trends in Alps-Adria region.* eds. R. Actis and A. Galmonte Cambridge University Press, 133–153.

Neuper, C., Scherer, R., Reiner, M., and Pfurtscheller, G. (2005). Imagery of motor actions: differential effects of kinesthetic and visual-motor mode of imagery in single-trial EEG. *Brain Res. Cogn. Brain Res.* 25, 668–77. doi: 10.1016/j.cogbrainres.2005.08.014

Ono, T., Shindo, K., Kawashima, K., Ota, N., Ito, M., Ota, T., et al. (2014). Brain-computer interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke. *Front. Neuroeng.* 7:19. doi: 10.3389/fneng.2014.00019

Ortner, R., Irimia, D. C., Scharinger, J., and Guger, C. (2012). A motor imagery based brain-computer interface for stroke rehabilitation. *Stud. Health Technol. Inform.* 181, 319–23.

Perera, S., Mody, S. H., Woodman, R. C., and Studenski, S. A. (2006). Meaningful change and responsiveness in common physical performance measures in older adults. *J. Am. Geriatr. Soc.* 54, 743–749. doi: 10.1111/j.1532-5415.2006.00701.x

Peurala, S. H., Tarkka, I. M., Pitkänen, K., and Sivenius, J. (2005). The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. *Arch. Phys. Med. Rehabil.* 86, 1557–1564. doi: 10.1016/j.apmr.2005.02.005

Pichiorri, F., Mrachacz-Kersting, N., Molinari, M., Kleih, S., Kübler, A., and Mattia, D. (2017). Brain-computer interface based motor and cognitive rehabilitation after stroke – state of the art, opportunity, and barriers: summary of the BCI meeting 2016 in Asilomar. *Brain Comput Inter* 4, 53–59. doi: 10.1080/2326263X.2016.1246328

Pohl, M., Werner, C., Holzgraefe, M., Kroczek, G., Wingendorf, I., Hoölig, G., et al. (2007). Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). *Clin. Rehabil.* 21, 17–27. doi: 10.1177/0269215506071281

Quinn, T. J., Langhorne, P., and Stott, D. J. (2011). Barthel index for stroke trials. *Stroke* 42, 1146–1151. doi: 10.1161/STROKEAHA.110.598540

Ramos-Murguialday, A., Broetz, D., Rea, M., Läer, L., Yilmaz, Ö., Brasil, F. L., et al. (2013). Brain-machine interface in chronic stroke rehabilitation: a controlled study. *Ann. Neurol.* 74, 100–108. doi: 10.1002/ana.23879

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/h0054651

Tong, R. K., Ng, M. F., and Li, L. S. (2006). Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* 87, 1298–1304. doi: 10.1016/j.apmr.2006.06.016

Wade, D. T. (1992). Measurement in neurological rehabilitation. *Curr. Opin. Neurol. Neurosurg.* 1:207. doi: 10.1136/qshc.1.3.207

Werner, C., von Frankenberg, S., Treig, T., Konrad, M., and Hesse, S. (2002). Treadmill training with partial body weight support and an electromechanical gait trainer for restoration of gait in subacute stroke patients. *Stroke* 33, 2895–2901. doi: 10.1161/01.STR.0000035734.61539.F6

Wolpaw, J. R., and Wolpaw, E. W. (2012). Brain–computer interfaces: Principles and Practice. New York, NY: Oxford University Press.

Woytowicz, E. J., Rietschel, J. C., Goodman, R. N., Conroy, S. S., Sorkin, J. D., Whitall, J., et al. (2017). Determining levels of upper extremity movement impairment by applying a cluster analysis to the Fugl-Meyer assessment of the upper extremity in chronic stroke. *Arch. Phys. Med. Rehabil.* doi: 10.1016/j.apmr.2016.06.023

Yeh, C.-Y., Tsai, K.-H., Su, F.-C., and Lo, H.-C. (2010). Effect of a bout of leg cycling with electrical stimulation on reduction of hypertonia in patients with stroke. *Arch. Phys. Med. Rehabil.* 91, 1731–1736. doi: 10.1016/j.apmr.2010.08.003

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Machine-learning assisted swallowing assessment: a deep learning-based quality improvement tool to screen for post-stroke dysphagia

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Introduction: Post-stroke dysphagia is common and associated with significant morbidity and mortality, rendering bedside screening of significant clinical importance. Using voice as a biomarker coupled with deep learning has the potential to improve patient access to screening and mitigate the subjectivity associated with detecting voice change, a component of several validated screening protocols.

Methods: In this single-center study, we developed a proof-of-concept model for automated dysphagia screening and evaluated the performance of this model on training and testing cohorts. Patients were admitted to a comprehensive stroke center, where primary English speakers could follow commands without significant aphasia and participated on a rolling basis. The primary outcome was classification either as a pass or fail equivalent using a dysphagia screening test as a label. Voice data was recorded from patients who spoke a standardized set of vowels, words, and sentences from the National Institute of Health Stroke Scale. Seventy patients were recruited and 68 were included in the analysis, with 40 in training and 28 in testing cohorts, respectively. Speech from patients was segmented into 1,579 audio clips, from which 6,655 Mel-spectrogram images were computed and used as inputs for deep-learning models (DenseNet and ConvNext, separately and together). Clip-level and participant-level swallowing status predictions were obtained through a voting method.

Results: The models demonstrated clip-level dysphagia screening sensitivity of 71% and specificity of 77% (F1 = 0.73, AUC = 0.80 [95% CI: 0.78–0.82]). At the participant level, the sensitivity and specificity were 89 and 79%, respectively (F1 = 0.81, AUC = 0.91 [95% CI: 0.77–1.05]).

Discussion: This study is the first to demonstrate the feasibility of applying deep learning to classify vocalizations to detect post-stroke dysphagia. Our findings suggest potential for enhancing dysphagia screening in clinical settings. https://github.com/UofTNeurology/masa-open-source.

KEYWORDS

stroke, dysphagia, machine learning, swallowing, neural technology, original research stroke, quality improvement, Artificial Intelligence

Introduction

Stroke is among the top three leading causes of mortality worldwide (Feigin et al., 2021). Acute stroke resulting in hospitalization is a serious health event with often life-long alteration of functional status (Singh and Hamdy, 2006). One of the most common serious complications of stroke is dysphagia, or swallowing dysfunction, which occurs in approximately 55% of acute stroke patients (Singh and Hamdy, 2006). Dysphagia places patients at increased risk of aspiration pneumonia which can be fatal, thus screening of swallowing status and/or a formal speech language pathologist assessment are commonplace as part of the admission process to stroke centers. It is important to note the distinction between screening tests and formal assessments, which are deployed either in succession or independently depending on a local stroke center protocol (Singh and Hamdy, 2006; Cohen et al., 2016). Screening tests such as the Toronto Bedside Swallowing Screening Test (TOR-BSST©) (Martino et al., 2009) can be performed by course-trained operators of varying backgrounds, whereas formal assessment of dysphagia is performed by a speech language pathologist (SLP). Screening test certification requires training time, coverage and/or resources including the cost of training and licensure. Furthermore, permission to use a particular screening tool may have its own associated resource burden. Clinical availability of SLPs may also be limited due to high case volumes and off-hours availability, often leading to reliance on screening tests. In some hospitals, lack of immediate access to an SLP to provide a swallowing assessment can result in patients receiving NG tubes as a precautionary measure even in those who would not otherwise receive such interventions for nutrition or hydration purposes. An increased risk of infection and aspiration, as well as increase in cost for patient care can manifest in these scenarios; these in addition to patient intrinsic factors such as overall health, oropharyngeal secretions, and feeding status. Inability to easily access dysphagia screening also impacts patient comfort, tolerance, and facilitation of early physiologic recovery.

In general, centers that use a screening test trigger an SLP assessment when the screening result is a failure. Despite these care pathways, many centers lack routine integration of validated screening tests or quick access to SLPs, and thus robust dysphagia screening has significant barriers. SLPs can diagnose and prescribe various diet consistencies and textures and can also, if indicated, perform a modified barium swallow and video fluoroscopic swallowing study (VFSS). This is considered a gold-standard of swallowing assessment, but it is not routinely deployed as a screening test. VFSS requires access to trained personnel, radioactive material (barium) and x-ray equipment. Validated screening tests such as the TOR-BSST© have been compared to the VFSS and have favorable characteristics from a screening test perspective (Martino et al., 2009). Moreover, even VFSS by SLP has an element of subjectivity and poor inter-rater reliability. This same issue of subjectivity permeates screening tests that rely on voice change. Furthermore, some screening tests that do not rely on voice alone, require repeated trials of oral fluid intake. These also often have a subjective component when it comes to voice change with successive intake trials and pose execution challenges. This was experienced during the COVID-19 pandemic in relation to both staffing availability but also risk of aerosol generation (Fritz et al., 2021). Voice change detected by audio alone could be used as an assistive tool for screening tools that rely on voice quality change.

Use of voice change, including those associated with sustained vowel sounds, have been used to screen for non-stroke dysphagia (Ryu et al., 2004). Further studies have demonstrated differences in extracted audio features between patients at risk of aspiration versus those not at risk even prior to swallowing (Kang et al., 2018). Additionally, the use of vocal recordings to detect pathologies has gained increasing research interest in recent years as various applications have been developed to automatically detect or monitor pathologies such as Parkinson's disease, and cognitive impairment (Milling et al., 2022). This has opened the possibility of voice as an adjunct biomarker in dysphagia screening. Taken together, there is a quality gap, and hence a quality improvement opportunity where machine learning algorithms, can be deployed to reduce subjectivity and perform classification as part of dysphagia screening.

In this study we assessed state-of-the-art deep-learning models (ConvNext, DenseNet, and an ensemble) to screen for dysphagia using vocal samples from post-stroke inpatients. An existing commonly used dysphagia screening tool (TOR-BSST) was used to label audio clips. Models were used to classify individual audio clips from post-stroke inpatients, and individual audio clip scores were aggregated to predict participant dysphagia screening status. This deep learning approach aims to reduce subjectivity and improve access to rapid dysphagia screening.

Methods

Participants

A total of 70 patients were recruited from the inpatient neurovascular unit at Sunnybrook Health Sciences Center

(comprehensive stroke center, Toronto, Canada). Patients were enrolled from 13 June 2022 to 19 January 2023 (epoch 1) and 24 January to 4 March 2023 (epoch 2) for training and testing datasets, respectively. Two patients, early in the study (study patients 7 and 9), had technical difficulties with their audio recordings resulting in poor audio quality during the first data collection epoch and were rejected, allowing for a total of 68 patient's audio recordings to be used (AB, HM, 94% inter-rater agreement of good audio quality, see **Supplementary Methods**). All patients, as part of their routine clinical care, were assessed using the Toronto Bedside Swallowing Screening Test (TOR-BSST©), which involves baseline assessment of voice change, as well as repetitive swallows and assessment for dysphonia by a trained assessor (Martino et al., 2009). Our center uses TOR-BSST©, and among 36 other screening tests in a Cochrane review, TOR-BSST© is among the three identified best performing tests, allowing this screening tool to be used for our supervised learning model and pass or fail status to be the training label (Kiekens and Tognonato, 2022). Overall, 27 patients were designated as fails and 41 patients passed screening. Our study included 40 patients (58.9% of total) in a training cohort and 28 patients (41.1% of total) in the testing cohort. Note that enrollment was on a rolling basis, across several sampling days, and on those random days, enrollments occurred by sampling successive admissions to the stroke unit that were within 72 h of admission. All patients provided informed consent for data collection and the study was approved by the research ethics board at Sunnybrook Health Sciences Centre. Patients with recent stroke admitted to the stroke unit who could speak English, follow commands and whom did not have significant aphasia precluding participation were included. Patients who did not speak English, had a significant speech impairment (from other medical/neurologic conditions), or were medically unstable were excluded.

Data collection

Two categories of speech were recorded: (a) recordings of the National Institutes of Health Stroke Scale (NIHSS) portions involving speech, and (b) sustained vowel sounds (**Figure 1A**). The NIHSS is a widely used, validated tool for assessing neurological deficits in stroke patients, including tests of articulation, naming, repetition, and comprehension with standardized sounds, words, and sentences; we used the NIHSS to avoid bias in selecting speech tests and given its wide use in stroke assessment (Lyden et al., 1994; Appelros and Terént, 2004). In this study the NIHSS language test was separated into three distinct categories based on the type of speech: continuous speech, sentences, and words (i.e., naming objects and repeating discrete words). During segmentation these categories of speech were labeled separately for further analysis. The second category of recordings were collected by asking participants to vocalize each vowel sound (/a/, /e/, /i/, /o/, and/u/) for a target duration of 3 s repeated three times each. Prior work has demonstrated vowel sounds to be discriminative for differentiating between swallowing abnormalities and closely mirrors the articulation tasks of existing dysphagia screening tools (Waito et al., 2011; Gerratt et al., 2016; Kang et al., 2018; Moore et al., 2020). Sustained vowels were chosen since they can be more easily administered in patients for whom English is not their first language and require less vocal effort. Data was collected on an encrypted iPhone 12 with a sampling rate of 44.1 kHz using the included Voice Recorder application with a resolution of 16-bits. The phone was placed on the patient's bedside table approximately 10 cm from their mouth. Data was collected on the inpatient stroke ward and background noise was minimized (**Supplementary Methods**). If there were overhead announcements during the recordings those vocalizations were asked to be repeated from the patient. The recordings were all done in a real-world setting, using an iPhone, encrypted, loss-less audio, with no other interventions to alter real-world recording conditions. This includes single and multi-patient rooms, in the ED, ward, and neurovascular step-down/observation ICU beds. Of note, investigators responsible for data collection/audio segmentation (AB, HM, LP) and the final testing phase of the model (RS) were blinded to each other's efforts. Specifically, for most of the training data (60% of recordings during epoch 1), and for all the recordings acquired for model testing (epoch 2), the investigator running the models (RS) was blinded to the label assignment and raw audio files (see **Supplementary Methods**). Model training and testing was done on the spectrogram images from the audio-data (see below).

Data analysis

Data were first assessed for quality and then analyzed through a 3-step data processing pipeline involving (1) segmentation, (2) transformation, and (3) machine learning (**Figure 1**). Firstly, prior to data segmentation, clips were independently evaluated for quality (**Supplementary Methods**). Data was segmented manually using Audacity© digital audio workstation software. Each vocalization of interest (i.e., either a vowel sound, word, sentence, or continuous speech) was segmented from the onset to the offset, labeled accordingly, and exported to an audio file. A custom data processing program was developed in Python (**Supplementary Methods**) to load segmented audio files, pre-process the signal, and convert them into Mel-spectrogram image representations. Given the variability in a participant's ability to sustain vocal production for the full target duration, and large discrepancies in clip lengths with diverse sound input types (i.e., words, vowels, and continuous speech), a windowing approach was used to ensure uniform scaling of resultant Mel-spectrogram images (Zhang et al., 2019; Khurana et al., 2023). Audio clips were segmented into 0.5 s clips with 50% overlap (**Figure 1B**). Clips shorter than 0.5 s were rejected, and power thresholding was applied to all clip windows to ensure that periods of silence were not used to train the classifier. A single audio clip was first processed into windows. The average power contained in these windows was then calculated and windows greater than 1.5 standard deviations lower than the mean window power were rejected.

Next, all post-segmentation audio files for each participant were transformed from time-series to corresponding Mel-spectrogram images (**Figure 1C**). Within the realm of audio classification, the decision to employ Mel-spectrograms as opposed to directly using raw audio waveforms was both strategic and evidence-based. Mel-spectrograms are notable for their ability to emulate

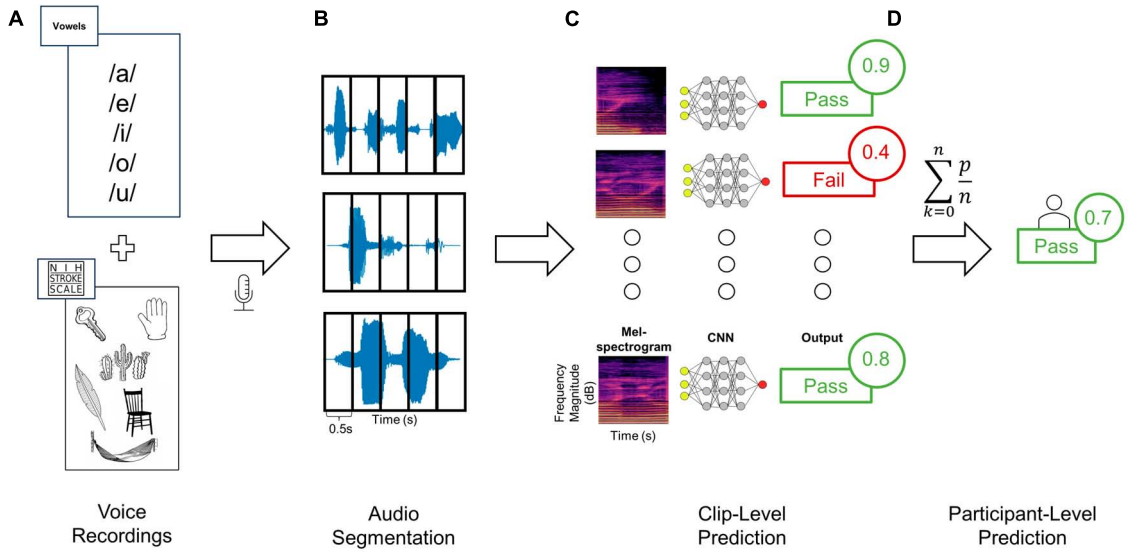

FIGURE 1
Training and testing deep learning classifiers to distinguish audio recordings based on dysphagia status. **(A)** Audio clips were recorded from each patient using a standardized assessment of vowels as well as words and sentences from the NIHSS language assessment, **(B)** and then segmented into 0.5 s windows. **(C)** Each clip from a given patient was then converted to Mel-spectrogram images using either the RGB (shown here) or three-channel approaches. Each Mel-spectrogram image was used as an input into the CNN (either DenseNet, ConvNext-Tiny or fusion networks) which generated an output class along with an output probability for each clip. **(D)** The average of all clip level output probabilities per patient were used to generate a final participant-level output class prediction.

the human ear's non-linear perception of pitch and frequency, making them especially powerful for tasks involving human speech (Zhang et al., 2019; Khurana et al., 2023). This is particularly salient in our study, as our ground truth anchors in evaluations by speech-language therapists. The direct mapping of these Mel-spectrograms to human auditory perception ensures that the patterns discerned by our model are grounded in clinically significant features.

Mel-spectrogram images were generated using the Librosa library resulting in images with the vertical axis representing Mel frequency bands, horizontal axis representing time, and the color intensity at each point indicating the magnitude of the spectral content of that frequency and time (Schmoldt et al., 1975; **Figure 2**). Mel-spectrograms were computed on each clip individually with a hop length of 2,048 samples (hamming window), 512 Mels and a minimum frequency of 20 Hz. Mel-spectrograms were then converted into the power-domain (decibels) and outputted into an image file (224 × 224).

Two types of Mel-spectrogram images were generated (detailed in **Supplementary Methods**) to be used to train machine learning classifiers separately. The first approach ("RGB Mel-spectrogram") used red-blue-green (RGB) images of Mel-spectrograms directly as inputs to the machine learning classifiers. The choice to use RGB Mel-spectrograms was influenced by the compatibility with transfer learning models originally trained on RGB images and the optimization of standard CNN architectures for RGB data. The second approach ("Three-channel Mel-spectrogram") involved the depth-wise concatenations of three-monochrome Mel-spectrograms with differing Fast Fourier Transform (FFT) lengths (1,024, 2,048 and 4,096) to generate a composite image. This approach has previously demonstrated superior performance compared to RGB images in some applications (Palanisamy et al., 2020).

Machine learning classifiers

The proposed approach relies on a type of Deep Neural Network called a convolutional neural network (CNN) which defines specialized spatial filters which allow more efficient extraction of features in images during learning (Lecun and Bengio, 1995). Extensive prior work has demonstrated the effectiveness of CNNs on other temporal and spatial data beyond images, including audio classification (Hershey et al., 2017; Zhang et al., 2019; Palanisamy et al., 2020; Dave and Srivastava, 2023; Khurana et al., 2023). CNNs were trained using transfer learning to classify Mel-spectrogram images based on TOR-BSST© screen status (**Figure 1C**). Transfer learning is a ML technique wherein a model is first trained on one task and then fine-tuned to solve a different task (Schmoldt et al., 1975; Hershey et al., 2017; Zhang et al., 2019; Ganaie et al., 2022; Dave and Srivastava, 2023). Large pre-trained CNN models which have been computed on large image datasets (e.g., ImageNet) have been shown to perform well in transfer learning applications when applied to images generated from audio files, even performing better than CNNs trained from scratch (i.e., with random weight initialization) (Palanisamy et al., 2020).

In this study, an ensemble method was implemented, integrating multiple classifiers trained via transfer learning, each utilizing different base models. This ensemble approach mitigates model variance stemming from random parameter initialization, thereby enhancing model robustness (Ganaie et al., 2022). Specifically, unweighted averaging was adopted for aggregating classifier outputs, a decision driven by the need for transparency and interpretability in clinical AI applications (Shortliffe and Sepúlveda, 2018). While alternative ensemble strategies, such as weighted majority voting, might offer marginal accuracy improvements by adjusting for the confidence level of individual

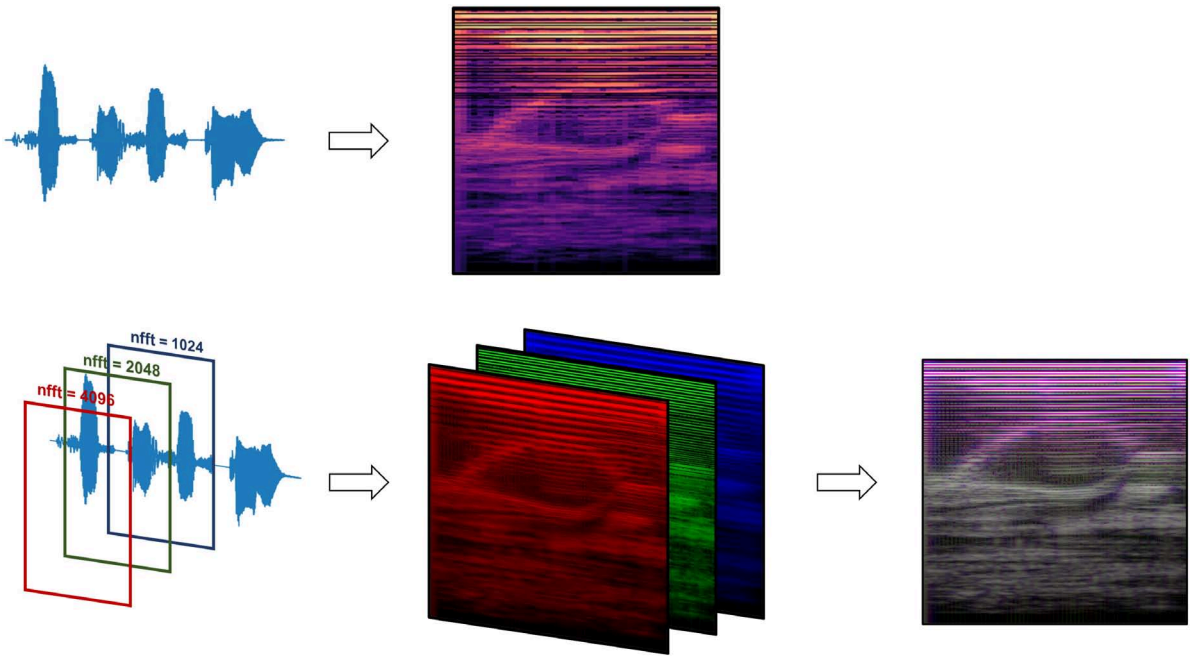

FIGURE 2
Mel-spectrogram processing methods, comparing data processing pipelines between the standard RGB Mel-spectrogram approach **(top)** and three-channel Mel-spectrogram **(bottom)** involving depth-wise concatenation of three separate Mel-spectrograms with different FFT lengths to produce a single composite image.

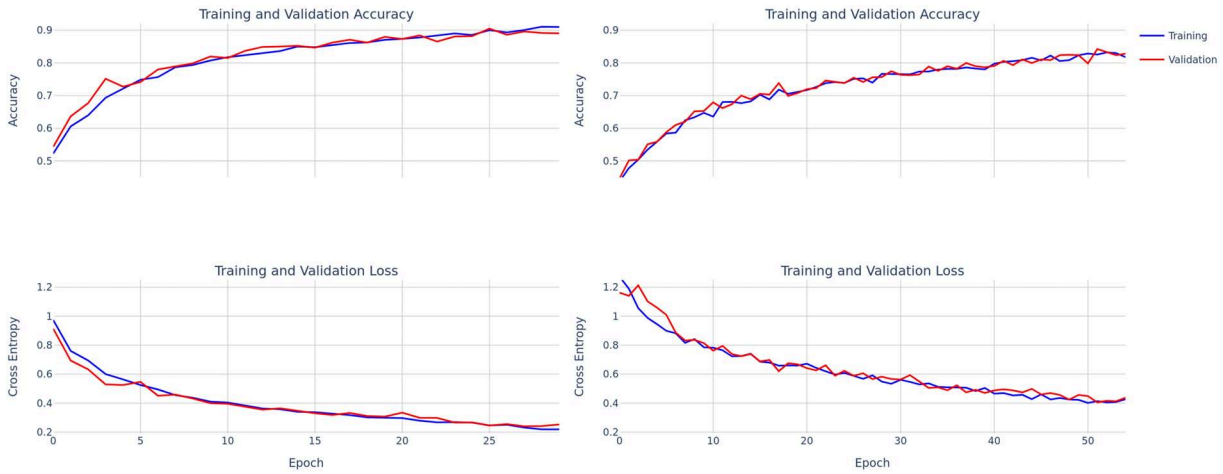

FIGURE 3
Training and validation accuracy and loss curves for ConvNext-Tiny **(left)** and DenseNet-121 **(right)**.

predictions, they introduce complexities that could obscure the decision rationale (Kuncheva, 2014). In contrast, the chosen method, though simpler, maintains clarity in the decision-making process, a critical factor in healthcare settings. Importantly, a study by Ju et al. (2018) affirms the robustness of unweighted averaging, particularly when the base models exhibit similar performance levels (Ganaie et al., 2022). An ensemble network using DenseNet-121 and ConvNext-Tiny was developed. The architecture of each of these networks provides unique advantages when used as an ensemble. DenseNet uses a feed-forward connections between each layer and each subsequent layer such that a given layer N has N-1 inputs (Huang et al., 2016). This architecture allows for a lower number of parameters, and results in improved feature propagation. In applications that use computer vision for audio signals, DenseNet has demonstrated state-of-the-art (SOTA) CNN performance superior to Inception and ResNet (Palanisamy et al., 2020). Based on prior work (Palanisamy et al., 2020), all pre-trained layers were frozen until the last DenseNet block and the remaining layers in the network were fine-tuned.

ConvNext is a CNN that aims to provide some of the advantages of vision transformers. Though vision transformers have achieved SOTA performance on the ImageNet dataset in

recent years they present many challenges including significant computational complexity, global rather than local attention, and reliance on large datasets (with high risk of overfitting when transfer learning is applied to smaller datasets) (Liu et al., 2022). The ConvNext includes architecture improvements that are inspired by vision transformers (ViTs) including larger kernel sizes, a processing layer ("patchify stem") akin to a ViT patchify layer, and improved training techniques (Liu et al., 2022), resulting in classification performance similar to ViTs but with much fewer parameters. Based on training data results, all layers up to stage 3 were frozen and the remaining layers fine-tuned.

The configuration of the network architecture for both DenseNet and ConvNext is detailed in the **Supplementary Methods**. The last layer of each pre-trained network was removed and replaced by a global average and dense layer with a single sigmoid output. A dropout rate of 80% was used to prevent overfitting. This was settled on through empiric testing on the validation set to mitigate overfitting which is especially problematic when utilizing transfer learning of large models to smaller datasets (Srivastava et al., 2014). The ensemble classifier outputs a label for each individual image, corresponding to a 0.5-s window of the original audio clip. The output probabilities of all images corresponding to a given audio clip were summed cumulatively and averaged to give a resultant aggregate participant classification (**Figure 1D**). A fixed decision boundary of 0.5 was used to classify participants as either a fail (< 0.5) or a pass (≥ 0.5).

Model training and testing

The first 40 participants' vocal samples were selected for the training set (58.9% of total data) and the final 28 participants' data (41.1% of the total data) for the test set. A testing split of 20% was used during the training phase. There was no overlap between training and testing sets. The decision to segregate data based on the order of participation rather than random sampling was deliberate. This choice aims to simulate a real-world scenario where the model is trained on existing data and is then required to generalize to new, unseen participants. Thirty and forty-five epochs were used to train ConvNext and DenseNet, respectively, with a learning rate of 1e-5 and a batch size of 32. A learning rate scheduler and early stopping were used to mitigate overfitting (**Figure 3**). Given differences in the number of parameters in each model, we used 55 and 30 target epochs with patience of 7 and 10 for DenseNet and ConvNext-Tiny, respectively, with validation loss as the early stopping parameter.

Results

The mean age of the patients was 69 years. Most patients had ischemic stroke (76%), with 46% involving middle cerebral artery, 18% brainstem, and 1.5% thalamic infarcts. Others had approximately 9% multifocal infarcts, 3% cerebellar and 16% intracerebral hemorrhage (ICH). Within the training and testing cohort, demographics between TOR-BSST© pass and fails were compared (two-sample *t*-test for continuous data, Chi-squared test for frequency data). There were no differences between pass and fail patients in both cohorts except for higher NIHSS in patients who failed (**Table 1**); lower NIHSS was associated with a pass status as expected. Comparing training and testing cohorts there was no difference in baseline demographics (**Supplementary Table 1**) in a similar manner.

The training and test performance of the classifiers on both clip and participant levels are shown in **Tables 2**, **3**. The performance metrics shown are sensitivity (recall), specificity, precision, F1 score, and area under the receiver operator curve (AUC). At the audio clip-level, DenseNet-121 demonstrated a sensitivity of 0.77, a specificity of 0.69, a precision of 0.56, an F1 score of 0.70, and an AUC of 0.79 [95% CI: 0.77, 0.81]. The ConvNext-Tiny model produced a sensitivity of 0.63, a specificity of 0.77, a precision of 0.58, an F1 score of 0.63, and an AUC of 0.78 [95% CI: 0.76, 0.80]. The ensemble fusion model, amalgamating DenseNet-121 and ConvNext-Tiny models, achieved a sensitivity of 0.71, a specificity of 0.77, a precision of 0.62, an F1 score of 0.73, and an AUC of 0.80 [95% CI: 0.78, 0.82] (see **Supplementary Table 1** and **Figure 4**).

TABLE 1 Demographic characteristics of pass and fail patients within training and testing patient cohorts.

Training cohort			
	Screening FAIL	Screening PASS	*p*-value
N	18	22	
Mean age, years (SD)	69 (17)	67 (16)	0.72
Female, *n* (%)	6 (38%)	12 (55%)	0.21
Mean NIHSS (SD)	9 (6)	4 (6)	0.010
Stroke type (%)			0.11
Ischemic MCA	44%	59%	
Ischemic lacunar	22%	14%	
Ischemic multifocal	6%	23%	
ICH	22%	0	
CVST	0	0	
Other	6%	4%	
Testing cohort			
N	10	18	
Mean age, years (SD)	73 (18)	65 (16)	0.28
Female, *n* (%)	3 (30%)	12 (67%)	0.19
Mean NIHSS (SD)	6 (6)	2 (1)	0.001
Stroke type (%)			0.65
Ischemic MCA	40%	44%	
Ischemic lacunar	40%	22%	
Ischemic multifocal	0	6%	
ICH	20%	22%	
CVST	0	6%	
Other	0	0	

Comparing within training and testing cohorts (two-sample *t*-test for continuous data, Chi-squared test for frequency data), there was no differences between pass and fail patients in both cohorts except for higher NIHSS in patients who failed. *P*-values for subtypes individually not computed as small subtype *n*-values. NIHSS, National Institute of Health Stroke Scale; CVST, cerebral venous sinus thrombosis; ICH, intracranial hemorrhage; MCA, middle cerebral artery.

TABLE 2 Comparing RGB Mel-spectrogram and three-channel Mel-spectrogram clip-level classifier performance across DenseNet-121, ConvNext-Tiny, and a fusion of the two networks.

	RGB Mel-spectrogram					Three-channel Mel-spectrograms				
	Sensitivity (recall)	Specificity	Precision	F1 score	AUC [95% CI]	Sensitivity (recall)	Specificity	Precision	F1 score	AUC [95% CI]
DenseNet-121	0.78	0.69	0.56	0.70	0.79 [0.77, 0.81]	0.71	0.7	0.56	0.69	0.75 [0.73, 0.77]
ConvNext-Tiny	0.63	0.77	0.58	0.63	0.78 [0.76, 0.80]	0.66	0.74	0.57	0.69	0.76 [0.74, 0.78]
Fusion	0.71	0.77	0.62	0.73	0.80 [0.78, 0.82]	0.67	0.76	0.60	0.71	0.77 [0.75, 0.79]

CI, confidence interval.

Participants were classified based on the cumulative sum of output scores of each individual clip. At the participant level (Table 3), DenseNet-121 achieved a sensitivity of 0.89, a specificity of 0.79, a precision of 0.67, an F1 score of 0.81, and an AUC of 0.89 [95% CI: 0.74–1.04]. In contrast, the ConvNext-Tiny model delivered a sensitivity of 0.78, a specificity of 0.89, a precision of 0.78, an F1 score of 0.84, and an AUC of 0.911 [95% CI: 0.77–1.05]. Again, the fusion model showed a sensitivity of 0.89, a specificity of 0.79, a precision of 0.67, an F1 score of 0.81, and achieved the highest AUC of 0.912 [95% CI: 0.77–1.05] (Hanley and McNeil, 1982). We have included the third decimal place to show marginal difference between the two approaches. Confidence interval calculations are detailed in the **Supplementary Methods** section.

Using three-channel Mel-spectrograms instead produced slightly worse performance than RGB Mel-spectrograms, as detailed in Table 2 (clip-level performance) and Table 3 (patient-level performance). While the RGB representation offered certain benefits due to compatibility with transfer learning and standard CNN architectures, the overall advantage over the three-channel representation was observed to be marginal. Nonetheless, both methods produced comparable performance, indicating that either representation could be employed based on specific application needs.

Finally, the contribution of vowels to classification performance was also studied by comparing the results of vowels alone to vowels plus the speech components of the NIH. At the participant level, the additional information provided by the NIH speech components provided a significant increase in performance (Table 4).

Discussion

The findings of our study support the use of deep learning, specifically convolutional neural networks employing transfer learning, as a tool for screening post-stroke dysphagia using real-world speech audio recordings. By leveraging established neural network architectures and ensemble methods, our approach achieved robust performance demonstrating its potential use as a non-invasive, time-efficient, and scalable screening tool in clinical settings. We hope that this tool can be used as an assistive technology (for example deployed on a mobile device), to aid any provider in performing a bedside swallow screening test. It also naturally lends itself to telehealth applications or other remote uses especially considering challenges introduced by the COVID-19 pandemic. Our proof-of-concept study supports the notion that this technology can be deployed in an assistive capacity to screen patients in low-resource settings constrained by person-power, off-hours access, or other challenges accessing screening services. Our models leveraged state-of-the-art CNN architectures (DenseNet-121 and ConvNext-Tiny), as well as a simple ensemble fusion approach to integrate the results of these architectures and improve classification performance. The fusion model's results are promising, achieving a sensitivity of 0.89, specificity of 0.79, F1 score of 0.81, and an AUC of 0.91 when evaluated at the patient level, demonstrating compelling proof-of-concept results. This gain in performance is marginal relative to single models at the participant level, however, difference in AUC at the clip

TABLE 3 Comparing RGB Mel-spectrogram and three-channel Mel-spectrogram participant level classifier performance across DenseNet-121, ConvNext-Tiny, and a fusion of the two networks.

	RGB Mel-spectrogram					Three-channel Mel-spectrograms				
	Sensitivity (recall)	Specificity	Precision	F1 score	AUC [95% CI]	Sensitivity (recall)	Specificity	Precision	F1 score	AUC [95% CI]
DenseNet-121	0.89	0.79	0.67	0.81	0.89 [0.74, 1.04]	0.78	0.74	0.58	0.73	0.88 [0.73, 1.03]
ConvNext-Tiny	0.78	0.89	0.78	0.84	0.91 [0.77, 1.05]	0.78	0.79	0.64	0.77	0.86 [0.69, 1.03]
Fusion	0.89	0.79	0.67	0.81	0.91 [0.77, 1.05]	0.78	0.79	0.64	0.77	0.87 [0.71, 1.03]

CI, confidence interval, please note max. AUC value is 1.0, computed numerically has upper bounds larger than this value and is listed herein to show the calculation result.

level suggests that the fusion approach would perform better when applied to a larger number of participants. Furthermore, the utilization of audio data, as opposed to other modalities allows for a less invasive collection method and integration into passive monitoring systems.

Prior approaches for classifying audio data predominantly employed classical statistical methods that necessitate the explicit extraction of signal features. While such methods are effective in specific scenarios, their application to voice-based dysphagia detection is constrained by the need for *a priori* knowledge of pathology-related acoustic features. These feature-centric methodologies have been utilized either in isolation or in conjunction with clinical variables for dysphagia identification (Roldan-Vasco et al., 2021; Park et al., 2022). Using a deep learning framework allows for reduced reliance on feature engineering and thus supports classification based on more complex signal characteristics using raw or minimally processed data. Some deep learning approaches have already demonstrated success in classifying speech into various classes such as identifying speakers by gender, accent, or other attributes (Khalifa et al., 2020; Wilhelm et al., 2020). Automatic dysphagia detection has also been studied using accelerometers or microphones attached directly to a patient's neck to record swallowing sounds (Khalifa et al., 2020; O'Brien et al., 2021). Additionally, CNNs have been used extensively for audio classification using audio signals converted into images in fields outside of medicine (Hershey et al., 2017; Zhang et al., 2019; Palanisamy et al., 2020; Dave and Srivastava, 2023; Khurana et al., 2023).

Our deep learning approach produced results that are biologically plausible in that our model's performance is within a range of reasonable expected values considering the limits of the studied population of patients. The underlying physiology of detecting dysphagia is quite complex, and thus no model or approach can be perfect for all populations. This is reflected in the current landscape of screening tests that have subjective interpretation and varied receiver-operator characteristics (Kiekens and Tognonato, 2022). With that said, our proof-of-concept study using deep learning suggests that with larger more diverse datasets this approach can converge to, or exceed, human operator performance with reduced subjectivity and variability. Our work, and indeed all established screening tests, are applicable only to patients with mild-to-moderate stroke as it requires a minimum awareness/consciousness and ability to follow some commands. In our case, the pass group expectantly had lower NIHSS scores.

Our study has several limitations, including a small dataset size, which can potentially introduce overfitting and limit the generalizability of our models. We did use real-world audio data gathered in clinical settings, which does improve certain aspects of generalizability and adoption by other centers; our code is also open source to facilitate wider use.[1] We additionally attempted to address generalizability concerns by implementing robust model evaluation strategies, including early stopping during model training and using chronologically separated training and test datasets to mimic real-world multi-cohort testing. In future work, larger datasets, including non-English speakers, patients

1 https://github.com/UofTNeurology/masa-open-source

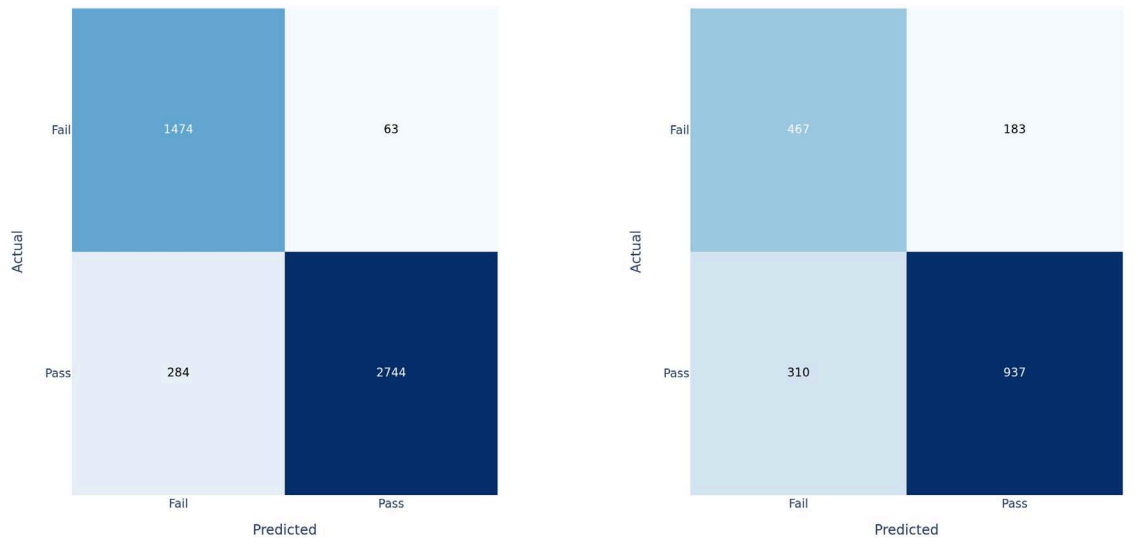

FIGURE 4
Confusion matrices for fusion model applied at the clip-level on training set **(left)** and test set **(right)**.

TABLE 4 Participant-level performance using RGB Mel-spectrograms and only vowel sounds as inputs yielded reduced performance compared to using all recorded voice sounds.

	RGB Mel-spectrogram (vowels only)				
	Sensitivity (recall)	Specificity	Precision	F1 score rage	AUC [95% CI]
DenseNet-121	0.67	0.79	0.6	0.72	0.79 [0.44, 1.14]
ConvNext-Tiny	0.67	0.79	0.6	0.72	0.78 [0.39, 1.17]
Fusion	0.67	0.79	0.6	0.72	0.79 [0.42, 1.16]

CI, confidence interval, please note max. AUC value is 1.0, computed numerically has upper bounds larger than this value and is listed herein to show the calculation result.

with accents, dental prosthesis, and other diverse populations will further expand generalizability.

Data-augmentation techniques in the audio domain such as time stretching, pitch shifting, or background noise injection could also be used to supplement our smaller dataset, however, this approach was not considered in this application given concerns about reduced explainability. However, the overlapping windows used to segment audio into spectrograms can be thought of as a type of cropping-based augmentation technique that maintains the integrity of the frequency-domain. Mel-spectrogram domain augmentation has also demonstrated promise in speech and acoustic scene classification and could be considered in future work (Wang et al., 2019). Additionally, input analysis should be explored in future work to determine the effects of varying recording conditions on model performance.

In this study we attempted to reduce the subjectivity involved with recognizing voice changes in dysphagia screening by developing a screening discriminator using TOR-BSST© "pass" or "fail" labels for the audio recordings as video fluoroscopy is not available for most patients. This is a limitation of our study, however, TOR-BSST© has been characterized as having excellent receiver operating characteristics that render it a good screening discriminator in a population assessed by VFSS, and in comparison, to many other screening tests (Kiekens and Tognonato, 2022). Our choice of labeling places this feasibility study as an assistive technology for care-providers and one that does not fully replace clinical judgment when coupled with bedside assessment (Liu et al., 2022). Furthermore, even in the setting of video assessment, there can be discordance between SLP reviewers reflecting the underlying physiological complexity of dysphagia.

Another consideration pertains to the manual segmentation of the audio data. Recognizing the potential scalability challenges associated with manual processing, we acknowledge the utility of automated segmentation techniques in streamlining the process. Nevertheless, the primary intent of this study was to establish the foundational feasibility of discriminating between dysphagia and non-dysphagia states via audio biomarkers. The manual approach was adopted considering challenges encountered in our real-world data collection environment (in hospital) and the occasional capture of the study data collector's voice in the recordings. Moving forward, as this approach is further refined, automated segmentation with its promise for increased scalability will certainly be an area of focus and exploration.

Although screening tools generally exhibit good sensitivity and specificity, stroke patients commonly have a non-linear clinical course that can result in a fluctuating swallowing status. We utilized the most up-to-date swallowing screening result as a label for our data. This property is inherent to stroke physiology (at least in mild to moderate stroke), as there is a degree of spontaneous improvement over the course of several days. We attempted to

mitigate this by assessing patients early in their clinical course. In the future, rapid ML-based clinical screening tools may allow fast serial assessments of dysphagia evolution and not simply one-time snapshots.

A further limitation we recognize are the challenges associated with applying CNNs, originally trained on image datasets, to spectrograms. This is due to the fundamental differences between these two types of data. Unlike images, spectrograms operate within unique parameter spaces, characterized by axes of frequency, time, and power. Furthermore, the non-local spectral properties of sound, and the inherent temporal nature of sound as noted by Hershey et al. (2017), Zhang et al. (2019), Palanisamy et al. (2020), Park et al. (2022), Dave and Srivastava (2023), add to this limitation. Nonetheless, CNNs are extensively used for analysis of audio signals and our findings and AUC measurements are congruent with these known limitations. We recognize the inherent variability and limitations that exist with real-world patient data, CNNs, and their ability to classify a physiologically complex pathology such as dysphagia.

Conclusion

Our study demonstrates the feasibility of deep learning as an effective application for the screening of post-stroke dysphagia from vocalizations alone. This approach offers an avenue for the development of future non-invasive, less subjective, and rapid screening tools for dysphagia. This could contribute to improved patient management, outcomes, and democratization of swallowing screening.

Data availability statement

The datasets presented in this article are not readily available because REB at Sunnybrook Health Sciences requires human voice data to be stored and analyzed locally. Requests to access the datasets should be directed to h.khosravani@utoronto.ca.

Ethics statement

The studies involving humans were approved by Lisa Di Prospero, Sunnybrook Hospital, REB. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review and editing. AB: Conceptualization, Methodology, Data curation, Investigation, Writing – original draft, Writing – review and editing. HM: Methodology, Software, Writing – review and editing. EN: Methodology, Writing – review and editing. LP: Methodology, Writing – review and editing. AW: Writing – review and editing. AS: Writing – review and editing. GR: Writing – review and editing. MC: Writing – review and editing. MB: Writing – review and editing. BM: Writing – review and editing. HK: Conceptualization, Methodology, Data curation, Investigation, Resources, Writing – original draft, Writing – review and editing, Supervision, Project administration, Funding acquisition.

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Conflict of interest

HK was an associate editor for Frontiers in Neurology.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1302132/full#supplementary-material

References

Appelros, P., and Terént, A. (2004). Characteristics of the National Institute of Health Stroke Scale: Results from a population-based stroke cohort at baseline and after one year. *Cerebrovasc. Dis.* 17, 21–27. doi: 10.1159/000073894

Cohen, D., Roffe, C., and Beavan, J. (2016). Post-stroke dysphagia: A review and design considerations for future trials. *Int. J. Stroke* 11, 399–411.

Dave, B., and Srivastava, K. (2023). Convolutional neural networks for audio classification: An ensemble approach. *Lecture Notes Netw. Syst.* 428, 253–262. doi: 10.1007/978-981-19-2225-1_23/COVER

Feigin, V., Stark, B., and Johnson, C. (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* 20, 795–820. doi: 10.1016/S1474-4422(21)00252-0

Fritz, M., Howell, R., Brodsky, M., Suiter, D., Dhar, S., Rameau, A., et al. (2021). Moving forward with dysphagia care: Implementing strategies during the COVID-19 pandemic and beyond. *Dysphagia* 36, 161–169. doi: 10.1007/s00455-020-10144-9

Ganaie, M., Hu, M., and Malik, A. (2022). Ensemble deep learning: A review. *Eng. Appl. Artif. Intell.* 115:105151.

Gerratt, B., Kreiman, J., and Garellek, M. (2016). Comparing measures of voice quality from sustained phonation and continuous speech. *J. Speech Lang. Hear. Res.* 59, 994–1001. doi: 10.1044/2016_JSLHR-S-15-0307

Hanley, J., and McNeil, B. (1982). The meaning and use of the area under a receiver operating characteristic (ROC) Curve1. *Radiology* 143, 29–36.

Hershey, S., Chaudhuri, S., and Ellis, D. (2017). CNN architectures for large-scale audio classification. *arXiv* [Preprint]. doi: 10.48550/arXiv.1609.09430

Huang, G., Liu, Z., van der Maaten, L., and Weinberger, K. (2016). "Densely Connected Convolutional Networks," in *Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition*, Honolulu.

Ju, C., Bibaut, A., and van der Laan, M. (2018). The relative performance of ensemble methods with deep convolutional neural networks for image classification. *J. Appl. Stat.* 45, 2800–2818. doi: 10.1080/02664763.2018.1441383

Kang, Y., Kim, J., Jee, S., Jo, C., and Koo, B. (2018). Detection of voice changes due to aspiration via acoustic voice analysis. *Auris Nasus Larynx.* 45, 801–806. doi: 10.1016/j.anl.2017.10.007

Khalifa, Y., Coyle, J., and Sejdić, E. (2020). Non-invasive identification of swallows via deep learning in high resolution cervical auscultation recordings. *Sci. Rep.* 10:8704. doi: 10.1038/s41598-020-65492-1

Khurana, A., Mittal, S., and Kumar, D. (2023). Tri-integrated convolutional neural network for audio image classification using Mel-frequency spectrograms. *Multimed. Tools Appl.* 82, 5521–5546. doi: 10.1007/s11042-022-13358-1

Kiekens, C., and Tognonato, C. (2022). Which screening tool should be used for identifying aspiration risk associated with dysphagia in acute stroke? A Cochrane Review summary with commentary. *NeuroRehabilitation* 51, 533–535. doi: 10.3233/NRE-228024

Kuncheva, L. (2014). *Combining Pattern Classifiers Methods and Algorithms*. Hoboken, NY: Wiley.

Lecun, Y., and Bengio, Y. (1995). "Convolutional networks for images, speech, and time-series," in *Handbook of Brain Theory and Neural Networks*, eds A. Michael and Arbib (London: MIT Press).

Liu, Z., Mao, H., and Wu, C. (2022). A ConvNet for the 2020s. *arXiv* [Preprint]. doi: 10.48550/arXiv.2201.03545

Lyden, P., Brott, T., Tilley, B., Welch, K., Mascha, E., Levine, S., et al. (1994). Improved reliability of the NIH Stroke Scale using video training. NINDS TPA stroke study group. *Stroke* 25, 2220–2226. doi: 10.1161/01.str.25.11.2220

Martino, R., Silver, F., Teasell, R., Bayley, M., Nicholson, G., Streiner, D., et al. (2009). The Toronto Bedside Swallowing Screening Test (TOR-BSST): development and validation of a dysphagia screening tool for patients with stroke. *Stroke* 40, 555–561. doi: 10.1161/STROKEAHA.107.510370

Milling, M., Pokorny, F., Bartl-Pokorny, K., and Schuller, B. (2022). Is Speech the New Blood? Recent progress in ai-based disease detection from audio in a nutshell. *Front. Digit Health.* 4:886615. doi: 10.3389/fdgth.2022.886615

Moore, M., Papreja, P., and Saxon, M. (2020). Uncommonvoice: A Crowdsourced dataset of dysphonic speech. *Interspeech* 2020, 2532–2536.

O'Brien, M., Botonis, O., Larkin, E., Carpenter, J., Martin-Harris, B., Maronati, R., et al. (2021). Advanced machine learning tools to monitor biomarkers of dysphagia: A wearable sensor proof-of-concept study. *Digit. Biomark.* 5, 167–175. doi: 10.1159/000517144

Palanisamy, K., Singhania, D., and Yao, A. (2020). Rethinking CNN Models for Audio Classification. *arXiv* [Preprint]. doi: 10.48550/arXiv.2007.11154

Park, H., Park, D., Kang, H., Kim, H., Lee, S., and Im, S. (2022). Post-stroke respiratory complications using machine learning with voice features from mobile devices. *Sci. Rep.* 12:16682. doi: 10.1038/s41598-022-20348-8

Roldan-Vasco, S., Orozco-Duque, A., Suarez-Escudero, J., and Orozco-Arroyave, J. (2021). Machine learning based analysis of speech dimensions in functional oropharyngeal dysphagia. *Comput. Methods Programs Biomed.* 208:106248. doi: 10.1016/j.cmpb.2021.106248

Ryu, J., Park, S., and Choi, K. (2004). Prediction of laryngeal aspiration using voice analysis. *Am. J. Phys. Med. Rehabil.* 83, 753–757. doi: 10.1097/01.phm.0000140798.97706.a5

Schmoldt, A., Benthe, H., and Haberland, G. (1975). Digitoxin metabolism by rat liver microsomes. *Biochem. Pharmacol.* 24, 1639–1641.

Shortliffe, E., and Sepúlveda, M. (2018). Clinical decision support in the era of artificial intelligence. *JAMA* 320, 2199–2200. doi: 10.1001/jama.2018.17163

Singh, S., and Hamdy, S. (2006). Dysphagia in stroke patients. *Postgrad. Med. J.* 82, 383–391. doi: 10.1136/pgmj.2005.043281

Srivastava, N., Hinton, G., Krizhevsky, A., and Salakhutdinov, R. (2014). Dropout: A simple way to prevent neural networks from overfitting. *J. Mach. Learn. Res.* 15, 1929–1958.

Waito, A., Bailey, G., Molfenter, S., Zoratto, D., and Steele, C. (2011). Voice-quality abnormalities as a sign of dysphagia: Validation against acoustic and videofluoroscopic data. *Dysphagia* 26, 125–134. doi: 10.1007/s00455-010-9282-4

Wang, H., Zou, Y., and Wang, W. (2019). SpecAugment++: A hidden space data augmentation method for acoustic scene classification. *arXiv* [Preprint]. doi: 10.31219/osf.io/3mwa7

Wilhelm, P., Reinhardt, J., and Van Daele, D. (2020). "A Deep Learning Approach to Video Fluoroscopic Swallowing Exam Classification," in *Proceedings - International Symposium on Biomedical Imaging. IEEE Computer Society*, Honolulu.

Zhang, B., Leitner, J., and Thornton, S. (2019). *Audio Recognition using Mel Spectrograms and Convolution Neural Networks*. San Diego, CA: Noiselab University of California.

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Stratified predictions of upper limb motor outcomes after stroke

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Introduction: Longitudinal observations of upper limb motor recovery after stroke have suggested that certain subgroups may exhibit distinct recovery patterns. Here we sought to examine whether the predictive ability for post-stroke upper limb motor outcomes could be enhanced by applying conventional stratification strategies.

Method: For 60 individuals who suffered the first stroke, upper limb motor impairment was assessed with the upper extremity Fugl-Meyer assessment (UE-FMA) at 2 weeks as a baseline and then 3 months post-stroke. Brain structural damage at baseline was assessed by MRI data-derived markers ranging from traditional lesion size to the lesion load and to the disconnectome. Linear regression models for predicting upper limb motor outcomes (UE-FMA score at 3 months post-stroke) based on baseline upper limb motor impairment (UE-FMA score at 2 weeks post-stroke), brain structural damage, and their combinations were generated, and those with the best predictive performance were determined for individual subgroups stratified according to initial impairment (severe and non-severe), lesion location (cortical and non-cortical), and neurophysiological status (motor evoked potential-positive and motor evoked potential-negative).

Results: The best predictions were made by baseline upper limb motor impairment alone for subgroups with less functional impairment (non-severe) or less structural involvement (non-cortical), but by the combination of baseline upper limb motor impairment and brain structural damage for the other subgroups. The predictive models tailored for subgroups determined according to initial impairment and neurophysiological status yielded a smaller overall error than that for the whole group in upper limb motor outcome predictions.

Discussion: The predictive ability for upper limb motor outcomes could be enhanced beyond the one-size-fits-all model for all individuals with stroke by applying specific stratification strategies, with stratification according to initial impairment being the most promising. We expect that predictive models tailored for individual subgroups could lead closer to the personalized prognosis of upper limb motor outcomes after stroke.

KEYWORDS

upper limb motor impairment, upper limb motor outcome, brain structural damage, proportional recovery, predictive model

1 Introduction

Numerous investigations have attempted to understand patterns of functional recovery after stroke, yielding longitudinal observations that have revealed recovery patterns regarding the time-dependency of functional recovery. With respect to the understanding of post-stroke recovery patterns, there appear to be some concerns; among others, identifying distinct recovery patterns to address inter-individual variability in recovery courses and linking the identified recovery patterns with markers collected at baseline to predict specific recovery patterns for individuals to follow appear to be the most pressing.

These concerns have led to the development of models enabling individualized outcome predictions. As artificial intelligence approaches become increasingly available, various machine learning algorithms ranging from linear regression to deep learning have been applied to demographic, clinical, electrophysiological, and neuroimaging data, as well as their combinations, as inputs, suggesting the potential of multidimensional markers for more accurate outcome predictions (for reviews, see (1, 2)).

Wide applications of the proportional recovery rule, notably to upper limb motor outcomes (3, 4), suggest that the severity of initial impairment affects the degree of outcomes. Considering confounders of the proportional recovery rule, however, initial impairment appears to explain a smaller amount of the variance in recovery than originally assumed (5). Furthermore, the existence of individuals not fitted to the proportional recovery rule indicates that outcomes may not be well predicted by initial impairment alone for some subgroups.

In this contribution, we employed two main strategies to generate models for predicting upper limb motor outcomes after stroke. First, as a follow-up to our previous study (6), we recognized the potential of lesion-induced brain structural damage in addition to baseline upper limb motor impairment. Among lots of markers that can be obtained from neuroimaging, we believe that lesion-induced brain structural damage could best characterize individual strokes, so we considered measures ranging from traditional lesion size to the lesion load and to the disconnectome as markers. Second, we assumed that predictive performance could be improved by generating models specific to distinct recovery patterns. Since distinct recovery patterns that best describe inter-individual variability in recovery courses remain unclear, we hypothetically considered conventional stratification strategies, such as the severity of initial impairment (7, 8), the location of lesions (9, 10), and neurophysiological status (11, 12), as potentially reflecting inter-individual variability in upper limb motor recovery.

Among the different combinations of baseline upper limb motor impairment and brain structural damage, we searched for the best predictive models for individual subgroups assigned according to the conventional stratification strategies. We sought to determine whether predictive models of upper limb motor outcomes for stratified subgroups could yield a reduction in the overall error compared with that for the whole group. We hypothesized that predictive performance could be improved for specific stratification strategies if they could at least partially reflect different recovery courses across individuals.

2 Methods

2.1 Participants

Sixty individuals (59.4 ± 12.5 years, 30 women) who suffered their first stroke and had a course of disease within 2 weeks (2 W) to 3 months (3 M) post-stroke participated in this study. They included those (i) with unilateral supratentorial lesions from ischemic or hemorrhagic stroke, (ii) aged between 18 and 80 years, and (iii) who were conscious and lacked indications of dementia or mental impairment. The absence of cognitive impairment for all individuals was checked by using the Mini-Mental State Examination as a screening instrument. The individuals' demographic and clinical characteristics are summarized in Table 1, with individual values listed in Supplementary Table S1. Lesions were manually segmented by an experienced physician, with their reliability checked by another experienced physician. An overlap map of the lesions is depicted in Figure 1. Seventy-seven healthy individuals (46.9 ± 16.5 years, 40 women) without any history of neurological or psychiatric diseases served as age- and sex-matched normative controls. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki and its later amendments, and the study was approved by the local institutional review board.

2.2 Stroke rehabilitation therapy

The individuals with stroke received comprehensive rehabilitation therapy to restore motor functions from the time of study participation until 3 months post-stroke. They participated in rehabilitation therapy 5 times a week in a rehabilitation hospital, with physical and occupational therapy received twice a day, each in the morning and afternoon, for a total treatment time of 4 h per day. Physical therapy consisted of gait training, strength strengthening exercises, balance training, and joint range of motion exercises, while occupational therapy included training for activities of daily living, hand function movement exercises, and swallowing facilitation therapy. For the individuals with aphasia or dysarthria, speech therapy was added to the program.

2.3 Assessment of upper limb motor impairment

For the individuals with stroke who suffered motor impairment of the contralesional upper limb, the degree of upper limb motor impairment at 2 W and 3 M after stroke was assessed using the upper extremity Fugl-Meyer assessment (UE-FMA) (13) by a trained occupational therapist blinded to the individuals' severity and not involved in administering the interventions. The UE-FMA score was based on direct observations of performance, such that each item was scored based on one's ability to complete the item using a three-point ordinal scale (0, unable to perform; 1, partially done; and 2, fully done). The UE-FMA score at 2 W was regarded as baseline upper limb motor impairment and the UE-FMA score at 3 M was considered as upper limb motor outcomes. The average UE-FMA scores were 25.2 ± 18.2 at 2 W and 39.9 ± 19.8 at 3 M against a full score of 66.

2.4 Measurement of motor evoked potentials

Motor evoked potentials (MEPs) were measured for 47 of the 60 individuals; the remaining individuals were unable to meet the schedules for MEP assessment. By using a BiStim^2 transcranial

TABLE 1 Summary characteristics of participants.

			Individuals with stroke (n = 60)	Normative controls (n = 77)	Statistical comparison
Demographics	Age (years) (mean ± SD)		28 ~ 80 (59.4 ± 12.5)	22 ~ 77 (46.9 ± 16.5)	NS
	Sex		Men:women = 30:30	Men:women = 37:40	NS
Lesion side	Hemispheric motor dominance		Dominant:non-dominant = 27:33	n/a	n/a
Upper limb motor impairment	UE-FMA score (mean ± SD)	2 W	4 ~ 63 (25.2 ± 18.2)	n/a	n/a
		3 M	4 ~ 66 (39.9 ± 19.8)	n/a	n/a
Stratification	Initial impairment		Severe:non-severe = 33:27	n/a	n/a
	Lesion location		Cortical:non-cortical = 26:34	n/a	n/a
	Neurophysiological status		MEP-negative:MEP-positive = 14:33	n/a	n/a
	Proportional recovery		Non-fitted:fitted = 22:38	n/a	n/a

For individuals with stroke, the dominant/non-dominant lesion side indicates that a lesion is located in the motor dominant/non-dominant hemisphere.
UE-FMA, upper extremity Fugl-Meyer assessment; 2 W, two weeks after stroke; 3 M, three months after stroke; MEP, motor evoked potential; SD, standard deviation; and NS, non-significant.

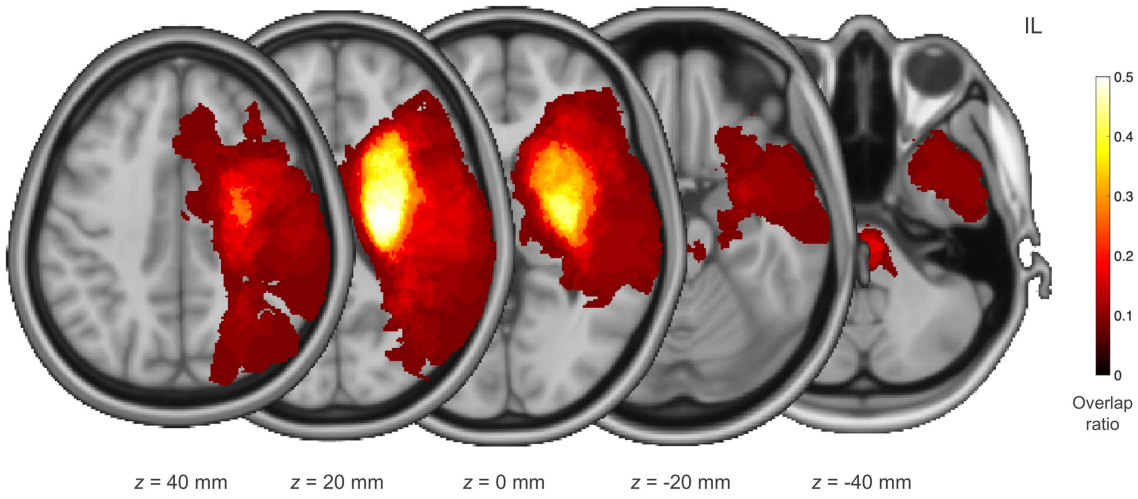

FIGURE 1
Distribution of lesions for individuals with stroke. Each individual's lesion was transformed to the standard space, oriented to be located on the same side, and then superimposed. The red–yellow colour maps the voxel-wise overlap ratio over the individuals. IL, ipsilesional hemisphere.

magnetic stimulation (TMS) system (Magstim, Carmarthenshire, UK) and a 70 mm figure-eight coil, a single-pulse TMS was repeatedly applied to the optimal scalp position to determine each individual's resting motor threshold, which was defined as the lowest stimulation intensity required to produce an MEP peak-to-peak amplitude ≥50 μV in 5 of 10 consecutive trials (14). By recording MEPs via surface electrodes from the contralateral first dorsal interosseous muscle, the absence of MEPs was defined if no MEP appeared after three consecutive discharges at full power (15).

2.5 Acquisition and analysis of MRI data

Using an Achieva 3 T MRI system (Philips Healthcare, Best, Netherlands), structural MRI (sMRI) and diffusion-weighed MRI (dMRI) data were collected for the individuals. For sMRI data, a T1-weighted volume image was acquired in axial planes with the following parameters: number of slices = 124, slice thickness = 1.60 mm, matrix size = 512 × 512, and in-plane resolution = 0.47 mm × 0.47 mm. For dMRI data, 46 volume images comprising 45 with diffusion weighting at b value = 1,000 s/mm^2 and one without diffusion

weighting were acquired in axial planes with the following parameters: number of slices = 60, slice thickness = 2.25 mm, matrix size = 112 × 112, and in-plane resolution = 1.96 mm × 1.96 mm.

Preprocessing of the dMRI data was conducted using tools in FSL[1] in such a way that eddy current-induced distortion and head movement were corrected and the skull was removed before modelling the diffusion tensor at each voxel. White matter (WM) tractography was performed for the preprocessed dMRI data to reconstruct WM fibers over the whole brain by using tools in MRtrix3.[2] For registration between the dMRI native space and the standard space, a deformation field was estimated for the sMRI data coregistered to the dMRI data by using tools in SPM12.[3]

2.6 Assessment of brain structural damage

As lesion-induced brain structural damage that could reflect an effect of a lesion on the CST or whole brain, we considered three types of measures as listed in Table 2, each identified by applying a specific damage map to a region of interest (ROI). Damage maps included (i) a weighted map of fractional anisotropy (FA) (16) derived from the diffusion tensor estimated using the post-stroke individuals' dMRI data, (ii) a binary map of a lesion identified using the post-stroke individuals' sMRI data, and (iii) a weighted map of a structural disconnectome estimated using the normative controls' dMRI data, as an ensemble of structural connections passing through a lesion (17, 18). Given a lesion identified for an individual with stroke, after the lesion was transformed to the dMRI data native space of a normative control, WM fibers passing through the lesion were selected among whole brain WM fibers estimated for the normative control. The distribution of voxel-wise counts of WM fibers was normalized to the maximum count and transformed to the standard space, and its average over the normative controls served as a structural disconnectome from the lesion.

ROIs included the (i) CST and (ii) whole brain. The territories of the CST were determined using either the post-stroke individuals' dMRI data (patient CST) or the normative controls' dMRI data (control CST) (19). For both patient and control CSTs, WM fibers commencing with the precentral gyrus, progressing to the posterior limb of the internal capsule (PLIC), and reaching the pons ipsilateral to the precentral gyrus were selected among whole brain WM fibers. The precentral gyrus was defined based on the respective label of the Destrieux atlas (20), and the PLIC and pons were delineated manually. Of the selected WM fibers, those extending into the cerebellum or contralateral hemisphere were excluded. The distribution of voxel-wise counts of WM fibers was normalized to the maximum count and then transformed to the standard space. The patient CST was identified for each individual with stroke, while the control CST was determined as the average of the CSTs of the normative controls.

A total of six measures of brain structural damage, including two CST disintegrity measures, two CST damage measures, and two brain damage measures, were evaluated for the individuals with stroke at baseline. CST disintegrity measures, including patient CST FA asymmetry and control CST FA asymmetry, were acquired by applying an FA map to the patient or control CST, averaging voxel-wise FA values in each hemisphere, and computing the asymmetry of the mean FA values between the two hemispheres: $(FA_{contralesional} - FA_{ipsilesional})/(FA_{contralesional} + FA_{ipsilesional})$. CST damage measures, including the CST lesion load and CST disconnectome load, were obtained by applying a lesion or disconnectome map to the control CST and computing the weighted volume of the overlap. Brain damage measures, including lesion volume and disconnectome volume, were acquired by applying a lesion or disconnectome map to the whole brain and computing the weighted volume of the overlap. To check whether there was multicollinearity between the six measures of brain structural damage, partial correlation between them was assessed after controlling for the individuals' age, sex, and hemispheric motor dominance.

2.7 Subgroup stratification

The individuals with stroke were allocated to subgroups according to (i) initial impairment, (ii) lesion location, and (iii) neurophysiological status. The severity of initial upper limb motor impairment was evaluated in terms of the UE-FMA score at 2 W. Among the 60 individuals, 33 with a score of 20 or lower were classified as severe (13), whereas the other 27 with a score higher than 20 were classified as non-severe. The criterion for the distribution of lesion location was determined according to whether lesions involved cortical areas beyond subcortical areas. Among the 60 individuals, 26 with lesions that involved both subcortical and cortical areas were classified as cortical, whereas the other 34 with lesions that involved subcortical areas only were classified as non-cortical. Neurophysiological status was assessed in terms of MEPs elicited by TMS. Among the 47 individuals for whom MEPs were evaluated, 14 without MEPs were classified as MEP-negative, whereas the other 33 with MEPs recorded in either contralateral target muscle were classified as MEP-positive.

For comparison with the stratification strategies considered above, the individuals were also assigned to subgroups according to whether they met the proportional recovery rule. Defining a model residual as the difference between the predicted change in the UE-FMA score according to the proportional recovery rule ((66 - UE-FMA score at 2 W) × 0.7) and the observed change in the UE-FMA score (UE-FMA score at 3 M - UE-FMA score at 2 W), larger model residuals indicated recovery-atypical individuals showing much poorer upper limb motor outcomes than predicted by the proportional recovery rule (21). Among the 60 individuals, 22 with a model residual of 20 or larger were classified as non-fitted (21), whereas the other 38 with a model residual smaller than 20 were classified as fitted, as displayed in the histogram of model residuals in Fig. S1.

2.8 Construction and comparison of predictive models

We used multiple linear regression to generate models for predicting upper limb motor outcomes. That is, upper limb motor outcomes served as the response variable and inputs including baseline upper limb motor impairment and brain structural damage served as predictor variables. Specifically, three kinds of models were generated according to inputs employed: (i) baseline upper limb motor impairment alone, (ii) brain structural damage alone, and (iii) a combination of baseline upper limb motor impairment and brain structural damage. In all the

1 https://fsl.fmrib.ox.ac.uk/

2 https://www.mrtrix.org/

3 http://www.fil.ion.ucl.ac.uk/spm/

TABLE 2 List of brain structural damage measures.

Type	Damage map	ROI	Structural damage measure
CST disintegrity	FA	Patient CST	Patient CST FA asymmetry
	FA	Control CST	Control CST FA asymmetry
CST damage	Lesion	Control CST	CST lesion load
	Structural disconnectome	Control CST	CST disconnectome load
Brain damage	Lesion	Whole brain	Lesion volume
	Structural disconnectome	Whole brain	Disconnectome volume

Each measure was defined by applying a specific damage map to a region of interest (ROI).
CST, corticospinal tract; and FA, fractional anisotropy.

models, the individuals' age, sex, and hemispheric motor dominance were included as confounding covariates. Model parameters were estimated by using the least square approximation without involving regularization. This model construction was repeated for the whole group and for each stratified subgroup.

To assess the predictive ability of each model, the in-sample error and the out-of-sample or generalization error in predicting upper limb motor outcomes were measured by the squared error per sample, that is, the mean squared error (MSE). While the in-sample error was estimated for samples already seen in the training phase, the generalization error was estimated for those unseen in the training phase. Specifically, the generalization error was measured via leave-one-out cross-validation (CV), in which a squared error was computed for each left-out sample when the remaining samples were used to estimate the model parameters. A model's superiority was primarily determined by a smaller MSE in CV in terms of the generalization error since the robustness of a model to a range of unseen samples beyond those used for estimating model parameters would be crucial for assessing the model's practical applicability. Moreover, the goodness of fit of each model was evaluated by the coefficient of determination, R^2, and the trade-off between the goodness of fit and model complexity was evaluated by the corrected Akaike information criterion (AICc) (22).

Between nested models, specifically between a reduced model composed of baseline upper limb motor impairment alone and an extended model comprising a combination of baseline upper limb motor impairment and brain structural damage, the likelihood-ratio χ^2 test was carried out to assess whether adding brain structural damage as an additional predictor variable could significantly improve the goodness of fit. In addition, between different models formed by a combination of baseline upper limb motor impairment and brain structural damage, a difference in the goodness of fit was evaluated by comparing R^2 values. In all statistical inferences, statistical significance was identified when a p value was less than 0.05, specifically corrected for multiple comparisons by a false discovery rate approach in the case of considering multiple models.

3 Results

3.1 Correlation between brain structural damage measures

The six measures of brain structural damage were highly correlated with each other ($p < 0.001$ for all pairs), with correlation coefficients ranging from 0.525 to 0.920 (Fig. S2). The average correlation coefficients between each and the others were 0.766, 0.803, 0.839, 0.698, 0.727, and 0.837 for the measures as ordered in Table 2, showing that the CST lesion load was the most correlated, whereas the CST disconnectome load was the least correlated on average. Specifically, the correlation coefficient was 0.920 between the two CST disintegrity measures, 0.809 between the two CST damage measures, and 0.862 between the two brain damage measures.

3.2 Predictive models for stratified subgroups

Since generally high correlation between the six measures of brain structural damage indicated multicollinearity between them, each of the measures was individually employed as a predictor variable, producing a total of 13 multiple linear regression models, as listed in Supplementary Table S2, for predicting upper limb motor outcomes. The statistics of the models are listed in Supplementary Table S3. In all models constructed, baseline upper limb motor impairment was a statistically significant predictor when it was combined with brain structural damage as well as when it was employed alone. When baseline upper limb motor impairment was combined with brain structural damage, brain structural damage was a statistically significant predictor for specific subgroups and, in connection with that, adding brain structural damage to baseline upper limb motor impairment could offer, but not always, a significant improvement in the goodness of fit. In addition, between the models comprised of a combination of baseline upper limb motor impairment and brain structural damage, the goodness of fit was not significantly different as specified in Supplementary Table S4.

The best predictive models developed for the whole group and for subgroups specified according to the different stratification strategies are summarized in Table 3. While the combination of baseline upper limb motor impairment and the CST lesion load (B + LL) composed the best predictive model with the greatest R^2 ($R^2 = 0.672$) and the smallest AICc (AICc = 474.253) as well as the smallest MSE in CV (MSE = 152.572) for the whole group, the best predictive models were variable between stratified subgroups. Whereas the best predictive models consisted of baseline upper limb motor impairment alone (B) in the non-severe subgroup determined by initial impairment and in the non-cortical subgroup determined by lesion location, the combination of baseline upper limb motor impairment and the CST disconnectome load (B + DL) formed the best predictive model for the severe subgroup determined by initial impairment, for the cortical subgroup determined by lesion location, and for the MEP-negative subgroup determined by neurophysiological status.

TABLE 3 Predictive ability of the best predictive models developed for the whole group and for stratified subgroups.

Subgroup		Generalization error			In-sample error		
		Best model	MSE	Overall MSE	Best model	MSE	Overall MSE
All individuals		B + LL	152.572	152.572 (100%)	B + LL	140.510	140.510 (100%)
Initial impairment	Severe	B + DL	149.457	130.982 (85.8%)	B + DL	122.040	106.068 (75.5%)
	Non-severe	B	108.402		B + PF	86.547	
Lesion location	Cortical	B + DL	193.887	162.572 (106.6%)	B + DL	161.464	135.831 (96.7%)
	Non-cortical	B	138.802		B + DV	116.230	
Neurophysiological status	MEP-negative	B + DL	156.777	112.877 (96.1%)	B + DL	128.301	92.011 (89.6%)
	MEP-positive	B + DV	9.398		B + DV	6.470	
Proportional recovery	Non-fitted	B + PF	43.753	46.434 (30.4%)	B + PF	31.732	37.648 (26.8%)
	Fitted	B	47.986		B + DL	41.073	

A smaller mean squared error (MSE) indicates better predictive ability.
CV, cross-validation; MEP, motor evoked potential; B, baseline upper extremity Fugl-Meyer assessment (UE-FMA) score; B + PF, baseline UE-FMA score + patient CST FA asymmetry; B + LL, baseline UE-FMA score + CST lesion load; B + DL, baseline UE-FMA score + CST disconnectome load; and B + DV, baseline UE-FMA score + disconnectome volume.

3.3 Overall error of predictive models for stratified subgroups

In predicting upper limb motor outcomes, having set the MSE of the best predictive model generated for the whole group at 100%, the best predictive models constructed via subgroup stratification according to initial impairment, lesion location, and neurophysiological status yielded overall MSEs ranging from 85.8 to 106.6% for the generalization error and those ranging from 75.5 to 96.7% for the in-sample error, as listed in Table 3, when the overall MSE was computed by weighting the MSEs of predictive models for stratified subgroups by the number of individuals in each subgroup. By comparison, for subgroups determined according to proportional recovery, as reference for those exhibiting different recovery courses, the best predictive model yielded an overall MSE reduced up to 30.4% for the generalization error and up to 26.8% for the in-sample error.

4 Discussion

In predicting upper limb motor outcomes in stroke recovery, we showed that predictive models tailored for subgroups of individuals with stroke could be furnished by applying conventional stratification strategies. While baseline upper limb motor impairment alone composed better predictive models for the non-severe subgroup determined by initial impairment and the non-cortical subgroup determined by lesion location, a combination of baseline upper limb motor impairment and brain structural damage formed superior predictive models for the other subgroups as well as for the whole group. We demonstrated that predictive models tailored for subgroups based on specific stratification strategies, such as initial impairment and neurophysiological status, could lead to reductions in the overall error in upper limb motor outcome predictions compared with the predictive model for the whole group.

An increasing number of studies of upper limb motor recovery after stroke have suggested numerous markers sourced from various clinical data, not least of which are upper limb motor impairment and neuroimaging-based brain structural damage evaluated at baseline (23), in predicting subsequent upper limb motor outcomes. While initial impairment is a well-known marker of outcomes several months later (24, 25), we showed that a combination of baseline upper limb motor impairment and brain structural damage could generally provide an improvement in predictive ability compared with the use of baseline upper limb motor impairment alone. Considering the relevance of proportional recovery to lesion-induced CST disintegrity (3, 21, 26) and CST damage (7), brain structural damage appears to have the potential to improve the predictive ability when used together with baseline upper limb motor impairment (6).

For the non-severe subgroup determined by initial impairment and the non-cortical subgroup determined by lesion location, upper limb motor outcomes were best predicted by baseline upper limb motor impairment alone, specifically in terms of the generalization error. Considering that variability in recovery courses could be associated with the heterogeneity of lesion characteristics between individuals (9, 10, 27–29), structurally or functionally less impairment would induce smaller inter-individual variability; hence, the greatest robustness to variations in upper limb motor outcome predictions could be achieved by the simpler predictive model composed of baseline upper limb motor impairment alone for the subgroups.

As the virtue of upper limb motor outcome predictions for stratified subgroups, we showed that predictive models tailored for subgroups determined according to specific stratification strategies could yield a smaller overall error compared with that for the so called one-size-fits-all model for all individuals with stroke. Of the stratification strategies considered here, subgroup stratification according to initial impairment appears to be most promising in that the predictive models for the stratified subgroups yielded smaller MSEs in terms of the generalization error for every subgroup than that for the one-size-fits-all model. Considering that many individuals not fitted to the proportional recovery rule are those with initially severe impairment (30), subgroup stratification according to initial impairment appears to partly reflect different recovery courses as implied by proportional recovery. In subgroup stratification according to neurophysiological status, the MSE in terms of the generalization error was greatly reduced for the MEP-positive subgroup, but not for the MEP-negative subgroup, indicating much larger variability in recovery courses in the absence of MEPs (31) in contrast to the robust predictive value in the presence of MEPs (12).

In upper limb motor recovery studies that considered follow-up outcomes as the response variable to be predicted, differing ability in outcome predictions according to subgroups has been often presented. For example, Feng and colleagues (7) showed that baseline upper limb motor impairment was a marker comparable to the CST lesion load in predicting upper limb motor outcomes for the whole sample, but not for a subgroup with initially severe impairment (UE-FMA score at baseline $\leq$ 10). Such changing contributions of a certain marker to predicting outcomes appear to suggest a need for predictive models for stratified subgroups as a possible way to improve predictive performance, as well as supporting the notion of grossly different recovery patterns across individuals. In this respect, we note that our unique attempt was to generate predictive models for individual subgroups assigned according to hypothetical differences in recovery patterns, while many of previous studies aimed to predict different recovery patterns themselves via the representation of the response variable by categories of outcomes, for example, two recovery patterns in the proportional recovery rule (32) and four recovery patterns in the Predict Recovery Potential algorithm (33). Our approach may find new applications as distinct recovery patterns that better describe inter-patient variability in recovery courses could be identified in the future.

This study has some limitations that should be accounted for in future studies. First, the predictive models suggested here are not yet considered conclusive primarily due to the small sample size. Subgroup stratification according to initial impairment appears to be a reasonable starting point for further development of predictive models for stratified subgroups, but it would be necessary to refine the stratification strategy and validate the performance of the predictive models against a larger sample for practical application to prognostic predictions in clinical practice. Second, although here we considered at most two subgroups for stratification strategies partly because of the limited pool of post-stroke individuals, the number of subgroups could vary greatly. For instance, by considering that the presence of MEPs could be a useful marker particularly for individuals with initially severe impairment (12), initial impairment and neurophysiological status might be applied together to provide subdivided subgroups according to a combination of stratification strategies. Third, more markers than those considered here could be added to establish more robust and accurate outcome predictions. High-dimensional markers from demographic, clinical, electrophysiological, and neuroimaging data would increase the opportunity to apply more complex artificial intelligence approaches and eventually render individualized outcome predictions practically feasible.

5 Conclusion

Despite growing momentum to develop precision medicine for stroke, the phenotypic diversity of stroke appears to be a main challenge specifically in predicting functional outcomes after stroke. In the current study, we put forward the value of subgroup stratification in developing prognostic predictive models of upper limb motor outcomes. We suppose that predictive models for stratified subgroups could serve as an intermediate step towards more complete precision medicine for personalized prognosis of upper limb motor outcomes, thus paving the way for promoting clinical application of such prognostic predictive models in stroke recovery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This studies involving humans were approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (No. 2022-07-084-001). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ChP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. M-SK: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1323529/full#supplementary-material

References

1. Bonkhoff AK, Grefkes C. Precision medicine in stroke: towards personalized outcome predictions using artificial intelligence. *Brain*. (2021) 145:457–75. doi: 10.1093/brain/awab439

2. Li Q, Chi L, Zhao W, Wu L, Jiao C, Zheng X, et al. Machine learning prediction of motor function in chronic stroke patients: a systematic review and meta-analysis. *Front Neurol*. (2023) 14:1039794. doi: 10.3389/fneur.2023.1039794

3. Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong JY, Lazar RM, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabil Neural Repair*. (2008) 22:64–71. doi: 10.1177/1545968307305302

4. Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehabil Neural Repair*. (2015) 29:614–22. doi: 10.1177/1545968314562115

5. Bonkhoff AK, Hope T, Bzdok D, Guggisberg AG, Hawe RL, Dukelow SP, et al. Bringing proportional recovery into proportion: Bayesian modelling of post-stroke motor impairment. *Brain*. (2020) 143:2189–206. doi: 10.1093/brain/awaa146

6. Park C-h, Ohn SH. The predictive value of lesion and disconnectome loads for upper limb motor impairment after stroke. *Neurol Sci*. (2022) 43:3097–104. doi: 10.1007/s10072-021-05600-9

7. Feng W, Wang J, Chhatbar PY, Doughty C, Landsittel D, Lioutas VA, et al. Corticospinal tract lesion load: an imaging biomarker for stroke motor outcomes. *Ann Neurol*. (2015) 78:860–70. doi: 10.1002/ana.24510

8. Binkofski F, Seitz R, Hackländer T, Pawelec D, Mau J, Freund H-J. Recovery of motor functions following hemiparetic stroke: a clinical and magnetic resonance-morphometric study. *Cerebrovasc Dis*. (2001) 11:273–81. doi: 10.1159/000047650

9. Feys H, Hetebrij J, Wilms G, Dom R, De Weerdt W. Predicting arm recovery following stroke: value of site of lesion. *Acta Neurol Scand*. (2000) 102:371–7. doi: 10.1034/j.1600-0404.2000.102006371.x

10. FtdN S, Reding MJ. Effect of lesion location on upper limb motor recovery after stroke. *Stroke*. (2001) 32:107–12. doi: 10.1161/01.str.32.1.107

11. Stinear CM, Byblow WD, Ackerley SJ, Smith M-C, Borges VM, Barber PA. Proportional motor recovery after stroke: implications for trial design. *Stroke*. (2017) 48:795–8. doi: 10.1161/STROKEAHA.116.016020

12. JnV E, Sancho J, Bautista D, Escudero M, López-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. *Stroke*. (1998) 29:1854–9. doi: 10.1161/01.str.29.9.1854

13. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med*. (1975) 7:13–31. doi: 10.2340/1650197771331

14. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann Neurol*. (1996) 40:367–78. doi: 10.1002/ana.410400306

15. Jo JY, Lee A, Kim MS, Park E, Chang WH, Shin YI, et al. Prediction of motor recovery using quantitative parameters of motor evoked potential in patients with stroke. *Ann Rehabil Med*. (2016) 40:806–15. doi: 10.5535/arm.2016.40.5.806

16. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson*. (2011) 213:560–70. doi: 10.1016/j.jmr.2011.09.022

17. Foulon C, Cerliani L, Kinkingnéhun S, Levy R, Rosso C, Urbanski M, et al. Advanced lesion symptom mapping analyses and implementation as bcbtoolkit. *Gigascience*. (2018) 7:1–17. doi: 10.1093/gigascience/giy004

18. Salvalaggio A, Filippo De Grazia M, Zorzi M, Thiebaut de Schotten M, Corbetta M. Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. *Brain*. (2020) 143:2173–88. doi: 10.1093/brain/awaa156

19. Park C-h, Kou N, Boudrias M-H, Playford ED, Ward NS. Assessing a standardised approach to measuring corticospinal integrity after stroke with DTI. *Neuroimage Clin*. (2013) 2:521–33. doi: 10.1016/j.nicl.2013.04.002

20. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*. (2010) 53:1–15. doi: 10.1016/j.neuroimage.2010.06.010

21. Buch ER, Rizk S, Nicolo P, Cohen LG, Schnider A, Guggisberg AG. Predicting motor improvement after stroke with clinical assessment and diffusion tensor imaging. *Neurology*. (2016) 86:1924–5. doi: 10.1212/WNL.0000000000002675

22. Hurvich CM, Tsai C-L. Regression and time series model selection in small samples. *Biometrika*. (1989) 76:297–307. doi: 10.1093/biomet/76.2.297

23. Stinear CM, Ward NS. How useful is imaging in predicting outcomes in stroke rehabilitation? *Int J Stroke*. (2013) 8:33–7. doi: 10.1111/j.1747-4949.2012.00970.x

24. König IR, Ziegler A, Bluhmki E, Hacke W, Bath PMW, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke. *Stroke*. (2008) 39:1821–6. doi: 10.1161/STROKEAHA.107.505867

25. Rost NS, Bottle A, Lee JM, Randall M, Middleton S, Shaw L, et al. Stroke severity is a crucial predictor of outcome: an international prospective validation study. *J Am Heart Assoc*. (2016) 5:e002433. doi: 10.1161/JAHA.115.002433

26. Guggisberg AG, Nicolo P, Cohen LG, Schnider A, Buch ER. Longitudinal structural and functional differences between proportional and poor motor recovery after stroke. *Neurorehabil Neural Repair*. (2017) 31:1029–41. doi: 10.1177/1545968317740634

27. Chen C-L, Tang F-T, Chen H-C, Chung C-Y, Wong M-K. Brain lesion size and location: effects on motor recovery and functional outcome in stroke patients. *Arch Phys Med Rehabil*. (2000) 81:447–52. doi: 10.1053/mr.2000.3837

28. Schiemanck SK, Kwakkel G, Post MW, Kappelle JL, Prevo AJ. Impact of internal capsule lesions on outcome of motor hand function at one year post-stroke. *J Rehabil Med*. (2008) 40:96–101. doi: 10.2340/16501977-0130

29. Fries W, Danek A, Scheidtmann K, Hamburger C. Motor recovery following capsular stroke: role of descending pathways from multiple motor areas. *Brain*. (1993) 116:369–82. doi: 10.1093/brain/116.2.369

30. Ward NS. Restoring brain function after stroke - bridging the gap between animals and humans. *Nat Rev Neurol*. (2017) 13:244–55. doi: 10.1038/nrneurol.2017.34

31. Pizzi A, Carrai R, Falsini C, Martini M, Verdesca S, Grippo A. Prognostic value of motor evoked potentials in motor function recovery of upper limb after stroke. *J Rehabil Med*. (2009) 41:654–60. doi: 10.2340/16501977-0389

32. Koch PJ, Park C-H, Girard G, Beanato E, Egger P, Evangelista GG, et al. The structural connectome and motor recovery after stroke: predicting natural recovery. *Brain*. (2021) 144:2107–19. doi: 10.1093/brain/awab082

33. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*. (2012) 135:2527–35. doi: 10.1093/brain/aws146

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The effect of transcranial alternating current stimulation on functional recovery in patients with stroke: a narrative review

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Stroke is a common neurological disorder worldwide that can cause significant disabilities. Transcranial alternating current stimulation (tACS) is an emerging non-invasive neuromodulation technique that regulates brain oscillations and reshapes brain rhythms. This study aimed to investigate the effect of tACS on functional recovery in patients with stroke. The MEDLINE (PubMed), Cochrane Library, Embase, SCOPUS, and Web of Science databases were searched for English-language articles on tACS and stroke, published up to October 20, 2023. The following key search phrases were combined to identify potentially relevant articles: 'tACS,' 'transcranial alternating current stimulation,' 'stroke,' 'cerebral infarct,' and 'intracerebral hemorrhage.' The inclusion criteria for study selection were as follows: (1) studies involving patients with stroke and (2) studies that used tACS for functional recovery. A total of 34 potentially relevant studies were identified. Five articles were included in this review after reading the titles and abstracts and assessing their eligibility based on the full-text articles. Among the included studies, one investigated the improvement in overall functional status in patients with stroke after tACS, and two investigated the effect of tACS on motor function and gait patterns. Moreover, one study reported the efficacy of tACS on aphasia recovery, and one study evaluated the effect of tACS on hemispatial neglect. Our findings suggest that tACS improves functional recovery in patients with stroke. The application of tACS was associated with improved overall functional recovery, sensorimotor impairment, aphasia, and hemispatial neglect. The potential clinical application of tACS should be supported by high-quality, evidence-based studies.

KEYWORDS

transcranial alternating current stimulation, stroke, treatment, rehabilitation, review

Introduction

Stroke is a common neurological disorder that occurs worldwide and causes significant disability (1). Patients with stroke have neurological deficits in different functional domains that can be permanent (2). Following a stroke, patients can have various sequelae, such as motor impairments, sensory loss, visual field defects, cognitive impairments, dysphagia, and language impairment (3). Such functional problems that persist after stroke can have a substantial negative impact on the quality of life and result in emotional stress. Rehabilitation therapy is crucial for ameliorating severe dysfunction resulting from strokes; it assists patients

TABLE 1 Search terms and strategies.

Database	Keywords
MEDLINE	("stroke"[All Fields] OR "cerebral infarct"[All Fields] OR "intracerebral hemorrhage"[All Fields]) AND ("tACS"[All Fields] OR "transcranial alternating current stimulation"[All Fields])
Cochrane library	#1 "stroke" OR "cerebral infarct" OR "intracerebral hemorrhage" 84,173 #2 "tACS" OR "transcranial alternating current stimulation" 3,397 #3 #1 and #2 in Trials 112
Embase	('stroke'/exp. OR 'stroke' OR 'cerebral infarct'/exp. OR 'cerebral infarct' OR 'intracerebral hemorrhage'/exp. OR 'intracerebral hemorrhage') AND ('tacs' OR 'transcranial alternating current stimulation'/exp. OR 'transcranial alternating current stimulation')
Scopus	ALL (("stroke" OR "cerebral infarct" OR "intracerebral hemorrhage") AND ("tACS" OR "transcranial alternating current stimulation"))
Web of Science	ALL = (("stroke" OR "cerebral infarct" OR "intracerebral hemorrhage") AND ("tACS" OR "transcranial alternating current stimulation"))

in regaining full functionality and reintegrating into their daily routines (4).

Normally, functional balance between the two hemispheres of the brain is achieved through interhemispheric inhibition (5). In patients with stroke, brain damage caused by the events leads to abnormal increases in interhemispheric inhibition and enhanced excitability of the contralesional hemisphere (6). Cortico-subcortical excitability and neural network changes can cause severe functional disabilities (7). Among the various rehabilitation methods, non-invasive brain stimulation (NIBS) modulates cortical excitability and helps regain balance between the two hemispheres (8). Moreover, NIBS aims to induce neuroplasticity and facilitate recovery by modulating neural processing. Repetitive transcranial magnetic stimulation (rTMS), transcranial direct-current stimulation (tDCS), and transcranial alternating current stimulation (tACS) are commonly used NIBS methods to induce a better recovery (9). rTMS activates axons through short-pulsed stimulation by inducing new action potentials, whereas tDCS manipulates the membrane potential of neurons and modulates spontaneous firing rates (10).

tACS is an emerging NIBS method used to regulate brain oscillations and reshape brain rhythms (11). Sinusoidal alternating electric currents are delivered to the head via scalp electrodes in specific brain regions to modulate brain activity. The duration of stimulation, frequency, amplitude, phase difference, and the site of stimulation are major parameters used in the application of tACS (12). The intensity of the alternating-current is provided within the range of 0.5–2 mA using metal or rubber electrodes with a skin-electrolyte contact area of 25–35 cm^2 (13). The electrical current alternates between two electrodes (a positive electrode is called an anode, and a negative electrode is called a cathode) back and forth as a sinusoidal wave. These weak and constant direct electrical currents affect cortical neurons and alter cortical excitability (14). Furthermore, tACS is believed to improve brain function by modulating the intrinsic oscillatory activity in a frequency-dependent manner (15).

Previous studies have investigated the relationship between tACS-induced neural oscillations and improvements in behavioral and cognitive functions (16). The networks of oscillatory activity are classified into frequency bands (delta-δ: 1–3 Hz; theta-θ: 4–7 Hz; alpha-α: 8–13 Hz; beta-β: 14–30 Hz; gamma-γ: 30–80 Hz; fast, 80–200 Hz; ultra-fast, 200–600 Hz) (17). The associations of alpha-band oscillations (8–13 Hz) with visual task performance (18), beta-band oscillations (14–30 Hz) with motor performance (19), and theta-band oscillations (4–7 Hz) with memory (20) have been reported. Therefore, tACS could be an effective therapeutic tool to enhance stroke rehabilitation. However, no previous studies have summarized the effect of tACS on functional recovery in patients with stroke. This review investigated tACS therapy for functional recovery in patients with stroke.

Methods

The MEDLINE (PubMed), Cochrane Library, Embase, SCOPUS, and Web of Science databases were searched for English-language articles about tACS and stroke, published up to October 20, 2023. The following key search phrases were combined to identify potentially relevant articles: 'tACS,' 'transcranial alternating-current stimulation,' 'stroke,' 'cerebral infarct,' and 'intracerebral hemorrhage' (Table 1). The inclusion criteria for study selection were as follows: (1) studies involving patients with stroke and (2) studies which used tACS for functional recovery. The exclusion criteria were as follows: (1) reviews, (2) case reports, (3) commentaries, (4) letters, (5) animal studies, and (6) study outcomes that were either insufficient or not reported.

Results

After the search, 1,742 potentially relevant articles were identified. The titles and abstracts of the articles were screened, and their eligibility was assessed based on the full-text articles. Five studies were included in this review (Figure 1). Details of the included articles are presented in Table 2. Among the included studies, only one study highlighted an improvement in overall functional status in patients with stroke after tACS (21), and two studies investigated the effect of tACS on motor function and gait patterns (22, 23). One study reported the efficacy of tACS on aphasia recovery (24), whereas one study evaluated the effect of tACS on hemispatial neglect (25).

A randomized controlled trial (RCT) conducted by Wu et al. in 2016 recruited 60 patients with stroke and demonstrated that tACS positively enhanced neurological function (26). Thirty patients received 15 sessions of tACS over the mastoids bilaterally (20 Hz and < 400 μA for 30 min). Mastoid regions, which are close to the subcortical structures around the medulla and cerebellum, are expected to increase cerebral blood flow and induce functional recovery as they are close to the cerebello-hypothalamic projections. The National Institutes of Health Stroke Scale (NIHSS) scores, which reflect the overall functional status of patients with stroke and cerebral hemodynamics using transcranial Doppler, of these patients were

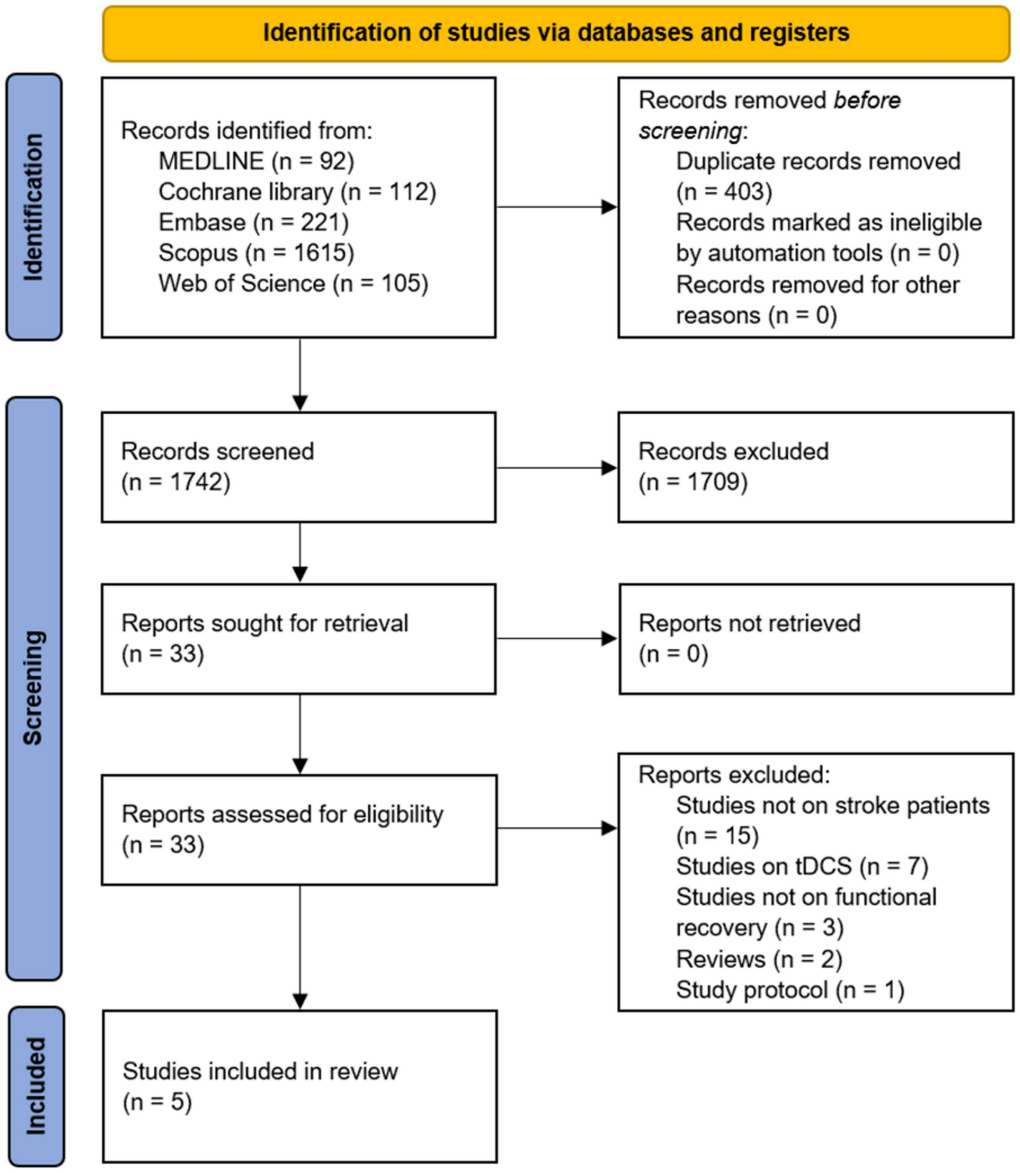

FIGURE 1
Flow diagram of the study selection process.

compared with those of 30 patients in the control group, who received the usual rehabilitation program only. When patients in the tACS group received the tACS in a quiet treatment room, patients in the control group were asked to sit on a chair for the same period in the same room with tACS. All patients received a standardized rehabilitation program, which included aerobic exercise, daily function training, and speech and cognitive training for 3 h. Patients were unaware of which group they belonged to or what treatment the other group received. The NIHSS is often used to measure neurological function in post-stroke patients and consists of 15 items, including levels of consciousness, visual fields, facial muscle function, extraocular movements, language, speech, motor strength, sensory function, coordination, and hemi-inattention (27). The results demonstrated that the tACS group had a significant decrease in mean NIHSS scores, a larger increase in blood flow velocity, and a decrease in the resistance of the vascular bed compared to the control group. The mechanism of tACS action in stroke recovery is that electrical stimulation to brain tissues enhances cerebral hemodynamics, including global and regional cerebral blood flow (28). This study also showed that tACS increased the cerebral blood flow velocity, which induced recovery of neurological function. Thus, this study concludes that tACS effectively improves sensorimotor function and cerebral hemodynamics in patients with stroke.

In 2020, Kitatani et al. conducted a small single-blind crossover study to investigate the effects of gait-synchronized oscillatory brain stimulation with tACS. Eight patients with chronic stroke received tACS over the ipsilesional primary motor cortex (M1) foot area (40 Hz for 10 sessions, twice a week for 5 weeks). The primary motor cortex is a brain region located anterior to the central sulcus, which is traditionally implicated in voluntary movement control (29). For stimulation over the foot area of M1, the positions of the electrodes were determined to be where the transcranial magnetic stimulation

TABLE 2 Characteristics of included studies.

#	First author	Year	Study design	No. of patients (active/control)	Patients	Site	Intensity (mA)	Duration (min)	No. of sessions	Outcome parameters	Results
1	Wu et al. (21)	2016	RCT	60 (30 tACS vs. 30 usual rehabilitation)	Subacute stroke between 15 and 60 days after the onset	Bilateral mastoids	20 Hz	30 min	15 sessions	Overall functional status (NIHSS score, mean blood flow velocity (MFVs), Gosling pulsatility index (PI))	The mean NIHSS scores and Gosling PI of the the tACS group demonstrated a significant decrease compared to the control group.
2	Kitatani et al. (17)	2020	PCO	8 (tACS and sham)	Single stroke ≥6 m	M1 (foot area)	40 Hz	10 min	10 sessions (tACS-sham crossver)	Gait (EMG)	Gait intervention with tACS was effective in modulating the cortical control of muscle activity during gait and enhancing gait function.
3	Xie et al. (19)	2022	RCT	30 (14 active tACS vs. 11 sham tACS)	Post-stroke aphasia ≥6 m	SMA	6 Hz	30 min	14 sessions	Aphasia (Aphasia Battery of Chinese (ABC))	The results demonstrated that the active tACS plus SLT group exhibited significantly greater improvements in AQ and auditory verbal comprehension than the sham tACS plus SLP group.
4	Yuan et al. (18)	2022	POS	13 (crossover, 10 Hz, 20 Hz, sham)	Unilateral stroke ≥6 m	Ipsilesional M1 (C3/C4) and contralesional supraorbital ridge (FP1/FP2)	10 Hz, 20 Hz	20 min	3 sessions	Motor (Fugl-Meyer Assessment, Action Research Arm Test, functional MRI)	10 Hz tACS mainly modulated FC within motor-related regions and 20 Hz tACS modulated regions beyond the motor-related areas.
5	Schuhmann et al. (20)	2022	POS	16 (crossover, 10 Hz, sham)	Stroke patients with hemispatial neglect	Contralateral posterior parietal cortex	10 Hz	30 min	2 sessions	Hemispatial neglect (CVDT)	Patients who received tACS demonstrated significant improvement in reducing neglect symptoms measured with a CVDT and BT.

BT, Bell's task; CVDT, computerized visual detection test; EMG, electromyography; LBT, line bisection task; FC, functional connectivity; SMA, supplementary motor area; M1, primary motor cortex; NIHSS, National Institute of Health Stroke Scale.

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elicited the best motor response in the tibialis anterior muscle. Patients performed a 10-min treadmill walking at a comfortable pace along with tACS, which was synchronized with the individual gait cycle frequency. Sham stimulation was performed in a crossover manner during the gait cycle. The results demonstrated that tACS in gait intervention, particularly targeting β-band (15–35 Hz) coherence, induced gait-specific plasticity and changes in gait function by enhancing the excitability of the cortical control of the paretic tibialis anterior muscle activity during gait.

The effect of tACS on recovery from aphasia in patients with stroke was reported in 2022 (24). Considering that neuronal oscillations in language-related brain areas may also be associated with speech and language processing (30), Xie et al. investigated whether tACS is effective in recovering post-stroke aphasia (24). Twenty-five patients with stroke suffering from aphasia were randomized into the active tACS (n = 14) or sham tACS (n = 11) groups. In the active tACS group, 6 Hz tACS was applied during 30 min of speech-language therapy (SLT) over the supplementary motor area (SMA) for 14 consecutive days. All patients believed that they received active tACS. tACS was delivered for the entire 30-min intervention period and 30-s ramp-up and-down phases in the study group. Patients in the sham group received tACS only during the ramp-up and-down phases. The stimulation site was SMA, which is involved in both speech production and comprehension (31, 32), and tACS over the SMA was expected to enhance the efficacy of SLT. Both groups received 30 min of SLT with active or sham tACS, followed by 90 min of SLT alone (14 sessions). The results demonstrated that in the active tACS plus SLT group the aphasia quotient and auditory verbal comprehension improved significantly more than the sham tACS and SLT group. This study suggests tACS over the SMA as an additive rehabilitative tool to strengthen the effect of SLT in patients with aphasia and stroke.

In 2022, Yuan et al. investigated whether tACS produced differential modulation effects according to frequency. Thirteen patients with chronic stroke were enrolled, and the effects of tACS at different frequencies (10 Hz, 20 Hz, sham) were evaluated using functional magnetic resonance imaging (fMRI). Additionally, tACS was applied over the ipsilesional M1, and 1 mA current was delivered for 20 min at 10 Hz and 20 Hz. At 10 Hz, tACS had a limited effect on motor-related regions, whereas tACS at 20 Hz modulated brain regions beyond motor-related areas. Therefore, this study concludes that applying 20 Hz tACS promotes a heightened functional interplay between the brain regions associated with executive control and the sensorimotor area, surpassing the effects observed with both 10 Hz tACS and sham stimulation.

Moreover, tACS was also effective in improving spatial attention deficits after stroke. In 2022, Schuhmann et al. conducted a crossover study to evaluate whether tACS alleviated attention deficits. Sixteen subacute patients with stroke with visuospatial neglect symptoms were enrolled and received 10 Hz tACS or sham stimulation. Alpha-band oscillations (8–12 Hz) over the posterior parietal cortex is known to be associated with attentional bias. Therefore, tACS at 10 Hz targeting the contralesional posterior parietal cortex was administered for 30 min. Patients who received tACS demonstrated a significant reduction in neglect symptoms, which were measured with a computerized visual detection task and Bell's task, compared to patients with sham stimulation. Therefore, the potential clinical utility of tACS was proposed for improving hemispatial neglect symptoms.

Four studies did not mention whether there were any side effects of tACS (23–26). Only the study by Kitatani et al. (22) reported that no patients experienced side effects, such as vertigo, skin pain or irritation, headaches, or phosphenes from the stimulation, which are commonly reported adverse effects of tACS (33).

Discussion

This review explored whether tACS can be considered an alternative treatment option for improving functional disabilities in patients with stroke. Studies included in this review demonstrated that applying tACS produced improvement in overall functional recovery, sensorimotor impairment, aphasia, and hemispatial neglect.

However, the mechanism of action of tACS is not fully understood. We hypothesized that the effects of tACS could be induced by entrainment and spike-timing-dependent plasticity (STDP) (16). Entrainment refers to the synchronization of the stimulated frequency with endogenous neural oscillations. As the stimulated frequency approaches the endogenous frequency of the targeted neural network, it can effectively modulate rhythmic oscillations (34). Additionally, STDP refers to synaptic plastic changes after stimulation that depend on synaptic events' timing. Synaptic strength increases when presynaptic spikes occur before postsynaptic spikes, whereas the strength is weakened when postsynaptic spikes occur before presynaptic spikes (16). Synaptic strengthening has been assumed to occur if the stimulation frequency is close to the endogenous frequency. In contrast, if the stimulation frequency is higher than the endogenous frequency, a postsynaptic spike occurs before the presynaptic spikes and the synapse may be weakened (16, 35). In addition, as tACS generates a weak oscillating extracellular field in the brain, subthreshold membrane potential shifts can increase or decrease membrane potentials (36). Changes in membrane potential affect spike timing at the single-neuron level and cause depolarization or hyperpolarization, which may trigger neuronal plasticity (37). Thus, tACS may facilitate neuroplasticity, which is essential in recovery (38).

The application of tACS may be recommended, considering the efficacy of stimulation in stroke recovery and its several advantages. First, tACS is usually well-tolerated and is both feasible and inexpensive (25). Moreover, tACS can also be easily applied in the clinical setting. Second, tACS is portable and can be used in a home setting (25). Third, tACS is safe and does not cause any serious adverse events (39). Therefore, tACS appears to be a readily available and safe alternative therapeutic approach to improve brain function. As tACS modulates oscillations and oscillatory connectivity in the brain, it may also be a potentially effective therapeutic tool to enhance brain plasticity, improving overall functional status, sensorimotor deficits, language problems, and attentional deficits.

The studies included in this review had a few limitations. First, the sample sizes of the included studies were small. Studies with large sample sizes are required to investigate the effects of tACS in patients with different functional impairments. Second, only a few studies have investigated the effect of tACS on functional recovery after stroke, and the functional status of patients with stroke differed across studies. Further studies on the effects of tACS on stroke recovery are warranted. Third, the long-term effects of tACS were not reported in these studies.

Further studies investigating the clinical efficacy of tACS, including repeated treatment sessions and evaluating the long-term effects of stimulation, are recommended.

Conclusion

Our findings suggest that tACS improves functional recovery in patients with stroke. The application of tACS was associated with improved overall functional recovery, sensorimotor impairment, aphasia, and hemispatial neglect. The potential clinical application of tACS should be supported by high-quality, evidence-based studies.

Author contributions

SY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. YY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. MC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol.* (2019) 18:459–80. doi: 10.1016/S1474-4422(18)30499-X

2. Fedorov A, Chibisova Y, Szymaszek A, Alexandrov M, Gall C, Sabel BA. Non-invasive alternating current stimulation induces recovery from stroke. *Restor Neurol Neurosci.* (2010) 28:825–33. doi: 10.3233/RNN-2010-0580

3. Buxbaum LJ, Ferraro MK, Veramonti T, Farne A, Whyte J, Ladavas E, et al. Hemispatial neglect. *Subtypes, neuroanatomy, and disability*. (2004) 62:749–56. doi: 10.1212/01.WNL.0000113730.73031.F4

4. Arantes AP, Bressan N, Borges LR, McGibbon CA. Evaluation of a novel real-time adaptive assist-as-needed controller for robot-assisted upper extremity rehabilitation following stroke. *PLoS One*. (2023) 18:e0292627. doi: 10.1371/journal.pone.0292627

5. Meyer BU, Röricht S, Gräfin von Einsiedel H, Kruggel F, Weindl A. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain*. (1995) 118:429–40. doi: 10.1093/brain/118.2.429

6. Bertolucci F, Chisari C, Fregni F. The potential dual role of transcallosal inhibition in post-stroke motor recovery. *Restor Neurol Neurosci*. (2018) 36:83–97. doi: 10.3233/RNN-170778

7. Shen QR, Hu MT, Feng W, Li KP, Wang W. Narrative review of noninvasive brain stimulation in stroke rehabilitation. *Med Sci Monit*. (2022) 28:e938298. doi: 10.12659/MSM.938298

8. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair*. (2009) 23:641–56. doi: 10.1177/1545968309336661

9. Veldema J, Gharabaghi A. Non-invasive brain stimulation for improving gait, balance, and lower limbs motor function in stroke. *J Neuroeng Rehabil*. (2022) 19:84. doi: 10.1186/s12984-022-01062-y

10. Kandić M, Moliadze V, Andoh J, Flor H, Nees F. Brain circuits involved in the development of chronic musculoskeletal pain: evidence from non-invasive brain stimulation. *Front Neurol*. (2021) 12:732034. doi: 10.3389/fneur.2021.732034

11. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. *Eur Arch Psychiatry Clin Neurosci*. (2021) 271:135–56. doi: 10.1007/s00406-020-01209-9

12. Bikson M, Esmaeilpour Z, Adair D, Kronberg G, Tyler WJ, Antal A, et al. Transcranial electrical stimulation nomenclature. *Brain Stimul*. (2019) 12:1349–66. doi: 10.1016/j.brs.2019.07.010

13. Pathak H, Sreeraj VS, Venkatasubramanian G. Transcranial alternating current stimulation (tACS) and its role in schizophrenia: a scoping review. *Clin Psychopharmacol Neurosci*. (2023) 21:634–49. doi: 10.9758/cpn.22.1042

14. Shirehjini SN, Shahrabi Farahani M, Ibrahim MK, Salman HM, Motevalli S, Mohammadi MH. Mechanisms of action of noninvasive brain stimulation with weak non-constant current stimulation approaches. *Iran J Psychiatry*. (2023) 18:72–82. doi: 10.18502/ijps.v18i1.11415

15. Lafleur LP, Murray A, Desforges M, Pacheco-Barrios K, Fregni F, Tremblay S, et al. No aftereffects of high current density 10 Hz and 20 Hz tACS on sensorimotor alpha and beta oscillations. *Sci Rep*. (2021) 11:21416. doi: 10.1038/s41598-021-00850-1

16. Vogeti S, Boetzel C, Herrmann CS. Entrainment and spike-timing dependent plasticity – a review of proposed mechanisms of transcranial alternating current stimulation. *Front Syst Neurosci*. (2022) 16:827353. doi: 10.3389/fnsys.2022.827353

17. Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci*. (2005) 6:285–96. doi: 10.1038/nrn1650

18. de Graaf TA, Gross J, Paterson G, Rusch T, Sack AT, Thut G. Alpha-band rhythms in visual task performance: phase-locking by rhythmic sensory stimulation. *PLoS One*. (2013) 8:e60035. doi: 10.1371/journal.pone.0060035

19. Espenhahn S, van Wijk BCM, Rossiter HE, de Berker AO, Redman ND, Rondina J, et al. Cortical beta oscillations are associated with motor performance following visuomotor learning. *NeuroImage*. (2019) 195:340–53. doi: 10.1016/j.neuroimage.2019.03.079

20. Rutishauser U, Ross IB, Mamelak AN, Schuman EM. Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature*. (2010) 464:903–7. doi: 10.1038/nature08860

21. Xu J, Wu Z, Nürnberger A, Sabel BA. Reorganization of brain functional connectivity network and vision restoration following combined tACS-tDCS treatment after occipital stroke. *Front Neurol*. (2021) 12:729703. doi: 10.3389/fneur.2021.729703

22. Kitatani R, Koganemaru S, Maeda A, Mikami Y, Matsuhashi M, Mima T, et al. Gait-synchronized oscillatory brain stimulation modulates common neural drives to ankle muscles in patients after stroke: a pilot study. *Neurosci Res*. (2020) 156:256–64. doi: 10.1016/j.neures.2019.11.001

23. Yuan K, Chen C, Lou WT, Khan A, Ti EC, Lau CC, et al. Differential effects of 10 and 20 Hz brain stimulation in chronic stroke: a tACS-fMRI study. *IEEE Trans Neural Syst Rehabil Eng*. (2022) 30:455–64. doi: 10.1109/TNSRE.2022.3153353

24. Xie X, Hu P, Tian Y, Wang K, Bai T. Transcranial alternating current stimulation enhances speech comprehension in chronic post-stroke aphasia patients: a single-blind sham-controlled study. *Brain Stimul*. (2022) 15:1538–40. doi: 10.1016/j.brs.2022.12.001

25. Schuhmann T, Duecker F, Middag-van Spanje M, Gallotto S, van Heugten C, Schrijnemaekers AC, et al. Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *Int J Clin Health Psychol*. (2022) 22:100326. doi: 10.1016/j.ijchp.2022.100326

26. Wu JF, Wang HJ, Wu Y, Li F, Bai YL, Zhang PY, et al. Efficacy of transcranial alternating current stimulation over bilateral mastoids (tACS (bm)) on enhancing recovery of subacute post-stroke patients. *Top Stroke Rehabil*. (2016) 23:420–9. doi: 10.1080/10749357.2016.1175218

27. Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS, et al. Utility of the NIH stroke scale as a predictor of hospital disposition. *Stroke*. (2003) 34:134–7. doi: 10.1161/01.STR.0000048217.44714.02

28. Yamamoto S, Golanov EV, Reis DJ. Reductions in focal ischemic infarctions elicited from cerebellar fastigial nucleus do not result from elevations in cerebral blood flow. *J Cereb Blood Flow Metab*. (1993) 13:1020–4. doi: 10.1038/jcbfm.1993.128

29. Tomasino B, Gremese M. The cognitive side of M1. *Front Hum Neurosci*. (2016) 10:298. doi: 10.3389/fnhum.2016.00298

30. Giraud AL, Poeppel D. Cortical oscillations and speech processing: emerging computational principles and operations. *Nat Neurosci*. (2012) 15:511–7. doi: 10.1038/nn.3063

31. Geranmayeh F, Chau TW, Wise RJS, Leech R, Hampshire A. Domain-general subregions of the medial prefrontal cortex contribute to recovery of language after stroke. *Brain*. (2017) 140:1947–58. doi: 10.1093/brain/awx134

32. Stockert A, Wawrzyniak M, Klingbeil J, Wrede K, Kümmerer D, Hartwigsen G, et al. Dynamics of language reorganization after left temporo-parietal and frontal stroke. *Brain*. (2020) 143:844–61. doi: 10.1093/brain/awaa023

33. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol*. (2017) 128:1774–809. doi: 10.1016/j.clinph.2017.06.001

34. Lakatos P, Gross J, Thut G. A new unifying account of the roles of neuronal entrainment. *Curr Biol*. (2019) 29:R890–r905. doi: 10.1016/j.cub.2019.07.075

35. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*. (2010) 5:e13766. doi: 10.1371/journal.pone.0013766

36. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat Commun*. (2018) 9:483. doi: 10.1038/s41467-018-02928-3

37. Hogan MK, Hamilton GF, Horner PJ. Neural stimulation and molecular mechanisms of plasticity and regeneration: a review. *Front Cell Neurosci*. (2020) 14:271. doi: 10.3389/fncel.2020.00271

38. Aderinto N, Abdul Basit MO, Olatunji G, Adejumo T. Exploring the transformative influence of neuroplasticity on stroke rehabilitation: a narrative review of current evidence. *Ann Med Surg (Lond)*. (2023) 85:4425–32. doi: 10.1097/MS9.0000000000|001137

39. Laurin A, Nard N, Dalmont M, Bulteau S, Bénard C, Bonnot O, et al. Efficacy and safety of transcranial electric stimulation during the perinatal period: a systematic literature review and three case reports. *J Clin Med*. (2022) 11:4048. doi: 10.3390/jcm11144048

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Study protocol of a double-blind randomized control trial of transcranial direct current stimulation in post-stroke fatigue

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Rationale: Post-stroke fatigue (PSF) is a frequent problem in stroke survivors and often hinders their rehabilitation. PSF is difficult to treat, and pharmacological therapy is often ineffective. Transcranial direct current stimulation (tDCS) can modulate motor, sensory, cognitive and behavioral responses, as it alters neuronal activity by delivering a small amount of current via the scalp to the cortex, resulting in prolonged alterations to brain function. tDCS has been studied for the treatment of fatigue associated with other neurological diseases, namely, multiple sclerosis, Parkinson's disease and post-polio syndrome.

Aims: This proposed project will examine the effect of tDCS on PSF.

Sample size estimates: We will recruit 156 participants aged 18 to 80 with chronic stroke and allocate them equally to two groups (i.e., $n = 78$ per group).

Methods and design: This proposed project will be a double-blind randomized control trial. The participants will be randomly divided into two groups. The control group will receive sham tDCS, and the treatment group will receive active tDCS. The latter treatment will involve application of a constant 2-mA current via one 5 × 5-cm anodal electrode positioned on the scalp over the C3 or C4 positions (motor cortex) of the lesioned hemisphere and one cathodal electrode positioned at the ipsilateral shoulder in two 20-min sessions per day for 5 days. The period of follow-up will be 4 weeks.

Study outcome(s): The primary outcome measure will be a change in fatigue severity, as measured using the modified fatigue impact scale (MFIS). The participants' scores on the MFIS (total score and physical, cognitive and psychosocial subscores) will be collected before treatment (T0), after 10 treatment sessions, i.e., 1 day after the fifth treatment day (T1), and 1 week (T2), 2 weeks (T3) and 4 weeks (T4) thereafter. Both per-protocol analysis and intention-to-treat analysis will be performed.

Discussion: This proposed project will provide proof-of-concept, i.e., demonstrate the benefits of tDCS for the treatment of PSF. The beneficiaries are the subjects participated in the study. This will stimulate further research to optimize tDCS parameters for the treatment of PSF.

Clinical trial registration: www.Chictr.org.cn, identifier: ChiCTR2100052515.

KEYWORDS

stroke, transcranial direct current stimulation (tDCS), rehabilitation, post-stroke fatigue (PSF), randomized control trial (RCT)

Introduction

Fatigue is defined as the "subjective lack of physical or mental energy to carry out usual and desired activities as perceived by the patient" (1). Patients with fatigue may experience a devastating sense of tiredness, exhaustion or lack of energy during or after mental or motor activity. Fatigue is a common symptom of neurological disorders (2).

Post-stroke fatigue (PSF) is a common and chronic problem (3), with a frequency that varies from 23 to 85% (3–7). For many stroke patients with good recovery, PSF is the sole major disability (8). It was found that up to 40% of stroke patients reported PSF as the most troublesome consequence of stroke (3). PSF can hinder rehabilitation (5) and predicts reduced functional independence, risk of institutionalization, impairment of cognition, poor quality of life and increased mortality (9). Female sex, older age and previous stroke are clinical correlates of PSF (9). Other causes of PSF include sleep apnea (10) and depression (3, 11).

Pathological mechanism of PSF

PSF is a complex problem with several contributing factors, many of which are not well understood. One theory holds that stroke may trigger biochemical imbalances, such as inflammatory responses, that generate fatigue in the early stages following stroke. Subsequently, neurophysiological and behavioral perturbations, such as beliefs about estimated action cost, may result in chronic PSF (11).

Potential treatments that have been explored for alleviation of PSF

Potential pharmacological treatments for PSF, such as antidepressants, stimulants, vitamin D and wakefulness-promoting agents (e.g., modafinil), have failed to demonstrate significant benefits (12). Similarly, the efficacy of non-pharmacological treatments, such as low-intensity training, cognitive therapy, fatigue education, a mindfulness-based stress-reduction program, treatment of associated depression, Chinese herbs, correction of risk factors and adaptation of activities, remains unproven (13).

Nature of transcranial direct current stimulation (tDCS)

tDCS can regulate sensory, cognitive, motor and behavioral responses (14), as it involves the application of a small amount of current to the cortex that regulates the activity of neurons and induces protracted after-effects in brain function. During tDCS, an anodal electrode is positioned over the targeted area and a cathodal electrode is positioned on a different part of the scalp or another body part, such as the shoulder. Importantly, tDCS does not cause severe adverse effects and is considered to be safe (15) and is a cost-effective and portable technique for neuromodulation (16).

Diverse effects on brain excitability can be achieved via tDCS, depending on the intensity, polarity and duration of the applied electric current. tDCS is a technique that in the short term is capable of modulating the resting potential of the membrane and in the long term of inducing for example functional plastic changes in the networks such as an increase or decrease in synaptic efficacy (17, 18).

The immediate effects of tDCS are caused by the modulation of resting membrane potential, whereas its long-lasting after-effects are due to the induction of enduring depression and potentiation (19). At the single-neuron level, tDCS generates glutamatergic plasticity that modulates the function of various ion channels and of neurotransmitters such as brain-derived neurotrophic factor and *N*-methyl-D-aspartate glutamate (19). In summary, tDCS can modulate neuronal excitability and induce prolonged functional changes in the brain (20). Stimulation of different levels of the neuromotor control system affects neuronal circuits in stroke patients, which causes neuroplastic changes. This reorganizes the damaged brain and produces improvements in function (19).

Effects of tDCS in stroke patients

There is growing interest in tDCS as a treatment to facilitate stroke recovery, and small-scale clinical trials have suggested that tDCS can be effective in the treatment of various motor and non-motor dysfunctions in stroke patients. For example, tDCS has been found to improve the capacity for activities of daily living (21), swallowing function (22), gait training (23), motor learning (24), visuospatial neglect (25), central pain (26), verbal learning (27) and depression (28) in stroke patients. tDCS may be more effective in patients with stroke with mild-to-moderate impairments than in those with major impairments (29).

Effects of tDCS in patients with PSF

An open-label trial of two sessions of tDCS per week for 5–6 weeks in 10 stroke patients did not result in any changes in PSF (30). Another recent clinical trial on 30 patients with PSF showed that compared with sham stimulation, one session of anodal tDCS over the bilateral primary motor cortex reduced symptoms of PSF for up to 7 days following treatment (31). One randomized control trial revealed no add-on effect of six sessions of tDCS on fatigue in 74 chronic stroke patients (32). Another randomized control trial of 6 sessions of tDCS per week for 4 weeks in 60 stroke patients reduced fatigue (33). Finally, there is an ongoing trial of six sessions of tDCS in 100 patients with PSF (34).

tDCS for treatment of fatigue related to neurological disease

tDCS has been explored as a potential treatment for fatigue associated with other neurological diseases, namely, multiple sclerosis (MS), Parkinson's disease and post-polio syndrome. For example, in a series of studies involving more than 50 patients with MS who received 5 sessions of tDCS applied over the motor cortex (35) or the somatosensory cortex (36, 37), results showed tDCS treatment led to a reduction of fatigue symptoms (35–37) and the improvement might persist up to 3 weeks (35). In a fourth study, 27 patients with MS were given 20 sessions of tDCS over the left dorsolateral prefrontal cortex, which which led to a decrease in their fatigue symptoms (37). In a fifth study, 17 patients with MS were given 10 sessions of random noise stimulation over the primary motor cortex, which led to a decrease in their fatigue symptoms (38). In two studies on patients with post-polio fatigue, 10 (39) and 15 (40) daily sessions of tDCS were found to decrease patients' fatigue symptoms. In a clinical trial involving 23 patients with Parkinson's disease, eight daily sessions of tDCS were found to decrease patients' fatigue symptoms (41). Crucially, mild side effects (headache and tingling sensations) but no serious side-effects have been reported in the above-mentioned studies.

It has been suggested that three neurophysiological mechanisms underlie central fatigue: slowed conduction in central motor pathways, resulting in decreased recruitment of spinal motoneurons; blockage of conduction at Ranvier's nodes; and impairment in the prefrontal cortex, which is responsible for motor planning (35). tDCS may alleviate PSF through several mechanisms. First, tDCS may restore activation in prefrontal and motor areas (35). Second, tDCS may improve connectivity between motor and frontal areas and the thalamus (35). Third, tDCS may increase positive mood and alleviate depressive symptoms (41).

In a recent review the effect of tDCS on fatigue in neurological disorders, 42 studies were identified. These studies included a total of 994 participants. Amongst these 42 studies, five of them, involving 290 subjects, examined the effect of tDCS in PSF. In 36 out of 42 (85.7%) of studies reported an improvement in fatigue scores in the tDCS group. Side effects of tDCS are usually mild (42). Hence tDCS proves to have a promising simple, low-cost, portable, non-invasive and risk-free procedure for reducing fatigue symptoms in alleviating PSF. The objective of this proposed project will be to examine the effect of tDCS on PSF. We hypothesize that active tDCS is more effective than sham tDCS.

Methods

Design

A double-blind randomized control trial of stroke survivors (Figure 1).

Patient population

Patients with chronic stroke will be recruited from the Neurology Unit of the Prince of Wales Hospital and the rehabilitation wards of Shatin Hospital (both in Hong Kong) and from the Hong Kong community through newspaper advertisements and word of mouth. A research assistant will visit the above facilities weekly to identify all eligible patients and obtain their written consent.

Inclusion and exclusion criteria

The *inclusion criteria* will be (1) either sex; (2) aged 18–80; (3) any level of literacy or education; (4) a history of stroke confirmed by an brain imaging examination such as a CT scan or Magnetic Resonance Imaging; (5) able to speak ethnic Chinese and Cantonese; (6) willing and able to give informed consent; and (6) presence of PSF (a Fatigue Severity Scale [FSS] score of 4.0 or more) (43–45). The cut-off score of 4.0 was chosen since it the most commonly used cut-off score. In a recent systematic review of 31 studies using FSS to examine the prevalence of PSF, all of them reported a cut-off point of 4 or more (46).

The *exclusion criteria* will be (1) acute and subacute stroke ($\leq$6 months after onset); (2) a history of depression (self-report or a Beck Depression Inventory (BDI) – II) (47) score $\geq$ 14; (3) a presence of schizophrenia, bipolar affective disorder, and/or substance/alcohol dependence/abuse; (4) a history of any neurological disorder (except stroke); (5) a history of sleep apnea, narcolepsy, hypothyroidism, heart failure, chronic obstructive pulmonary disease or cancer; (6) a history of unexplained spells of fainting; (7) current pregnancy; (8) a history of neurosurgery; (9) presence of dementia, defined as a Hong Kong version of the Montreal Cognitive Assessment (MoCA) score of less than 19 (48); (10) presence of aphasia, defined as a score > 0 in the best language instructions item of the National Institute of Health Stroke Scale (NIHSS) (49); (11) presence of major depression, as confirmed by a research assistant using the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) – Fourth Edition (SCID-DSMIV) (50) and according to the DSM – Fifth Edition Diagnostic Criteria (51); (12) taking hypnotics or other medications that can cause fatigue; (13) taking antiepileptic or other medications that can weaken the effect of tDCS; (14) current or past use of tDCS; (15) contraindications to tDCS, e.g., skin damage at the proposed site of stimulation or presence of a pacemaker, a metal implant in the head or a medical device in the brain; and (16) participation in rehabilitative therapy or physical exercise program during the trial. The above criteria will be assessed by examination of patients' medical record.

Measurement overview

The data collection schedule is detailed in Table 1. The number of patients excluded and the reasons for their exclusion will be recorded. Data on sex, age, level of education, risk factors of vascular diseases (e.g., smoking, hyperlipidemia, diabetes mellitus and hypertension), date of stroke onset and length of stay in rehabilitation facilities will be collected from all of the participants. Neurological impairment (i.e., the NIHSS total score data) at admission will be extracted from the stroke registry, which will be maintained by a full-time, well-trained research nurse who will also be responsible for administration of the NIHSS.

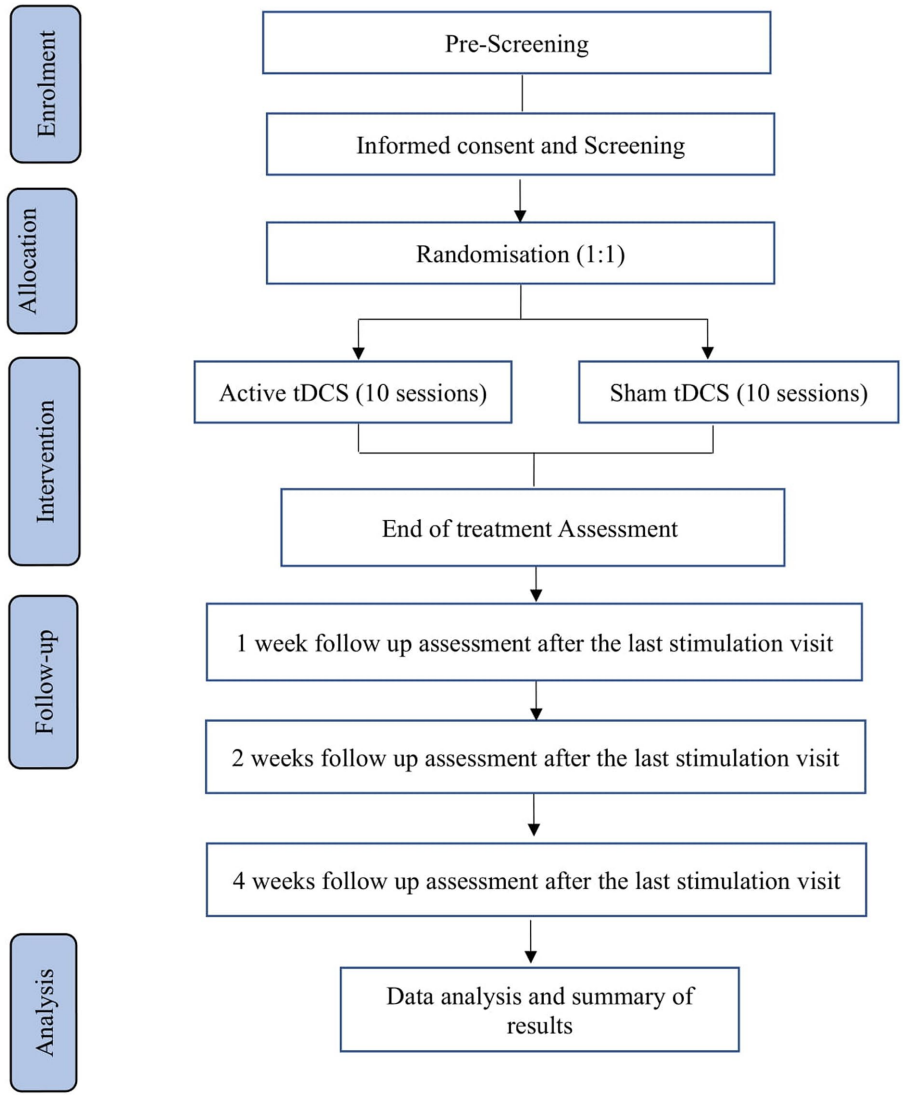

FIGURE 1
Flow chart of the study.

Baseline measures

A research assistant will assess the participants' PSF by administering the validated Chinese version of FSS and the MFIS (52–55, 56). The FSS is the most frequently used tool to measure PSF (57–59) and consists of nine Likert items scored on a 7-point scale (e.g., "I am easily fatigued," "My motivation is lower when I am fatigued than when I am not" and "Exercise brings on my fatigue"). A higher score on an item indicates the presence of greater fatigue, and the scores for all items are averaged to give a total fatigue score. In an assessment of the FSS in patients with neurological diseases, its Cronbach's α was 0.90–0.94, its intraclass correlation coefficient was 0.73–0.93, and its correlation coefficients with other fatigue scales were 0.62–0.84, indicating that the FSS has good internal consistency, reliability and convergent validity in such patients (58). In addition, information on previous treatment of PSF will be collected using a questionnaire.

The MFIS is administered via a 5–10-min interview that assesses how fatigue affects people's daily lives, in terms of their psychosocial, cognitive and physical functioning. The MFIS contains 21 items that are scored from 0 to 4, which represent different frequencies, i.e., "never," "seldom," "sometimes," "often" and "always," respectively. Subscores are obtained for cognitive functioning (0–36), physical functioning (0–40) and psychosocial functioning (0–8) and are summed to give a total score (0–84). A higher score indicates severer fatigue. The MFIS has been used to assess PSF (60) and measure outcomes in clincial trials of interventions for fatigue (61), including tDCS (37, 39, 62, 63).

A research assistant will use the Physical Activity Scale for the Elderly (PASE) (64), the Barthel Index (BI) (65), the MoCA, the anxiety subscale of the Chinese version of the Hospital Anxiety Depression Scale (HADSA), the Chinese version of the Geriatric Depression Scale (GDS), the Pittsburgh Sleep Quality Index (PSQI) (66) and the Chinese version of the Stroke-Specific Quality

TABLE 1 Data collection schedule.

Study period	Screening	Treatment	EOT	FUV
Visit	**1**	**2–6**	**7**	**8–10**
Weeks after Randomization	**-2**	**1**	**1**	**2,3,5**
Review of inclusion / exclusion criteria	X			
Informed consent	X			
Demographics, vascular risk factors, stroke characteristics, previous treatment of PSF	X			
Montreal Cognitive Assessment	X			
MFIS, FFS, PSAE, BI, GDS, HADSA, SSQoL	X		X	X
tDCS		X		
Randomization	X			
tDCS adverse effects questionnaire		X	X	
Experience, preferences, concerns and belief on tDCS questionnaire			X	

Screen denotes Screening visit.
EOT denotes End of treatment.
FUV denotes Follow up visits.

of Life (SSQoL) scale to, respectively, assess the participants' level of physical activity, level of disability, global cognitive function, anxiety symptoms, depressive symptoms, sleep disturbances and health-related quality of life. The anxiety subscale of the HADSA consists of seven items, each of which is scored on a 4-point Likert scale, with higher scores representing severer anxiety. The Chinese version of the HADSA has been previously validated (67). The Chinese version of GDS contains 15 items, has a maximum possible score of 15, and has been previously validated (68). The PSQI measures seven components across 19 items, each of which is rated on a scale from 0 to 3, and the total possible score ranges from 0 to 21.

The Chinese version of the SSQoL scale (69, 70) is designed to measure quality of life in stroke survivors. It is a self-report questionnaire that contains 49 items covering 12 domains: family roles (three items), energy (three items), mobility (six items), language (five items), mood (five items), personality (three items), social roles (five items), self-care (five items), upper extremity function (five items), thinking (three items), work/productivity (three items) and vision (three items). Individual items are scored on a 5-point Likert scale representing answers from "completely true" to "not true at all," with higher scores implying a better quality of life. Thus, the Chinese version of the SSQoL scale generates both domain and total scores. It has been previously shown to have excellent internal consistency, intertest reliability and test–retest reliability (69).

Randomization and blinding procedure

A statistician will apply a block randomization procedure to afford a concealed randomization list. As mentioned, there with be 78 participants in each group (the sham tDCS group and the active tDCS group). Upon recruitment of each participant, the technician responsible for the tDCS delivery will receive information on the participant's assigned treatment.

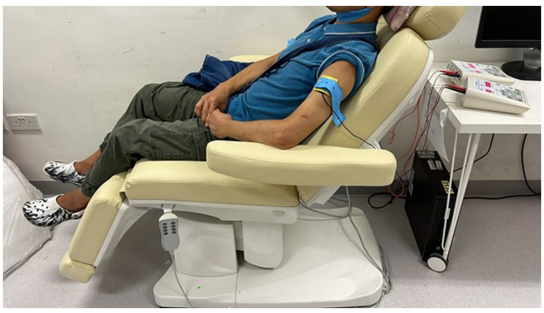

FIGURE 2
Demonstration of the setup on the arm.

Intervention

A trained research assistant will administer tDCS at Shatin Hospital. The participants will recline on a comfortable chair with their eyes closed during tDCS, which will be delivered by one battery-driven constant-current stimulator (Soterix Medical 1 × 1 Clinical Trials Device) through one 5 × 5-cm conductive-rubber anodal electrode. The electrodes will be inserted into an EASYpad (Soterix Medical), which contains sponge material and will be moistened by application of approximately 10–15 mL of saline. The EASYpad will examined every minute to check whether additional saline needs to be added to prevent it from drying out. Each participant will be allocated a set of EASYpads that will be used for the entire treatment course to maintain good hygiene. Elastic straps will be used to fasten the EASYpad to the scalp. The anodal electrode will be positioned on the scalp over the C3 or C4 positions (motor cortex) of the lesioned hemisphere, based on the international electroencephalogram 10/20 system, and a cathodal electrode will be positioned on the ipsilateral shoulder (34) (Figures 2, 3). A constant current of 2 mA (with a current density of 0.08 mA/cm^2) will be applied to the anode by one

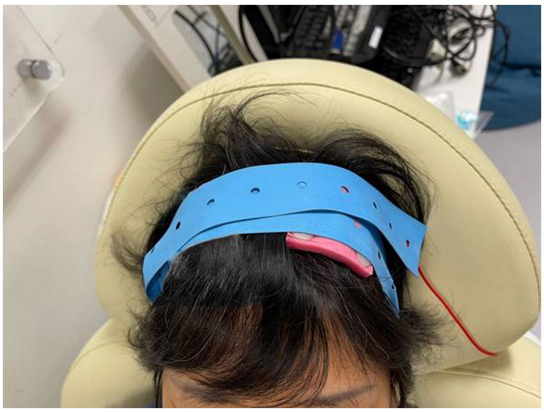

FIGURE 3
Demonstration of the setup on the scalp (C3).

of the constant-current stimulators in two 20-min sessions, separated by a 10-min break (34), every day for 5 consecutive days. Sham tDCS will consist of 30 s of constant current at the beginning and end of each 20-min session, such that all of the participants will experience the initial itching sensation at the beginning of stimulation. The participants will be asked about skin sensations they experienced during and at the end of the stimulation to determine if they are able to distinguish between sham and real stimulation. The above stimulation site and parameters were chosen based on the following rationale. First, association observed between increased fatigue scores and decreased functional connectivity of supplementary and primary motor areas (42). In addition, stimulation of motor cortex has been shown to improve fatigue in stroke patients and healthy individuals (31, 71). Second, the duration of stimulation per session was 20 min in all five published studies of tDCS on PSF (42). Third, consecutive sessions of tDCS has been employed were employed in previous studies of tDCS on PSF (32, 34, 71).

Safety measures

The Adverse Event Checklist (AEC) will be administered at the end of each stimulation session. The AEC covers adverse events (AEs; symptoms) in various systems, namely, the circulatory, digestive, cardiovascular, musculoskeletal, metabolic, urogenital and nervous systems, and the whole body (72).

Withdrawal criteria

The participants should be able to complete the 10 sessions of tDCS treatment within 1 week. If they miss a scheduled session, they can receive another session when convenient. If the participants cannot complete the 10 sessions, they will be regarded as dropouts. In addition, participants will be removed from the study if they (i) withdraw their consent for tDCS treatment and/or (ii) have a severe AE that may lead to significant distressful consequences (seizure, skin burn or blister).

We will continue to follow withdrawn participants and perform outcome measures as far as possible.

Primary outcome measure

The MFIS will be administered before treatment (T0), after 10 treatment sessions (T1, 1 day after the fifth treatment day), and 1 week (T2), 2 weeks (T3) and 4 weeks (T4) thereafter (36), at the same time of day. The time window of administration will be adjusted to assess changes between time points (4 weeks for T0, 1 day for T1, 1 week for T2 and T3, and 2 weeks for T4). The participants and the research assistant who administers the MFIS will be blinded to the delivered treatment.

Secondary outcome measures

The FSS, the Chinese version of the GDS, the Chinese version of the HADSA, the PSQI, the BI and the PASE will be administered at T0, T1, T2, T3, and T4 (36), at the same time of day. The Chinese version of the SSQoL will be administered at T0 and T4. The time window of administration will be adjusted to assess changes between time points, as stated above. Data on the participants' experience of, preferences for, and concerns and beliefs about tDCS will be collected at T4 via a brief questionnaire (33).

Data monitoring body

An independent Data Safety Monitoring Board will be formed (DSMB) and will consist of a stroke neurologist, a psychiatrist, a statistician and a tDCS clinical trial specialist. The DSMB will meet regularly and examine AEs, perform an interim analysis and make recommendations on the safety of the study and the need to stop or extend the study.

Sample size estimates

Statistical power was computed using Power Analysis & Sample Size 2005. We assumed that the standard deviation of the MFIS score at baseline will be 3.9 (60), that the sham stimulation will not cause any change in fatigue and that a decrease of at least 3.0 MFIS points will be clinically relevant (36). Hence, the effect size of tDCS will be (3.0/3.9 = 0.77). Given that such a large effect size is unusual in clinical contexts, we will instead use a more realistic effect size, i.e., 0.50. One pairwise comparison will be performed in the analysis of variance. A sample size of 63 per group (a total of 126 participants) will give rise to 80% power in identifying the main effect of tDCS (73). Thus, assuming a dropout rate of 20%, 156 (126/0.8) participants will be recruited.

Statistical analysis

We will perform a per-protocol analysis and an intention-to-treat analysis. Only participants who complete treatment will be included in the per-protocol analysis, whereas all of the participants who receive at least one tDCS session will be included in the intention-to treat-analysis. A last-observation-carried-forward approach will be adopted for the analysis of outcome data. The mean score of the FSS will be calculated. The sum of individual item scores will be computed for the MFIS and the total score and physical, cognitive and psychosocial subscores will

be derived. Demographic characteristics will comprise age, sex, and scores on the Chinese version of the GDS, the Chinese version of the HADSA, the PASE, the BI, the PSQI, and the NIHSS, and the severity of PSF will be measured using the FSS and the MFIS. Chi-square tests (for categorical variables such as sex) and t-tests (for continuous variables such as age) will be used to compare baseline performance. The effects of tDCS upon completion of treatment (T1) will be studied by entering the participants' scores on the MFIS (total score and subscores) into a mixed-model analysis of variance with baseline MFIS scores as covariates, and the tDCS intervention (T0, T1) and stimulation (active, sham) as between-participant factors. The trend of tDCS effects will be studied by entering the participants' scores on the MFIS (total score and subscores) into a linear mixed model with the tDCS intervention (T0, T1, T2, T3 and T4) and stimulation (active, sham) as within-participant factors. Pairwise comparisons between baseline and individual post-measurement-day significant results will conducted using Bonferroni t-tests for related samples. Withdrawals will be analyzed by logistic regression. The level of significance will be 0.05.

The safety analysis will be descriptive and exploratory. Key safety measures will be based on the tDCS AEs questionnaire and include the overall incidence and intensity of AEs; the number of AEs leading to treatment discontinuation; skin reactions; and other AEs.

Organization and funding

The proposed project will be performed in the acute stroke unit of the Prince of Wales Hospital, Shatin, Hong Kong, China, where research coordination and analyzes will also be conducted. The proposed project has received support from the General Research Fund of the Research Grants Council of Hong Kong, China.

Access to data

Only the Principal Investigator (WKT) will have access to the final dataset.

Discussion and summary

We will endeavor to obtain a homologous sample by obtaining a set of participants with a narrow range of ages, ethnicities, handedness and duration of PSF. Potential participants with other causes of fatigue, such as depression, psychiatric disorders, alcohol/substance abuse and neurological disorders, will be excluded. We will use two tDCS devices to achieve bilateral stimulation of the motor cortex with a relatively high current and long duration of stimulation. The MFIS will be used to measure the primary outcome (a change in PSF severity), as it is commonly used in clinical trials of interventions for fatigue. A variety of secondary outcomes will be assessed, such as mood, quality of life and functioning. A conservative estimate of effect size has been used to calculate an adequate sample size. On the other hand, exclusion of patients with aphasia will limit the generalizability of the study's results to this subgroup of patients. This proposed project will provide proof-of-concept, i.e., will demonstrate the benefits of tDCS in the treatment of PSF, thereby stimulating further research to determine the optimal tDCS parameters to alleviate PSF.

Ethics statement

The studies involving humans were approved by the Joint CUHK-NTEC CREC (CREC: ref 2020.550). (The Chinese University of Hong Kong (CUHK) and New Territories East Cluster (NTEC) Clinical Research Ethics Committee). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WT: Writing – original draft. HL: Writing - review & editing, Conceptualization and methodology. TL: Writing – review & editing. JK: Writing – review & editing. KF: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two Centre phase 2 study. *J Neurol Neurosurg Psychiatry*. (2002) 72:179–83. doi: 10.1136/jnnp.72.2.179

2. Penner I-K, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol*. (2017) 13:662–75. doi: 10.1038/nrneurol.2017.117

3. Paciaroni M, Acciarresi M. Poststroke Fatigue. *Stroke*. (2019) 50:1927–33. doi: 10.1161/STROKEAHA.119.023552

4. Van Zandvoort MJE, Kappelle LJ, Algra A, De Haan EHF. Decreased capacity for mental effort after single supratentorial lacunar infarct may affect performance in everyday life. *J Neurol Neurosur Ps*. (1998) 65:697–702. doi: 10.1136/jnnp.65.5.697

5. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Arch Phys Med Rehabil*. (1999) 80:173–8. doi: 10.1016/S0003-9993(99)90116-8

6. Staub F, Bogousslavsky L. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis*. (2001) 12:75–81. doi: 10.1159/000047685

7. Tang WK, Chen YK, Mok V, Chu WC, Ungvari GS, Ahuja AT, et al. Acute basal ganglia infarcts in poststroke fatigue: an MRI study. *J Neurol*. (2010) 257:178–82. doi: 10.1007/s00415-009-5284-2

8. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet*. (2004) 363:978–88. doi: 10.1016/S0140-6736(04)15794-2

9. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke*. (2002) 33:1327–33. doi: 10.1161/01.STR.0000014248.28711.D6

10. Sandberg O, Franklin KA, Bucht G, Gustafson Y. Sleep apnea, delirium, depressed mood, cognition, and ADL ability after stroke. *J Am Geriatr Soc*. (2001) 49:391–7. doi: 10.1046/j.1532-5415.2001.49081.x

11. De Doncker W, Dantzer R, Ormstad H, Kuppuswamy A. Mechanisms of poststroke fatigue. *J Neurol Neurosurg Psychiatry*. (2018) 89:287–93. doi: 10.1136/jnnp-2017-316007

12. Kennedy C, Kidd L. Interventions for post-stroke fatigue: a Cochrane review summary. *Int J Nurs Stud*. (2018) 85:136–7. doi: 10.1016/j.ijnurstu.2017.11.006

13. Wu SM, Kutlubaev MA, Chun HYY, Cowey E, Pollock A, Macleod MR, et al. Interventions for post-stroke fatigue. *Cochrane Db Syst Rev*. (2015) 2015:CD007030. doi: 10.1002/14651858.CD007030.pub3

14. Vallar G, Bolognini N. Behavioural facilitation following brain stimulation: implications for neurorehabilitation. *Neuropsychol Rehabil*. (2011) 21:618–49. doi: 10.1080/09602011.2011.574050

15. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull*. (2007) 72:208–14. doi: 10.1016/j.brainresbull.2007.01.004

16. Lu H, Chan SSM, Chan WC, Lin C, Cheng CPW, Wa LC, et al. Randomized controlled trial of TDCS on cognition in 201 seniors with mild neurocognitive disorder. *Ann Clin Transl Neurol*. (2019) 6:1938–48. doi: 10.1002/acn3.50823

17. Furubayashi T, Terao Y, Arai N, Okabe S, Mochizuki H, Hanajima R, et al. Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Exp Brain Res*. (2007) 185:279–86. doi: 10.1007/s00221-007-1149-z

18. Hodkinson DJ, Jackson SR, Jung J. Task-dependent plasticity in distributed neural circuits after transcranial direct current stimulation of the human motor cortex: a proof-of-concept study. *Front. Pain Res.* (2022) 3:1005634. doi: 10.3389/fpain.2022.1005634

19. Bao SC, Khan A, Song R, Kai-Yu TR. Rewiring the lesioned brain: electrical stimulation for post-stroke motor restoration. *J Stroke*. (2020) 22:47–63. doi: 10.5853/jos.2019.03027

20. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. *Arch Neurol*. (2008) 65:1571–6. doi: 10.1001/archneur.65.12.1571

21. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tdcs) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. *Cochrane Database Syst Rev*. (2020) 11:CD009645. doi: 10.1002/14651858.CD009645.pub4

22. Shigematsu T, Fujishima I, Ohno K. Transcranial direct current stimulation improves swallowing function in stroke patients. *Neurorehabil Neural Repair*. (2013) 27:363–9. doi: 10.1177/1545968312474116

23. Picelli A, Chemello E, Castellazzi P, Roncari L, Waldner A, Saltuari L, et al. Combined effects of transcranial direct current stimulation (tDCS) and transcutaneous spinal direct current stimulation (tsDCS) on robot-assisted gait training in patients with chronic stroke: a pilot, double blind, randomized controlled trial. *Restor Neurol Neurosci*. (2015) 33:357–68. doi: 10.3233/RNN-140474

24. Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. (2016) 87:345–55. doi: 10.1136/jnnp-2015-311242

25. Bang DH, Bong SY. Effect of combination of transcranial direct current stimulation and feedback training on visuospatial neglect in patients with subacute stroke: a pilot randomized controlled trial. *J Phys Ther Sci*. (2015) 27:2759–61. doi: 10.1589/jpts.27.2759

26. Bae SH, Kim GD, Kim KY. Analgesic effect of transcranial direct current stimulation on central post-stroke pain. *Tohoku J Exp Med*. (2014) 234:189–95. doi: 10.1620/tjem.234.189

27. Yun GJ, Chun MH, Kim BR. The effects of transcranial direct-current stimulation on cognition in stroke patients. *J Stroke*. (2015) 17:354–8. doi: 10.5853/jos.2015.17.3.354

28. Li Y, Li H-P, Wu M-X, Wang Q-Y, Zeng X. Effects of transcranial direct current stimulation for post-stroke depression: a systematic review and meta-analysis. *Clin Neurophysiol*. (2022) 142:1–10. doi: 10.1016/j.clinph.2022.07.369

29. Baltar A, Piscitelli D, Marques D, Shirahige L, Monte-Silva K. Baseline motor impairment predicts transcranial direct current stimulation combined with physical therapy-induced improvement in individuals with chronic stroke. *Neural Plast*. (2020) 2020:1–8. doi: 10.1155/2020/8859394

30. Cleland BT, Galick M, Huckstep A, Lenhart L, Madhavan S. Feasibility and safety of transcranial direct current stimulation in an outpatient rehabilitation setting after stroke. *Brain Sci*. (2020) 10:719. doi: 10.3390/brainsci10100719

31. De Doncker W, Ondobaka S, Kuppuswamy A. Effect of transcranial direct current stimulation on post-stroke fatigue. *J Neurol*. (2021) 268:2831–42. doi: 10.1007/s00415-021-10442-8

32. Ulrichsen KM, Kolskår KK, Richard G, Pedersen ML, Alnæs D, Dørum ES, et al. No add-on effect of tDCS on fatigue and depression in chronic stroke patients: a randomized sham-controlled trial combining tDCS with computerized cognitive training. *Brain Behav.* (2022) 12:e2643. doi: 10.1002/brb3.2643

33. Dong X-L, Sun X, Sun W-M, Yuan Q, Yu G-H, Shuai L, et al. A randomized controlled trial to explore the efficacy and safety of transcranial direct current stimulation on patients with post-stroke fatigue. *Medicine*. (2021) 100:e27504. doi: 10.1097/MD.0000000000027504

34. Sun X, Dong X, Yuan Q, Yu G, Shuai L, Ma C, et al. Effects of transcranial direct current stimulation on patients with post-stroke fatigue: a study protocol for a double-blind randomized controlled trial. *Trials*. (2022) 23:200. doi: 10.1186/s13063-022-06128-9

35. Ferrucci R, Vergari M, Cogiamanian F, Bocci T, Ciocca M, Tomasini E, et al. Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. *NeuroRehabilitation*. (2014) 34:121–7. doi: 10.3233/NRE-131019

36. Tecchio F, Cancelli A, Cottone C, Zito G, Pasqualetti P, Ghazaryan A, et al. Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. *J Neurol*. (2014) 261:1552–8. doi: 10.1007/s00415-014-7377-9

37. Charvet LE, Dobbs B, Shaw MT, Bikson M, Datta A, Krupp LB. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. *Mult Scler*. (2018) 24:1760–9. doi: 10.1177/1352458517732842

38. Salemi G, Vazzoler G, Ragonese P, Bianchi A, Cosentino G, Croce G, et al. Application of tRNS to improve multiple sclerosis fatigue: a pilot, single-blind, sham-controlled study. *J Neural Transm*. (2019) 126:795–9. doi: 10.1007/s00702-019-02006-y

39. Curatolo M, La Bianca G, Cosentino G, Baschi R, Salemi G, Talotta R, et al. Motor cortex tRNS improves pain, affective and cognitive impairment in patients with fibromyalgia: preliminary results of a randomised sham-controlled trial. *Clin Exp Rheumatol*. (2017) 35 Suppl 105(3):100–5.

40. Acler M, Bocci T, Valenti D, Turri M, Priori A, Bertolasi L. Transcranial direct current stimulation (tDCS) for sleep disturbances and fatigue in patients with post-polio syndrome. *Restor Neurol Neurosci*. (2013) 31:661–8. doi: 10.3233/RNN-130321

41. Forogh B, Rafiei M, Arbabi A, Motamed MR, Madani SP, Sajadi S. Repeated sessions of transcranial direct current stimulation evaluation on fatigue and daytime sleepiness in Parkinson's disease. *Neurol Sci*. (2016) 38:249–54. doi: 10.1007/s10072-016-2748-x

42. Jagadish A, Shankaranarayana AM, Natarajan M, Solomon JM. Transcranial direct current stimulation for fatigue in neurological conditions: a systematic scoping review. *Physiother Res Int*. (2023) 15:e254. doi: 10.1002/pri.2054

43. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. *J Psychosom Res*. (1993) 37:753–62. doi: 10.1016/0022-3999(93)90104-N

44. Chen SXYF. Syndrome differentiation and treatment of post-stroke fatigue. *J Pract Tradit Chin Int Med*. (2008) 22:17–9.

45. Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS. The impact of pain on health-related quality of life 3 months after stroke. *Top Stroke Rehabil*. (2015) 22:194–200. doi: 10.1179/1074935714Z.0000000024

46. Alghamdi I, Ariti C, Williams A, Wood E, Hewitt J. Prevalence of fatigue after stroke: a systematic review and meta-analysis. *Eur Stroke J*. (2021) 6:319–32. doi: 10.1177/23969873211047681

47. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck depression inventories-IA and -II in psychiatric outpatients. *J Pers Assess*. (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13

48. Yeung PY, Wong LL, Chan CC, Yung CY, Leung LJ, Tam YY, et al. Montreal cognitive assessment — single Cutoff achieves screening purpose. *Neuropsychiatr Dis Treat*. (2020) 16:2681–7. doi: 10.2147/NDT.S269243

49. Lyden P. Using the National Institutes of Health stroke scale. *Stroke*. (2017) 48:513–9. doi: 10.1161/STROKEAHA.116.015434

50. So E, Kam I, Leung CM, Chung D, Liu Z, Fong S. The Chinese-bilingual SCID-I/P project: stage 1 — reliability for mood disorders and schizophrenia. *Hong Kong J Psychiatry*. (2003) 13:7–18.

51. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Association.

52. Multiple Sclerosis Council for Clinical Practice Guidelines. *Fatigue and multiple sclerosis: Evidence-based management strategies for fatigue in multiple sclerosis*. Washington, DC: Paralyzed Veterans of America (1998).

53. Chen K, Fan Y, Hu R, Yang T, Li K. Impact of depression, fatigue and disability on quality of life in Chinese patients with multiple sclerosis. *Stress Health*. (2013) 29:108–12. doi: 10.1002/smi.2432

54. Ng SS, Liu TW, Tsoh J. Translation and initial validation of Chinese (Cantonese) version of modified fatigue impact scale (mfis-C) in people with stroke. *BMC Neurol*. (2022) 22:300. doi: 10.1186/s12883-022-02832-w

55. Wang M-Y, Liu I-C, Chiu C-H, Tsai P-S. Cultural adaptation and validation of the Chinese version of the fatigue severity scale in patients with major depressive disorder and nondepressive people. *Qual Life Res*. (2015) 25:89–99. doi: 10.1007/s11136-015-1056-x

56. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist*. (2011) 17:37–53. doi: 10.1177/1073858410386614

57. Tang WK, Lu JY, Chen YK, Mok VC, Ungvari GS, Wong KS. Is fatigue associated with short-term health-related quality of life in stroke? *Arch Phys Med Rehabil*. (2010) 91:1511–5. doi: 10.1016/j.apmr.2010.06.026

58. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res*. (2012) 21:925–44. doi: 10.1007/s11136-011-0009-2

59. Tang WK, Liang HJ, Chen YK, Chu WNCW, Abrigo J, Mok VCT, et al. Poststroke fatigue is associated with caudate infarcts. *J Neurol Sci*. (2013) 324:131–5. doi: 10.1016/j.jns.2012.10.022

60. Hubacher M, Calabrese P, Bassetti C, Carota A, Stocklin M, Penner IK. Assessment of post-stroke fatigue: the fatigue scale for motor and cognitive functions. *Eur Neurol*. (2012) 67:377–84. doi: 10.1159/000336736

61. De Giglio L, De Luca F, Prosperini L, Borriello G, Bianchi V, Pantano P, et al. A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study. *Neurorehabil Neural Repair*. (2015) 29:453–61. doi: 10.1177/1545968314554623

62. Saiote C, Goldschmidt T, Timaus C, Steenwijk MD, Opitz A, Antal A, et al. Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. *Restor Neurol Neurosci*. (2014) 32:423–36. doi: 10.3233/RNN-130372

63. Cancelli A, Cottone C, Giordani A, Migliore S, Lupoi D, Porcaro C, et al. Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis. *Mult Scler*. (2018) 24:1366–74. doi: 10.1177/1352458517720528

64. Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): development and evaluation. *J Clin Epidemiol*. (1993) 46:153–62. doi: 10.1016/0895-4356(93)90053-4

65. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J*. (1965) 14:61–5.

66. Tsai PS, Wang SY, Wang MY, Su CT, Yang TT, Huang CJ, et al. Psychometric evaluation of the Chinese version of the Pittsburgh sleep quality index (CPSQI) in primary insomnia and control subjects. *Qual Life Res*. (2005) 14:1943–52. doi: 10.1007/s11136-005-4346-x

67. Lam CL, Pan P-C, Chan AW, Chan S-Y, Munro C. Can the hospital anxiety and depression (HAD) scale be used on Chinese elderly in general practice? *Fam Pract*. (1995) 12:149–54. doi: 10.1093/fampra/12.2.149

68. Chau J, Martin CR, Thompson DR, Chang AM, Woo J. Factor structure of the Chinese version of the geriatric depression scale. *Psychol Health Med*. (2006) 11:48–59. doi: 10.1080/13548500500093688

69. Wang YL, Ma JG, Li JT. The study on reliability,validity andresponsiveness of the Chinese version of stroke-specific Qualityof life. *Chin J Geriatr Heart Brain Vessel D*. (2003) 5:391–4.

70. Hsueh IP, Jeng JS, Lee Y, Sheu CF, Hsieh CL. Construct validity of the stroke-specific quality of life questionnaire in ischemic stroke patients. *Arch Phys Med Rehabil*. (2011) 92:1113–8. doi: 10.1016/j.apmr.2011.02.008

71. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol*. (2006) 117:845–50. doi: 10.1016/j.clinph.2005.12.003

72. Lu H, Lam LCW. Cathodal skin lesions induced by transcranial direct current stimulation (tDCS). *Neuromodulation*. (2019) 22:989–91. doi: 10.1111/ner.12892

73. Edwards L. *Applied analysis of variance in behavioral science*. New York, NY: Marcel Dekker, Inc (1993).

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Transcranial magnetic stimulation therapy for central post-stroke pain: systematic review and meta-analysis

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Introduction: Although rare, central post-stroke pain remains one of the most refractory forms of neuropathic pain. It has been reported that repetitive transcranial magnetic stimulation (rTMS) may be effective in these cases of pain.

Aim: The aim of this study was to investigate the efficacy of rTMS in patients with central post-stroke pain (CPSP).

Methods: We included randomized controlled trials or Controlled Trials published until October 3rd, 2022, which studied the effect of rTMS compared to placebo in CPSP. We included studies of adult patients (>18 years) with a clinical diagnosis of stroke, in which the intervention consisted of the application of rTMS to treat CSP.

Results: Nine studies were included in the qualitative analysis; 6 studies (4 RCT and 2 non-RCT), with 180 participants, were included in the quantitative analysis. A significant reduction in CPSP was found in favor of rTMS compared with sham, with a large effect size (SMD: −1.45; 95% CI: −1.87; −1.03; $p < 0.001$; I2: 58%).

Conclusion: The findings of the present systematic review with meta-analysis suggest that there is low quality evidence for the effectiveness of rTMS in reducing CPSP.

Systematic review registration: Identifier (CRD42022365655).

KEYWORDS

meta-analysis, stroke, transcranial magnetic stimulation, pain management, pain

Introduction

According to the International Association for the Study of Pain (IASP), neuropathic pain is any pain caused by a lesion or disease of the somatosensory system (Jensen et al., 2011; Treede et al., 2015). Central post-stroke pain (CPSP) is defined by the IASP as 'pain initiated or caused by a primary lesion or dysfunction of the central nervous system (IASP, 2011) and

occurs in the absence of other nociceptive, peripheral and psychogenic pain (Şahin-Onat et al., 2016).

A recent meta-analysis involving a total of 69 studies by Liampas et al. (2020) estimated that approximately 1 in 10 of all stroke patients will experience neuropathic pain. Other studies (Bowsher et al., 1993; Stitik et al., 2005) indicate that in the USA, the prevalence of CPSP reported in one study ranged from 2 to 8% in 250,000 people who suffered a cerebrovascular accident in the course of 1 year. Other authors widen the range even further, establishing a prevalence between 1 and 35% (Oh and Seo, 2015). This broad estimate is possibly due to variabilities in the definition of this pain category, the inclusion criteria, and the length of patients' evaluation post-stroke (Kumar et al., 2009).

Once stroke patients overcome the acute phase of the event, they need early neurorehabilitation treatment to alleviate the consequences of the injury, such as spasticity or CSPS. Currently, there is no globally accepted and approved pharmacological therapy to accelerate the recovery of these patients (Figueroa et al., 2015). Therefore, new therapies, such as transcranial magnetic stimulation (TMS), have emerged. TMS consist of a high voltage and high intensity discharge system attached to a transducing coil. This system generates short lasting (<1 ms) magnetic fields of 1–2.5 Tesla, which penetrates the skull and induces secondary electric currents in the cerebral cortex that depolarizes neurons (Groppa et al., 2012). This phenomenon could be used as evaluation tool to assess corticospinal pathway integrity, applying a single pulse at cortical level and registering electric activity at the motor end-plate (Spampinato et al., 2023). Also, it could be used to evaluate intra-cortical excitability changes applying paired pulses with different time intervals (Wagle-Shukla et al., 2009).

For CPSP treatment one of the most used TMS techniques is repetitive transcranial magnetic stimulation (rTMS). rTMS is a noninvasive brain stimulation technique that generates brief, rapidly changing magnetic fields capable of inducing electric currents in the brain (Young et al., 2014). It is safe, well tolerated, and has a very favorable side effect profile, provided that safety recommendations are followed (Burke et al., 2019). Depending on stimulation parameters, rTMS can have an excitatory or inhibitory effect on the underlying neural networks (Young et al., 2014). At frequencies ≥5 Hz (high-frequency rTMS), rTMS has been shown to produce an increment in cortical excitability in healthy humans (Fitzgerald et al., 2006) and stroke patients (Belardinelli et al., 2021). This improvement in cortical excitability is the result of a modulation of the GABAergic and glutamatergic systems (Esser et al., 2006; Belardinelli et al., 2021) producing a long-term potentiation phenomenon in the stimulated neural networks (Esser et al., 2006). Moreover, ≤1 Hz frequencies (low-frequency rTMS) produce the opposite effect via long-term depression (Chen et al., 1997). These neuroplastic changes could induce reorganization of neural networks in the motor cortex, supplementary motor area, premotor area, cerebellum, thalamus and corpus callosum (Tosun et al., 2017; Guo et al., 2021; Wanni Arachchige et al., 2023). As well as reversal of functional connectivity changes (Grefkes et al., 2010; Guo et al., 2021; Juan et al., 2022) that occur after the stroke (Li et al., 2017; Vecchio et al., 2019).

According to the scientific literature, rTMS has numerous applications as analgesic tool in different neuropathic pain conditions. A long lasting analgesic effect has been reported when applying 5 sessions of high-frequency rTMS in CPSP or trigeminal neuralgia patients, compared to sham stimulation (Khedr et al., 2005). This reduction in pain intensity is also observed in other neuropathic pain conditions after receiving a rTMS treatment (Ahmed et al., 2011; Attal et al., 2021). In the only one systematic review conducted on the effect of non-invasive brain stimulation on CPSP, Ramger et al. (2019) concluded that noninvasive brain stimulation can have a therapeutic effect on the pain level of people with CPSP, as evidenced by significant decreases in clinical and experimental pain scores. Although no more systematic reviews or meta-analysis have been conducted on the analgesic effect of rTMS on CPSP, we can observe the same effect across other chronic neuropathic pain conditions (Gatzinsky et al., 2021).

To date no quantitative synthesis of the effect of rTMS on CPSP has been performed. Therefore, the aim of this study was to perform a meta-analysis of the randomized clinical trials (RCTs) or non-randomized clinical trials (CTs) that investigated the efficacy of rTMS in patients with CPSP.

Methods

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement were consulted to develop this systematic review (Moher et al., 2010). The computerized databases Medline (Pubmed), SCOPUS, Cochrane Library, Embase, and Web of Science were used to search for relevant studies. Keywords referring to the intervention were used, combined with Boolean operators (complete search strategy is shown in Supplementary Appendix S1).

Searches were performed between September 3rd 2022, and October 3rd 2022, (from the date of inception of each database) using a combination of controlled vocabulary (i.e., medical subject headings) and free-text terms. Search strategies were modified to meet the specific requirements of each database. Searches of the reference lists of included studies and previously published systematic reviews were also conducted.

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no: CRD42022365655).

Criteria for considering studies and study selection

We used the Population, Intervention, Comparison, Outcomes, Time, and Study design (PICOTS) as a framework to formulate eligibility criteria (Lira and Rocha, 2019).

Population

Individuals diagnosed with CPSP secondary to an ischemic or hemorrhagic stroke in the central nervous system.

Intervention

Treatment must consist of the application of at least one session of rTMS in the motor cortex.

Comparison

Comparison groups could be another type of intervention or non-intervention.

Outcomes

The measurement used to assess the outcomes and effects of the exercise was pain intensity. Measurements were to be recorded by objective methods, using validated and reliable scales or questionnaires (e.g., pain intensity by visual analog scale or numerical rating scale). Variables were to be assessed before and after the intervention.

Time

No temporal restrictions were applied to the duration of the intervention or outcome measures.

Studies

Only RCTs or CTs were included.

Data extraction

At first, two blinded investigators (JLS-G and FG-A) examined the studies obtained from the databases by screening by title and abstract according to the established inclusion criteria. In the case of discrepancies, a third investigator (SV-R) intervened. After this first screening, the selected articles were read in full to see if they definitely met the criteria and could be included in the analysis. The authors of the included studies were contacted by e-mail, with the aim of accessing possible unclear data. If no response was received, the data were excluded from the analysis.

Risk of bias and assessment of methodological quality of the studies

Two reviewers independently assessed the risk of bias in the studies (FGA and JLSG).

The risk of bias in non-randomized studies of interventions (NRSI) was assessed through the Risk of Bias In Non-randomized Studies of interventions (ROBINS-I) (Sterne et al., 2016). This tool focuses on assessing the risk of bias (RoB) in the results of NRSIs. The types of NRSIs that can be assessed with this tool are quantitative studies estimating the efficacy (harm or benefit) of an intervention, which did not use randomization to assign units (individuals or groups of individuals) to comparison groups. ROBINS-I takes into account 6 domains: Randomization process (D1), Bias arising from period and carryover effects (DS), Deviations from the intended interventions (D3), missing outcome data (D4), Selection of the reported result (D5).

On the other hand, a revised tool to assess the risk of bias in randomized clinical trials (RoB2) (Higgins et al., 2011) was used to assess the risk of bias in randomized trials. The tool is structured into five domains through which bias could be introduced into the outcome. These were identified based on empirical evidence and theoretical considerations. Because the domains cover all types of bias that may affect the results of randomized trials, each domain is mandatory, and no additional domains should be added. The five domains for individually randomized trials (including crossover trials) are: bias arising from the randomization process (D1); bias due to deviations from intended interventions (D2); bias due to missing outcome data (D3); bias in the measurement of the outcome (D4); bias in the selection of the reported result (D5).

In addition, methodological quality was evaluated using the PEDro list (de Morton, 2009), which assesses the internal and external validity of a study and consists of 11 criteria: (1) specified study eligibility criteria; (2) random allocation of subjects; (3) concealed allocation; (4) measure of similarity between groups at baseline; (5) subject blinding; (6) therapist blinding; (7) assessor blinding; (8) fewer than 15% dropouts; (9) intention-to-treat analysis; (10) between group statistical comparisons; and (11) point measures and variability data. The methodological criteria were scored as follows: yes (one point), no (zero points), or unknown (zero points). The PEDro score of each selected study provided an indicator of the methodological quality (9–10 = excellent; 6–8 = good; 4–5 = fair; 3–0 = poor) (Higgins et al., 2011).

Overall quality of the evidence

The overall quality of evidence was based on the classification of the results into levels of evidence according to the Grading Of Recommendations Assessments, Development, and Evaluation (GRADE), which is based on 5 domains: (1) Study design; (2) Imprecision; (3) Indirectness; (4) Inconsistency; (5) Publication bias.

Evidence was categorized into the following 4 levels accordingly: (a) High quality: further research is very unlikely to change our confidence in the estimate of effect, all 5 domains are also met; (b) Moderate quality: further research is likely to have an important impact on our confidence and might change the estimate of effect, one of the 5 domains is not met; (c) Low quality: further research is very likely to have an important impact on our confidence and is likely to change the estimate of effect, two of the 5 domains are not met; and (d) Very low quality: any estimate of effect is very uncertain, 3 of the 5 domains are not met (Balshem et al., 2011; Andrews et al., 2013).

Data synthesis and analysis

Meta-analysis was performed using ReviewManager statistical software (version 5.4; Cochrane, London, UK). Effects were investigated by calculating standardized mean differences (SMDs) for change scores from baseline to intervention. For this, the sample size, mean difference, and standard deviations (SDs) were extracted. When the study only reported median and first and third quartile values, they were converted to means and SDs (Luo et al., 2018).

When the authors presented only standard errors, these were converted to SDs. If the study did not present the results, the authors were contacted to request them. If results were not available in this way, means and SDs were estimated from graphs (Image J program;

National Institute of Health in Bethesda, Maryland, United States). If none of this was possible, the study was excluded from the quantitative analysis and the information was presented narratively.

If the study did not report the preintervention postintervention mean difference in each group, the mean difference was obtained using the pre-postintervention values. In the absence of SD of the difference, we imputed from other data reported in the study: (1) using other measures reported in the study (e.g., confidence intervals and *p* values, following the principles described in Chapter 6.5.2.2 of the Cochrane Handbook) (Higgins et al., 2023); or, if that was not possible, (2) using the correlation coefficient of the most similar study included (following the principles described in Chapter 6.5.2.8 of the Cochrane Handbook) (Higgins et al., 2023); or if that was not possible, (3) using a conservative correlation coefficient of 0.5 (Deeks et al., 2022). This methodology has been performed in other meta-analyses (Gurdiel-Álvarez et al., 2023).

Meta-analysis was performed using the inverse variance method and a random effects model with 95% confidence intervals, as it provides more conservative results in case of heterogeneity between studies, which is expected. *p* values < 0.05 were considered statistically significant. An effect size (SMD) of 0.8 or greater was considered large, an effect size between 0.5 and 0.8 was considered moderate, and an effect size between 0.2 and 0.5 was considered small.

A sensitivity analysis was performed to evaluate the results. For this purpose, the meta-analysis was performed only with studies with low RoB, and then with the correlation coefficient of 0.5, instead of being estimated from the other studies. Sensitivity analysis was performed when the analysis could be performed in at least 5 studies. Study heterogeneity was assessed by the degree of between study inconsistency (I2). The Cochrane Group has established the following interpretation of the I2 statistic: 0–40% may not be relevant/important heterogeneity, 30–60% suggests moderate heterogeneity, 50–90% represents substantial heterogeneity, and 75–100% represents considerable heterogeneity (Balk et al., 2012). Skewness was assessed using funnel plots according to application method (cathodic, anodic), and stimulation site. These analyses were performed only if the subgroups had at least three studies.

Inter-rater reliability

Inter-rater reliability for screening, risk of bias assessment, and quality of the evidence rating were assessed using percentage agreement and Cohen's kappa coefficient (Cohen, 1968; McHugh, 2012). There was strong agreement between reviewers for the screening records and full texts (98.51% agreement rate and $k = 0.91$), the risk of bias assessment (92.86% agreement rate and $k = 0.83$), and the quality and strength of the evidence assessment (97.73% rate and $k = 0.95$).

Results

The search found 851 records, of which 384 were duplicates and 467 were screened by title and abstract. Twenty five studies were potentially relevant and full reports were obtained and screened. Seventeen studies were justifiably excluded. Nine studies met the eligibility criteria and were included for review (Figure 1).

Characteristics of included studies

Nine studies (180 participants; 78 women) were included for review (Table 1). Six were RCTs and three were CTs. The mean age of participants was 56.73 ± 9.78 years. Mean pain duration was 39.08 ± 23.42 months. Mean pain intensity was 66.57 ± 12.20 in a 0 to 100 scale.

Quality assessment

Methodological quality scores ranged from 3 to 10 out of a maximum of 10 points. Three studies (33%) were of high methodological quality (greater than or equal to 6 points). Table 2 show the details of the PEDro scale.

Risk of bias

We assessed the quality of the included studies using the RoB 2 tool for the RCTs and the ROBINS-E tool for the non-randomized clinical trials. We only judged 1 study to be at low risk of bias. The majority of the RCTs presented limitations in the randomization process or the report of the outcomes. While in the CTs, there was a risk of selection bias. Assessment of the risk of bias in the included studies is shown in Figures 2, 3.

Effects of rTMS on neuropathic pain

Meta-analysis showed that significantly ($p < 0.001$), rTMS-based intervention produces a reduction in pain compared to sham based interventions with a large effect size (SMD: −1.45; 95% CI: −1.87; − 1.03; *Z*: 6.79; $p < 0.001$), and a moderate-substantial heterogeneity (I^2: 58%; $p = 0.001$) (Figure 4). Sensitivity analysis by RoB could not be performed since only one study showed a low risk of bias. In the sensitivity analysis, a conservative correlation coefficient of 0.5 was applied, instead of being estimated from the other studies, the effect size was reduced from large to medium, but the significance remained in favor of the rTMS (SMD: −1.45; 95% CI: −1.87; −1.03; Z: 6.79; $p < 0.001$ to SMD: −1.81; 95% CI: −1.07; −0.54; *Z*: 6.06; $p < 0.001$). Heterogeneity was reduced from I^2: 58%; $p = 0.001$ to $I^2 = 13\%$; $p = 0.3$ (Figure 5). The funnel plot presents asymmetry, indicating the risk of publication bias (Figure 6).

Adverse effects of intervention

Two non-randomized clinical trials did not mention adverse effects when reporting their results (Khedr et al., 2005; Matsumura et al., 2013). In one RCT, two patients reported transient, slight scalp discomfort after real rTMS (Kobayashi et al., 2015). Another RCT reported mild and transient adverse effects, such as headaches, tiredness, paresthesia, transient increase of pain, collapse, increased spasticity, or dizziness (Ojala et al., 2022). Lastly, other RCT reported short periods of numbness in the scalp or twitching of the fascial muscle during the stimulation in three participants (Zhao et al., 2021).

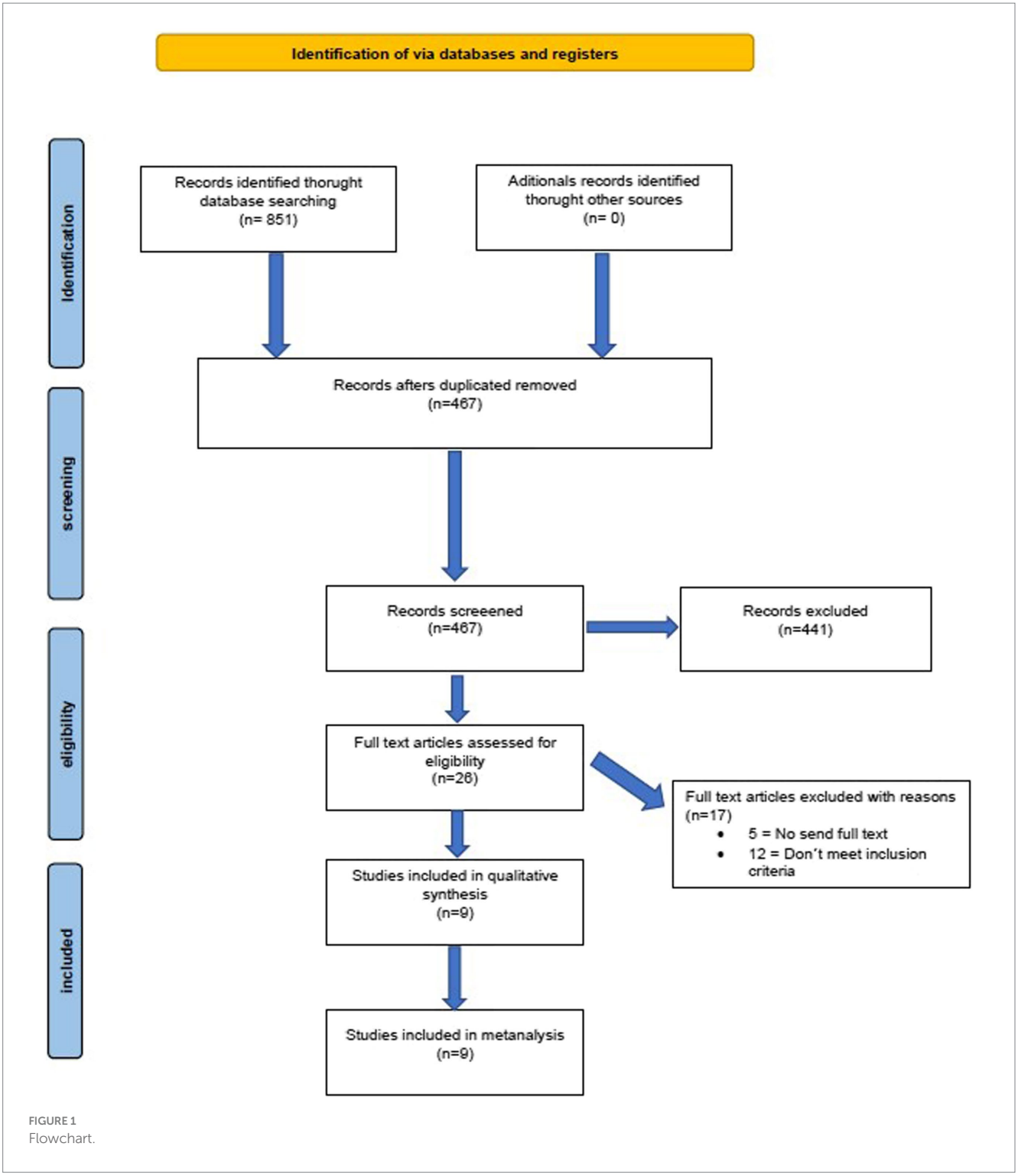

FIGURE 1
Flowchart.

The rest of the studies reported no adverse effects experienced during the duration of the intervention or follow-up (Lefaucheur et al., 2001a,b; André-Obadia et al., 2006; Hosomi et al., 2013).

Quality of evidence

Table 3 collects the details of the GRADE assessment. Three levels of evidence were downgraded due to the serious inconsistency of the results, publication bias, and overall risk of bias, which suggests a very small level of evidence regarding the effects of rTMS in patients with CPSP.

Discussion

This systematic review included nine studies, of which six were RCTs, the largest cohort of clinical studies on the effects of rTMS on CPSP. This meta-analysis of data from six trials provides very small level of evidence of a large effect size on pain reduction when active

TABLE 1 Studies characteristics.

Study	Design	Group (sample size)	Gender, male (female)	Age, years	Pain duration (months)	Localization of injury (*n*)	Etiology of injury	Stimulation site	Adverse effects	Stimulation protocol	Pain outcome
Hosomi et al. (2013)	RCT (cross-over)	G1	16 (13)	61.5 ± 10.9	56.4 ± 63.1	Thalamus (15) Lenticular nucleus (6) Subcortex (1) Other (7)	NR	M1 contralateral corresponding to painful site	Deterioration of squeezing (3%), deterioration of numbness (1%) and hypoglycemia (1%)	A stimulation session was carried out daily for 10 consecutive days. A real rTMS session consisted of 10 trains at 90% intensity of resting motor threshold (one train, 50 pulses at 5 Hz; intertrain interval, 50 s). A total of 500 pulses were applied in a session	VAS SF-MPQ
		G2	14 (11)	60.1 ± 10.5	59.5 ± 47.0	Thalamus (14) Lenticular nucleus (12) Subcortex (2) Brain stem (2) Other (5)				A stimulation session was carried out daily for 10 consecutive days. Ten trains of electrical stimuli at 2 times the intensity of the sensory threshold (one train, 50 stimuli at 5 Hz; intertrain interval, 50 s) were delivered with a conventional electrical stimulator through the electrodes fixed on the head	
Khedr et al. (2005)	CT	G1	14 (Sex distribution NR)	52.3 ± 10.3	18 ± 17	Thalamic infarction (12) Thalamic hemorrhage (6) Parietal infarction (2) Other (4)		M1 contralateral of abductor digiti minimi	NR	Real-rTMS involved applying a train of rTMS once per minute for 10 min. Each train consisted of 200 pulses at 20 Hz and 80% RMT (total duration of 10 s) applied through a figure of eight coil over the identified motor cortical area corresponding to the hand of the painful side. The treatment was repeated every day for five consecutive days	VAS
		G2	10 (Sex distribution NR)							Sham-rTMS was applied using the same parameters but with the coil elevated and angled away from the head to reproduce some of the subjective sensation of rTMS and yet avoid induction of current in the brain	
Kobayashi et al. (2015)	RCT (cross-over)	G1	4 (2)	63 ± 9.9	9 ± 6.83		Ischemic (5) Hemorrhagic (11)	M1 contralateral to most painful arm/leg	Transient slight scalp discomfort	Real focal 5 Hz rTMS was delivered to the scalp over the primary motor cortex of the affected hemisphere. The intensity of rTMS was set at 90% of the active motor threshold for the targeted hemisphere. Real rTMS involved a train of 50 pulses at 5 Hz (total duration 10 s). The train was repeated ten times, and a total of 500 pulses were delivered over a 10-min session, with a 50-s inter-train interval	VAS

(Continued)

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TABLE 1 (Continued)

Study	Design	Group (sample size)	Gender, male (female)	Age, years	Pain duration (months)	Localization of injury (*n*)	Etiology of injury	Stimulation site	Adverse effects	Stimulation protocol	Pain outcome
		G2								Sham rTMS was performed with the coil held at an angle of 90° to the scalp using the same stimulation parameters (noise, time, frequency) as those for real rTMS.	
Lefaucheur et al. (2001a)	RCT (cross-over)	G1	6 (8)	57.2	NR	NR	NR	M1 contralateral to painful site	None	For "real" TMS a series of 20 trains of 5 s in duration (55-s intertrain interval) at a stimulation rate of 10 Hz and 80% of rest motor threshold intensity	VAS
		G2								The same protocol was used for sham stimulation, but using a "sham" 8-shaped coil	
Lefaucheur et al. (2001b)	RCT (cross-over)	G1	11 (7)	54. 7	NR	thalamic (6) Brain Stem (6) brachial plexus (6)	NR	M1 contralateral to painful site	None	(1) a series of 20 10 Hz trains of 5 s duration (55 -s intertrain interval) at 80% of rest motor threshold intensity using a real TMS coil; (2) the same protocol using a sham 8-shaped coil (Magstim Placebo Coil System 1730-23-00, The Magstim Co., Whitland, UK); (3) a 20 min stimulation at 0.5 Hz and at 80% of rest motor threshold intensity using a real TMS coil	VAS
Matsumura et al. (2013)	CT (cross-over)	G1	12 (8)	63.6 ± 8.1	2.95 ± 1.36	Thalamic (11) Putamen (5) Brainstem (4)	Ischemic (7) Hemorrhagic (13)	M1 contralateral to most painful site	NR	For rTMS, the subjects sat relaxed on a stimulation chair while a total of 500 stimuli at 5 Hz were delivered to the part of the motor cortex that corresponded to the site of most severe pain on the lesion side. The stimulation intensity was 100% resting motor threshold of the unaffected primary motor cortex of the hand area, with 50 pulses per train at 25-s intertrain intervals	VAS
		G2								Sham rTMS was performed under the same conditions, but the stimulation coils were elevated at an angle of 45° from the skull	
André-Obadia et al. (2006)	RCT (cross-over)	G1	10 (4)	53 ± 11	82.8 ± 48	Brainstem (10) Other (4)		M1 contralateral to painful site	None	Cortical inhibitory stimulation at M1: 1 Hz repetitive stimulation at 90% of motor threshold during 26 min, i.e., a total of 1,600 stimulations	VAS
		G2								Cortical excitatory stimulation at M1: 20 consecutive trains of 80 stimulations at 20 Hz (90% motor threshold), separated by inter-trains intervals of 84 s, i.e., a total of 1,600 stimulations	

(Continued)

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TABLE 1 (Continued)

Study	Design	Group (sample size)	Gender, male (female)	Age, years	Pain duration (months)	Localization of injury (*n*)	Etiology of injury	Stimulation site	Adverse effects	Stimulation protocol	Pain outcome
		G3								Sham stimulation at M1: same protocol as 1 Hz stimulation using the coil oriented perpendicular to, and separated from, the skull, thus preventing actual cortical stimulation	
Ojala et al. (2022)	RCT (cross-over)	G1	8 (9)	55.8 ± 7.1	NR	NR	Ischemic (10) Hemorrhagic (7)	M1 contralateral representation of the abductor pollicis brevis of the painful site	Headache (*n* = 1) Tiredness (*n* = 2) Paresthesia (*n* = 2) Transient increase in pain (*n* = 2) Collapse (*n* = 1)	The nrTMS was applied at 10 Hz during a 50-min period with an intensity of 90% of the MT. Altogether, 5,050 pulses per session were given in trains of 101 pulses (10-s stimulation with a 50-s intertrain interval). The electric fields induced by the nrTMS ranged from 31 to 127 V/m in the underlying M1 cortex	NRS
		G2						S2 in the parietal operculum lateral upper lip of the Sylvian fissure	Headache (*n* = 3) Tiredness (*n* = 3) Paresthesia (*n* = 3) Transient increase in pain (*n* = 3) Increase spasticity (*n* = 2) Dizziness (*n* = 1)	The nrTMS was applied at 10 Hz during a 50-min period with an intensity of 90% of the MT. Altogether, 5,050 pulses per session were given in trains of 101 pulses (10-s stimulation with a 50-s intertrain interval) The corresponding values in the chosen lateral cortical site for S2 ranged from 39 to 109 V/m	
		G3						Same as M1 group	Headache (*n* = 4) Tiredness (*n* = 2) Paresthesia (*n* = 3) Transient increase in pain = 2	Sham nrTMS was delivered over the M1 cortex by attaching a 75-mm non-conductive plastic block on the coil to increase the coil-to-scalp distance and to minimize the electric field induced in the cortex	

(Continued)

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TABLE 1 (Continued)

Study	Design	Group (sample size)	Gender, male (female)	Age, years	Pain duration (months)	Localization of injury (*n*)	Etiology of injury	Stimulation site	Adverse effects	Stimulation protocol	Pain outcome
Zhao et al. (2021)	RCT	G1	19 (Sex distribution NR)	50.16 ± 11.34	0.2 ± 0.10	Right cerebellum (1) Right thalamus (4) Right basal ganglia (7) Right external capsule (2) Right lateral periventricular (1) Right frontal lobe (2) Left cerebellum (1) Left thalamus (4) Left frontal lobe (2) Left basal ganglia (10) Left external capsule (1) Left lateral periventricular (3)	Ischemic (17) Hemorrhagic (21)	M1 contralateral to painful site	Numbness in the scalp or twitching of facial muscles during procedure ($n = 3$)	In the active rTMS stimulation group, rTMS was applied over the motor cortical area (M1) corresponding to the painful zone at a frequency of 10 Hz, as 15 pulse trains (1.5 s), with intertrain intervals of 3 s (total of 1,500 pulses) and at an intensity of 80% of the RMT (AH), or 100% (UH) when the RMT could not be detected in the AH	NRS SF-MPQ2
		G2	19 (Sex distribution NR)	48.95 ± 11.51	0.21 ± 0.41					The sham stimulation was delivered using a coil identical to the one in the active group (same shape and color), but with no magnetic stimulation output (only emitting the same sound) Patients in the active rTMS and sham groups received stimulation once a day, 6 days per week, for a total of 3 weeks	

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TABLE 2 Methodological score of randomized clinical trials using the Physiotherapy Evidence Database (PEDro) scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Hosomi et al. (2013)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
Khedr et al. (2005)	N	N	N	Y	Y	N	Y	N	N	Y	N	4
Kobayashi et al. (2015)	N	N	N	N	Y	N	N	Y	N	Y	N	3
Lefaucheur et al. (2001a)	N	Y	N	Y	N	N	N	Y	N	Y	N	4
Lefaucheur et al. (2001b)	N	Y	N	Y	N	N	N	Y	Y	Y	N	5
Matsumura et al. (2013)	N	N	N	Y	N	N	N	Y	N	Y	N	3
André-Obadia et al. (2006)	N	Y	N	N	Y	N	Y	N	N	Y	N	4
Ojala et al. (2022)	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	7
Zhao et al. (2021)	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	9

Y: yes; N: no. 1: eligibility criteria specify; 2: random allocation of participants; 3: concealed allocation; 4: similarity between groups at baseline; 5: participant blinding; 6: therapist blinding; 7: assessor blinding; 8: dropout rate less than 15%; 9: intention-to-treat analysis; 10: between-group statistical comparisons; 11: point measures and variability data.

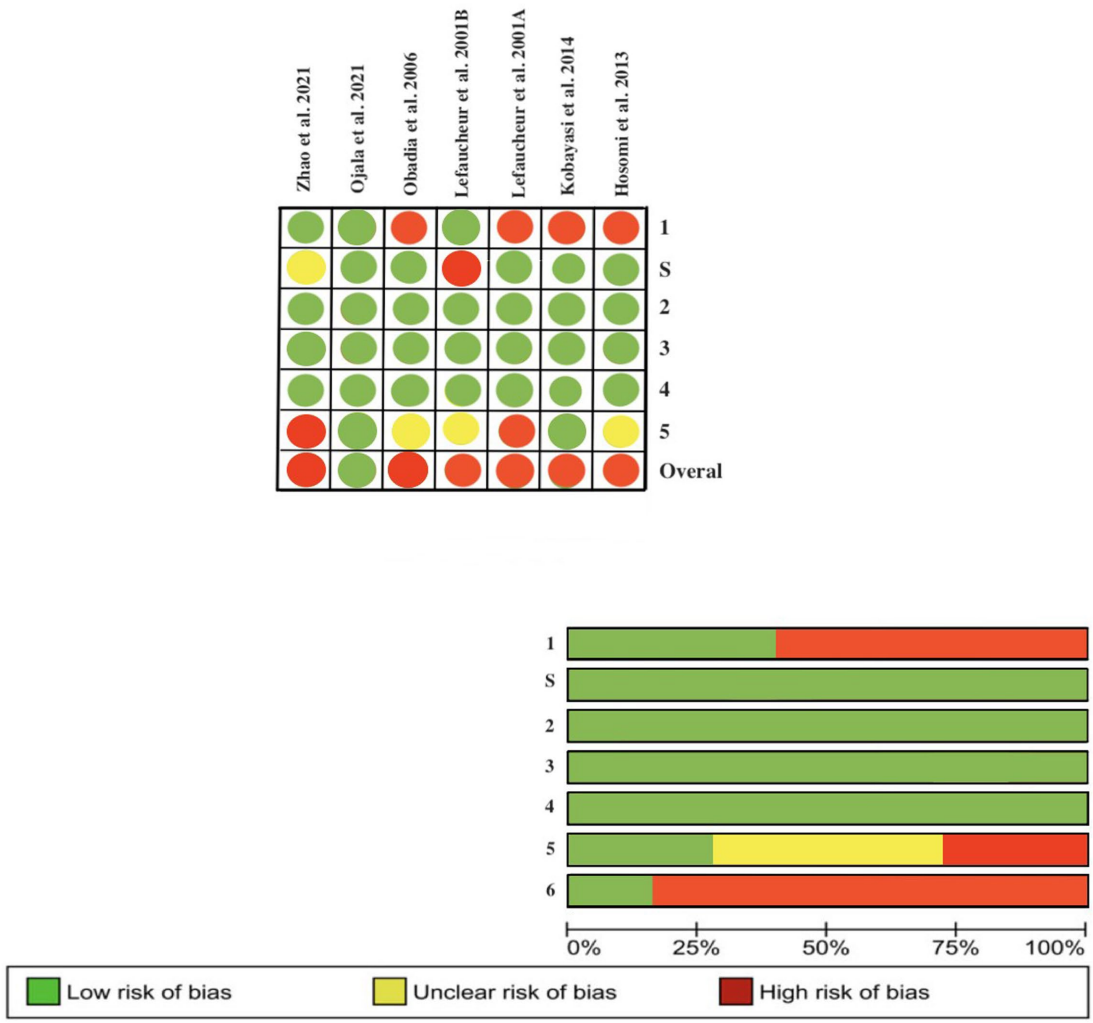

FIGURE 2
Assessment of the risk of bias according to the revised Cochrane risk-of-bias tool for randomized trials (ROB-2).

rTMS is delivered on affected M1 in CPSP compared to a sham intervention. However, after carrying a sensitivity analysis, the effect size of the intervention is determined to be moderate with a low heterogeneity.

To date, this is the first meta-analysis evaluating the analgesic effect of rTMS on CPSP. Other studies have reviewed the antalgic effect of non-invasive physical modalities on CPSP, including rTMS. In other systematic review (Chen et al., 2016), a reduction of 10.8–32.6%

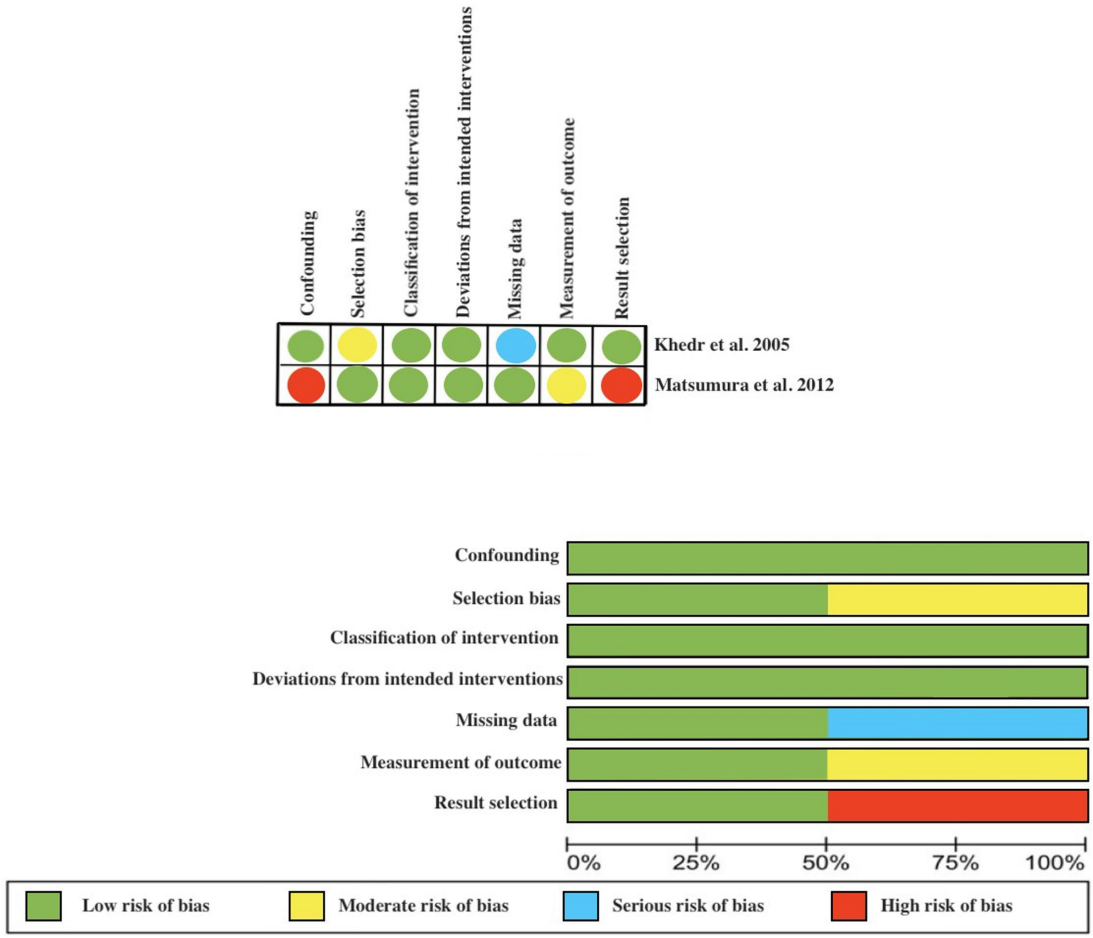

FIGURE 3
Assessment of the risk of bias according to the Robins scale.

Study or Subgroup	rTMS Mean	rTMS SD	rTMS Total	Sham therapy Mean	Sham therapy SD	Sham therapy Total	Weight	Std. Mean Difference IV, Random, 95% CI
Khedr et al. 2005 3 sessions	-3.74	1.04	13	-0.7	0.23	13	4.8%	-3.91 [-5.29, -2.52]
Lefaucheur et al. 2021A 1 day post	-2.65	1.96	7	0.9	0.71	7	4.6%	-2.25 [-3.69, -0.82]
Lefaucheur et al. 2021A 2 day post	-2.95	3.06	7	1.5	0.71	7	5.0%	-1.88 [-3.21, -0.55]
Lefaucheur et al. 2021A 8 day post	-2.3	2.56	7	1.45	0.79	7	5.1%	-1.85 [-3.18, -0.53]
Lefaucheur et al. 2021A 11 day post	-2.3	2.68	7	1.55	0.92	7	5.1%	-1.80 [-3.11, -0.49]
Lefaucheur et al. 2021A 3 day post	-3.1	2.94	7	0.95	0.81	7	5.2%	-1.76 [-3.06, -0.46]
Lefaucheur et al. 2021A 4 day post	-2.45	2.94	7	1.4	0.71	7	5.2%	-1.69 [-2.97, -0.40]
Lefaucher et al., 2001B 10Hz	-1.6	1.41	6	0.3	0.59	6	4.8%	-1.62 [-3.00, -0.24]
Lefaucheur et al. 2021A 10 day post	-2.15	2.8	7	1.4	0.92	7	5.3%	-1.59 [-2.85, -0.34]
Lefaucheur et al. 2021A 12 day post	-2	3.18	7	1.8	0.49	7	5.3%	-1.56 [-2.81, -0.31]
Kobayashi et al. 2015	-20.42	8.49	6	-4.13	12.29	6	5.0%	-1.42 [-2.75, -0.10]
Lefaucheur et al. 2021A 6 day post	-2	2.8	7	1.3	1.41	7	5.5%	-1.39 [-2.61, -0.18]
Lefaucheur et al. 2021A 9 day post	-2.15	2.8	7	1	1.16	7	5.5%	-1.38 [-2.58, -0.17]
Lefaucheur et al. 2021A 5 day post	-2.35	2.9	7	0.9	1.4	7	5.6%	-1.34 [-2.54, -0.14]
Lefaucheur et al. 2021A 7 day post	-2.15	3.95	7	1.6	0.54	7	5.6%	-1.25 [-2.43, -0.06]
Zhao et al. 2021 18 sessions	-1.16	0.4	20	-0.05	1.41	20	8.1%	-1.05 [-1.72, -0.38]
Lefaucher et al., 2001B 0.5Hz	0.3	1.6	6	0.3	0.59	6	5.9%	0.00 [-1.13, 1.13]
Ojala et al. 2021 10 sessions	-0.9	1.5	17	-0.9	1.9	21	8.2%	0.00 [-0.64, 0.64]
Total (95% CI)			**152**			**156**	**100.0%**	**-1.45 [-1.87, -1.03]**

Heterogeneity: Tau² = 0.45; Chi² = 40.07, df = 17 (P = 0.001); I² = 58%
Test for overall effect: Z = 6.79 (P < 0.00001)

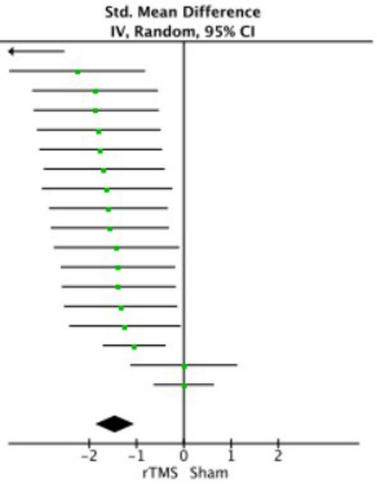

FIGURE 4
rTMS versus sham forest plot. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI) for the effects of rTMS compared with sham in post-stroke central pain. The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

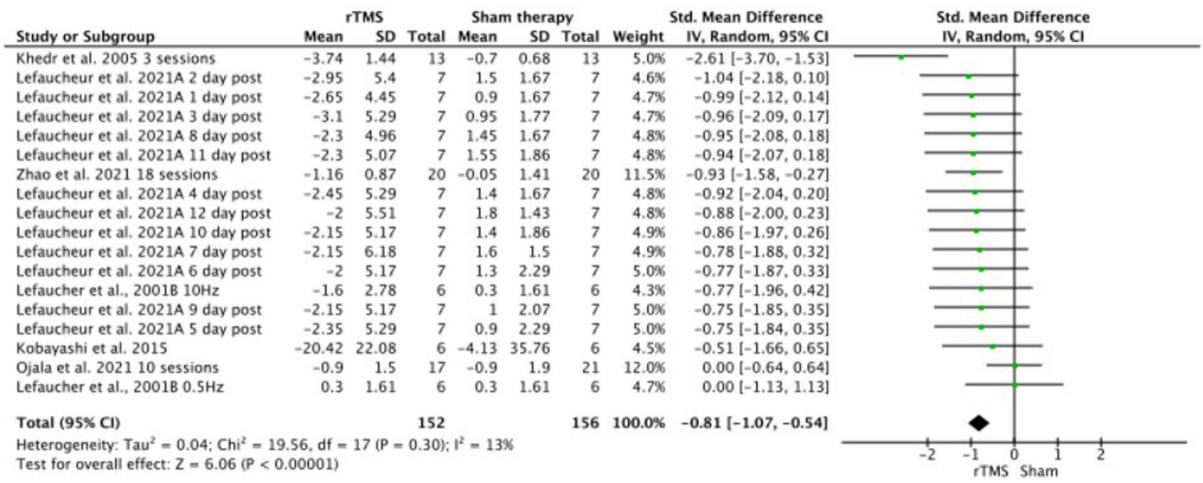

FIGURE 5
Sensitivity analysis of rTMS versus sham forest plot. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI) for the effects of rTMS compared with sham in post-stroke central pain. The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond rep-resents the overall mean difference of the studies.

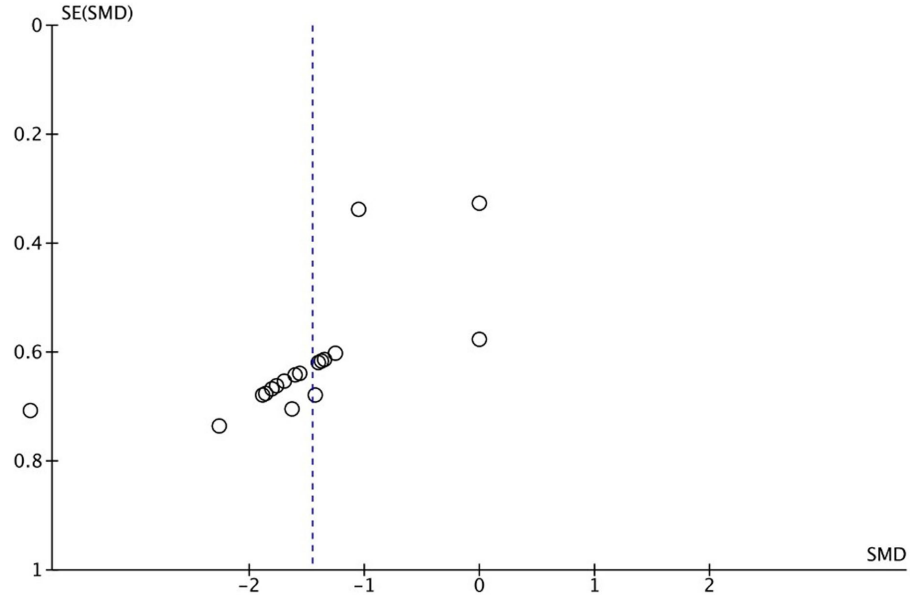

FIGURE 6
Central post-stroke pain funnel plot.

in pain intensity was found in four non-randomized controlled trials (Hirayama et al., 2006; Goto et al., 2008; Ohn et al., 2012; Hosomi et al., 2013) and 1 case study (Lefaucheur et al., 2004) but no effect was seen in 2 RCTs (Lefaucheur et al., 2001b; de Oliveira et al., 2014). As a result, a Level B of evidence was given to rTMS as an analgesic tool for the treatment of CPSP (Chen et al., 2016). Another systematic review evaluated the effect of non-invasive brain stimulation on CPSP (Ramger et al., 2019). It found that of the 5 studies about rTMS (Ohn et al., 2012; Matsumura et al., 2013; de Oliveira et al., 2014; Hasan et al., 2014), 2 RCTs (Matsumura et al., 2013; Kobayashi et al., 2015) and 2 non-randomized clinical trials (Ohn et al., 2012; Hasan et al., 2014) reported a decrease in pain intensity after the treatment with high-frequency rTMS on the affected hemisphere (Ramger et al., 2019).

After the stroke, there is a remapping of the motor cortex that has been observe by functional magnetic resonance imaging (fMRI) or TMS (Cicinelli et al., 1997, 2003; Traversa et al., 1997). In animal stroke models, we can observe a significant reduction of the affected area in the motor cortex (Nudo, 2007). In addition, neuronal connections on the side contralateral to the lesion appear to be altered resulting in a lateralization of the neural activity (Bütefisch et al., 2008). In consequence, a decrease in short interval intracortical

TABLE 3 GRADE evidence for rTMS to treat central post-stroke pain.

Number of studies	Risk of bias*	Inconsistency†	Indirectness‡	Imprecision§	Publication Bias¶	MD or SMD (95% CI)	Quality of evidence
Five trials ($n = 197$)	Serious (mainly by blinding the therapist)	Serious ($I^2 = 67\%$)	No serious	No serious	Serious	MD = −1.65 (−2.46, −0.84) SMD = −1.21 (−1.95, −0.47)	Very small

GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; SMD, standardized mean difference.
*"No" = most information is from results at low risk of bias; "Serious" = crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect; "Very serious" = crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect.
†"Serious" = $I^2 > 40\%$; "Very serious" = $I^2 > 80\%$.
‡No indirectness of evidence was found in any study.
§Based on sample size. "Serious" = $n < 250$ subjects; "Very serious" = $n < 250$ and the estimated effect is little or absent.
¶Based on funnel plots. No publication bias was found. Funnel plots are not shown because the number of trials was less than 10.

inhibition in both hemispheres, and an increase in intracortical facilitation in the non lesioned hemisphere can be observed (Liepert et al., 2000; Swayne et al., 2008). This results in an imbalance in the interhemispheric inhibition that could result in an obstacle for recovery (Vallone et al., 2016).

With regard to CPSP treatment, motor cortex stimulation has been researched since 1991 (Tsubokawa et al., 1991) as an invasive procedure to treat drug-resistant central pain. In motor cortex stimulation, higher frequencies are used, and the electrode is implanted in the affected hemisphere. High-frequency rTMS of the affected hemisphere tends to be the most common type of stimulation seen in CPSP trials, whereas low-frequency rTMS of the affected hemisphere is less common and tends to not have an effect (Lefaucheur et al., 2001a). Several mechanisms for high-frequency rTMS modulation of CPSP have been proposed (Pan et al., 2023; Radiansyah and Hadi, 2023). Electrical stimulation of the motor cortex increases blood flow to the lateral thalamus, the anterior cingulate cortex, the anterior insula, and the brainstem of CPSP patients (García-Larrea et al., 1999). Similar patterns of activity had been reported on fMRI after rTMS of M1 (Bestmann et al., 2004), implying common mechanisms of action. This analgesic effect of motor cortex stimulation in CPSP patients seems to be determined by the availability of opioid receptors in the anterior cingulate cortex, the insula, the thalamus, and the periaqueductal gray matter (Maarrawi et al., 2013). Meaning that rTMS of affected M1 in CPSP patients could modulate these structures of the medial system of pain (Xie et al., 2009), which has been shown to mediate the affective processing of the pain experience (Vogt and Sikes, 2000). Regarding this, animal CPSP models exhibit a reduction in the number of fibers in the thalamocortical pathway between the ventral posterolateral nucleus of the thalamus and the somatosensory cortices (Kadono et al., 2021) and increased functional connectivity between the medial thalamus and the amygdala (Mitchell and Chakraborty, 2013). The analgesic effect of rTMS in these models is associated with a reduction in the strength of the functional connectivity between medial thalamus and amygdala, normalizing during the rTMS treatment (Kadono et al., 2021).

Another proposed mechanism is the increase in excitability of the affected M1, that seems to be reduced in CPSP patients as a result of an asymmetric interhemispheric inhibition (Pan et al., 2023; Radiansyah and Hadi, 2023). The lesion of one M1 reduces its inhibitory activity in the contralateral M1. This results in an increase on the excitability of the contralateral M1 and a higher inhibitory output from the contralateral M1 to the injured M1 (Boddington and Reynolds, 2017). The application of high frequency rTMS to the injured M1 produce an increment on the excitability of the affected cortex, and an inhibition of the augmented excitability of the contralateral M1 (Bai et al., 2022). Finally, the activation of the descending inhibitory system is another mechanism that could explain the analgesic effect of non-invasive brain stimulation (DosSantos et al., 2018). However, in CPSP patients, heterotopic noxious conditioning stimulation, which activates the descending inhibitory system, has failed to reduce ongoing pain and dynamic mechanical allodynia (Tuveson et al., 2009).

Pharmacological treatment of the CPSP tend to use some drugs that could interact with the mechanism of action of TMS, and therefore alter its effects (Ziemann et al., 2015). Amitriptyline is used as first line treatment for CPSP (Ziemann et al., 2015), but its interaction with TMS is not known. It acts inhibiting voltage gated ion channels (Yan et al., 2010; Wu et al., 2012) and could act as agonist of TrkA and TrkB receptors, which mediate neural plasticity (Jang et al., 2009). Also, it seems to decrease GABAergic transmission (Bang et al., 2021). These mechanisms could potentially result in the increase of the facilitatory effect of the high frequency rTMS, and in the decrease of the inhibitory effect of the low frequency rTMS. Anticonvulsants like gabapentin or pregabalin, are other type of drugs that have been implemented in the management of CPSP (Hesami et al., 2015). Gabapentin and pregabalin have been shown to block voltage-gated ion channels, increase the synthesis and brain concentrations of GABA (Löscher et al., 1991) and reduce the synaptic release of glutamate (Taylor et al., 2007). These effects could produce an increase in the motor threshold measured by TMS (Menzler et al., 2014), a more sustained intracortical inhibition (Rizzo et al., 2001; Sommer et al., 2012) and a diminished intracortical facilitation (Rizzo et al., 2001). Accordingly, to this, stroke patients receiving anticonvulsant treatment could benefit less from high frequency rTMS treatment.

Considering the results of the present systematic review with meta-analysis, rTMS could be considered useful tool in the clinical context for management CPSP. Not only it has several possible mechanisms of action on the pathophysiological processes underlying CPSP as previously presented (Bestmann et al., 2004; Bai et al., 2022; Pan et al., 2023; Radiansyah and Hadi, 2023), but it is also a less invasive treatment that motor cortex stimulation (Tsubokawa et al., 1991). Also, high frequency rTMS protocols last only about 10 min and its adverse effects tend to be rare and mild in nature. Due to its suitability for the clinical practice, future studies should consider evaluating rTMS effectiveness compared to other treatments recommended for the management of patients with CPSP (e.g., adrenergic antidepressants or anticonvulsants) or its interaction with them.

Strengths and limitations

Several limitations should be kept in mind when interpreting the results of the meta-analysis. Two of the studies included in the meta-analysis were not RCTs, so there exists some risk of selection bias. Regarding the duration of pain, some studies did not report it, while others ranged between acute (<3 months) to chronic presentation (>3 months). Mixing patients with acute and chronic CPSP in the study sample could account to an increased variability in the results, due to differences in the underlying pathophysiological processes. So future studies should consider these differences when stablishing their inclusion criteria. Also, the dosage of the rTMS varied between studies, with the frequency of stimulation ranging between 5 and 20 Hz, the intensity of stimulation ranging between 80 and 100% resting motor threshold, and the total number of sessions ranging between 1 and 18 sessions. Analyzing together studies with different rTMS protocols could in fact account to differences in the measured effects, accounting to increased heterogeneity in the results. Due to scarcity in studies applying same rTMS protocols in CPSP, future studies should take into account replicating the methodology of stimulation of previous studies to reduce this problem. Lastly, there seems to be a common risk of bias between the included studies regarding the randomization process or the clarity in the report of the outcomes. Researchers must consider reporting clearly the randomization processes to reduce possible biases and facilitate replicability, as well as expressing measures of centralization and dispersion to improve transparency and better understanding of the results.

The mains strengths of this study, is that this is the first systematic review with meta-analysis that has investigated the efficacy of rTMS on patients with CPSP. An analysis methodology has been applied in which pre-post mean differences were compared, which provides robustness to the results. The analysis has been developed based on the most recommended guidelines so that the study is replicable. The sensitivity analysis allowed to reduce the heterogeneity of the analyzed data sample, increasing the robustness of the results. Future studies should aim to improve the randomization and blinding processes to reduce the risk of bias, and define better the characteristics of the included subjects to provide homogeneous samples.

Conclusion

The findings of the current systematic review with meta-analysis suggest that there is low quality evidence for the effectiveness of rTMS in reducing CPSP intensity with a large effect size. Future studies should consider improving methodology by blinding the therapist and taking into account patients' characteristics and rTMS parameters to reduce heterogeneity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FG-Á: Conceptualization, Methodology, Supervision, Writing – original draft. VN-L: Data curation, Formal analysis, Investigation, Software, Writing – original draft. SV-R: Investigation, Validation, Visualization, Writing – review & editing. RJ-V: Data curation, Project administration, Writing – review & editing. AC-R: Data curation, Formal analysis, Resources, Validation, Writing – review & editing. JS-G: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer ER-A declared a past co-authorship with the author RJ-V to the handling editor.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1345128/full#supplementary-material

References

Ahmed, M. A., Mohamed, S. A., and Sayed, D. (2011). Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. *Neurol. Res.* 33, 953–958. doi: 10.1179/1743132811Y.0000000045

André-Obadia, N., Peyron, R., Mertens, P., Mauguière, F., Laurent, B., and Garcia-Larrea, L. (2006). Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin. Neurophysiol.* 117, 1536–1544. doi: 10.1016/j.clinph.2006.03.025

Andrews, J., Guyatt, G., Oxman, A. D., Alderson, P., Dahm, P., Falck-Ytter, Y., et al. (2013). GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J. Clin. Epidemiol.* 66, 719–725. doi: 10.1016/j.jclinepi.2012.03.013

Attal, N., Poindessous-Jazat, F., De Chauvigny, E., Quesada, C., Mhalla, A., Ayache, S. S., et al. (2021). Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. *Brain* 144, 3328–3339. doi: 10.1093/brain/awab208

Bai, Z., Zhang, J., and Fong, K. N. K. (2022). Effects of transcranial magnetic stimulation in modulating cortical excitability in patients with stroke: a systematic review and meta-analysis. *J. Neuroeng. Rehabil.* 19:24. doi: 10.1186/s12984-022-00999-4

Balk, E. M., Earley, A., Patel, K., Trikalinos, T. A., and Dahabreh, I. J. *Empirical assessment of within-arm correlation imputation in trials of continuous outcomes*. *12. 13* Rockville, MD: Agency for Healthcare Research and Quality (US); (2012).

Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., et al. (2011). GRADE guidelines: 3. Rating the quality of evidence. *J. Clin. Epidemiol.* 64, 401–406. doi: 10.1016/j.jclinepi.2010.07.015

Bang, E., Tobery, A., Montgomery, K. S., Fincher, A. S., Earnest, D. J., Murchison, D. A., et al. (2021). Amitriptyline decreases GABAergic transmission in basal forebrain neurons using an Optogenetic model of aging. *Front. Aging Neurosci.* 13:13. doi: 10.3389/fnagi.2021.673155

Belardinelli, P., König, F., Liang, C., Premoli, I., Desideri, D., Müller-Dahlhaus, F., et al. (2021). TMS-EEG signatures of glutamatergic neurotransmission in human cortex. *Sci. Rep.* 11:8159. doi: 10.1038/s41598-021-87533-z

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., and Frahm, J. (2004). Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur. J. Neurosci.* 19, 1950–1962. doi: 10.1111/j.1460-9568.2004.03277.x

Boddington, L. J., and Reynolds, J. N. J. (2017). Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimul.* 10, 214–222. doi: 10.1016/j.brs.2017.01.006

Bowsher, D., Vantrappen, G., Mabey, D., Treasure, T., Woods Kent, L., Treasure, T., et al. (1993). Cerebrovascular disease. *Lancet* 341:156. doi: 10.1016/0140-6736(93)90015-9

Burke, M. J., Fried, P. J., and Pascual-Leone, A. (2019). Transcranial magnetic stimulation: Neurophysiological and clinical applications. *Handb. Clin. Neurol.* 163, 73–92. doi: 10.1016/B978-0-12-804281-6.00005-7

Bütefisch, C. M., Weßling, M., Netz, J., Seitz, R. J., and Hömberg, V. (2008). Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. *Neurorehabil. Neural Repair* 22, 4–21. doi: 10.1177/1545968307301769

Chen, C.-C., Chuang, Y.-F., Huang, A. C.-W., Chen, C.-K., and Chang, Y.-J. (2016). The antalgic effects of non-invasive physical modalities on central post-stroke pain: a systematic review. *J. Phys. Ther. Sci.* 28, 1368–1373. doi: 10.1589/jpts.28.1368

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 48, 1398–1403. doi: 10.1212/WNL.48.5.1398

Cicinelli, P., Pasqualetti, P., Zaccagnini, M., Traversa, R., Oliveri, M., and Rossini, P. M. (2003). Interhemispheric asymmetries of motor cortex excitability in the Postacute stroke stage. *Stroke* 34, 2653–2658. doi: 10.1161/01.STR.0000092122.96722.72

Cicinelli, P., Traversa, R., and Rossini, P. M. (1997). Post-stroke reorganization of brain motor output to the hand: a 2–4 month follow-up with focal magnetic transcranial stimulation. Electroencephalography and clinical neurophysiology/electromyography and motor. *Control* 105, 438–450. doi: 10.1016/S0924-980X(97)00052-0

Cohen, J. (1968). Weighted kappa: nominal scale agreement provision for scaled disagreement or partial credit. *Psychol. Bull.* 70, 213–220. doi: 10.1037/h0026256

de Morton, N. A. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust. J. Physiother.* 55, 129–133. doi: 10.1016/S0004-9514(09)70043-1

de Oliveira, R. A. A., de Andrade, D. C., Mendonça, M., Barros, R., Luvisoto, T., Myczkowski, M. L., et al. (2014). Repetitive transcranial magnetic stimulation of the left premotor/dorsolateral prefrontal cortex does not have analgesic effect on central Poststroke pain. *J. Pain* 15, 1271–1281. doi: 10.1016/j.jpain.2014.09.009

Deeks, J. J., Higgins, P. T., and Altman, D. G. Analysing data and undertaking meta-analyses. In: J. Higgins and J. Thomas, editors. *Cochrane handbook for systematic reviews of interventions*, *3*; *6*. Bristol; (2022).

DosSantos, M. F., Oliveira, A. T., Ferreira, N. R., Carvalho, A. C. P., and Rosado de Castro, P. H. (2018). The contribution of endogenous modulatory systems to TMS-and tDCS-induced analgesia: evidence from PET studies. *Pain Res. Manag.* 2018:2368386. doi: 10.1155/2018/2368386

Esser, S. K., Huber, R., Massimini, M., Peterson, M. J., Ferrarelli, F., and Tononi, G. (2006). A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. *Brain Res. Bull.* 69, 86–94. doi: 10.1016/j.brainresbull.2005.11.003

Figueroa, J., Villamayor, B., and Antelo, A. (2015). *Reeducación funcional tras un ictus*. Spain: Elsevier.

Fitzgerald, P., Fountain, S., and Daskalakis, Z. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin. Neurophysiol.* 117, 2584–2596. doi: 10.1016/j.clinph.2006.06.712

García-Larrea, L., Peyron, R., Mertens, P., Gregoire, C. M., Lavenne, F., Le Bars, D., et al. (1999). Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* 83, 259–273. doi: 10.1016/S0304-3959(99)00114-1

Gatzinsky, K., Bergh, C., Liljegren, A., Silander, H., Samuelsson, J., Svanberg, T., et al. (2021). Repetitive transcranial magnetic stimulation of the primary motor cortex in management of chronic neuropathic pain: a systematic review. *Scand J Pain* 21, 8–21. doi: 10.1515/sjpain-2020-0054

Goto, T., Saitoh, Y., Hashimoto, N., Hirata, M., Kishima, H., Oshino, S., et al. (2008). Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. *Pain* 140, 509–518. doi: 10.1016/j.pain.2008.10.009

Grefkes, C., Nowak, D. A., Wang, L. E., Dafotakis, M., Eickhoff, S. B., and Fink, G. R. (2010). Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. *NeuroImage* 50, 233–242. doi: 10.1016/j.neuroimage.2009.12.029

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., et al. (2012). A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin. Neurophysiol.* 123, 858–882. doi: 10.1016/j.clinph.2012.01.010

Guo, Z., Jin, Y., Bai, X., Jiang, B., He, L., McClure, M. A., et al. (2021). Distinction of high-and low-frequency repetitive transcranial magnetic stimulation on the functional reorganization of the motor network in stroke patients. *Neural Plast.* 2021, 1–11. doi: 10.1155/2021/8873221

Gurdiel-Álvarez, F., González-Zamorano, Y., Lerma-Lara, S., Gómez-Soriano, J., Sánchez-González, J. L., Fernández-Carnero, J., et al. (2023). Transcranial direct current stimulation (tDCS) effects on quantitative sensory testing (QST) and nociceptive processing in healthy subjects: a systematic review and Meta-analysis. *Brain Sci.* 14:9. doi: 10.3390/brainsci14010009

Hasan, M., Whiteley, J., Bresnahan, R., MacIver, K., Sacco, P., Das, K., et al. (2014). Somatosensory change and pain relief induced by repetitive transcranial magnetic stimulation in patients with central Poststroke pain. Neuromodulation: Technology at the Neural. *Interface* 17, 731–736. doi: 10.1111/ner.12198

Hesami, O., Gharagozli, K., Beladimoghadam, N., Assarzadegan, F., Mansouri, B., and Sistanizad, M. (2015). The efficacy of gabapentin in patients with central Post-stroke pain. *Iran. J. Pharm. Res.* 14, 95–101.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trialss. *BMJ.* 18,343: d5928. doi: 10.1136/bmj.d5928

Higgins, P. T., Li, T., and Deeks, J. J. (2023). "Chapter 6: Choosing effect measures and computing estimates of effect" in *Cochrane Handbook for Systematic Reviews of Interventions*

Hirayama, A., Saitoh, Y., Kishima, H., Shimokawa, T., Oshino, S., Hirata, M., et al. (2006). Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *Pain* 122, 22–27. doi: 10.1016/j.pain.2005.12.001

Hosomi, K., Kishima, H., Oshino, S., Hirata, M., Tani, N., Maruo, T., et al. (2013). Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain. *Pain* 154, 1352–1357. doi: 10.1016/j.pain.2013.04.017

Hosomi, K., Shimokawa, T., Ikoma, K., Nakamura, Y., Sugiyama, K., Ugawa, Y., et al. (2013). Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. *Pain* 154, 1065–1072. doi: 10.1016/j.pain.2013.03.016

IASP (2011). "Classification of chronic pain" in *Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2 (Revised) ed

Jang, S.-W., Liu, X., Chan, C.-B., Weinshenker, D., Hall, R. A., Xiao, G., et al. (2009). Amitriptyline is a TrkA and TrkB receptor agonist that promotes TrkA/TrkB Heterodimerization and has potent neurotrophic activity. *Chem. Biol.* 16, 644–656. doi: 10.1016/j.chembiol.2009.05.010

Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S. C., et al. (2011). A new definition of neuropathic pain. *Pain* 152, 2204–2205. doi: 10.1016/j.pain.2011.06.017

Juan, D., Yao, W., Li, J., Yang, F., Hu, J., Xu, Q., et al. (2022). Motor network reorganization after repetitive transcranial magnetic stimulation in early stroke patients: a resting state fMRI study. *Neurorehabil. Neural Repair* 36, 61–68. doi: 10.1177/15459683211054184

Kadono, Y., Koguchi, K., Okada, K., Hosomi, K., Hiraishi, M., Ueguchi, T., et al. (2021). Repetitive transcranial magnetic stimulation restores altered functional connectivity of central poststroke pain model monkeys. *Sci. Rep.* 11:6126. doi: 10.1038/s41598-021-85409-w

Khedr, E. M., Kotb, H., Kamel, N. F., Ahmed, M. A., Sadek, R., and Rothwell, J. C. (2005). Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J. Neurol. Neurosurg. Psychiatry* 76, 833–838. doi: 10.1136/jnnp.2004.055806

Kobayashi, M., Fujimaki, T., Mihara, B., and Ohira, T. (2015). Repetitive transcranial magnetic stimulation once a week induces sustainable long-term relief of central Poststroke pain. *Neuromodulation* 18, 249–254. doi: 10.1111/ner.12301

Kumar, B., Kalita, J., Kumar, G., and Misra, U. K. (2009). Central Poststroke pain: a review of pathophysiology and treatment. *Anesth. Analg.* 108, 1645–1657. doi: 10.1213/ane.0b013e31819d644c

Lefaucheur, J. P., Drouot, X., Keravel, Y., and Nguyen, J.-P. (2001a). Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *Neuroreport* 12, 2963–2965. doi: 10.1097/00001756-200109170-00041

Lefaucheur, J.-P., Drouot, X., Ménard-Lefaucheur, I., and Nguyen, J. P. (2004). Neuropathic pain controlled for more than a year by monthly sessions of repetitive

transcranial magnetic stimulation of the motor cortex. *Clin. Neurophysiol.* 34, 91–95. doi: 10.1016/j.neucli.2004.02.001

Lefaucheur, J. P., Drouot, X., and Nguyen, J. P. (2001b). Interventional neurophysiology for pain control: Duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol. Clin.* 31, 247–252. doi: 10.1016/S0987-7053(01)00260-X

Li, Y., Wang, Y., Liao, C., Huang, W., and Wu, P. (2017). Longitudinal brain functional connectivity changes of the cortical motor-related network in subcortical stroke patients with acupuncture treatment. *Neural Plast.* 2017, 1–9. doi: 10.1155/2017/5816263

Liampas, A., Velidakis, N., Georgiou, T., Vadalouca, A., Varrassi, G., Hadjigeorgiou, G. M., et al. (2020). Prevalence and management challenges in central Post-stroke neuropathic pain: a systematic review and Meta-analysis. *Adv. Ther.* 37, 3278–3291. doi: 10.1007/s12325-020-01388-w

Liepert, J., Hamzei, F., and Weiller, C. (2000). Motor cortex disinhibition of the unaffected hemisphere after acute stroke. *Muscle Nerve* 23, 1761–1763. doi: 10.1002/1097-4598(200011)23:11<1761::AID-MUS14>3.0.CO;2-M

Lira, R. P. C., and Rocha, E. M. (2019). PICOT: imprescriptible items in a clinical research question. *Arq. Bras. Oftalmol.* 82:1. doi: 10.5935/0004-2749.20190028

Löscher, W., Hönack, D., and Taylor, C. P. (1991). Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. *Neurosci. Lett.* 128, 150–154. doi: 10.1016/0304-3940(91)90249-S

Luo, D., Wan, X., Liu, J., and Tong, T. (2018). Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat. Methods Med. Res.* 27, 1785–1805. doi: 10.1177/0962280216669183

Maarrawi, J., Peyron, R., Mertens, P., Costes, N., Magnin, M., Sindou, M., et al. (2013). Brain opioid receptor density predicts motor cortex stimulation efficacy for chronic pain. *Pain* 154, 2563–2568. doi: 10.1016/j.pain.2013.07.042

Matsumura, Y., Hirayama, T., and Yamamoto, T. (2013). Comparison between pharmacologic evaluation and repetitive transcranial magnetic stimulation-induced analgesia in poststroke pain patients. *Neuromodulation* 16, 349–354. doi: 10.1111/ner.12019

McHugh, M. L. (2012). Interrater reliability: the kappa statistic. *Biochem. Med. (Zagreb)* 22, 276–282. doi: 10.11613/BM.2012.031

Menzler, K., Hermsen, A., Balkenhol, K., Duddek, C., Bugiel, H., Bauer, S., et al. (2014). A common splice-site polymorphism modifies the effect of carbamazepine on cortical excitability—a pharmacogenetic transcranial magnetic stimulation study. *Epilepsia* 55, 362–369. doi: 10.1111/epi.12515

Mitchell, A. S., and Chakraborty, S. (2013). What does the mediodorsal thalamus do? *Front. Syst. Neurosci.* 7:37. doi: 10.3389/fnsys.2013.00037

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., et al. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 340:c869. doi: 10.1136/bmj.c869

Nudo, R. J. (2007). Postinfarct cortical plasticity and behavioral recovery. *Stroke* 38, 840–845. doi: 10.1161/01.STR.0000247943.12887.d2

Oh, H., and Seo, W. (2015). A comprehensive review of central Post-stroke pain. *Pain Manag. Nurs.* 16, 804–818. doi: 10.1016/j.pmn.2015.03.002

Ohn, S. H., Chang, W. H., Park, C., Kim, S. T., Il, L. J., Pascual-Leone, A., et al. (2012). Neural correlates of the Antinociceptive effects of repetitive transcranial magnetic stimulation on central pain after stroke. *Neurorehabil. Neural Repair* 26, 344–352. doi: 10.1177/1545968311423110

Ojala, J., Vanhanen, J., Harno, H., Lioumis, P., Vaalto, S., Kaunisto, M. A., et al. (2022). A randomized, sham-controlled trial of repetitive transcranial magnetic stimulation targeting M1 and S2 in central Poststroke pain: a pilot trial. *Neuromodulation* 25, 538–548. doi: 10.1111/ner.13496

Pan, L.-J., Zhu, H.-Q., Zhang, X.-A., and Wang, X.-Q. (2023). The mechanism and effect of repetitive transcranial magnetic stimulation for post-stroke pain. *Front. Mol. Neurosci.* 15:15. doi: 10.3389/fnmol.2022.1091402

Radiansyah, R. S., and Hadi, D. W. (2023). Repetitive transcranial magnetic stimulation in central post-stroke pain: current status and future perspective. *Korean J. Pain* 36, 408–424. doi: 10.3344/kjp.23220

Ramger, B. C., Bader, K. A., Davies, S. P., Stewart, D. A., Ledbetter, L. S., Simon, C. B., et al. (2019). Effects of non-invasive brain stimulation on clinical pain intensity and experimental pain sensitivity among individuals with central Post-stroke pain: a systematic review. *J. Pain Res.* 12, 3319–3329. doi: 10.2147/JPR.S216081

Rizzo, V., Quartarone, A., Bagnato, S., Battaglia, F., Majorana, G., and Girlanda, P. (2001). Modification of cortical excitability induced by gabapentin: a study by transcranial magnetic stimulation. *Neurol. Sci.* 22, 229–232. doi: 10.1007/s100720100002

Şahin-Onat, Ş., Ünsal-Delialioğlu, S., Kulaklı, F., and Özel, S. (2016). The effects of central post-stroke pain on quality of life and depression in patients with stroke. *J. Phys. Ther. Sci.* 28, 96–101. doi: 10.1589/jpts.28.96

Sommer, M., Gileles, E., Knappmeyer, K., Rothkegel, H., Polania, R., and Paulus, W. (2012). Carbamazepine reduces short-interval interhemispheric inhibition in healthy humans. *Clin. Neurophysiol.* 123, 351–357. doi: 10.1016/j.clinph.2011.07.027

Spampinato, D. A., Ibanez, J., Rocchi, L., and Rothwell, J. (2023). Motor potentials evoked by transcranial magnetic stimulation: interpreting a simple measure of a complex system. *J. Physiol.* 601, 2827–2851. doi: 10.1113/JP281885

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., et al. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355:i4919. doi: 10.1136/bmj.i4919

Stitik, T., Klecz, R., and Grenwald, B. Pharmacotherapy of disability. In: LisaJ. De, editor. *Physical medicine and rehabilitation*. *4*, Philadelphia: Lippincott Williams Wilkins; (2005), p. 1207–1247.

Swayne, O. B. C., Rothwell, J. C., Ward, N. S., and Greenwood, R. J. (2008). Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cereb. Cortex* 18, 1909–1922. doi: 10.1093/cercor/bhm218

Taylor, C. P., Angelotti, T., and Fauman, E. (2007). Pharmacology and mechanism of action of pregabalin: the calcium channel α2–δ (alpha2–delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res.* 73, 137–150. doi: 10.1016/j.eplepsyres.2006.09.008

Tosun, A., Türe, S., Askin, A., Yardimci, E. U., Demirdal, S. U., Kurt Incesu, T., et al. (2017). Effects of low-frequency repetitive transcranial magnetic stimulation and neuromuscular electrical stimulation on upper extremity motor recovery in the early period after stroke: a preliminary study. *Top. Stroke Rehabil.* 24, 361–367. doi: 10.1080/10749357.2017.1305644

Traversa, R., Cicinelli, P., Bassi, A., Rossini, P. M., and Bernardi, G. (1997). Mapping of motor cortical reorganization after stroke. *Stroke* 28, 110–117. doi: 10.1161/01.STR.28.1.110

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., et al. (2015). A classification of chronic pain for ICD-11. *Pain* 156, 1003–1007. doi: 10.1097/j.pain.0000000000000160

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., and Koyama, S. (1991). Chronic motor cortex stimulation for the treatment of central. *Pain* 52, 137–139. doi: 10.1007/978-3-7091-9160-6_37

Tuveson, B., Leffler, A.-S., and Hansson, P. (2009). Influence of heterotopic noxious conditioning stimulation on spontaneous pain and dynamic mechanical allodynia in central post-stroke pain patients. *Pain* 143, 84–91. doi: 10.1016/j.pain.2009.02.002

Vallone, F., Lai, S., Spalletti, C., Panarese, A., Alia, C., Micera, S., et al. (2016). Post-stroke longitudinal alterations of inter-hemispheric correlation and hemispheric dominance in mouse pre-motor cortex. *PLoS One* 11:e0146858. doi: 10.1371/journal.pone.0146858

Vecchio, F., Tomino, C., Miraglia, F., Iodice, F., Erra, C., Di Iorio, R., et al. (2019). Cortical connectivity from EEG data in acute stroke: a study via graph theory as a potential biomarker for functional recovery. *Int. J. Psychophysiol.* 146, 133–138. doi: 10.1016/j.ijpsycho.2019.09.012

Vogt, B. A., and Sikes, R. W. (2000). The medial pain system, cingulate cortex, and parallel processing of nociceptive information. *Prog. Brain Res.* 122, 223–235. doi: 10.1016/S0079-6123(08)62141-X

Wagle-Shukla, A., Ni, Z., Gunraj, C. A., Bahl, N., and Chen, R. (2009). Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. *J. Physiol.* 587, 5665–5678. doi: 10.1113/jphysiol.2009.181446

Wanni Arachchige, P. R., Ryo, U., Karunarathna, S., and Senoo, A. (2023). Evaluation of fMRI activation in hemiparetic stroke patients after rehabilitation with low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy. *Int. J. Neurosci.* 133, 705–713. doi: 10.1080/00207454.2021.1968858

Wu, W., Ye, Q., Wang, W., Yan, L., Wang, Q., Xiao, H., et al. (2012). Amitriptyline modulates calcium currents and intracellular calcium concentration in mouse trigeminal ganglion neurons. *Neurosci. Lett.* 506, 307–311. doi: 10.1016/j.neulet.2011.11.031

Xie, Y., Huo, F., and Tang, J. (2009). Cerebral cortex modulation of pain. *Acta Pharmacol. Sin.* 30, 31–41. doi: 10.1038/aps.2008.14

Yan, L., Wang, Q., Fu, Q., Ye, Q., Xiao, H., and Wan, Q. (2010). Amitriptyline inhibits currents and decreases the mRNA expression of voltage-gated sodium channels in cultured rat cortical neurons. *Brain Res.* 1336, 1–9. doi: 10.1016/j.brainres.2010.04.016

Young, N. A., Sharma, M., and Deogaonkar, M. (2014). Transcranial magnetic stimulation for chronic pain. *Neurosurg. Clin. N. Am.* 25, 819–832. doi: 10.1016/j.nec.2014.07.007

Zhao, C. G., Sun, W., Ju, F., Jiang, S., Wang, H., Sun, X. L., et al. (2021). Analgesic effects of navigated repetitive transcranial magnetic stimulation in patients with acute central Poststroke pain. *Pain Ther.* 10, 1085–1100. doi: 10.1007/s40122-021-00261-0

Ziemann, U., Reis, J., Schwenkreis, P., Rosanova, M., Strafella, A., Badawy, R., et al. (2015). TMS and drugs revisited 2014. *Clin. Neurophysiol.* 126, 1847–1868. doi: 10.1016/j.clinph.2014.08.028

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Comparative efficacy of different repetitive transcranial magnetic stimulation protocols for lower extremity motor function in stroke patients: a network meta-analysis

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Background: Lower extremity motor dysfunction is one of the most severe consequences after stroke, restricting functional mobility and impairing daily activities. Growing evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can improve stroke patients' lower extremity motor function. However, there is still controversy about the optimal rTMS protocol. Therefore, we compared and analyzed the effects of different rTMS protocols on lower extremity motor function in stroke patients using network meta-analysis (NMA).

Methods: We systematically searched CNKI, WanFang, VIP, CBM, PubMed, Embase, Web of Science, and Cochrane Library databases (from origin to 31 December 2023). Randomized controlled trials (RCTs) or crossover RCTs on rTMS improving lower extremity motor function in stroke patients were included. Two authors independently completed article screening, data extraction, and quality assessment. RevMan (version 5.4) and Stata (version 17.0) were used to analyze the data.

Results: A total of 38 studies with 2,022 patients were eligible for the NMA. The interventions included HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, dTMS-M1, and Placebo. The results of NMA showed that LFrTMS-M1 ranked first in FMA-LE and speed, and HFrTMS-M1 ranked first in BBS, TUGT, and MEP amplitude. The subgroup analysis of FMA-LE showed that HFrTMS-M1 was the best stimulation protocol for post-stroke time > 1 month, and LFrTMS-M1 was the best stimulation protocol for post-stroke time ≤ 1 month.

Conclusion: Considering the impact of the stroke phase on the lower extremity motor function, the current research evidence shows that HFrTMS-M1 may be the preferred stimulation protocol to improve the lower extremity motor function of patients for post-stroke time > 1 month, and LFrTMS-M1 for post-stroke time ≤ 1 month. However, the above conclusion needs further analysis and validation by more high-quality RCTs.

Systematic Review Registration: www.crd.york.ac.uk/prospero/, identifier (CRD42023474215).

KEYWORDS

stroke, lower extremity, motor function, repetitive transcranial magnetic stimulation, network meta-analysis

1 Introduction

Stroke is a local brain dysfunction caused by acute cerebrovascular disease (Park et al., 2011). By 2019, the proportion of stroke patients had increased to 2.58% among residents aged ≥40 years in China (Wang et al., 2022). Stroke is the leading cause of adult death and disability in China, with the five characteristics of high incidence, high disability rate, high mortality rate, high recurrence rate, and high economic burden, which has seriously endangered the health of Chinese people. With the development of medical technology, the mortality rate of stroke has decreased year by year, but 72% of the survivors still have lower extremity dysfunction (Ng and Hui-Chan, 2010), which affects the walking function of patients. Walking dysfunction is one of the most severe consequences of stroke. Nearly 30% of stroke patients are unable to walk even in the chronic recovery stage (Park et al., 2011), which significantly affects the patients' social interactions and can lead to lifelong disability in severe cases (Park and An, 2016). Therefore, improving the motor function of the lower extremity, restoring independent walking as soon as possible, and improving activities of daily living (ADL) are the problems that many stroke patients are eager to solve urgently. However, pharmacological therapy (Mead et al., 2013) and traditional rehabilitation therapies [e.g., neurodevelopmental therapy (Langhammer and Stanghelle, 2011), proprioceptive neuromuscular facilitation (Eng and Tang, 2007), and electromyography biofeedback (Woodford and Price, 2007)] seem to have limited effects on improving motor function of the lower extremity after stroke. Therefore, a more effective treatment is needed.

Repetitive transcranial magnetic stimulation (rTMS), one of the brain stimulation techniques without any trauma, can induce neuroplastic changes and promote brain function restoration (Nathou et al., 2018). At present, the interhemispheric competition (IHC) model is the primary theoretical basis for applying rTMS in stroke rehabilitation. This model suggests that stroke destroys the balance of mutual inhibition of the bilateral cerebral hemispheres through the corpus callosum, resulting in the decreased inhibition of the ipsilateral hemisphere to the contralateral hemisphere and the increased inhibition of the contralateral hemisphere to the ipsilateral hemisphere (Di Pino et al., 2014). Therefore, in clinical practice, there are two main ways to use rTMS to promote functional recovery after stroke. One is to reduce the excitability of the contralateral hemisphere through low-frequency (≤1 Hz) rTMS to reduce the inhibitory effect of the contralateral hemisphere on the ipsilateral hemisphere. The other is to restore the balance of competitive inhibition between the bilateral cerebral hemispheres by stimulating the ipsilateral hemisphere with high-frequency (≥5 Hz) rTMS to increase its excitability (George and Aston-Jones, 2010). Both stimulation modes have been used to treat motor/non-motor dysfunction after stroke.

Theta burst stimulation (TBS), a novel mode of rTMS, saves time in the rehabilitation of motor function after stroke (Huang et al., 2005). There are two types of TBS: intermittent TBS (iTBS) and continuous TBS (cTBS), which generate excitatory and inhibitory effects, respectively (Larson et al., 1986; Huang et al., 2011). Compared with conventional rTMS protocols, TBS provides significant advantages due to its reduced stimulation time (Chung et al., 2015) and long-lasting effects with lower-intensity stimulation (Cárdenas-Morales et al., 2010). Deep transcranial magnetic stimulation (dTMS) is a new non-invasive neuromodulation technique based on rTMS technology, which uses a different coil type (Hesed coil). dTMS has the advantages of deeper and wider stimulation, more precise localization, and less damage to the superficial cortex than conventional TMS (Roth et al., 2014). The primary motor cortex (M1) is typically the target of rTMS. However, some studies have shown that the cerebellum is one of the alternative targets of M1, and rTMS targeting the cerebellum can also improve motor function in stroke patients (Wessel and Hummel, 2018). In conclusion, rTMS can regulate the asymmetry of excitability between the bilateral cerebral hemispheres by changing the stimulation mode, stimulation target, stimulation frequency, and coil type to promote the recovery of lower extremity motor dysfunction after stroke (Kesikburun, 2022).

The effect of rTMS on lower extremity motor function in stroke patients has been demonstrated in previous meta-analysis (Li et al., 2018; Tung et al., 2019). However, an important drawback is that conventional meta-analysis can only compare two interventions simultaneously. At the same time, in these studies, the intervention protocols of the experimental group were roughly classified, and the effects of different stimulation frequencies, stimulation targets, stimulation modes, and post-stroke times on treatment effects were not comprehensively considered. Although Fan et al. (2021) conducted a detailed systematic review of rTMS to improve lower extremity motor function in stroke patients, this study did not consider the new stimulation mode-iTBS, the new stimulation target-cerebellum, and the effect of stroke phase on the efficacy of rTMS.

Network meta-analysis (NMA) is developed from conventional meta-analysis, and its primary function is to comprehensively evaluate and rank multiple interventions simultaneously (Rouse et al., 2017). Therefore, we took the stimulation mode, stimulation frequency, and stimulation target of rTMS into account and summarized the following five different rTMS protocols: high-frequency rTMS-M1 (HFrTMS-M1), low-frequency rTMS-M1 (LFrTMS-M1), iTBS-Cerebellum, iTBS-M1, and dTMS-M1. Then, we compared and analyzed the effects of different protocols on lower extremity motor dysfunction in stroke patients by NMA. In addition, considering the effects of the stroke phase on the efficacy of rTMS at different protocols, we also carried out a subgroup analysis for FMA-LE according to the phase of the stroke to provide sufficient evidence for future clinical practice.

2 Materials and methods

2.1 Study enrollment and reporting

Our NMA was conducted using the Cochrane Handbook for Systematic Reviews of Interventions, and the findings were reported according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyzes (PRISMA) statement (Page et al., 2021). This NMA was prospectively registered in PROSPERO (registration ID: CRD42023474215).

2.2 Search strategy

Two authors separately searched for randomized controlled trials (RCTs) and crossover RCTs about rTMS improving lower extremity motor function in stroke patients from China National Knowledge Infrastructure (CNKI), Wanfang database, VIP database, China Biomedical Literature Database (CBM), PubMed, Embase, Web of Science, and Cochrane Library. The search time limit was from the establishment of the database to 31 December 2023. By combining medical subject headings (MeSH) with free words using Boolean logic operators, we integrated the following terms for a comprehensive search: "Stroke," "cerebrovascular accident," "CVA," "Brain Vascular Accident," "hemiplegia," "apoplexy," "hemiparesis," "repetitive transcranial magnetic stimulation," "Transcranial Magnetic Stimulation," "TMS," "rTMS," "Theta burst stimulation," "θ-brust stimulation," "random," "randomized controlled trial," "RCT." In addition, we also reviewed meta-analysis, reviews, and references of the included studies to supplement the search. PubMed was used as an example, and the specific search strategy was provided in Supplementary Table 1.

2.3 Eligibility criteria

Eligibility criteria were defined in accordance with the PICOS framework (Hutton et al., 2015).

2.3.1 Inclusion criteria

1. Populations: Stroke patients with lower extremity dysfunction who were diagnosed according to the stroke diagnostic criteria formulated by The Fourth National Cerebrovascular Disease Conference in 1995.
2. Interventions: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and dTMS-M1.
3. Comparators: The placebo included conventional rehabilitation and sham rTMS (or conventional rehabilitation alone). Sham rTMS refers to the analog sound without any effective magnetic stimulation. Conventional rehabilitation, such as physiotherapy, occupational therapy, physical therapy, treadmill training, motor imagery practice, task-oriented training, and mirror therapy, was acceptable as cointervention.
4. Outcomes: The primary outcome indicator was the Fugl-Meyer Assessment of Lower Extremity (FMA-LE). The secondary outcome indicators included the Berg Balance Scale (BBS), Timed Up and Go Test (TUGT), Motor Evoked Potential amplitude (MEP amplitude), and speed.
5. Study designs: RCTs or crossover RCTs.

2.3.2 Exclusion criteria

1. Patients with lower extremity motor dysfunction were not caused by stroke but by traumatic brain injury, cerebral palsy, Parkinson's disease, and other diseases.
2. Conference abstracts, researcher protocols, reviews, meta-analysis, dissertations, and non-RCTs (e.g., case reports, observational studies, cross-sectional studies, and studies without a control group).
3. Lack of outcome indicators related to the lower extremity motor function.
4. Studies with more patients withdrawing midway.
5. Studies that could not be downloaded.
6. Studies with incomplete outcome data and contacting the authors three times without response.
7. Repeatedly published studies.

2.4 Study selection

First, two authors (CSW and QZ) used EndnoteX9 software to eliminate duplicate articles. Then, they screened out articles that did not meet the criteria by reading their titles and abstracts. Finally, they browsed the full text to select articles that met the criteria. In case of any disagreement during the review process, the decision was made by consultation between the two authors or by joint decision with the third author (LLZ).

2.5 Data extraction

Two authors (DYZ and YNX) independently reviewed all articles and extracted data. The extracted data included basic published information: first author's name, year of publication, country of origin, participant characteristics (age and sample size), intervention characteristics (intervention protocol, coil type, rTMS target, rTMS frequency, rTMS intensity, No. of pulses, and duration of intervention), and outcome indicators (FMA-LE, BBS, TUGT, MEP amplitude, and speed) at baseline and at last observation to obtain their change scores. The collected data were put into an Excel spreadsheet and cross-checked by two authors (DYZ and YNX). In case of disagreement during data extraction, the third author (ZJL) participated in discussion and decision-making.

2.6 Quality assessment

Two authors (CLW and SZW) independently assessed the risk of bias for the included articles through the Cochrane Risk of Bias Tool (Savović et al., 2014), which mainly included seven indicators: (I) Random sequence generation; (II) Allocation concealment; (III) Blinding of participants and personnel; (IV) Blinding of outcome assessment; (V) Incomplete outcome data; (VI) Selective reporting; (VII) Other bias. Assessment indicators were rated "low risk," "unclear," or "high risk" based on the available information. If there was any dispute during the evaluation, the third author (ZJL) would participate in the discussion and make decisions together.

2.7 Statistical analysis

Odds ratio (OR) for binary variables and mean difference (MD) for continuous variables were used as the effect indicators, and the

95% confidence interval (CI) was provided for each effect size. If a particular study used different methods or scales to measure the same outcome, standardized MD (SMD) was calculated instead of MD. We calculated the difference before and after treatment for continuous variable indicators and the standard deviation (SD) according to the method provided in 16.1.3.2 of Cochrane Handbook 5.0.2 and then performed the statistical analysis. We used RevMan (version 5.4) for pairwise meta-analysis. The *p*-value of the chi-square test and the I^2 index from the heterogeneity test were used to express the level of statistical heterogeneity. Different effect models were selected according to the test data's heterogeneity level. When the level of heterogeneity was low ($p \geq 0.1$, $I^2 \leq 50\%$), we selected the fixed effect model for analysis. Otherwise, a random effect model ($p < 0.1$, $I^2 > 50\%$) was used (Higgins et al., 2003; Tufanaru et al., 2015).

We used Stata (version 17.0) to perform the NMA and produce various charts, such as network meta-analysis diagrams of eligible comparisons, surface under the cumulative ranking area (SUCRA), funnel plot of publication bias, etc (Shim et al., 2017). When there were closed loops between interventions, we first needed to assess global inconsistency. If $p > 0.05$, the inconsistent model was not significant, and the consistent model was selected (White et al., 2012). We used a node-splitting approach to assess local inconsistency (Dias et al., 2010). At the same time, it was also necessary to evaluate the loop inconsistency and calculate the inconsistency factors (IF) and 95% CI for each closed loop. If the lower limit of 95% CI included or was close to 0, the consistency between the direct and indirect comparison results was good; otherwise, the closed loop was considered to have apparent inconsistency. If no closed loops existed between interventions, the consistency model was used directly for analysis. We used the SUCRA to rank interventions. The closer SUCRA was to 100%, the better the effect of the intervention. Finally, the publication bias of the included articles was evaluated using the funnel plot of publication bias and Egger's test. Asymmetry in the funnel plot of publication bias and $p < 0.05$ in Egger's test indicated publication bias in the included articles (Fleiss, 1993).

3 Results

3.1 Search results

We strictly searched the above 8 databases according to the inclusion and exclusion criteria and preliminarily obtained 12,814 articles. After the duplicate articles were removed, 10,166 articles remained in the database. By reading the titles and abstracts of the articles, we excluded articles that did not meet the inclusion criteria, leaving 176 remaining in the database. By reading the full text, we again excluded 138 articles. Ultimately, 38 articles met our study requirements. Figure 1 shows the article search process and results.

3.2 Characteristics of the included studies

Characteristics of studies adopted are shown in Table 1, published between 2012 and 2023. We finally included 38 studies with a total of 2,022 patients. 4 studies were crossover RCTs, and 34 studies were RCTs. Among the included studies, most of them were carried out in China (28/38), and the others were conducted in Korea (5/38), Italy (2/38), Egypt (1/38), India (1/38), and Japan (1/38). Outcome indicators included FMA-LE (29 studies), BBS (11 studies), TUGT (8 studies), MEP amplitude (8 studies), and speed (13 studies). Interventions included HFrTMS-M1 (16 studies), LFrTMS-M1 (18 studies), iTBS-Cerebellum (5 studies), iTBS-M1 (1 study), and dTMS-M1 (2 studies).

3.3 Quality evaluation

25 studies (65.8%) had a low risk of bias concerning random sequence generation. 9 studies (23.7%) had a low risk of bias concerning allocation concealment. 24 studies (63.2%) had a low risk of bias concerning blinding of participants and personnel. 27 studies (71.1%) had a low risk of bias concerning blinding of outcome assessment. 37 studies (97.4%) had a low risk of bias concerning incomplete outcome data. 38 studies (100.0%) had a low risk of bias concerning selective reporting. Other biases were not known. Details of the evaluation of bias results for the included articles are shown in Figure 2.

3.4 Pairwise meta-analysis

A pairwise meta-analysis was used to compare the two interventions comprehensively. We carried out 6 pairwise meta-analysis to compare FMA-LE, 6 to compare FMA-LE (post-stroke time > 1 month), 3 to compare FMA-LE (post-stroke time ≤ 1 month), 5 to compare BBS, 4 to compare TUGT, 4 to compare MEP amplitude, and 2 to compare speed, respectively, which can be summarily seen in Table 2. The detailed results of pairwise meta-analysis are shown in Supplementary Figures 1–7.

3.5 Network of evidence

Figure 3 shows the network meta-analysis diagrams of eligible comparisons, where the blue circles represent the different interventions. The circle size represents the sample size. The straight line between the two circles represents a direct comparison between the two different interventions. The thicker the solid line, the greater the number of studies in that pairwise comparison.

3.5.1 FMA-LE

A total of 29 included studies evaluated FMA-LE, involving 6 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, dTMS-M1, and Placebo. A total of 1,685 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.0772$ (>0.05; Supplementary Figure 8A). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The test of local inconsistency from the node-splitting model showed a small percentage of inconsistency (1 of 6 comparisons), as detailed in Supplementary Table 2. 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the

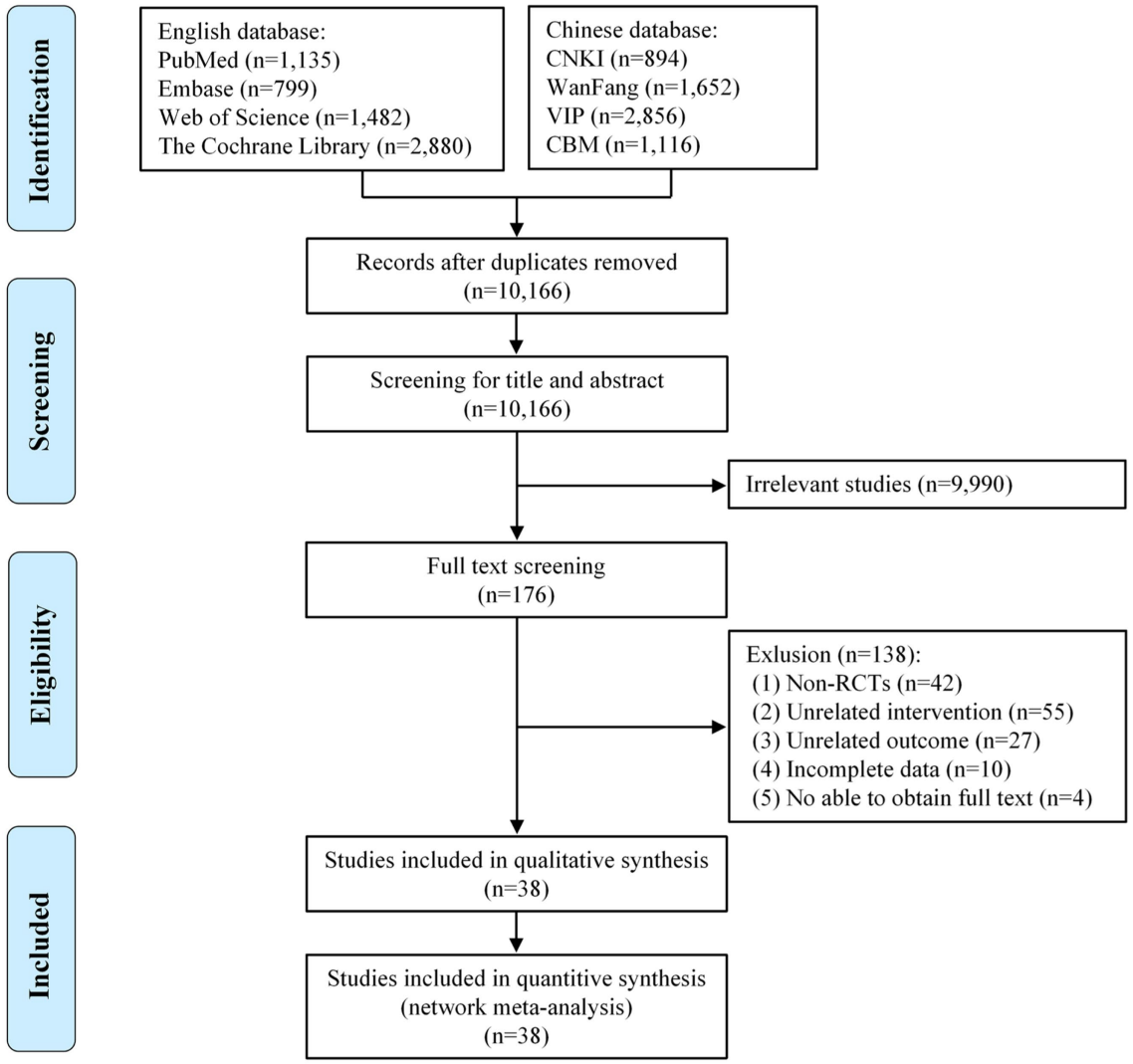

FIGURE 1
Flow diagram of the eligible studies selection process. CNKI, China National Knowledge Infrastructure; WanFang, WanFang Knowledge Service Platform; VIP, Chinese Scientific Journals Database; CBM, Chinese Biomedical Literature Service System; n, number of publications.

closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9A).

The NMA results showed that FMA-LE generated a total of 15 pairwise comparisons. Compared with Placebo, LFrTMS-M1 (MD = 2.83, 95% CI: 1.96 to 3.70) and HFrTMS-M1 (MD = 2.74, 95% CI: 1.60 to 3.87) significantly improved FMA-LE in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5A and Table 3 show the SUCRA rankings for all interventions. According to the analysis, LFrTMS-M1 (SUCRA, 84.6%) may be the most effective intervention to improve FMA-LE in stroke patients.

Different phases of stroke may lead to different therapeutic effects of rTMS. Therefore, we performed a subgroup analysis for FMA-LE according to the phase of stroke, including post-stroke time > 1 month and post-stroke time ≤ 1 month (Brunelli et al., 2019). The global consistency model of FMA-LE (post-stroke time > 1 month) and FMA-LE (post-stroke time ≤ 1 month) showed that the inconsistency test was not significant (Supplementary Figures 8B,C). There was a small percentage of inconsistency (1 of 3 comparisons) only for the local inconsistency test of FMA-LE (post-stroke time ≤ 1 month), details of which are provided in Supplementary Tables 3, 4.

For post-stroke time > 1 month, Figure 4 demonstrated that HFrTMS-M1 significantly improved FMA-LE (post-stroke time > 1 month) compared to iTBS-M1 (MD = 3.84, 95% CI: 0.52 to 7.16) and Placebo (MD = 3.94, 95% CI: 2.50 to 5.38). Figure 5B and Table 3 showed that the HFrTMS-M1 (SUCRA, 95.8%) was the best protocol. For post-stroke time ≤ 1 month, Figure 4 demonstrated that compared with the placebo, the LFrTMS-M1 (MD = 1.49, 95% CI: 0.05 to 2.93) and HFrTMS-M1 (MD = 2.47, 95% CI: 1.41 to 3.53) had better curative effects, with a statistically significant difference ($p < 0.05$). Figure 5C and Table 3 showed that the LFrTMS-M1 (SUCRA, 98.9%) was the best protocol. We found no publication bias by the funnel plot of publication bias and Egger's test (Supplementary Figures 10B,C).

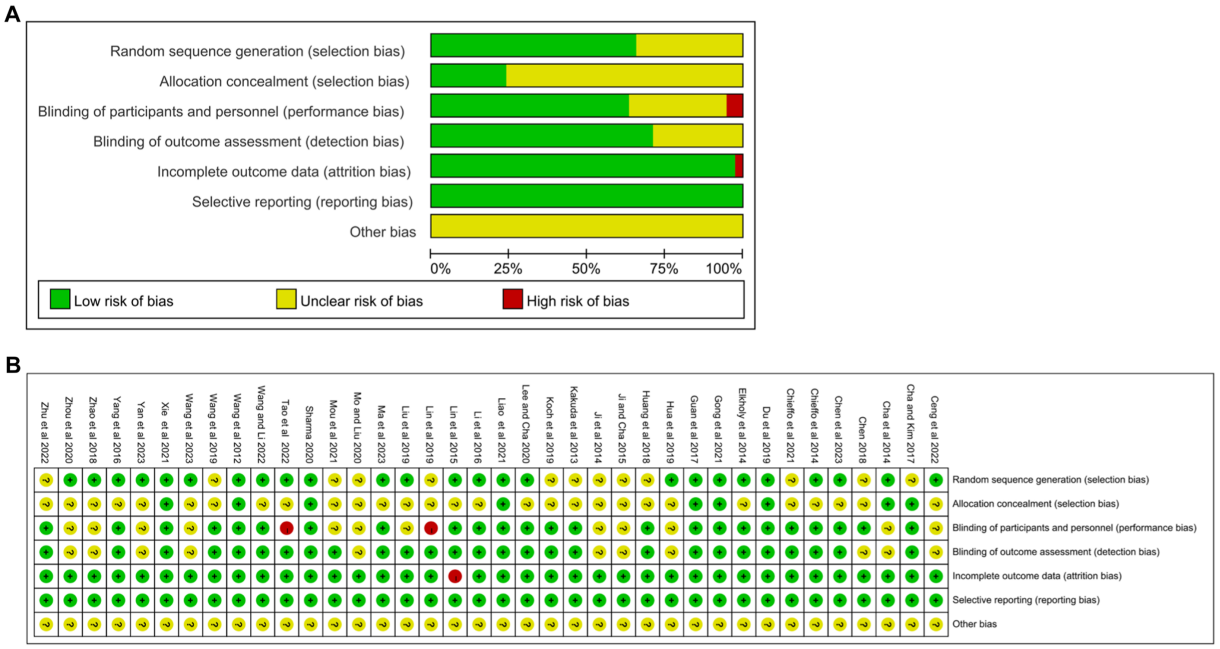

FIGURE 2
Quality assessment of selected studies by the Cochrane Risk Of Bias Tool. **(A)** Risk of bias graph: review authors' judgments about each risk of bias item presents as percentages across all included studies. **(B)** Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

3.5.2 BBS

A total of 11 included studies evaluated BBS, involving 5 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and Placebo. A total of 820 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.2800$ (>0.05; Supplementary Figure 8D). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The measured p-values were all greater than 0.05, indicating good local consistency (Supplementary Table 5). 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9D).

The NMA results showed that BBS generated a total of 10 pairwise comparisons. Compared with Placebo, HFrTMS-M1 (MD = 6.97, 95% CI: 3.95 to 9.98), LFrTMS-M1 (MD = 4.36, 95% CI: 2.00 to 6.72), and iTBS-Cerebellum (MD = 3.29, 95% CI: 0.63 to 5.95) significantly improved BBS in stroke patients. In addition, HFrTMS-M1 (MD = 6.36, 95% CI: 0.65 to 12.07) was significantly better than iTBS-M1 in improving BBS. Other pairwise comparisons showed no statistically significant differences ($p > 0.05$; Figure 4). Figure 5D and Table 3 show the SUCRA rankings for all interventions. According to the results of SUCRA analysis, HFrTMS-M1 (SUCRA, 96.8%) may be the most effective intervention to improve BBS in stroke patients.

3.5.3 TUGT

A total of 8 included studies evaluated TUGT, involving 5 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, iTBS-M1, and Placebo. A total of 382 patients were included. There was no closed loop, so we did not need to perform a consistency check. The NMA results showed that TUGT generated a total of 10 pairwise comparisons.

Compared with Placebo, HFrTMS-M1 (MD = −3.25, 95% CI: −5.19 to −1.30) and LFrTMS-M1 (MD = −2.72, 95% CI: −3.95 to −1.49) significantly improved TUGT in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5E and Table 3 show the SUCRA rankings for all interventions. According to the analysis, HFrTMS-M1 (SUCRA, 80.3%) may be the most effective intervention to improve TUGT in stroke patients.

3.5.4 MEP amplitude

A total of 8 included studies evaluated MEP amplitude, involving 4 intervention protocols: HFrTMS-M1, LFrTMS-M1, iTBS-Cerebellum, and Placebo. A total of 246 patients were included. The inconsistency model evaluated global inconsistency, which showed $p = 0.5656$ (>0.05; Supplementary Figure 8E). The inconsistency test was not significant, so we used the consistency model. The node-splitting approach was used to evaluate local inconsistency. The measured p-values were all greater than 0.05, indicating good local consistency (Supplementary Table 3). 1 closed loop was formed for the 3 interventions, so we assessed the inconsistency of the closed loop. The results showed that the 95% CI included 0, and IF was close to 0, indicating that our NMA was highly credible (Supplementary Figure 9E).

The NMA results showed that MEP amplitude generated a total of 6 pairwise comparisons. Compared with Placebo, HFrTMS-M1 (SMD = 0.99, 95% CI: 0.17 to 1.82) significantly improved MEP amplitude in stroke patients. There was no statistically significant

TABLE 1 Characteristics of included studies.

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Yang et al. (2016)	China	56.4 ± 7.8/57.5 ± 9.2	14/14	HFrTMS-M1/Placebo	75-mm figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	2,000	6 times per week for 4 weeks	①③
Ma et al. (2023)	China	56.75 ± 7.07/54.85 ± 5.65	20/20	HFrTMS-M1/Placebo	NR	Ipsi-M1	10 Hz	80% RMT	1,200	5 times per week for 4 weeks	①③⑤
Mo and Liu (2020)	China	56.68 ± 3.12/57.75 ± 2.86	53/52	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	2,000	7 times per week for 4 weeks	①②⑤
Cha et al. (2014)	Korea	54.83 ± 6.32/51.33 ± 8.71	12/12	HFrTMS-M1/LF-ZrTMS	70-mm figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/1 Hz	90% RMT	2,000/1,200	5 times per week for 4 weeks	②④
Cha and Kim (2017)	Korea	53.80 ± 13.28/55.80 ± 16.40	10/10	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	90% RMT	1,000	5 times per week for 8 weeks	④⑤
Wang et al. (2019)	China	53.5 ± 13.7/54.7 ± 12.2	8/6	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	5 Hz	90% RMT	900	3 times per week for 3 weeks	①④⑤
Lee and Cha (2020)	Korea	66.85 ± 4.05/64.00 ± 3.57	7/6	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	5 Hz	90% RMT	900	5 times per week for 3 weeks	③
Ji et al. (2014)	Korea	49.00 ± 11.01/44.28 ± 8.52	15/15	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	NR	NR	3 times per week for 6 weeks	⑤
Ji and Kim (2015)	Korea	55.65 ± 8.95/56.36 ± 10.44	20/19	HFrTMS-M1/Placebo	70-mm figure-of-8 coil	Ipsi-M1	10 Hz	NR	2,000	5 times per week for 4 weeks	⑤
Ceng et al. (2022)	China	60.22 ± 2.73/61.41 ± 2.24	40/40	HFrTMS-M1/Placebo	NR	Ipsi-M1	10 Hz	80% RMT	NR	5 times per week for 8 weeks	①
Kakuda et al. (2013)	Japan	52.1 ± 11.9	9/9	HFrTMS-M1/Placebo	80-mm double-cone coil	Bi-M1	10 Hz	90% RMT	2,000	1 time	⑤
Guan et al. (2017)	China	59.7 ± 6.8/57.4 ± 14.0	21/21	HFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1	5 Hz	120% RMT	1,000	10 consecutive weekdays	①
Wang et al. (2023)	China	63.85 ± 9.54/63.92 ± 10.28/ 64.10 ± 9.96	80/80/80	HFrTMS-M1/ LFrTMS-M1/Placebo	NR	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	NR	NR	6 times per week for 3 weeks	①
Hua et al. (2019)	China	63.2 + 9.5/63.4 + 10.7/65.4 + 10.8	15/15/15	HFrTMS-M1/ LFrTMS-M1/Placebo	Figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	80% RMT	1,290/1,090	6 times per week for 3 weeks	①②
Liu et al. (2019)	China	58.78 ± 6.97/60.78 ± 6.73/58.44 ± 5.94	18/18/18	HFrTMS-M1/ LFrTMS-M1/Placebo	NR	Ipsi-M1/ Contra-M1	10 Hz/0.5 Hz	90% MT	NR	5 times per week for 3 weeks	①

(Continued)

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TABLE 1 (Continued)

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Du et al. (2019)	China	54 ± 12/56 ± 9/56 ± 11	20/20/20	HFrTMS-M1/ LFrTMS-M1/Placebo	90-mm figure-of-8 coil	Ipsi-M1/ Contra-M1	10 Hz/1 Hz	100% RMT	1,200/1,200	5 consecutive weekdays	④
Sharma et al. (2020)	India	54.85 ± 13.39/ 52.89 ± 14.95	47/49	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	110% RMT	750	5 times per week for 2 weeks	①
Zhao et al. (2018)	China	56.2 ± 12.7/54.0 ± 11.4	36/39	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	80–120% RMT	1,000	20 consecutive weekdays	①②
Zhou et al. (2020)	China	58.80 ± 7.58/58.32 ± 7.61	50/50	LFrTMS-M1/Placebo	70-mm double-cone coil	Contra-M1	1 Hz	70% RMT	1,200	5 times per week for 3 weeks	①
Li et al. (2016)	China	56.7 ± 6.0/58.0 ± 6.5	30/30	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	90% RMT	NR	5 times per week for 4 weeks	①⑤
Yan et al. (2023)	China	67.82 ± 9.97/69.11 ± 10.03	88/88	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	70% RMT	NR	5 times per week for 6 weeks	①②⑤
Mou et al. (2021)	China	52.10 ± 14.96/48.40 ± 15.58	20/20	LFrTMS-M1/Placebo	Circular coil	Contra-M1	1 Hz	90% RMT	1,000	6 times per week for 6 weeks	①
Huang et al. (2018)	China	62.2 ± 10.4/61.2 ± 9.4	18/20	LFrTMS-M1/Placebo	110-mm double-cone coil	Contra-M1	1 Hz	120% RMT	900	15 consecutive weekdays	①③④
Lin et al. (2015)	China	58.3 ± 10.8/62.3 ± 11.7	16/16	LFrTMS-M1/Placebo	70-mm figure-of-8 coil	Contra-M1	1 Hz	130% MT	900	15 consecutive weekdays	①
Chen (2018)	China	55.2 ± 11.5/51.3 ± 12.1	70/70	LFrTMS-M1/Placebo	90-mm figure-of-8 coil	Contra-M1	1 Hz	90% RMT	1,000	5 times per week for 1 week	①②③
Wang et al. (2012)	China	64.90 ± 12.37/62.98 ± 10.88	14/14	LFrTMS-M1/Placebo	Figure-of-8 coil	Contra-M1	1 Hz	90% RMT	600	5 times per week for 2 weeks	①④⑤
Elkholy et al. (2014)	Egypt	44.06 ± 3.71/45.66 ± 4.27	30/15	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	2 G	NR	3 times per week for 6 weeks	③⑤
Zhu et al. (2022)	China	59.48 ± 7.04/58.36 ± 5.38	25/25	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	90% RMT	NR	5 times per week for 4 weeks	①③⑤
Tao et al. (2022)	China	57.5 ± 6.4/58.2 ± 4.8	20/20	LFrTMS-M1/Placebo	Figure-of-8 coil	Contra-M1	1 Hz	80% RMT	600	5 times per week for 4 weeks	①②
Gong et al. (2021)	China	63.40 ± 10.37/59.66 ± 14.31	16/16	LFrTMS-M1/Placebo	NR	Contra-M1	1 Hz	NR	NR	5 times per week for 4 weeks	①④

(Continued)

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TABLE 1 (Continued)

Study	Country	Age (E/C, year)	Sample size (E/C)	Intervention							Outcomes
				Intervention protocol (E/C)	Coil type	rTMS target	rTMS frequency (Hz)	rTMS intensity (%)	No. of pulses	Duration of intervention	
Koch et al. (2019)	China	63 ± 11/65 ± 12	18/18	iTBS-Cerebellum/ Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	1,200	3 weeks	①②
Chen et al. (2023)	China	58.88 ± 15.79/62.38 ± 12.66	16/16	iTBS-Cerebellum/ Placebo	Figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	600	6 times per week for 3 weeks	①
Wang and Li (2022)	China	52.62 ± 8.61/54.62 ± 7.85	21/21	iTBS-Cerebellum/ Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	80% RMT	600	5 times per week for 4 weeks	①②
Liao et al. (2021)	China	51.53 ± 9.22/55.40 ± 8.10	15/15	iTBS-Cerebellum/ Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	90% AMT	600	5 times per week for 2 weeks	②④
Xie et al. (2021b)	China	52.35 ± 8.62/54.41 ± 7.01	18/18	iTBS-Cerebellum/ Placebo	70-mm figure-of-8 coil	Contra-cerebellar	iTBS	90% AMT	600	10 consecutive weekdays	①③
Lin et al. (2019)	China	60.8 ± 8.1/61.1 ± 9.7	10/10	iTBS-M1/Placebo	70-mm figure-of-8 coil	Bi-M1	iTBS	100% RMT	1,200	2 times per week for 5 weeks	①②③
Chieffo et al. (2014)	Italy	62.20 ± 10.23	5/5	dTMS-M1/Placebo	H-coil	Bi-M1	20 Hz	90% RMT	1,500	11 times for 3 weeks	①
Chieffo et al. (2021)	Italy	58.67 ± 10.33/61.17 ± 8.70	6/6	dTMS-M1/Placebo	H-coil	Bi-M1	20 Hz	80–90% RMT	1,600	11 times for 3 weeks	①

E, experimental group; C, control group; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; Ipsi, ipsilateral; Contra, contralateral; Bi, bilateral; NR, not reported; MT, motor threshold; RMT, resting motor threshold; AMT, active motor threshold. ①: FMA-LE; ②: BBS; ③: TUGT; ④: MEP amplitude; ⑤: Speed.

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TABLE 2 Pairwise meta-analysis.

Comparison	Number of studies	MD/SMD (95% CI)	Heterogeneity test	
			I^2 (%)	*p*-value
FMA-LE				
HFrTMS-M1/Placebo	9	**3.36 (2.01, 4.72)**	81	<0.00001
LFrTMS-M1/Placebo	16	**2.62 (1.71, 3.54)**	81	<0.00001
iTBS-Cerebellum/Placebo	4	0.41 (−0.74, 1.56)	0	0.88
iTBS-M1/Placebo	1	0.10 (−1.29, 1.49)	NR	NR
dTMS-M1/Placebo	2	**1.60 (0.59, 2.61)**	0	1
LFrTMS-M1/HFrTMS-M1	3	**2.37 (1.35, 3.38)**	12	32
FMA-LE (post-stroke time > 1 month)				
HFrTMS-M1/Placebo	6	**4.52 (2.85, 6.19)**	76	0.001
LFrTMS-M1/Placebo	9	**2.84 (1.56, 4.12)**	88	<0.00001
iTBS-Cerebellum/Placebo	4	0.41 (−0.74, 1.56)	0	0.88
iTBS-M1/Placebo	1	0.10 (−1.29, 1.49)	NR	NR
dTMS-M1/Placebo	2	**1.60 (0.59, 2.61)**	0	1
LFrTMS-M1/HFrTMS-M1	1	0.89 (−3.16, 4.94)	NR	NR
FMA-LE (post-stroke time ≤ 1 month)				
HFrTMS-M1/Placebo	3	**1.25 (0.44, 2.06)**	0	0.82
LFrTMS-M1/Placebo	7	**2.39 (1.16, 3.63)**	52	0.05
LFrTMS-M1/HFrTMS-M1	2	**2.47 (1.41, 3.52)**	42	0.19
BBS				
HFrTMS-M1/Placebo	2	**6.64 (4.37, 8.91)**	75	0.05
LFrTMS-M1/Placebo	4	**4.49 (1.75, 7.24)**	90	<0.00001
iTBS-Cerebellum/Placebo	4	**3.23 (0.99, 5.47)**	57	0.07
iTBS-M1/Placebo	1	0.60 (−1.68, 2.88)	NR	NR
HFrTMS-M1/LFrTMS-M1	2	4.34 (−5.73, 14.41)	84	0.01
TUGT				
HFrTMS-M1/Placebo	2	**−3.25 (−5.19, −1.30)**	37	0.21
LFrTMS-M1/Placebo	4	**−2.72 (−3.95, −1.49)**	0	0.94
iTBS-Cerebellum/Placebo	1	−0.38 (−12.70, 11.94)	NR	NR
iTBS-M1/Placebo	1	−0.70 (−4.63, 3.23)	NR	NR
MEP amplitude				
HFrTMS-M1/Placebo	3	**0.92 (0.08, 1.77)**	61	0.08
LFrTMS-M1/Placebo	3	0.36 (−0.48, 1.21)	78	0.01
iTBS-Cerebellum/Placebo	1	−0.10 (−0.81, 0.62)	NR	NR
HFrTMS-M1/LFrTMS-M1	2	0.71 (−0.99, 2.41)	89	0.003
Speed				
HFrTMS-M1/Placebo	8	**0.91 (0.68, 1.13)**	26	0.21
LFrTMS-M1/Placebo	5	**1.04 (0.81, 1.26)**	46	0.12

Red and bold numbers are statistically significant. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; NR, not reported.

difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5F and Table 3 show the SUCRA rankings for all interventions. According to the analysis, HFrTMS-M1 (SUCRA, 93.7%) may be the most effective intervention to improve MEP amplitude in stroke patients.

3.5.5 Speed

A total of 13 included studies evaluated speed, involving 3 intervention protocols: HFrTMS-M1, LFrTMS-M1, and Placebo. A total of 667 patients were included. There was no closed loop, so

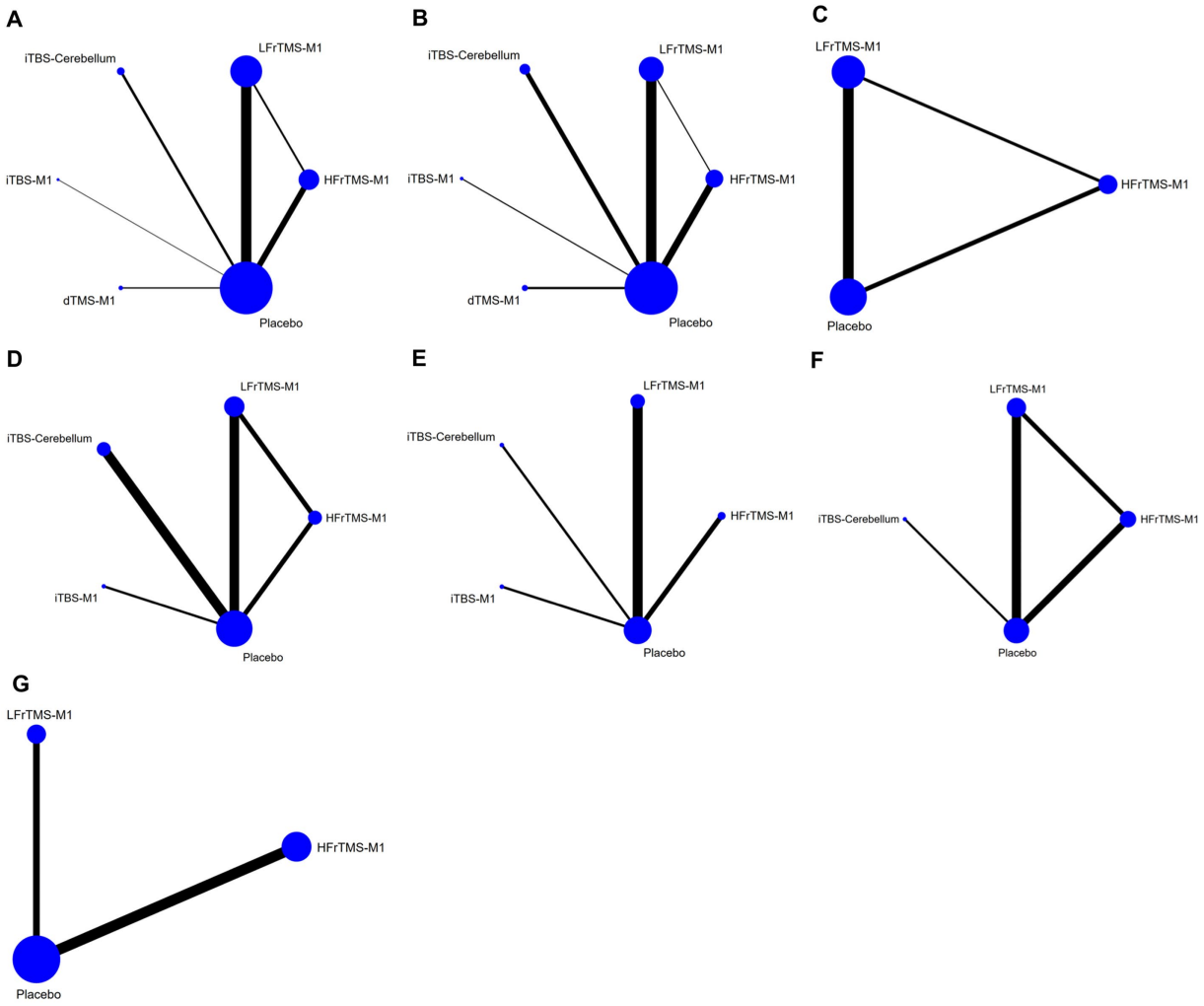

FIGURE 3
Network meta-analysis diagrams of eligible comparisons. The width of the lines is proportional to the number of trials. The size of every circle is proportional to the number of randomly assigned participants (sample size). **(A)** FMA-LE; **(B)** FMA-LE (post-stroke time > 1 month); **(C)** FMA-LE (post-stroke time ≤ 1 month); **(D)** BBS; **(E)** TUGT; **(F)** MEP amplitude; **(G)** Speed. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

we did not need to perform a consistency check. The NMA results showed that speed generated a total of 3 pairwise comparisons.

Compared with Placebo, LFrTMS-M1 (SMD = 1.01, 95% CI: 0.64 to 1.38) and HFrTMS-M1 (SMD = 0.82, 95% CI: 0.49 to 1.15) significantly improved speed in stroke patients. There was no statistically significant difference between the other two interventions ($p > 0.05$; Figure 4). Figure 5G and Table 3 show the SUCRA rankings for all interventions. According to the analysis, LFrTMS-M1 (SUCRA, 88.7%) may be the most effective intervention to improve speed in stroke patients.

3.6 Publication bias

This study evaluated publication bias for FMA-LE, FMA-LE (post-stroke time > 1 month), FMA-LE (post-stroke time ≤ 1 month), BBS, TUGT, MEP amplitude, and speed using the funnel plot of publication bias (Figure 6) and Egger's test. The findings revealed that most points were evenly distributed along both sides of the midline and were primarily focused there, indicating that our results were robust and there was no significant publication bias. In addition, we used Egger's test for secondary validation of publication bias. The results showed FMA-LE (Egger's test $p = 0.273$; Supplementary Figure 10A), FMA-LE (post-stroke time > 1 month; Egger's test $p = 0.807$; Supplementary Figure 10B), FMA-LE (post-stroke time ≤ 1 month; Egger's test $p = 0.601$; Supplementary Figure 10C), BBS (Egger's test $p = 0.843$; Supplementary Figure 10D), TUGT (Egger's test $p = 0.123$; Supplementary Figure 10E), MEP amplitude (Egger's test $p = 0.089$; Supplementary Figure 10F), and speed (Egger's test $p = 0.556$; Supplementary Figure 10G), indicating that there was no publication bias in this study.

3.7 Adverse events

Among the 38 included studies, 16 had no adverse events during the course of the experiment, 7 reported adverse events in detail, and the remaining studies did not describe adverse events

Intervention						
FMA-LE MD (95%CI)	LFrTMS-M1					
	0.09 (−1.23, 1.42)	HFrTMS-M1				
	1.23 (−1.17, 3.63)	1.13 (−1.37, 3.64)	dTMS-M1			
	1.26 (−0.85, 3.37)	1.16 (−1.07, 3.40)	0.03 (−2.92, 2.98)	iTBS-Cerebellum		
	2.73 (−0.50, 5.95)	2.63 (−0.67, 5.94)	1.50 (−2.33, 5.33)	1.47 (−2.18, 5.12)	iTBS-M1	
	2.83 (1.96, 3.70)	**2.74 (1.60, 3.87)**	1.60 (−0.63, 3.84)	1.57 (−0.35, 3.50)	0.10 (−3.00, 3.21)	Placebo
Intervention						
FMA-LE (post-stroke time >1 month) MD (95%CI)	HFrTMS-M1					
	1.02 (−0.75, 2.79)	LFrTMS-M1				
	2.34 (−0.26, 4.93)	1.32 (−1.11, 3.74)	dTMS-M1			
	2.36 (0.00, 4.73)	1.34 (−0.83, 3.52)	0.03 (−2.83, 2.88)	iTBS-Cerebellum		
	3.84 (0.52, 7.16)	2.82 (−0.37, 6.01)	1.50 (−2.19, 5.19)	1.47 (−2.06, 5.01)	iTBS-M1	
	3.94 (2.50, 5.38)	**2.92 (1.82, 4.02)**	1.60 (−0.56, 3.76)	1.58 (−0.30, 3.45)	0.10 (−2.89, 3.10)	Placebo
Intervention						
FMA-LE (post-stroke time ≤1 month) MD (95%CI)	LFrTMS-M1					
	1.49 (0.05, 2.93)	HFrTMS-M1				
	2.47 (1.41, 3.53)	0.98 (−0.32, 2.28)	Placebo			
Intervention						
BBS MD (95%CI)	HFrTMS-M1					
	2.60 (−0.74, 5.95)	LFrTMS-M1				
	3.68 (−0.33, 7.68)	1.07 (−2.50, 4.64)	iTBS-Cerebellum			
	6.36 (0.65, 12.07)	3.76 (−1.64, 9.15)	2.69 (−2.85, 8.22)	iTBS-M1		
	6.97 (3.95, 9.98)	**4.36 (2.00, 6.72)**	**3.29 (0.63, 5.95)**	0.60 (−4.25, 5.45)	Placebo	
Intervention						
TUGT MD (95%CI)	HFrTMS-M1					
	−0.53 (−2.83, 1.77)	LFrTMS-M1				
	−2.87 (−15.34, 9.61)	−2.34 (−14.72, 10.04)	iTBS-Cerebellum			
	−2.55 (−6.93, 1.84)	−2.02 (−6.14, 2.10)	0.32 (−12.61, 13.25)	iTBS-M1		
	−3.25 (−5.19, −1.30)	**−2.72 (−3.95, −1.49)**	−0.38 (−12.70, 11.94)	−0.70 (−4.63, 3.23)	Placebo	
Intervention						
MEP amplitude SMD (95%CI)	HFrTMS-M1					
	0.66 (−0.22, 1.54)	LFrTMS-M1				
	1.09 (−0.63, 2.81)	0.43 (−1.24, 2.09)	iTBS-Cerebellum			
	0.99 (0.17, 1.82)	0.33 (−0.37, 1.03)	−0.10 (−1.61, 1.41)	Placebo		
Intervention						
Speed SMD (95%CI)	LFrTMS-M1					
	0.19 (−0.31, 0.69)	HFrTMS-M1				
	1.01 (0.64, 1.38)	**0.82 (0.49, 1.15)**	Placebo			

FIGURE 4
Network meta-analysis of head-to-head comparisons. Red and bold numbers are statistically significant. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

(Supplementary Table 7). The adverse events reported were mild, such as headache, dizziness, nausea, and vomiting.

4 Discussion

Stroke is a common disease worldwide and causes severe disabilities for patients. More than two-thirds of stroke survivors have post-stroke sequelae, including impairment in motor function, balance, gait, and ADL (Paul et al., 2007). Improving lower extremity motor function and balance ability can significantly impact gait function, ADL, and quality of life in stroke patients (Smith et al., 2017). Although the use of rTMS for stroke has attracted considerable attention, there is still a lack of consensus on the optimal protocol for rTMS to improve lower extremity motor function in stroke patients. To the best of our knowledge, this is the first NMA to compare the effects of different rTMS protocols on lower extremity motor function in stroke patients by taking stimulation frequency, stimulation target, and stimulation mode of rTMS and post-stroke time into account simultaneously.

The FMA-LE can predict lower extremity motor recovery in individuals with stroke (Balasubramanian et al., 2016). This assessment exhibits good internal consistency and reliability, discriminative validity, and responsiveness to interventions

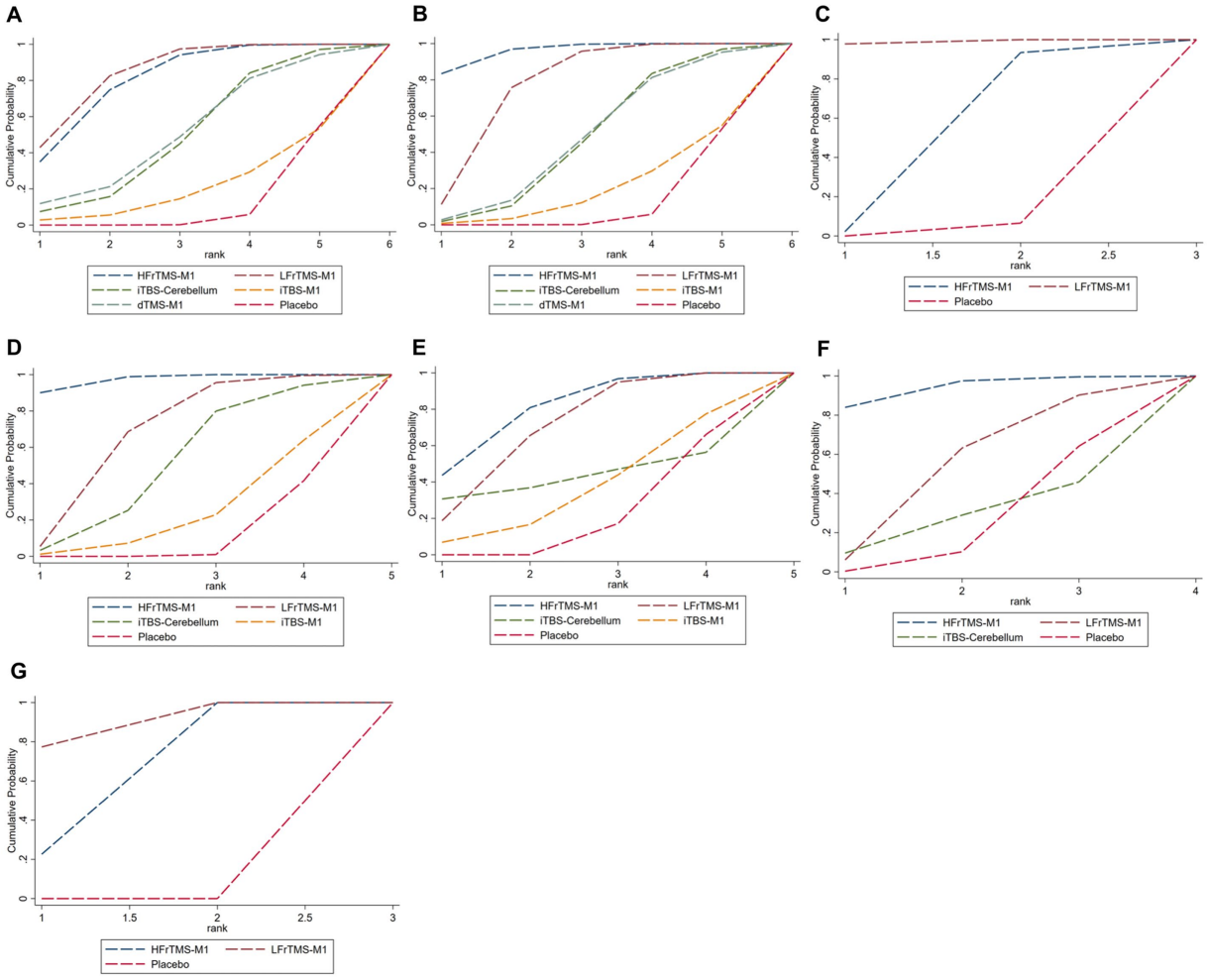

FIGURE 5
Cumulative probability ranking curve of different interventions. The vertical axis represents cumulative probabilities, while the horizontal axis represents ranks. **(A)** FMA-LE; **(B)** FMA-LE (post-stroke time > 1 month); **(C)** FMA-LE (post-stroke time ≤ 1 month); **(D)** BBS; **(E)** TUGT; **(F)** MEP amplitude; **(G)** Speed. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

TABLE 3 SUCRA values of different interventions for outcomes.

Outcomes	HFrTMS-M1	LFrTMS-M1	iTBS-cerebellum	iTBS-M1	dTMS-M1	Placebo
FMA-LE	80.7%[b]	84.6%[a]	49.9%	21.2%	51.5%	12.2%
FMA-LE (post-stroke time > 1 month)	95.8%[a]	76.8%[b]	47.4%	20.0%	28.0%	11.9%
FMA-LE (post-stroke time ≤ 1 month)	47.8%[b]	98.9%[a]	NR	NR	NR	3.3%
BBS	96.8%[a]	67.7%[b]	51.8%	22.7%	NR	11.0%
TUGT	80.3%[a]	69.8%[b]	42.8%	36.2%	NR	20.8%
MEP amplitude	93.7%[a]	53.2%[b]	28.2%	NR	NR	24.9%
Speed	63.1%[b]	88.7%[a]	NR	NR	NR	0.0%

[a]Presents the first-ranking. [b]Presents the second-ranking.
HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation, iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex; NR, not reported.

(Hsieh et al., 2009). This study found that compared with Placebo, LFrTMS-M1 and HFrTMS-M1 significantly improved FMA-LE in stroke patients, and LFrTMS in the contralateral hemisphere was more effective than HFrTMS in the ipsilateral hemisphere. Xie et al. (2021a) suggested that LFrTMS in the contralateral hemisphere was more effective than HFrTMS in the ipsilateral hemisphere, which was consistent with our findings. However, a novel finding from this NMA is that the subgroup analyses of FMA-LE showed that at ≤1 month after stroke, HFrTMS-M1 was the optimal stimulation protocol for improving stroke patients' lower extremity motor function. At

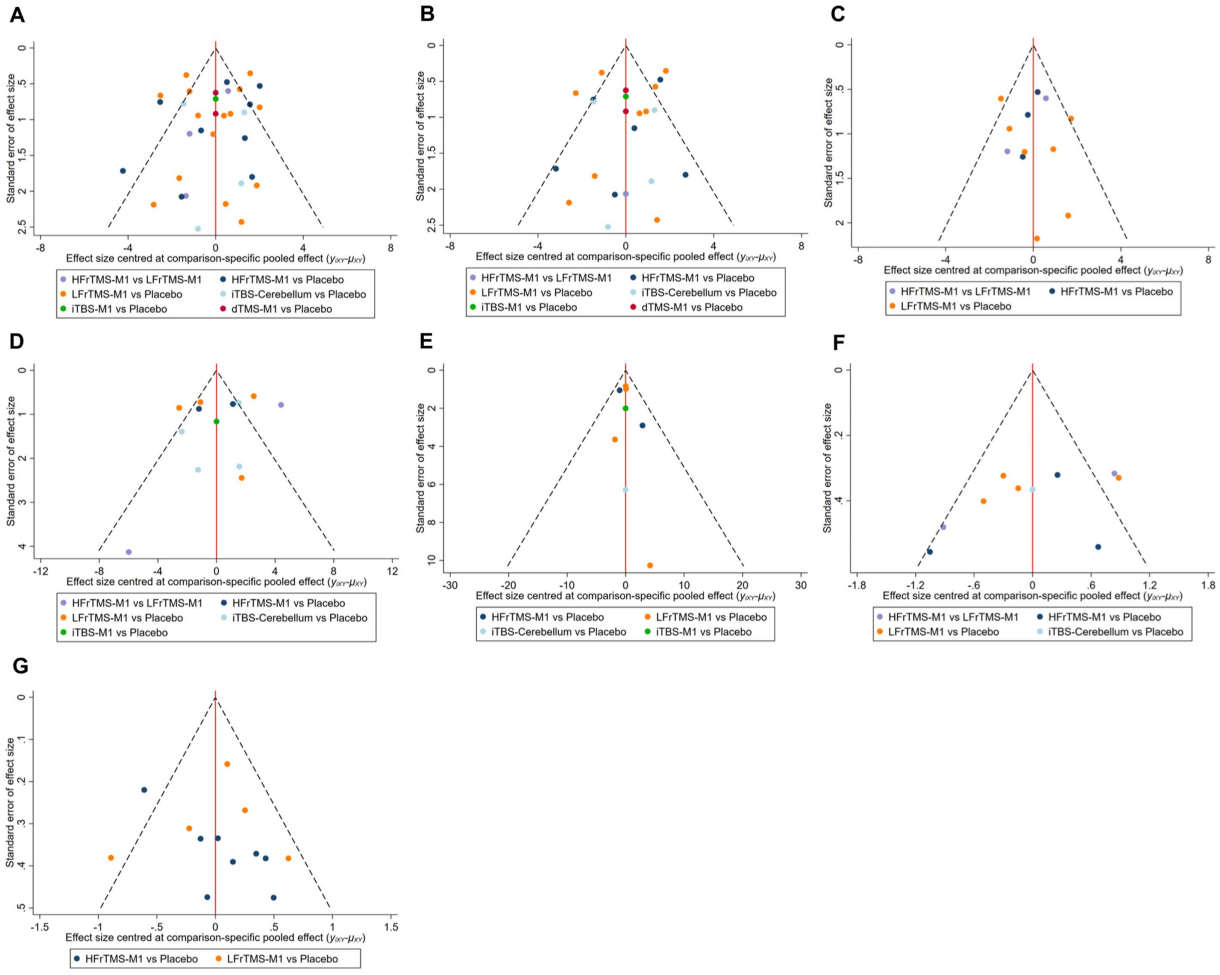

FIGURE 6
Funnel plot of publication bias. **(A)** FMA-LE; **(B)** FMA-LE (post-stroke time > 1 month); **(C)** FMA-LE (post-stroke time ≤ 1 month); **(D)** BBS; **(E)** TUGT; **(F)** MEP amplitude; **(G)** Speed. HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; dTMS, deep transcranial magnetic stimulation; M1, primary motor cortex.

≤1 month after stroke, LFrTMS-M1 was the best protocol, which was superior to HFrTMS-M1. The difference between these two studies was that when grouping rTMS protocols, we considered that the same rTMS mode applied to different stimulation targets would produce different therapeutic effects. Therefore, we divided stimulation targets into M1 and Cerebellum rather than simply grouping very different stimulation targets together, which allowed the intervention protocol to be more refined. Second, we included more articles that met our research objectives to expand the sample size. Finally, we also carried out a subgroup analysis of the patients on the efficacy of rTMS at different protocols to improve the accuracy of the outcome evidence. In addition, we also found that 10 Hz and 1 Hz were the most commonly used stimulation frequencies for HFrTM and LFrTMS, respectively, regarding rTMS prescription settings, which was the same conclusion as Fan et al. (2021). Meanwhile, rTMS sessions of 15 or 20 min each and lasting 3 or 4 weeks were the most common. In clinical practice, clinicians or rehabilitation therapists can flexibly formulate the best stimulation prescription according to the specific situation of patients and the recommended protocols mentioned above.

In fact, early hyperexcitability and increased interhemispheric inhibition of the contralesional motor cortex have been demonstrated using TMS after unilateral stroke. Therefore, LFrTMS can effectively improve the motor function of stroke patients by reducing the excitability of the motor cortex of the contralateral hemisphere to restore the balance of competitive inhibition between the two hemispheres in the acute phase of stroke. However, in the post-stroke convalescent phase, the interhemispheric competition is less pronounced than in the acute phase, as it is commonly observed that the transcallosal asymmetry decreases with time (Swayne et al., 2008). LFrTMS may reduce the compensatory effect of the contralateral hemisphere by inhibiting its excitability, thereby hindering functional recovery after stroke. Therefore, HFrTMS-M1 may be more effective than LFrTMS-M1 in the convalescent phase of stroke. Xia et al. (2022) also recommended the application of HFrTMS in patients with stroke patients during the convalescent phase.

The BBS is the most widely used clinical scale for assessing balance performance in individuals with neurological conditions, including static and dynamic balance (Neuls et al., 2011). The sum of the scores for the 14 items (each item was rated from 0 to 4) yielded a balance score ranging from 0 to 56 (Neuls et al., 2011). TUGT is a rapid and quantitative assessment of dynamic balance and functional walking ability and is closely related to other measures of gait and balance in stroke patients (Flansbjer et al., 2005). TUGT assesses the time taken to complete a series of actions, including standing up from a chair,

walking forward three meters, turning, and returning to the chair. According to the ranking probability of our NMA, HFrTMS-M1 was more advantageous in improving BBS and TUGT. Therefore, we recommend HFrTMS-M1 as a complementary rehabilitation therapy to improve balance function in stroke patients in clinical practice.

Walking speed can reflect the recovery of lower extremity function and walking quality in stroke patients (Patterson et al., 2008). Our NMA results showed that compared with Placebo, LFrTMS-M1 and HFrTMS-M1 significantly improved the speed in stroke patients. LFrTMS-M1 had more advantages in improving the speed of stroke patients. However, Tung et al. (2019) found that HFrTMS was superior to LFrTMS in improving speed in stroke patients. Further understanding of the relationship between different rTMS protocols and walking speed is needed in the future. Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that produces pulsed magnetic fields that form induced currents in the motor cortex of the brain. After the induced current stimulates one side of the motor cortex, the conduction nerve impulses are transmitted downward, which will cause the target muscle on the opposite side of the subject to produce action potentials, called motor-evoked potentials (MEPs). MEPs is a quantitative evaluation index of central motor conduction function, which can objectively reflect the excitability of the motor cortex. In this study, we used MEP amplitude to assess the functional status of motor conduction pathways, and the results showed that HFrTMS-M1 was the most effective in improving MEP amplitude. However, MEP amplitude included only a few studies, meaning this ranking result should be treated critically. In addition, to ensure the objectivity of the study results, more high-quality RCTs with large sample sizes are needed for further verification.

Like TMS, functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and other neuroimaging techniques are also of great significance in the assessment of motor function in stroke. fMRI can evaluate the neurovascular response induced by rTMS, and the activity changes of brain nerves can be observed through intuitive and visual images (Bergmann et al., 2016). In addition, fMRI can also be used to study the excitability and functional connectivity of the cerebral cortex and subcortex in stroke patients under rTMS intervention. Guo et al. (2021) used fMRI to find that both LFrTMS stimulation in the unaffected hemisphere and HFrTMS stimulation in the affected hemisphere could promote the reorganization of the motor network, and the changes in functional connectivity between the contralateral PMA and the ipsilateral M1, and between the bilateral M1 induced by rTMS were related to motor recovery. Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) is a new evaluation method in recent years. TMS-EEG can reflect the direct relationship between brain regions and motor function in stroke patients and predict the recovery of motor function after stroke. Koch et al. (2019) performed motor assessment on 34 stroke subjects who received iTBS-Cerebellum or sham iTBS treatment by Fugl-Meyer scale, gait analysis, and so on, and recorded cerebral cortical activity through TMS-EEG to achieve the combination of treatment and assessment feedback. At present, there are relatively few studies using fMRI and EEG to explore the treatment of rTMS to promote the recovery of dysfunction after stroke, and most of the trials are small in sample size and scale. In the future, large-sample, multi-center, and high-quality RCTs should be carried out, and the results of imaging and electrophysiology of stroke patients should be comprehensively analyzed to improve the accuracy and scientificity of rehabilitation efficacy evaluation.

The M1 is the most essential part of the motor cortex in the human cerebral cortex, located in the precentral gyrus. M1 is the most frequently stimulated target in noninvasive brain stimulation studies for post-stroke gait and balance recovery (Parikh et al., 2023). Among the 38 studies included in this article, 33 studies selected M1 as the stimulation target. Recent electrophysiological and imaging evidence underlined that a large motor network includes other key brain areas during the process of post-stroke functional recovery (Koch and Hummel, 2017). The cerebellum is a crucial structure involved in balance and motor control, and it is essential in motor adaptation and learning processes. Therefore, the cerebellum has been proposed as one of the alternative targets of M1. A total of 5 studies in our NMA used the cerebellum as the stimulation target and selected the iTBS mode for intervention. iTBS is a new rTMS mode that lasts only about 5 min, with the characteristics of short time-consuming, low intensity, and strong effect. iTBS can induce long-term potentiation, which helps promote neural plasticity and produce a safer and lasting intervention effect for stroke patients. Our findings showed that iTBS-Cerebellum can significantly improve balance function in stroke patients. Liao et al. (2024) compared the efficacy and safety of iTBS to the cerebellum or M1 on balance and motor recovery in stroke patients. They found that both iTBS-M1 and iTBS-Cerebellum could improve balance function and that iTBS-Cerebellum, but not iTBS-M1, had a more significant effect on motor recovery. Like our findings, Manto et al. (2012) suggested that iTBS-Cerebellum could be a potential therapeutic approach to improve balance and gait function in stroke patients. Thus, iTBS-Cerebellum may be a valuable new therapeutic option in stroke rehabilitation programs. At the same time, our NMA also included a study on the iTBS-M1 protocol, but the limited number of studies and participants may have led to inaccurate results.

It is worth noting that among the included studies, Chieffo et al. (2014) and Chieffo et al. (2021) used H-coil. The H-coil differs from conventional figure-of-8 coil and circular coil in that it can stimulate deeper cortical areas and neural networks (Roth et al., 2014). Roth et al. (2007) found that H-coil, figure-of-8 coil, and double-cone coil could generate the maximum induced electric field in the surface region of the saline head model at 0.9% concentration. With the increased distance from the simulated skull to the brain tissue, the induced electric field generated by the figure-of-8 coil and the double-cone coil decreased to less than 10% of the maximum induced electric field at 6 cm. In comparison, the electric field intensity of the H-coil was more than 63% of the maximum induced electric field. H-coil can theoretically stimulate deeper leg-related cortical motor areas within the intercerebral fissure approximately 3 to 4 cm below the skull. However, the results of Chieffo et al. (2014) and Chieffo et al. (2021) did not show a favorable advantage of dTMS. We suspect this may be due to the small number of current studies. In the future, more RCTs are needed to confirm the applicability and safety of dTMS in stroke patients.

5 Limitations

The study also has some limitations, including: (1) Coil type, stimulation intensity, total number of pulses, and duration of intervention were not exactly the same among the included studies, resulting in potential heterogeneity. (2) Despite including the full stimulation protocol in this analysis, the iTBS-M1 and dTMS-M1

groups accounted for 2.6 and 5.3% of the total data, respectively. This affects, to some extent, the quality of the conclusions of this study. (3) The age and disease severity of the included patients were slightly different, and some data indicators will be affected. Further subgroup analysis according to age and disease severity is needed in the future. (4) Adverse events may not be strictly reported in the included studies, so the safety of each intervention protocol needs to be further studied.

6 Conclusion

In this NMA, we found differences in the therapeutic effects between different rTMS protocols. Considering the impact of the stroke phase on the lower extremity motor function, the current research evidence shows that HFrTMS-M1 may be the preferred stimulation protocol to improve the lower extremity motor function of patients for post-stroke time > 1 month, and LFrTMS-M1 for post-stroke time ≤ 1 month. In the future, high-quality, large-sample, multi-center, and long-term follow-up RCTs are needed to verify the conclusions of this study.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

CWa: Software, Writing – original draft. QZ: Software, Writing – original draft. LZ: Data curation, Methodology, Supervision, Writing – review & editing. DZ: Data curation, Methodology, Supervision, Writing – review & editing. YX: Data curation, Methodology, Supervision, Writing – review & editing. ZL: Data curation, Methodology, Supervision, Writing – review & editing. CWu: Supervision, Writing – review & editing, Data curation, Methodology. SW: Supervision, Writing – review & editing, Data curation, Methodology. MY: Supervision, Writing – review & editing. LW: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1352212/full#supplementary-material

References

Balasubramanian, C. K., Li, C.-Y., Bowden, M. G., Duncan, P. W., Kautz, S. A., and Velozo, C. A. (2016). Dimensionality and item-difficulty hierarchy of the lower extremity Fugl-Meyer assessment in individuals with subacute and chronic stroke. *Arch. Phys. Med. Rehabil.* 97, 582–589.e2. doi: 10.1016/j.apmr.2015.12.012

Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., and Siebner, H. R. (2016). Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. *Neuroimage* 140, 4–19. doi: 10.1016/j.neuroimage.2016.02.012

Brunelli, S., Iosa, M., Fusco, F. R., Pirri, C., Di Giunta, C., Foti, C., et al. (2019). Early body weight-supported overground walking training in patients with stroke in subacute phase compared to conventional physiotherapy: a randomized controlled pilot study. *Int. J. Rehabil. Res.* 42, 309–315. doi: 10.1097/MRR.0000000000000363

Cárdenas-Morales, L., Nowak, D. A., Kammer, T., Wolf, R. C., and Schönfeldt-Lecuona, C. (2010). Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr.* 22, 294–306. doi: 10.1007/s10548-009-0084-7

Ceng, B., Fan, S., Li, Y., and Wang, P. (2022). Transcranial magnetic stimulation combined with the dual task training on stroke patients with hemiplegia lower limb motor function. *Chin J Integr Med Cardio Cererovasc Dis* 20, 4585–4588. doi: 10.12102/j.issn.1672-1349.2022.24.034

Cha, H. G., and Kim, M. K. (2017). Effects of strengthening exercise integrated repetitive transcranial magnetic stimulation on motor function recovery in subacute stroke patients: a randomized controlled trial. *Technol. Health Care* 25, 521–529. doi: 10.3233/THC-171294

Cha, H. G., Kim, M. K., Nam, H. C., and Ji, S. G. (2014). Effects of high frequency repetitive transcranial magnetic stimulation on function in subacute stroke patients. *J Magn* 19, 192–196. doi: 10.4283/JMAG.2014.19.2.192

Chen, Y. (2018). Effects of repetitive transcranial magnetic stimulation on spasm and motor function of lower limbs in patients with stroke. *Chongqing Med J* 47, 3292–3295+3298. doi: 10.3969/j.issn.1671-8348.2018.25.012

Chen, J., Shi, M., Chen, J., Zhang, J., Chen, R., Tu, J., et al. (2023). The effects of supplementing theta burst stimulation of the cerebellum with physical therapy on balance and gait recovery after a stroke: a randomized clinical trial. *Chin J Phys Med Rehabil* 45, 402–407. doi: 10.3760/cma.j.issn.0254-1424.2023.05.004

Chieffo, R., De Prezzo, S., Houdayer, E., Nuara, A., Di Maggio, G., Coppi, E., et al. (2014). Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function in chronic stroke: a pilot study. *Arch. Phys. Med. Rehabil.* 95, 1141–1147. doi: 10.1016/j.apmr.2014.02.019

Chieffo, R., Giatsidis, F., Santangelo, R., Alyagon, U., Comola, M., Zangen, A., et al. (2021). Repetitive transcranial magnetic stimulation with H-coil coupled with cycling for improving lower limb motor function after stroke: An exploratory study. *Neuromodulation* 24, 916–922. doi: 10.1111/ner.13228

Chung, S. W., Hoy, K. E., and Fitzgerald, P. B. (2015). Theta-burst stimulation: a new form of TMS treatment for depression? *Depress. Anxiety* 32, 182–192. doi: 10.1002/da.22335

Dias, S., Welton, N. J., Caldwell, D. M., and Ades, A. E. (2010). Checking consistency in mixed treatment comparison meta-analysis. *Stat. Med.* 29, 932–944. doi: 10.1002/sim.3767

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., et al. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol.* 10, 597–608. doi: 10.1038/nrneurol.2014.162

Du, J., Yang, F., Hu, J., Hu, J., Xu, Q., Cong, N., et al. (2019). Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. *Neuroimage Clin* 21:101620. doi: 10.1016/j.nicl.2018.101620

Elkholy, S. H., Atteya, A. A., Hassan, W. A., Sharaf, M., and Gohary, A. M. E. (2014). Low rate repetitive transcranial magnetic stimulation (rTMS) and gait rehabilitation after stroke. *Int J Neurorehabil* 1:109. doi: 10.4172/2376-0281.1000109

Eng, J. J., and Tang, P.-F. (2007). Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. *Expert Rev. Neurother.* 7, 1417–1436. doi: 10.1586/14737175.7.10.1417

Fan, H., Song, Y., Cen, X., Yu, P., Bíró, I., and Gu, Y. (2021). The effect of repetitive transcranial magnetic stimulation on lower-limb motor ability in stroke patients: a systematic review. *Front. Hum. Neurosci.* 15:620573. doi: 10.3389/fnhum.2021.620573

Flansbjer, U.-B., Holmbäck, A. M., Downham, D., Patten, C., and Lexell, J. (2005). Reliability of gait performance tests in men and women with hemiparesis after stroke. *J. Rehabil. Med.* 37, 75–82. doi: 10.1080/16501970410017215

Fleiss, J. L. (1993). The statistical basis of meta-analysis. *Stat. Methods Med. Res.* 2, 121–145. doi: 10.1177/096228029300200202

George, M. S., and Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology.* 35, 301–316. doi: 10.1038/npp.2009.87

Gong, Y., Long, X.-M., Xu, Y., Cai, X.-Y., and Ye, M. (2021). Effects of repetitive transcranial magnetic stimulation combined with transcranial direct current stimulation on motor function and cortex excitability in subacute stroke patients: a randomized controlled trial. *Clin. Rehabil.* 35, 718–727. doi: 10.1177/0269215520972940

Guan, Y.-Z., Li, J., Zhang, X.-W., Wu, S., Du, H., Cui, L.-Y., et al. (2017). Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: a one-year longitudinal randomized trial. *CNS Neurosci. Ther.* 23, 940–946. doi: 10.1111/cns.12762

Guo, Z., Jin, Y., Bai, X., Jiang, B., He, L., McClure, M. A., et al. (2021). Distinction of high- and low-frequency repetitive transcranial magnetic stimulation on the functional reorganization of the motor network in stroke patients. *Neural Plast.* 2021, 8873221–8873211. doi: 10.1155/2021/8873221

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ* 327, 557–560. doi: 10.1136/bmj.327.7414.557

Hsieh, Y., Wu, C., Lin, K., Chang, Y., Chen, C., and Liu, J. (2009). Responsiveness and validity of three outcome measures of motor function after stroke rehabilitation. *Stroke* 40, 1386–1391. doi: 10.1161/STROKEAHA.108.530584

Hua, Y., Li, B., Wang, K., Guo, H., and Gou, L. (2019). Different frequency repetitive transcranial magnetic stimulation treatment of ischemic cerebral apoplexy patients curative effect observation. *Chin J Phys Med Rehabil* 41, 745–748. doi: 10.3760/cma.j.issn.0254-1424.2019.10.006

Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., and Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron* 45, 201–206. doi: 10.1016/j.neuron.2004.12.033

Huang, Y.-Z., Lin, L.-F., Chang, K.-H., Hu, C.-J., Liou, T.-H., and Lin, Y.-N. (2018). Priming with 1-Hz repetitive transcranial magnetic stimulation over Contralesional leg motor cortex does not increase the rate of regaining ambulation within 3 months of stroke: a randomized controlled trial. *Am. J. Phys. Med. Rehabil.* 97, 339–345. doi: 10.1097/PHM.0000000000000850

Huang, Y.-Z., Rothwell, J. C., Chen, R.-S., Lu, C.-S., and Chuang, W.-L. (2011). The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clin. Neurophysiol.* 122, 1011–1018. doi: 10.1016/j.clinph.2010.08.016

Hutton, B., Salanti, G., Caldwell, D. M., Chaimani, A., Schmid, C. H., Cameron, C., et al. (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann. Intern. Med.* 162, 777–784. doi: 10.7326/M14-2385

Ji, S.-G., Cha, H.-G., Kim, K.-J., and Kim, M.-K. (2014). Effects of motor imagery practice in conjunction with repetitive transcranial magnetic stimulation on stroke patients. *J Magn* 19, 181–184. doi: 10.4283/JMAG.2014.19.2.181

Ji, S. G., and Kim, M. K. (2015). The effects of repetitive transcranial magnetic stimulation on the gait of acute stroke patients. *J Magn* 20, 129–132. doi: 10.4283/JMAG.2015.20.2.129

Kakuda, W., Abo, M., Nakayama, Y., Kiyama, A., and Yoshida, H. (2013). High-frequency rTMS using a double cone coil for gait disturbance. *Acta Neurol. Scand.* 128, 100–106. doi: 10.1111/ane.12085

Kesikburun, S. (2022). Non-invasive brain stimulation in rehabilitation. *Turk J Phys Med Rehabil* 68, 1–8. doi: 10.5606/tftrd.2022.10608

Koch, G., Bonnì, S., Casula, E. P., Iosa, M., Paolucci, S., Pellicciari, M. C., et al. (2019). Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. *JAMA Neurol.* 76, 170–178. doi: 10.1001/jamaneurol.2018.3639

Koch, P. J., and Hummel, F. C. (2017). Toward precision medicine: tailoring interventional strategies based on noninvasive brain stimulation for motor recovery after stroke. *Curr. Opin. Neurol.* 30, 388–397. doi: 10.1097/WCO.0000000000000462

Langhammer, B., and Stanghelle, J. K. (2011). Can physiotherapy after stroke based on the Bobath concept result in improved quality of movement compared to the motor relearning programme. *Physiother Res Int.* 16, 69–80. doi: 10.1002/pri.474

Larson, J., Wong, D., and Lynch, G. (1986). Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res.* 368, 347–350. doi: 10.1016/0006-8993(86)90579-2

Lee, S. A., and Cha, H. G. (2020). The effect of high frequency repetitive transcranial magnetic stimulation combined with treadmill training on the recovery of lower limb function in chronic stroke patients: a randomized controlled trial. *J Magn* 25, 402–408. doi: 10.4283/JMAG.2020.25.3.402

Li, Y., Fan, J., Yang, J., He, C., and Li, S. (2018). Effects of repetitive transcranial magnetic stimulation on walking and balance function after stroke: a systematic review and meta-analysis. *Am. J. Phys. Med. Rehabil.* 97, 773–781. doi: 10.1097/PHM.0000000000000948

Li, Y., Huang, L., Zhang, J., Tian, J., and Yu, X. (2016). Effects of repetitive transcranial magnetic stimulation on the lower limbmotor functionof cerebral infarctior patients. *Chin J Phys Med Rehabil* 38, 839–842. doi: 10.3760/cma.j.issn.0254-1424.2016.11.010

Liao, L.-Y., Xie, Y.-J., Chen, Y., and Gao, Q. (2021). Cerebellar theta-burst stimulation combined with physiotherapy in subacute and chronic stroke patients: a pilot randomized controlled trial. *Neurorehabil. Neural Repair* 35, 23–32. doi: 10.1177/1545968320971735

Liao, L.-Y., Zhu, Y., Peng, Q.-Y., Gao, Q., Liu, L., Wang, Q.-H., et al. (2024). Intermittent theta-burst stimulation for stroke: primary motor cortex versus cerebellar stimulation: a randomized sham-controlled trial. *Stroke* 55, 156–165. doi: 10.1161/STROKEAHA.123.044892

Lin, L.-F., Chang, K.-H., Huang, Y.-Z., Lai, C.-H., Liou, T.-H., and Lin, Y.-N. (2019). Simultaneous stimulation in bilateral leg motor areas with intermittent theta burst stimulation to improve functional performance after stroke: a feasibility pilot study. *Eur. J. Phys. Rehabil. Med.* 55, 162–168. doi: 10.23736/S1973-9087.18.05245-0

Lin, Y.-N., Hu, C.-J., Chi, J., Lin, L.-F., Yen, T.-H., Lin, Y.-K., et al. (2015). Effects of repetitive transcranial magnetic stimulation of the unaffected hemisphere leg motor area in patients with subacute stroke and substantial leg impairment: a pilot study. *J. Rehabil. Med.* 47, 305–310. doi: 10.2340/16501977-1943

Liu, M., Meng, Y., Li, H., and Zhang, G. (2019). Effects of repetitive transcranial magnetic stimulation on motor function and serum levels of MMP-9/hs-CRP of ischemic stroke patients. *Tianjin Med J* 47, 184–188. doi: 10.11958/20181534

Ma, Q., Li, Z., Fu, W., and Lin, Q. (2023). Effect of repetitive transcranial magnetic stimulation on walking of stroke patients at recovery stage. *Chin J Rehabil Theory Pract* 29, 167–173. doi: 10.3969/j.issn.1006-9771.2023.02.005

Manto, M., Bower, J. M., Conforto, A. B., Delgado-García, J. M., da Guarda, S. N. F., Gerwig, M., et al. (2012). Consensus paper: roles of the cerebellum in motor control--the diversity of ideas on cerebellar involvement in movement. *Cerebellum* 11, 457–487. doi: 10.1007/s12311-011-0331-9

Mead, G. E., Hsieh, C.-F., Lee, R., Kutlubaev, M., Claxton, A., Hankey, G. J., et al. (2013). Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. *Stroke* 44, 844–850. doi: 10.1161/STROKEAHA.112.673947

Mo, L., and Liu, A. (2020). Effects of transcranial Maanetic Stimuation combined with Behabilitation training on gait, balance and FMA score in patients with post stroke hemiplegia. *Chin J Integr Med Cardio-Cererovasc Dis* 18, 4065–4068. doi: 10.12102/j.issn.1672-1349.2020.23.038

Mou, G., Liu, Y., Ruan, Z., Dai, Y., Xie, L., Ai, Q., et al. (2021). Effects of low frequency repetitive transcranial magnetic stimulation on motor function of lower extremity in early re-covery stroke patients. *Chin J Rehabil* 36, 465–468. doi: 10.3870/zgkf.2021.08.004

Nathou, C., Duprey, E., Simon, G., Razafimandimby, A., Leroux, E., Dollfus, S., et al. (2018). Effects of low- and high-frequency repetitive transcranial magnetic stimulation on long-latency auditory evoked potentials. *Neurosci. Lett.* 686, 198–204. doi: 10.1016/j.neulet.2018.09.002

Neuls, P. D., Clark, T. L., Van Heuklon, N. C., Proctor, J. E., Kilker, B. J., Bieber, M. E., et al. (2011). Usefulness of the berg balance scale to predict falls in the elderly. *J. Geriatr. Phys. Ther.* 34, 3–10. doi: 10.1097/JPT.0b013e3181ff2b0e

Ng, S. S. M., and Hui-Chan, C. W. Y. (2010). Transcutaneous electrical stimulation on acupoints combined with task-related training to improve motor function and walking performance in an individual 7 years poststroke: a case study. *J. Neurol. Phys. Ther.* 34, 208–213. doi: 10.1097/NPT.0b013e3181fe0ab0

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. doi: 10.1136/bmj.n71

Parikh, V., Medley, A., Chung, Y.-C., and Goh, H.-T. (2023). Optimal timing and neural loci: a scoping review on the effect of non-invasive brain stimulation on post-stroke gait and balance recovery. *Top. Stroke Rehabil.* 30, 84–100. doi: 10.1080/10749357.2021.1990467

Park, C. S., and An, S. H. (2016). Reliability and validity of the modified functional ambulation category scale in patients with hemiparalysis. *J. Phys. Ther. Sci.* 28, 2264–2267. doi: 10.1589/jpts.28.2264

Park, H.-J., Oh, D.-W., Kim, S.-Y., and Choi, J.-D. (2011). Effectiveness of community-based ambulation training for walking function of post-stroke hemiparesis: a randomized controlled pilot trial. *Clin. Rehabil.* 25, 451–459. doi: 10.1177/0269215510389200

Patterson, K. K., Parafianowicz, I., Danells, C. J., Closson, V., Verrier, M. C., Staines, W. R., et al. (2008). Gait asymmetry in community-ambulating stroke survivors. *Arch. Phys. Med. Rehabil.* 89, 304–310. doi: 10.1016/j.apmr.2007.08.142

Paul, S. L., Srikanth, V. K., and Thrift, A. G. (2007). The large and growing burden of stroke. *Curr. Drug Targets* 8, 786–793. doi: 10.2174/138945007781077418

Roth, Y., Levkovitz, Y., Pell, G. S., Ankry, M., and Zangen, A. (2014). Safety and characterization of a novel multi-channel TMS stimulator. *Brain Stimul.* 7, 194–205. doi: 10.1016/j.brs.2013.09.004

Roth, Y., Padberg, F., and Zangen, A. (2007). Transcranial magnetic stimulation of deep brain regions: principles and methods. *Adv Biol Psychiatr.* 23, 204–225. doi: 10.1159/000101039

Rouse, B., Chaimani, A., and Li, T. (2017). Network meta-analysis: an introduction for clinicians. *Intern. Emerg. Med.* 12, 103–111. doi: 10.1007/s11739-016-1583-7

Savović, J., Weeks, L., Sterne, J. A. C., Turner, L., Altman, D. G., Moher, D., et al. (2014). Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst. Rev.* 3:37. doi: 10.1186/2046-4053-3-37

Sharma, H., Vishnu, V. Y., Kumar, N., Sreenivas, V., Rajeswari, M. R., Bhatia, R., et al. (2020). Efficacy of low-frequency repetitive transcranial magnetic stimulation in ischemic stroke: a double-blind randomized controlled trial. *Arch Rehabil Res Clin Transl* 2:100039. doi: 10.1016/j.arrct.2020.100039

Shim, S., Yoon, B.-H., Shin, I.-S., and Bae, J.-M. (2017). Network meta-analysis: application and practice using Stata. *Epidemiol Health* 39:e2017047. doi: 10.4178/epih.e2017047

Smith, M.-C., Byblow, W. D., Barber, P. A., and Stinear, C. M. (2017). Proportional recovery from lower limb motor impairment after stroke. *Stroke* 48, 1400–1403. doi: 10.1161/STROKEAHA.116.016478

Swayne, O. B. C., Rothwell, J. C., Ward, N. S., and Greenwood, R. J. (2008). Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cereb. Cortex* 18, 1909–1922. doi: 10.1093/cercor/bhm218

Tao, F., Wang, C., Chen, B., Qiu, M., and Jiang, L. (2022). Effects of low frequency repetitive transcranial magnetic stimulation combined with mirror therapy on lower limb motor function and balance in stroke patients with hemiplegia. Chin. *J. Rehabil. Med.* 37, 611–615+622. doi: 10.3969/j.issn.1001-1242.2022.05.007

Tufanaru, C., Munn, Z., Stephenson, M., and Aromataris, E. (2015). Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int. J. Evid. Based Healthc.* 13, 196–207. doi: 10.1097/XEB.0000000000000065

Tung, Y.-C., Lai, C.-H., Liao, C.-D., Huang, S.-W., Liou, T.-H., and Chen, H.-C. (2019). Repetitive transcranial magnetic stimulation of lower limb motor function in patients with stroke: a systematic review and meta-analysis of randomized controlled trials. *Clin. Rehabil.* 33, 1102–1112. doi: 10.1177/0269215519835889

Wang, S., and Li, L. (2022). Effects of cerebellar theta-burst stimulation on lower extremity motor function in stroke patients. *Chin J Rehabil Theory Pract* 28, 1205–1210. doi: 10.3969/j.issn.1006-9771.2022.10.011

Wang, D., Peng, B., Zhang, H., Wang, Y., Liu, N., Shan, C., et al. (2022). Brief report on stroke prevention and treatment in China, 2020. *Chin J Cerebrovasc Dis* 19, 136–144. doi: 10.3969/j.issn.1672-5921.2022.02.011

Wang, R.-Y., Tseng, H.-Y., Liao, K.-K., Wang, C.-J., Lai, K.-L., and Yang, Y.-R. (2012). rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. *Neurorehabil. Neural Repair* 26, 222–230. doi: 10.1177/1545968311423265

Wang, R.-Y., Wang, F.-Y., Huang, S.-F., and Yang, Y.-R. (2019). High-frequency repetitive transcranial magnetic stimulation enhanced treadmill training effects on gait performance in individuals with chronic stroke: a double-blinded randomized controlled pilot trial. *Gait Posture* 68, 382–387. doi: 10.1016/j.gaitpost.2018.12.023

Wang, C., Zeng, Q., Yuan, Z., Wang, W., and Shen, M. (2023). Effects of low-frequency (0.5 Hz) and high-frequency (10 Hz) repetitive transcranial magnetic stimulation on neurological function, motor function, and excitability of cortex in ischemic stroke patients. *Neurologist* 28, 11–18. doi: 10.1097/NRL.0000000000000435

Wessel, M. J., and Hummel, F. C. (2018). Non-invasive cerebellar stimulation: a promising approach for stroke recovery? *Cerebellum* 17, 359–371. doi: 10.1007/s12311-017-0906-1

White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. T. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res. Synth. Methods* 3, 111–125. doi: 10.1002/jrsm.1045

Woodford, H., and Price, C. (2007). EMG biofeedback for the recovery of motor function after stroke. *Cochrane Database Syst. Rev.* 2010:CD004585. doi: 10.1002/14651858.CD004585.pub2

Xia, Y., Xu, Y., Li, Y., Lu, Y., and Wang, Z. (2022). Comparative efficacy of different repetitive transcranial magnetic stimulation protocols for stroke: a network meta-analysis. *Front. Neurol.* 13:918786. doi: 10.3389/fneur.2022.918786

Xie, Y.-J., Chen, Y., Tan, H.-X., Guo, Q.-F., Lau, B. W.-M., and Gao, Q. (2021a). Repetitive transcranial magnetic stimulation for lower extremity motor function in patients with stroke: a systematic review and network meta-analysis. *Neural Regen. Res.* 16, 1168–1176. doi: 10.4103/1673-5374.300341

Xie, Y.-J., Wei, Q.-C., Chen, Y., Liao, L.-Y., Li, B.-J., Tan, H.-X., et al. (2021b). Cerebellar theta burst stimulation on walking function in stroke patients: a randomized clinical trial. *Front. Neurosci.* 15:688569. doi: 10.3389/fnins.2021.688569

Yan, Y., Yu, L., and Shao, Y. (2023). Effect of low frequency repetitive transcranial magnetic stimulation on lower limb spasticity and balance gait in patients with hemiplegia after stroke. *China Med Her* 20, 81–85. doi: 10.20047/j.issn1673-7210.2023.14.17

Yang, L., Sheng, Y., Xie, L., Wei, H., and Peng, T. (2016). The effect of repetitive transcranial magnetic stimulation combined with rehabilitation training on the walking function of stroke patients. *Chin J Phys Med Rehabil* 38, 907–909. doi: 10.3760/cma.j.issn.0254-1424.2016.12.007

Zhao, X., Liu, T., Zhou, Y., and Zhang, L. (2018). The effect of repetitive transcranial magnetic stimulation on dyskinesia in stroke patients. *Chin J Rehabil Med* 33, 800–805. doi: 10.3969/j.issn.1001-1242.2018.07.009

Zhou, J., Zhang, L., Li, R., Xu, K., and Wu, C. (2020). Effect of repetitive transcranial magnetic stimulation combined with exercise therapy on the motor function in stroke patients with hemiplegia. *Rehabil Med* 30, 235–239. doi: 10.3724/SP.J.1329.2020.03013

Zhu, D., Liu, S., Wang, L., Huang, Z., and Ni, J. (2022). Effects of repetitive transcranial magnetic stimulation combined with task-oriented training on lower limb function in stroke patients. *Chin J Rehabil Med* 37, 1046–1050. doi: 10.3969/j.issn.1001-1242.2022.08.006

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Peripheral nerve blocks of wrist and finger flexors can increase hand opening in chronic hemiparetic stroke

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Introduction: Hand opening is reduced by abnormal wrist and finger flexor activity in many individuals with stroke. This flexor activity also limits hand opening produced by functional electrical stimulation (FES) of finger and wrist extensor muscles. Recent advances in electrical nerve block technologies have the potential to mitigate this abnormal flexor behavior, but the actual impact of nerve block on hand opening in stroke has not yet been investigated.

Methods: In this study, we applied the local anesthetic ropivacaine to the median and ulnar nerve to induce a complete motor block in 9 individuals with stroke and observed the impact of this block on hand opening as measured by hand pentagonal area. *Volitional* hand opening and *FES*-driven hand opening were measured, both while the arm was fully supported on a haptic table (*Unloaded*) and while lifting against gravity (*Loaded*). Linear mixed effect regression (LMER) modeling was used to determine the effect of *Block*.

Results: The ropivacaine block allowed increased hand opening, both volitional and FES-driven, and for both unloaded and loaded conditions. Notably, only the *FES*-driven and *Loaded* condition's improvement in hand opening with the block was statistically significant. Hand opening in the *FES* and *Loaded* condition improved following nerve block by nearly 20%.

Conclusion: Our results suggest that many individuals with stroke would see improved hand-opening with wrist and finger flexor activity curtailed by nerve block, especially when FES is used to drive the typically paretic finger and wrist extensor muscles. Such a nerve block (potentially produced by aforementioned emerging electrical nerve block technologies) could thus significantly address prior observed shortcomings of FES interventions for individuals with stroke.

KEYWORDS

nerve block, stroke, anesthesia, hand opening, grasp, FES, upper extremity synergies, paresis

1 Introduction

An estimated 9.4 million Americans 20 years of age or older self-reported having had a stroke, with projections suggesting that an additional 3.4 million Americans may join them by 2030 (1). Moderately impaired individuals have a reduced ability to open their hands, while severely impaired individuals are often unable to open their impaired hand at all—especially due to involuntary flexion forces at wrist and fingers linked to increasing abduction load at the shoulder (2) and flexor hypertonia (3). While motor impairments at the paretic hand are due to multiple factors (4), of particular importance are *overactive wrist and finger flexors* and simultaneous *extensor weakness* (5). In particular, the proportional reduction of hand opening in relation to shoulder abduction loading results largely from the expression of the "*flexion synergy*" (i.e., abnormal coupling between shoulder abduction and elbow/wrist and finger flexion) (6–8), thought to be due to greater reliance on reticulospinal projections following a hemiparetic stroke (9). Furthermore, the flexor hypertonia may be related to the possible upregulation of monoaminergic coeruleospinal projections (10). The presence of hyperactive stretch reflexes, in comparison, may not play a major role in stroke disability (5) compared to the expression of said flexion synergy (11). As passive muscle properties are also largely unchanged (4, 12), it is likely the overactive wrist and finger flexors (*particularly* the flexion synergy) and extensor weakness that limits hand use in stroke.

The reduction in hand opening while lifting, induced by said flexion synergy expression (2), persists even when assisted by functional electrical stimulation (FES), limiting the effectiveness of FES interventions (13–15). Limited ability to open one's hand can also lead to the "learned disuse" of the whole paretic arm (16), potentially worsening patient outcomes over time. Without the useful end-effector necessary for many activities of daily living, the impact of reach-focused rehabilitation interventions (17, 18) can be reduced as well.

A possible method for improving hand opening during lifting is thus to inhibit the "over-activated" flexors. One of the most commonly utilized clinical methods for reducing hyperactive flexor activity is the use of botulinum toxin A, which temporarily reduces function at the neuromuscular junction (19, 20). This approach has been employed with initially encouraging results (21–23). However, the approach also has a number of limitations. While the "therapeutic effect" is reported to last 3 months, the magnitude of that effect varies significantly within this window with peak effect occurring around 5 weeks and gradual reduction of effect thereafter (24). Therefore, most patients require repeat injections, often in combination with physical therapies, every 3 to 4 months (25). A review article has shown strong evidence that botulinum toxins reduce hypertonia and spasticity (i.e., hyperactive stretch reflex), but its effect on improving hand and arm function is less compelling (26). Botulinum toxins further reduce the strength of the already paretic muscle, which may negatively impact function (27). Some individuals even develop neutralizing antibodies to the toxin, rendering the intervention ineffective with repeat injections (28). Finally, evidence also indicates potential long-term concerns related to increased muscle passive stiffness, possibly due to muscle extracellular matrix proliferation (12, 29–32). An alternative worth exploring is the use of FES-based methods that provide instantaneous, controllable, and reversible blocking of peripheral nerve transmission (33–35). However, these methods are still under development, and their feasibility in improving voluntary hand opening and/or FES-driven hand opening, with or without arm lifting, has yet to be evaluated.

In this study we temporarily relaxed the finger flexor muscles using an anesthesia block of the median and ulnar nerves as a proxy for future electrical block techniques. Specifically, ropivacaine was selected for perineural injection into both median and ulnar nerves to provide an adequate motor block duration (~8.7 h) (36, 37) with low required dosages (5 mL) (38). The efficacy of such a temporary nerve block approach was then assessed by measuring improvements in volitional- and FES-assisted hand opening after the application of the anesthesia nerve block, both when the arm was in a relaxed state and when participants had to raise their paretic arm against gravity by abducting at the shoulder.

2 Materials and methods

2.1 Participants

Having conducted a power analysis based on earlier hand opening data involving stroke participants (2), in which we assumed a nerve block effect size of a 20% increase in hand opening and similar variance, we enrolled a total of 10 individuals with chronic stroke (occurring more than 1 year ago) for this proof-of-concept study. The respective demographics of these participants are detailed in Table 1. Participants were recruited from the Shirley Ryan AbilityLab/Physical Therapy and Human Movement Sciences Clinical Research Registry and from the greater Chicago area. Other main inclusion/exclusion criteria included: (1) paresis confined to one side, with an ability to lift the arm up to the horizontal plane while maintaining 90 degrees elbow flexion; (2) no allergies to lidocaine or ropivacaine, and no use of contraindicated medications; (3) no recent or prior long-term use of other chemodenervation approaches, such as botulinum toxin, in the hand and wrist flexor muscles; (4) absence of any severe concurrent medical problems (such as cardiorespiratory impairment) or any acute/chronic pain conditions in the upper extremities or spine greater than 5 on the 10-point visual analog scale; (5) no use of a

TABLE 1 Participant demographic and clinical data.

ID	FMA UE (/66)	Impaired arm	Dominant hand pre-stroke	Age	Sex	Years post stroke
S01	33	L	R	57	M	24
S02	18	R	R	64	M	12
S03	29	L	L	68	M	13
S04	24	R	R	41	M	7
S05	20	L	L	63	M	15
S06	20	R	R	74	F	18
S07	43	L	R	67	M	11
S08	47	L	R	61	M	7
S09	13	L	R	73	F	30
S10	47	L	R	52	M	12

FMA UE: Fugl–Meyer assessment of the upper extremity, a measure of impairment where the maximum score of 66 suggests a level of ability indistinguishable from able-bodied individuals. L, Left; R, right; M, male; F, female.

cardiac pacemaker, implanted defibrillator, neurostimulation device, or similar implanted electrical equipment.

All participants gave written informed consent for participation in this study and the publication of any potentially identifiable images or data included in this article, as approved by the Northwestern University Institutional Review Board (IRB #STU00213403).

2.2 Experimental setup

The experiment was performed on the Arm Coordination Training 3D (ACT^{3D}) system (39, 40), which consists of a modified HapticMaster robot (Moog-FCR BV, the Netherlands) and a Biodex chair and T-Base support system (Biodex Medical Systems, Shirley, NY). The ACT^{3D} was used to measure arm configuration and modulate shoulder abduction load. Under the "*Unloaded*" condition, a frictionless virtual haptic table was provided by the ACT^{3D}, and under the "*Loaded*" condition, a shoulder abduction load of 100% of the participant's limb weight (41) was imposed.

Participants were seated in the Biodex chair with the trunk and shoulder strapped securely to prevent compensatory movements. Following a short series of wrist and finger stretches, the participant's impaired arm was attached to the forearm orthosis of the ACT^{3D} and placed in a "Home Position" of 85° shoulder abduction (SABD), 90° elbow flexion (EF), 40° shoulder flexion (SF), and 0° wrist extension (WE) (see Figure 1). The participant's fingers, thumb, and palm were placed around a cylinder attached to the distal end of the forearm orthosis. On the cylinder, a pressure sensor mat (Custom TactArray Sensing System, Pressure Profile Systems Inc., Los Angeles, CA) was mounted circumferentially. This pressure mat contained 27 by 21 sensors across a 6.4 by 5.1-inch surface area, with each sensor able to record up to 50 PSI with a pressure sensitivity of 0.15%. Furthermore, five Model 180 sensors from two linked trakSTAR systems (Northern Digital Company, Waterloo, ON, Canada) were placed on each of the tips of the 5 fingers to record the hand aperture to an accuracy of 1.4 mm Root Mean Square Error.

2.2.1 Assistive functional electrical stimulation parameters

A 2-channel E-Wave surface stimulator (Zynex Medical, Englewood, CO) was used to stimulate forearm compartment finger muscles, with one set of bipolar cutaneous electrodes placed over the flexor digitorum superficialis (FDS), and the other bipolar electrode pair placed over the extensor digitorum communis (EDC). The E-Wave was set up with a 200 µs pulse width duration and a 28 Hz biphasic stimulation paradigm that balances participant comfort with minimization of fatigue (42, 43). For each participant, each channel's appropriate intensity was found by incrementally increasing the current amplitude until a visible plateau of effect was reached, or the participant expressed discomfort.

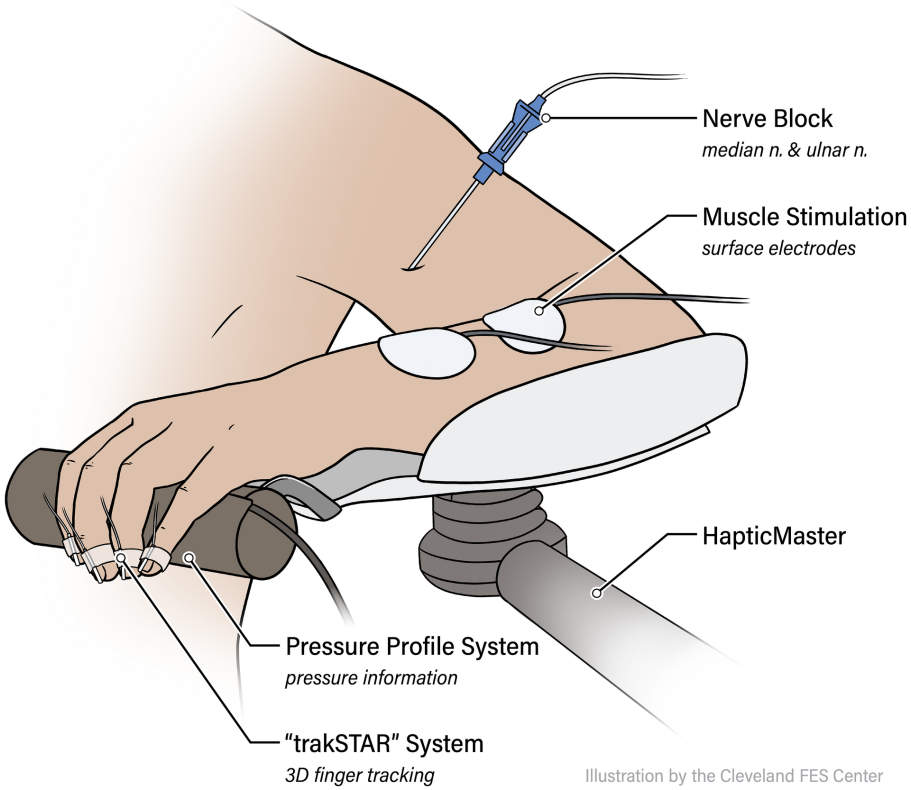

FIGURE 1
Experimental setup. Participants are attached via an orthosis to the ACT^{3D} assistive/loading device, and instrumented with the trakSTAR position sensors and PPS pressure mat. Functional electrical stimulation (FES) electrodes are placed on forearm flexors (flexor digitorum superficialis, or FDS) and extensors (extensor digitorum communis, or EDC).

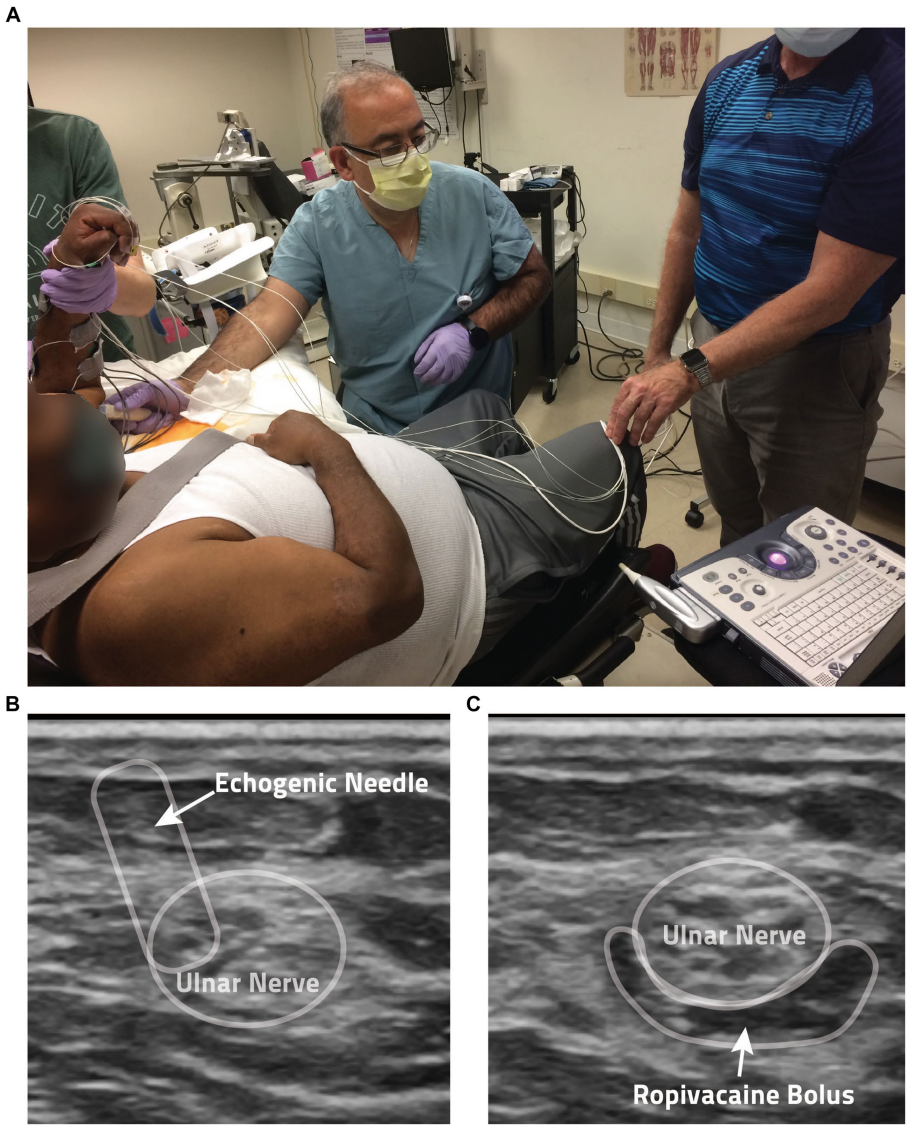

FIGURE 2
Anesthesia protocol. **(A)** Shown is a photo of the anesthesia application process. **(B)** Ultrasound guidance is used by the anesthesiologist in the administration of the local anesthesia ropivacaine. Shown here is the perineural injection method employed, with the echogenic needle noted by the arrow. **(C)** In this ultrasound image, you can see the anesthesia bolus surrounding a participant's ulnar nerve following injection.

2.3 Protocol

2.3.1 Before anesthesia (*Unblocked*)

After the instrumentation setup, each participant performed a series of hand *Opening* and *Closing* tasks. These tasks were done as groups of at least 3 repetitions per set of conditions, under the following 2-by-2 conditions, themselves selected in random order: shoulder abduction loading condition (*Loaded* vs. *Unloaded*) and driving condition (*Volitionally* vs. *FES* driven).

All tasks were performed with the tested arm/hand at the "Home Position." An auditory cue, 200 ms after the start of data collection, was used to trigger the participant to start the required task. Under the *Unloaded* condition, the participant opened or closed their hand volitionally (if a *Volitional* trial) or simply relaxed to let FES drive the task (if *FES* trial) for 6 s with the arm resting on the table. Under the *Loaded* condition, after hearing the auditory cue the participant first lifted their arm to the horizontal (90° SABD) level, then performed the open or close task *Volitionally* or with *FES* for 6 additional seconds. A rest period of at least 30 s was provided between trials to minimize fatigue.

2.3.2 Peripheral nerve anesthesia block

After the data collection for the *Unblocked* condition described above, the participant was prepped for applications of Ropivacaine to the ulnar and median nerves in the upper arm to induce a block of all wrist and finger flexors. After cleaning the skin with ChloraPrep (Becton, Dickinson and Company, Franklin Lakes, NJ), a trained anesthesiologist identified the position of each nerve via Ultrasound (GE LOGIQ e Ultrasound, 12L transducer, GE, Buc, France) and a SonoPlex echogenic nerve block needle (PAJUNK, Geisingen, Germany). Once a nerve was located, 5 mL of 0.5% Ropivacaine (Naropin, AstraZeneca, Wilmington, DE) was applied via perineural injection (see Figure 2). Throughout these injections, electrocardiogram, heart rate, and blood pressure were closely

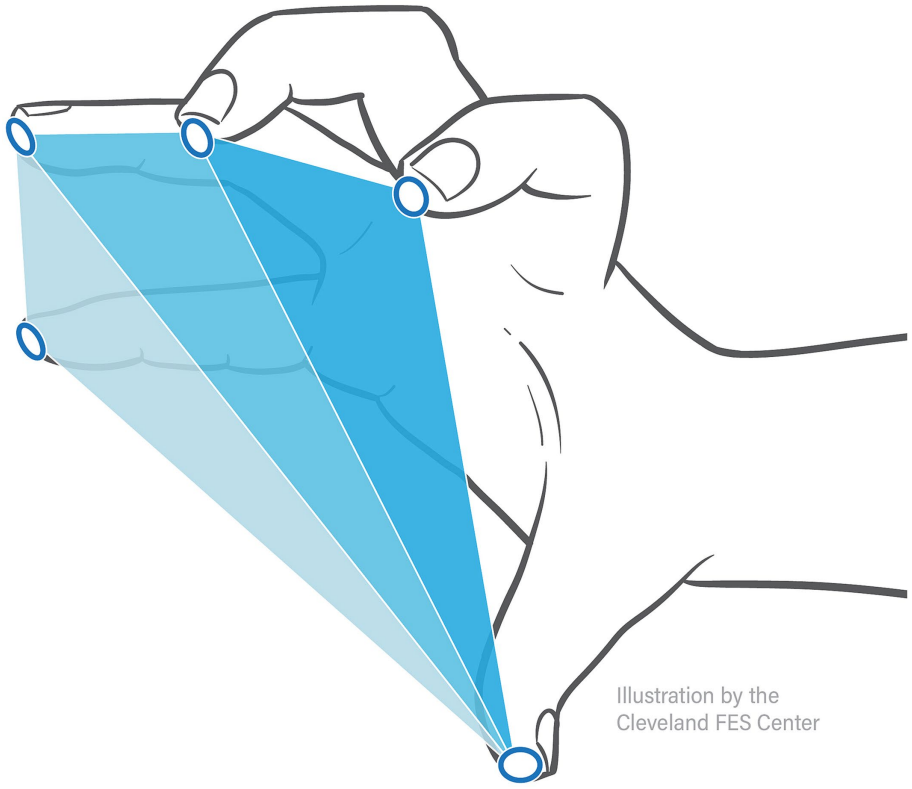

FIGURE 3
Hand pentagon area. Hand pentagon area, or HPA, is found using the trakSTAR sensor positions by calculating the surface area of three triangles made by the 5 fingertips: thumb-index-middle, thumb-middle-ring, and thumb-ring-pinky.

monitored (GE Carescape B105, GE Healthcare, Chicago, IL) for any adverse reactions.

2.3.3 After anesthesia (*Blocked* condition)

After a 1.5 h rest period during which the block effect was allowed to plateau, the same data collection under all the various conditions described in the *Unblocked* condition was repeated for the *Blocked* condition.

2.4 Data collection

Data was recorded using a custom MATLAB program (Mathworks, Natick, MA) using API libraries from Pressure Profile Systems and Northern Digital. The flexion force was measured by the pressure sensor mat sampled at 16.5 Hz. The finger position was measured by the trakSTAR system sampled at 30 Hz.

2.5 Data analysis

2.5.1 Outcome measures/metrics

Hand pentagon area (HPA), shown to be an effective measure in evaluating hand opening ability (2), was used as the primary outcome measure when quantifying hand opening. As shown in Figure 3, this area (in mm^2) was calculated as the sum of the surface area of three triangles formed by the participant's fingertip sensor locations in 3D space: thumb-index-middle, thumb-middle-ring, and thumb-ring-pinky. The maximum HPA presented during each *Hand Opening* trial was calculated. The average of these max HPAs across trials of the same conditions was then normalized by each participant's largest HPA (across all conditions), providing a 0–100% hand opening metric that could be readily compared across participants and between conditions.

To determine block success and gauge the impact of nerve block on FES function, the total grasp force generated by each participant's fingers and wrist in pounds (lbs) was calculated from pressure mat data by multiplying the PSI value of each sensor by each sensor's size (6 by 6 mm). The maximum presented grasp force during a *Hand Closing* trial was determined, ensemble-averaged across each participant's trials within the same condition, and finally normalized by each participant's largest *Volitional* grasp force.

An example of the collected HPA of two *Hand Opening* trials (*Unblocked* and *Blocked* of the same conditions) and the grasp force values of two *Hand Closing* trials (*Unblocked* and *Blocked* of the same conditions) can be seen in Figure 4.

2.5.2 Statistical analysis

At the individual level, paired *t*-tests were used per participant for *Volitionally*-driven Close and for *FES*-induced Close, separately, to verify that the nerve block significantly reduced grasp forces while not having any impact on FES behavior.

A linear mixed effects regression (LMER) model was then created to determine if observed significant differences in

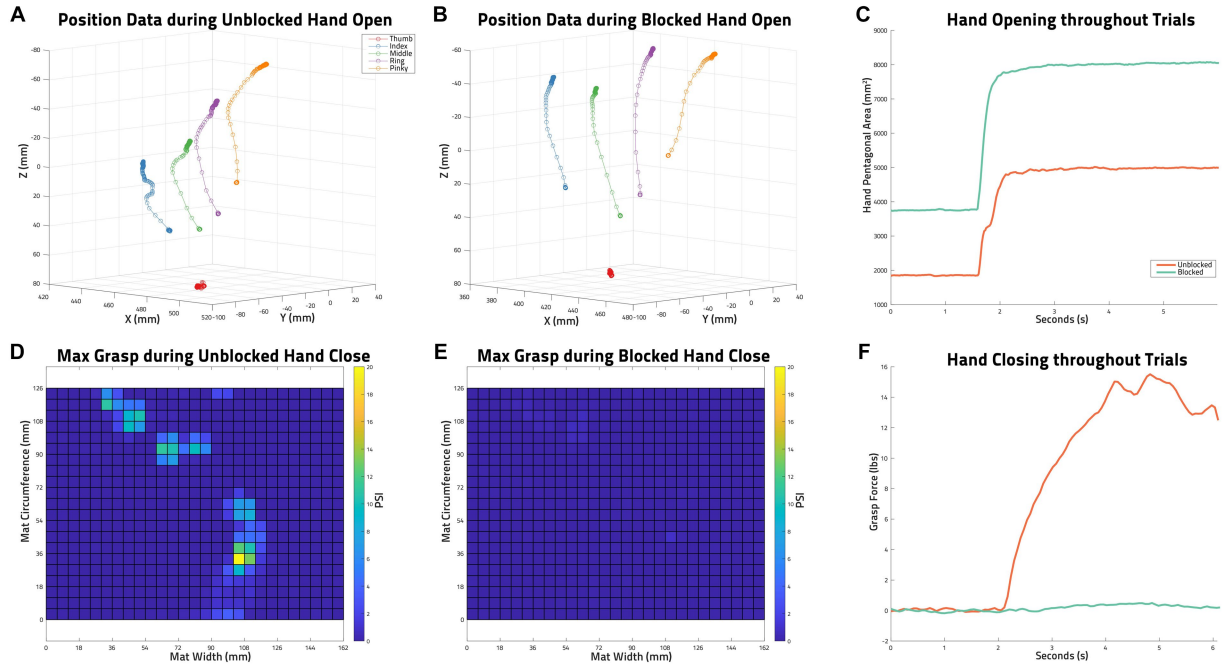

FIGURE 4
Example of Collected Data. **(A)** trakSTAR position data of all sensors during an unblocked hand opening task by S03: functional electrical stimulation (FES), unloaded, trial 3. **(B)** trakSTAR position data of all sensors during a blocked hand opening task by S03 (FES, unloaded, trial 2). **(C)** Hand pentagon area (HPA) as calculated from the sensor positions shown in **(A,B)** throughout the two mentioned trials. **(D)** The maximum grasp force measured with the PPS pressure mat during an unblocked volitional hand closing task by S03 (unloaded, trial 2). **(E)** The maximum grasp force measured with the PPS pressure mat during a blocked volitional hand closing task by s03 (unloaded, trial 1). **(F)** The grasp forces in lbs calculated from PPS pressure mat data (maxes of which are shown in **D,E**) throughout the two mentioned trials.

FES-induced grasp force followed a consistent trend dependent on the *Block* condition.

LMER models were also used to determine the impact of *Block* on hand-opening. Four models were made for the following conditions: *Volitional* and *Unloaded*, *Volitional* and *Loaded*, *FES*-driven and *Unloaded*, and *FES*-driven and *Loaded*. All data used in these models were normally distributed (Shapiro–Wilk test) so as to satisfy LMER assumptions.

Statistical significance was set at $p < 0.05$. All statistical analyses were performed in R (The R Foundation, Indianapolis, IN).

3 Results

3.1 Determining block success

The ability of the anesthesia block of the median and ulnar nerves to reduce hand flexor muscle forces is illustrated in Figure 5, which shows flexion forces before and after the block for each of the participants in this study. To ensure a successful block, grasping forces were measured during (1) voluntary hand closing while the arm was supported (*Unloaded*) and (2) simultaneous voluntary and synergy-driven hand closing from lifting the arm against a load (*Loaded*). For all participants except one (S09), the anesthesia block produced large decreases (average 75%) in grasp force; S09 is denoted with an asterisk in all figures for this reason.

A paired *t*-test per participant (using *all* of their *Volitional* Close trials, both *Unloaded* and *Loaded*) indicated a significant ($p < 0.05$) drop in grasp force following the nerve block in all participants except S09 (whose means are represented by an asterisk in Figure 5 instead of a circle). Table 2 shows both the grasp forces of each participant and the percent drop in *Volitional* grasp force due to anesthesia nerve block per participant. Participant S09 had a much lower grasp force than any of the other participants, and the relative decrease (36.5%) in grasp force was significantly lower than the other participants. A successful nerve block was defined as a drop of at least 50% *Volitional* grasp forces following the application of anesthesia (4). Thus, S09 was not included in any subsequent statistical analyses.

3.2 FES behavior post nerve block

The impact of the anesthesia block on the hand flexion forces elicited by FES (applied at the forearm, below the elbow) is illustrated in Figure 6. The mean normalized FES-induced grasp forces before and after the nerve blocks are shown for the participants, along with their accompanying standard deviations. The average change in normalized FES-elicited grasp forces across participants before and after the block was very small—it is shown by the darker line, along with its associated standard deviation.

A paired *t*-test per participant using all *FES Unloaded* trial data indicated that the nerve block did change the FES-induced grasping force ($p < 0.05$) for 6 out of 9 eligible participants. Furthermore, an LMER model that included only *Block* as the Fixed Effect and *Participant* as the Random Effect was used to determine whether nerve block has any effect on FES-driven hand closing forces under the *Unloaded* condition (Table 3). The model did not find *Block* statistically significant ($p \gg 0.05$).

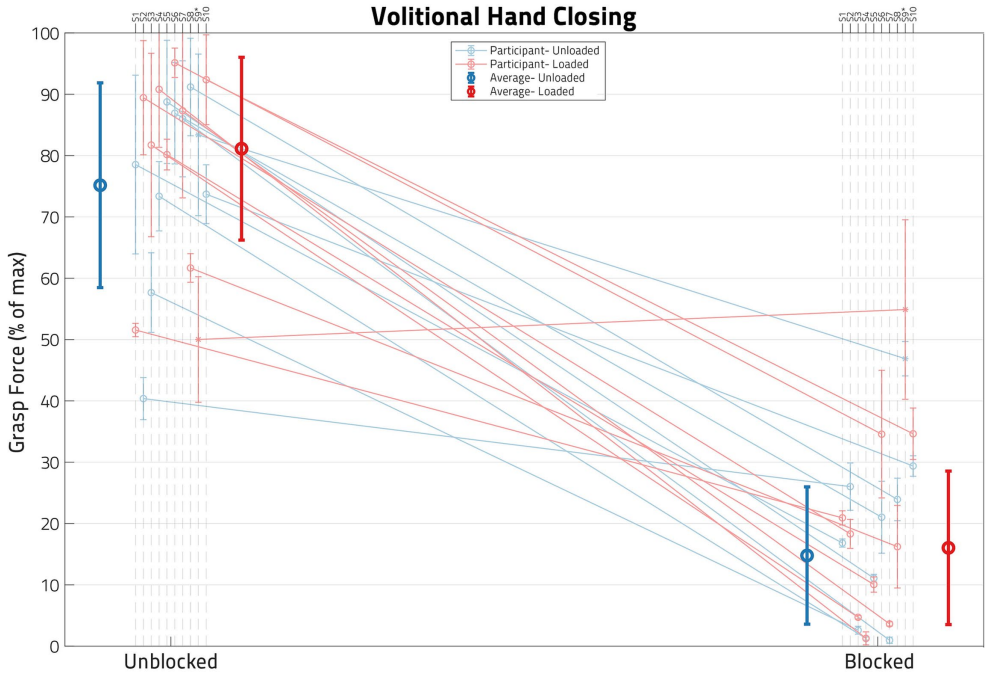

FIGURE 5
Impact of block on volitional hand closing. Each dot represents the normalized mean grasp force for a set of load and block conditions, with the error bars denoting standard deviation. Unblocked means are on the left and blocked means on the right. The blue lines represent *Unloaded* shoulder trials and the red lines represent *Loaded* shoulder trials. The blue and red circles on the left are the cross-participant averages for the *Unblocked* condition, while the corresponding circles on the right are for the *Blocked* condition. Note that, following block, grasp forces are reduced in most participants, verified by a paired *t*-test ($p < 0.05$). Only one participant, S09, failed to demonstrate statistical difference between pre- and post-nerve Block.

TABLE 2 **Maximum possible block impact per participant.**

ID	FMA UE (/66)	Maximum vol grasp (lbs)	%Vol grasp drop by block	% open increase by block	% Vol open increase by block	% FES open increase by block
S01	33	47.47	61.71	47.45	3.87	47.43
S02	18	27.76	71.14	35.40	15.36	1.36
S03	29	25.10	79.12	77.96	41.20	36.94
S04	24	32.70	89.55	68.75	4.43	50.57
S05	20	55.33	78.70	3.41	−2.04	0.07
S06	20	6.92	74.10	71.79	65.12	19.66
S07	43	29.73	86.35	−6.93	−7.96	−13.79
S08	47	34.99	74.96	68.95	67.97	66.92
S09	13	3.18	36.50	60.26	32.21	23.15
S10	47	18.58	62.99	49.60	49.61	32.09

All data within the four % columns were calculated from the means of each set of conditions (Open/Close, *Vol*/*FES*, *Unloaded*/*Loaded*, *Unblocked*/*Blocked*), taking the largest mean value from applicable conditions and subtracting from it the smallest mean value from the unblocked corollaries. "Vol" stands for "Volitional," FES stands for Functional Electrical Stimulation, and FMA UE stands for Fugl–Meyer assessment of the upper extremity.

3.3 Hand opening

Figure 7 shows the hand opening expressed as hand pentagon area (HPA) of all 10 participants, normalized per participant to their largest observed HPA. While most participants demonstrated an increase in hand opening following block for most conditions, this behavior was not ubiquitous in our 9-person sample (see S05 and S07 in Figure 7 and Table 2). The block had its largest and most consistent effect for FES-elicited contractions while supporting a load at the shoulder.

Four LMER models were created to determine the impact of *Block* on hand opening under the conditions of interest (*Loaded* vs. *Unloaded* and *Volitional* vs. *FES*). While all four models found that *Block* had, when viewed across the 9 participants included, a positive impact on hand opening, only in the *FES*-driven and shoulder-*Loaded* condition was the effect found to be significant ($p < 0.05$). In this model, the

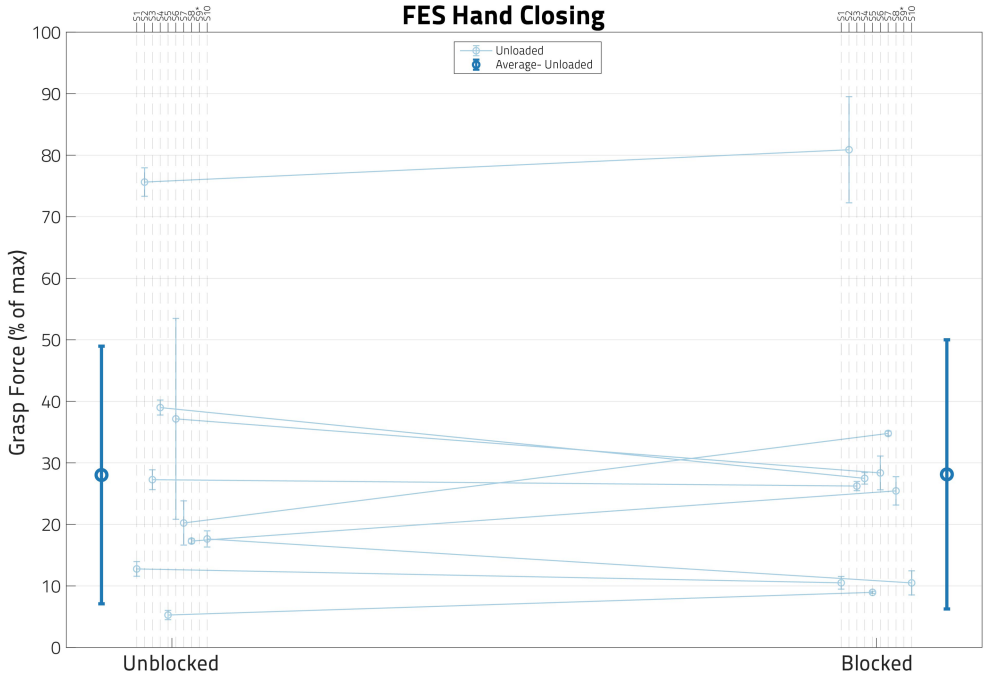

FIGURE 6
Impact of block on FES behavior. In this figure, each dot represents the normalized mean functional electrical stimulation (or FES) induced grasp force from the trials for one participant, with the error bars denoting standard deviations. While paired *t*-tests showed that these two populations were significantly different in some participants, a linear mixed effects regression (LMER) model found that there was no global trend. S09's data is not shown in this figure as their FES grasp forces surpassed the volitional grasp force 0–100% range.

TABLE 3 LMER results.

FES unloaded hand closing LMER				
Normalized Grasp ~1 + Block + (1|Subject: Trial) + (1|Block: Subject)				
Term	*Estimate*	95% *Confidence intervals*		*p-value*
Block	0.2994	−19.25	19.83	0.97652
Hand Opening LMERs				
Normalized opening ~1 + Block + (1|Subject: Trial) + (1|Block: Subject)				
Volitional and Unloaded				
Term	*Estimate*	95% *Confidence intervals*		*p-value*
Block	11.838	−8.49	32.17	0.273
Volitional and Loaded				
Term	*Estimate*	95% *Confidence intervals*		*p-value*
Block	12.538	−8.02	33.10	0.252
FES and Unloaded				
Term	*Estimate*	95% *Confidence intervals*		*p-value*
Block	3.129	−7.88	14.15	0.587
FES and Loaded*				
Term	*Estimate*	95% *Confidence intervals*		*p-value*
Block	19.431	1.56	37.30	0.0499*

Shown below are the linear mixed effect regression (LMER) models created for the functional electrical stimulation (FES) hand closing and all hand opening results. While individual *t*-test results for FES hand closing found significant differences pre/post *Block* for 6 of the 9 eligible participants, the LMER model did not find *Block* to be significant, and the coefficient estimate is near 0, suggesting no consistent trend. Regarding hand opening LMER data, all four models provided a positive coefficient for *Block*, but only in the *FES + Load* case was the difference found to be significant.

coefficient of block was found to be 19.431, or a roughly 20% increase in hand opening following the application of the nerve block.

To verify that the nerve block reduced the impact of shoulder loading on FES hand opening, we performed an additional one-tailed paired *t*-test on the change in FES hand opening brought on by loading, shown in Table 4. The drop in FES hand opening induced by *Load* was found to be significantly less in the *Blocked* case than in the *Unblocked* case ($p = 0.02198$).

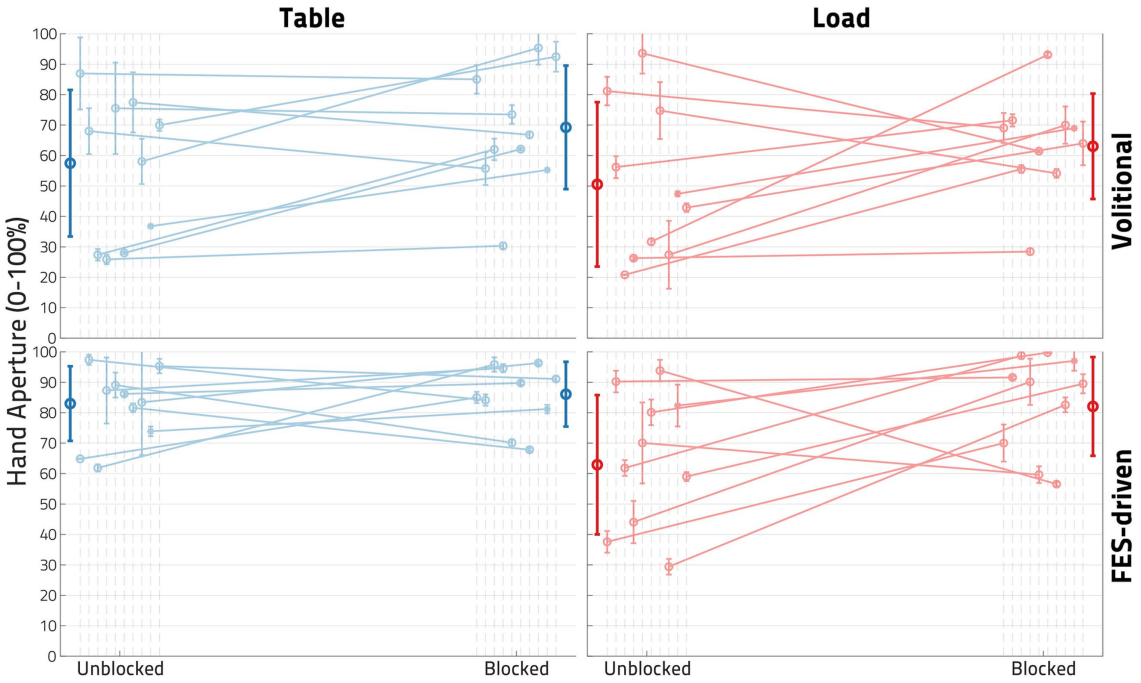

FIGURE 7
Impact of block on hand opening. In each plot, each dot represents the normalized mean hand pentagon area (HPA) from the trials of one participant in the denoted conditions, with the error bars denoting standard deviations. The left column of plots showcases the *Unloaded* (or table) condition, while the right represents the *Loaded* condition. The top row shows the *Volitional* condition, while the bottom row shows the functional electrical stimulation (*FES*)-driven condition. Four linear mixed effects regression (LMER) models were created for the four plots shown. In the bottom right plot- the FES-driven w/load condition- the *Block* term was found to be statistically significant ($p < 0.05$).

4 Discussion

4.1 Summary of findings and previous research

Our results demonstrated that Ropivacaine injection in the median and ulnar nerves induced a block of hand grasp in 9 out of 10 participants with moderate to severe stroke, averaging 75% of their maximum hand grasp force. Furthermore, we demonstrated that FES was able to produce flexion forces distal of the flexor nerve block sites. The effectiveness of FES distal to the nerve block injection sites is critical as it allows for the possibility of performing a functional hand task with FES assistance following a block. Most importantly, this study has shown that blocking the median and ulnar nerves responsible for wrist and finger flexion *can* improve FES-assisted hand opening outcomes even during shoulder abduction loading conditions. Previous literature had demonstrated the potential of nerve block approaches to address abnormal passive and active torques at the first MCP joint (4). Our current study demonstrated the effect of nerve block on a more functionally relevant measurement of hand opening (HPA), and, for the first time, in reducing the detrimental impact of shoulder abduction loading induced flexion synergy on hand opening.

Assistive FES has been employed to improve hand opening in individuals with stroke (13), but its functionality has been significantly limited by flexion synergy expression. There have been multiple attempts to reduce this synergy expression to increase hand opening outcomes, such as by also utilizing FES for shoulder muscles to reduce synergy presentation (15), or designing arm support devices (44) such as the SaeboMAS. The combination of flexor nerve block and extensor FES shown here addresses these prior limitations with FES interventions and improves the feasibility of using modern FES approaches (14) to enhance hand function following stroke, even in the most severely impaired individuals with tremendous extensor weakness.

TABLE 4 Load impact on FES opening, unblocked vs. blocked.

ID	Load delta, unblocked	Load delta, blocked
S01	−27.2609	−14.9751
S02	−7.14372	7.469255
S03	−0.02571	2.925072
S04	−43.2273	−4.49613
S05	−19.0013	−10.5008
S06	−6.0757	10.02314
S07	12.22537	−11.2919
S08	−54.0182	−13.7437
*S09	8.474343	15.8219
S10	−36.3131	−1.59081

Load Delta in this table is defined as the average Functional Electrical Stimulation (FES) -driven Hand Opening per participant (normalized by each participant's maximum Hand Pentagon Area, or HPA) in the Unloaded condition minus that of the Loaded condition. These values were calculated per participant, both before nerve block (middle column) and after (rightmost column). FES Hand Opening has been known to suffer severely following the addition of a load at the shoulder (as shown by large negative deltas), but the nerve block has reduced this issue for most participants; a one-tailed paired T-Test (*excluding S09) found that nerve block significantly reduced the impact of Load on FES-driven Hand Opening.

4.2 Study limitations and future work

4.2.1 Sample size

The original power analysis (G*Power, Heinrich-Heine-Universität, Dusseldorf, Germany) for this proof-of-concept study used an estimated effect size and standard deviation based on work that used an alternate measure of load at the shoulder (see 4.2.2). While 9 participants were sufficient to establish statistical significance in one set of conditions, a larger sample size could provide greater clarity on the impact of nerve block across the wide level of impairment encompassed by our participants. Of note is that the impact of nerve block on *Volitional* hand opening was still quite staggering in some individuals (such as S06), suggesting that *some* individuals could already benefit tremendously from nerve block alone without any assistance from FES. Determining which individuals may see such outcomes depends not only on a better understanding of mechanisms (4.2.5) but also on a larger sample size.

4.2.2 The effect of shoulder abduction loading

This study included trials with loading at the shoulder to evaluate the ability of nerve block to reduce the negative consequences of the flexion synergy on hand opening (2, 8). We studied two simple loading conditions: *Unloaded*, or when the participant was resting on a haptic table generated by the ACT^{3D}, and *Loaded*, when the participant had to lift the full weight of their limb (100% limb weight, or 100%LW, as used in prior studies (41)). Future studies should more completely take into account the varying levels of participant impairment and shoulder strength so as to remove the variability introduced by relying upon participant limb weight. One such metric that better normalizes results between participants of varying levels of impairment, strength, and limb weight is percentage of maximum voluntary torque (MVT) expression at the shoulder (45, 46); using metrics such as these should reduce the variability in resulting data and may provide greater insight into the variation in efficacy of nerve block in hand opening across different levels of stroke impairment.

4.2.3 Block success and impairment levels

Block success was determined by measuring the drop in volitional hand closing forces following the administration of ropivacaine using a within-subject comparison *t*-test. Nine out of 10 participants indeed showed large drops in volitional hand closing forces, averaging 75%. Some participants had particularly low volitional grasp forces prior to the nerve block as compared to those generated by FES, which made determining block efficacy in these participants more difficult. We believe that S09's failure to reach statistical significance and the 50% drop cutoff is due, in part, to the reduced dynamic range of the pressure mat at S09's lower grasp force levels. Although ropivacaine did not result in significantly reduced hand closing in S09 (for which their data was excluded from further statistical analysis), we still observed a ~60% increase in hand opening from S09 following the nerve block, indicating that this block improved hand opening (S09's data in the figures is denoted by an asterisk).

Regarding FES hand closing we observed minor, but statistically significant, variations in grasp forces before and after nerve block in 6 individuals (some increasing and others decreasing). The *Unblock* and *Block* FES Close cases have 2+ hours between them; many changes, such as fatigue and electrode site property changes, could occur during this period that can explain the change in grasp force. The statistical analysis based on the group data (see Table 3) did not show significant change in FES-induced flexion force. This result-that FES efficacy downstream of a nerve block site would perform similarly to the unblocked condition— was anticipated and supported by current understanding of the mechanisms of FES stimulation of muscle, but no prior scientific literature has technically demonstrated this. Now that this has been shown, FES assistance for flexors could arguably be applied alongside nerve block approaches in future interventions that might be unable to provide the required partial blocking or immediate on/off control of flexors necessary for an intervention useful for activities of daily living.

4.2.4 Mechanical side effects of nerve block

Though the LMER models showed a significant increase in FES hand opening ability during Load across our 9 participants, a few participants (S05 and S07) exhibited a decrease in FES or Volitional hand opening following the nerve block (Figure 7 and Table 2). We have considered two possible explanations for this: Firstly, ropivacaine nerve blocks affect not only motor, but also sensory nerve fibers, and the impact of this loss of afferent information in the spinal motor neuron loop on antagonist (extensor) behavior is not entirely clear. Secondly, loss of intrinsic hand muscles has often impaired FES hand outcomes in Spinal Cord Injury interventions, resulting in "claw hand" (47). This presents as strong finger flexion at the second and third MCP joint, reducing the HPA and thereby the potential for grasp functionality. We had occasionally observed such presentations in some of our participants, but our HPA metric did not take the orientation of the sensor into account. Future work could potentially omit ulnar nerve block or include FES of intrinsic hand muscles. Using implanted FES electrodes would, in general, provide precise, selective activation of the hand muscles needed to provide a more normal hand grasp pattern (48).

4.2.5 Disability mechanism contributions

Using electromyography (EMG) signals of relevant musculature as well as by calculating the purely flexion synergy-driven grasp forces exerted on the pressure mat during lifting, we next plan to analyze more directly the impact of the nerve block on certain known mechanisms of stroke disability. Of particular interest are the impacts of nerve block on the expression of hypertonia (tonic activation of wrist and finger flexors even while at rest), co-contraction (simultaneous activation of wrist and finger flexors and extensors during certain tasks (8)), and the expression of the flexion synergy (activation of wrist, finger, and elbow flexors proportional to the activity of shoulder abductors). This could help to explain why some participants improved in hand opening while others did not.

4.2.6 Electrical nerve block

There are a variety of electrically driven nerve block approaches currently in development (33) that could perform a similar function as Ropivacaine did in this study. KiloHertz frequency alternating current in particular (KHFAC) could provide a means for user-controlled, on/off, instant, and reversible flexor nerve block. Some studies have also demonstrated the potential for partial blocks using KHFAC (49). Regardless of whether managed by KHFAC block alone, or combined with newer emerging DC block approaches (50), a temporary and instant reduction of flexor activity combined with

FES-assisted extension could provide a permanent solution to functional losses at the hand in individuals with moderate to severe chronic stroke.

4.2.7 Alternate hand ability metrics

More work needs to be done to evaluate the impact of a general increase in hand opening (as measured by HPA) on activities of daily living. The "clawhand" presentation we observed in some participants may limit functional gain for certain individuals. A possible means to better account for "clawhand" while measuring hand aperture could be a hand hexagon area (HHA), where an additional sensor on the center of the back of the hand could serve as a reference (ref) for four triangles: ref-thumb-index, ref-index-middle, ref-middle-ring, and ref-ring-pinky. Lastly, comparing HPA, HHA, or any other hand-opening metrics against functional tests such as box and blocks or clothespin task could provide greater insight into the true value of a combination nerve block and assistive FES approach.

5 Conclusion

Blocking undesirable and abnormal hand flexor contractions in individuals following hemiparetic stroke using local anesthesia of the median and ulnar nerves was shown to improve the ability of most individuals to open their hands using assistive functional electrical stimulation of the hand extensor muscles. These results indicate that controllable and deployable methods for blocking peripheral nerves, such as electrical block, may facilitate the deployment of better, proven FES methods for hand functional restoration for individuals with hemiparetic stroke.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, upon request.

Ethics statement

The studies involving humans were approved by Northwestern University Institutional Review Board (IRB #STU00213403). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this article.

Author contributions

HD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing, Resources. JY: Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing. JD: Investigation, Methodology, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Supervision. AN: Conceptualization, Methodology, Writing – review & editing, Investigation. RK: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author declares that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke Statistics-2023 update: a report from the American Heart Association. *Circulation*. (2023) 147:e93–e621. doi: 10.1161/CIR.0000000000001123

2. Lan Y, Yao J, Dewald JPA. The impact of shoulder abduction loading on volitional hand opening and grasping in chronic hemiparetic stroke. *Neurorehabil Neural Repair*. (2017) 31:521–9. doi: 10.1177/1545968317697033

3. Li S, Kamper DG, Rymer WZ. Effects of changing wrist positions on finger flexor hypertonia in stroke survivors. *Muscle Nerve*. (2006) 33:183–90. doi: 10.1002/mus.20453

4. Kamper DG, Harvey RL, Suresh S, Rymer WZ. Relative contributions of neural mechanisms versus muscle mechanics in promoting finger extension deficits following stroke. *Muscle Nerve*. (2003) 28:309–18. doi: 10.1002/mus.10443

5. Kamper DG, Fischer HC, Cruz EG, Rymer WZ. Weakness is the primary contributor to finger impairment in chronic stroke. *Arch Phys Med Rehabil*. (2006) 87:1262–9. doi: 10.1016/j.apmr.2006.05.013

6. Brunnstrom S. (1970). *Movement therapy in hemiplegia: a neurophysiological approach*. New York: Harper & Row.

7. Dewald JP, Pope PS, Given JD, Buchanan TS, Rymer WZ. Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain*. (1995) 118:495–510. doi: 10.1093/brain/118.2.495

8. McPherson LM, Dewald JPA. Abnormal synergies and associated reactions post-hemiparetic stroke reflect muscle activation patterns of brainstem motor pathways. *Front Neurol*. (2022) 13:934670. doi: 10.3389/fneur.2022.934670

9. McPherson JG, Chen A, Ellis MD, Yao J, Heckman CJ, Dewald JPA. Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke. *J Physiol*. (2018a) 596:1211–25. doi: 10.1113/JP274968

10. Beauchamp J, Hassan A, Mcpherson L, Negro F, Pearcey G, Cummings M, et al. (2023) Motor unit firing rate modulation is more impaired during flexion synergy-driven contractions of the biceps brachii in chronic stroke. *medRxiv*. Available at: https://doi.org/10.1101/2023.11.22.23298905. [Epub ahead of preprint]

11. Ellis MD, Schut I, Dewald JPA. Flexion synergy overshadows flexor spasticity during reaching in chronic moderate to severe hemiparetic stroke. *Clin Neurophysiol*. (2017) 128:1308–14. doi: 10.1016/j.clinph.2017.04.028

12. Binder-Markey BI, Murray WM, Dewald JPA. Passive properties of the wrist and fingers following chronic hemiparetic stroke: Interlimb comparisons in persons with and without a clinical treatment history that includes botulinum neurotoxin. *Front Neurol*. (2021) 12:687624. doi: 10.3389/fneur.2021.687624

13. Chae J, Hart R. Intramuscular hand neuroprosthesis for chronic stroke survivors. *Neurorehabil Neural Repair*. (2003) 17:109–17. doi: 10.1177/0888439003017002005

14. Knutson JS, Chae J, Hart RL, Keith MW, Hoyen HA, Harley MY, et al. Implanted neuroprosthesis for assisting arm and hand function after stroke: a case study. *J Rehabil Res Dev*. (2012) 49:1505–16. doi: 10.1682/JRRD.2011.09.0171

15. Makowski NS, Knutson JS, Chae J, Crago PE. Functional electrical stimulation to augment poststroke reach and hand opening in the presence of voluntary effort: a pilot study. *Neurorehabil Neural Repair*. (2014) 28:241–9. doi: 10.1177/1545968313505913

16. Hunter SM, Crome P. Hand function and stroke. *Rev Clin Gerontol*. (2002) 12:68–81. doi: 10.1017/S0959259802012194

17. Ellis MD, Carmona C, Drogos J, Dewald JPA. Progressive abduction loading therapy with horizontal-plane viscous resistance targeting weakness and flexion synergy to treat upper limb function in chronic hemiparetic stroke: a randomized clinical trial. *Front Neurol*. (2018) 9:71. doi: 10.3389/fneur.2018.00071

18. Ellis MD, Sukal-Moulton T, Dewald JP. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. *Neurorehabil Neural Repair*. (2009) 23:862–9. doi: 10.1177/1545968309332927

19. Sommerfeld DK, Gripenstedt U, Welmer AK. Spasticity after stroke: an overview of prevalence, test instruments, and treatments. *Am J Phys Med Rehabil*. (2012) 91:814–20. doi: 10.1097/PHM.0b013e31825f13a3

20. Ward AB, Aguilar M, De Beyl Z, Gedin S, Kanovsky P, Molteni F, et al. Use of botulinum toxin type a in the management of adult spasticity—a European consensus statement. *J Rehabil Med*. (2003) 35:98–9. doi: 10.1080/16501970306112

21. Foley N, Pereira S, Salter K, Fernandez MM, Speechley M, Sequeira K, et al. Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. (2013) 94:977–89. doi: 10.1016/j.apmr.2012.12.006

22. Sampaio C, Ferreira JJ, Pinto AA, Crespo M, Ferro JM, Castro-Caldas A. Botulinum toxin type a for the treatment of arm and hand spasticity in stroke patients. *Clin Rehabil*. (1997) 11:3–7. doi: 10.1177/026921559701100102

23. Shaw LC, Price CI, van Wijck FM, Shackley P, Steen N, Barnes MP, et al. Botulinum toxin for the upper limb after stroke (BoTULS) trial: effect on impairment, activity limitation, and pain. *Stroke*. (2011) 42:1371–9. doi: 10.1161/STROKEAHA.110.582197

24. Ojardias E, Ollier E, Lafaie L, Celarier T, Giraux P, Bertoletti L. Time course response after single injection of botulinum toxin to treat spasticity after stroke: systematic review with pharmacodynamic model-based meta-analysis. *Ann Phys Rehabil Med*. (2022) 65:101579. doi: 10.1016/j.rehab.2021.101579

25. Turner-Stokes L, Jacinto J, Fheodoroff K, Brashear A, Maisonobe P, Lysandropoulos A. Longitudinal goal attainment with integrated upper limb spasticity management including repeat injections of botulinum toxin a: findings from the prospective, observational upper limb international spasticity (ULIS-III) cohort study. *J Rehabil Med*. (2021) 53:jrm00157. doi: 10.2340/16501977-2801

26. Levy J, Molteni F, Cannaviello G, Lansaman T, Roche N, Bensmail D. Does botulinum toxin treatment improve upper limb active function? *Ann Phys Rehabil Med*. (2019) 62:234–40. doi: 10.1016/j.rehab.2018.05.1320

27. Chen YT, Zhang C, Liu Y, Magat E, Verduzco-Gutierrez M, Francisco GE, et al. The effects of botulinum toxin injections on spasticity and motor performance in chronic stroke with spastic hemiplegia. *Toxins*. (2020) 12:492. doi: 10.3390/toxins12080492

28. Rahman E, Banerjee PS, Asghar A, Gupta NK, Mosahebi A. Botulinum toxin type a immunogenicity across multiple indications: an overview systematic review. *Plast Reconstr Surg*. (2022) 149:837–48. doi: 10.1097/PRS.0000000000008904

29. Minamoto VB, Suzuki KP, Bremner SN, Lieber RL, Ward SR. Dramatic changes in muscle contractile and structural properties after 2 botulinum toxin injections. *Muscle Nerve*. (2015) 52:649–57. doi: 10.1002/mus.24576

30. Pingel J, Wienecke J, Lorentzen J, Nielsen JB. Botulinum toxin injection causes hyper-reflexia and increased muscle stiffness of the triceps surae muscle in the rat. *J Neurophysiol*. (2016) 116:2615–23. doi: 10.1152/jn.00452.2016

31. Thacker BE, Tomiya A, Hulst JB, Suzuki KP, Bremner SN, Gastwirt RF, et al. Passive mechanical properties and related proteins change with botulinum neurotoxin a injection of normal skeletal muscle. *J Orthop Res*. (2012) 30:497–502. doi: 10.1002/jor.21533

32. Ward SR, Minamoto VB, Suzuki KP, Hulst JB, Bremner SN, Lieber RL. Recovery of rat muscle size but not function more than 1 year after a single botulinum toxin injection. *Muscle Nerve*. (2018) 57:435–41. doi: 10.1002/mus.25707

33. Bhadra N, Vrabec TL, Bhadra N, Kilgore KL. Reversible conduction block in peripheral nerve using electrical waveforms. *Bioelectron Med*. (2018) 1:39–54. doi: 10.2217/bem-2017-0004

34. Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. *Neuromodulation*. (2014) 17:242–55. doi: 10.1111/ner.12100

35. Vrabec T, Bhadra N, Wainright J, Kilgore K. Non-damaging nerve conduction block using direct current. *Int FES Soc*. (2012):4–6.

36. Koraki E, Stachtari C, Kapsokalyvas I, Stergiouda Z, Katsanevaki A, Trikoupi A. Dexmedetomidine as an adjuvant to 0.5% ropivacaine in ultrasound-guided axillary brachial plexus block. *J Clin Pharm Ther*. (2018) 43:348–52. doi: 10.1111/jcpt.12657

37. Fresenius Kabi (2018) Naropin ® (ropivacaine HCl) injection. Fresenius Kabi. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020533s035lbl.pdf. (Accessed August 7, 2023)

38. Safa B, Flynn B, McHardy PG, Kiss A, Haslam L, Henry PD, et al. Comparison of the analgesic duration of 0.5% bupivacaine with 1:200,000 epinephrine versus 0.5% ropivacaine versus 1% ropivacaine for low-volume ultrasound-guided interscalene brachial plexus block: a randomized controlled trial. *Anesth Analg*. (2021) 132:1129–37. doi: 10.1213/ANE.0000000000005373

39. Dewald JP, Ellis MD, Acosta AM, Sohn MH, Plaisier TA. Implementation of impairment-based neurorehabilitation devices and technologies following brain injury In: *Neurorehabilitation technology*. Cham: Springer (2022). 89–112.

40. Sukal TM, Ellis MD, Dewald JPA. (2005). Dynamic characterization of upper limb discoordination following hemiparetic stroke. IEEE 9th International Conference on Rehabilitation Robotics. Chicago, IL

41. Sukal TM, Ellis MD, Dewald JP. Shoulder abduction-induced reductions in reaching work area following hemiparetic stroke: neuroscientific implications. *Exp Brain Res*. (2007) 183:215–23. doi: 10.1007/s00221-007-1029-6

42. Gregory CM, Dixon W, Bickel CS. Impact of varying pulse frequency and duration on muscle torque production and fatigue. *Muscle Nerve*. (2007) 35:504–9. doi: 10.1002/mus.20710

43. Wilson RD, Page SJ, Delahanty M, Knutson JS, Gunzler DD, Sheffler LR, et al. Upper-limb recovery after stroke: a randomized controlled trial comparing EMG-triggered, cyclic, and sensory electrical stimulation. *Neurorehabil Neural Repair*. (2016) 30:978–87. doi: 10.1177/1545968316650278

44. Ghassemi M, Kamper DG. The hand after stroke and SCI: restoration of function with technology In: *Neurorehabilitation technology*. Cham: Springer (2022). 113–34.

45. McPherson JG, Stienen AH, Drogos J, Dewald JPA. (2011). The relationship between the flexion synergy and stretch reflexes in individuals with chronic hemiparetic

stroke. IEEE International Conference on Rehabilitation Robotics. Zurich, Switzerland. 1–7.

46. McPherson JG, Stienen AH, Drogos JM, Dewald JP. Modification of spastic stretch reflexes at the elbow by flexion synergy expression in individuals with chronic hemiparetic stroke. *Arch Phys Med Rehabil*. (2018b) 99:491–500. doi: 10.1016/j.apmr.2017.06.019

47. Binder-Markey BI, Dewald JPA, Murray WM. The biomechanical basis of the claw finger deformity: a computational simulation study. *J Hand Surg Am*. (2019) 44:751–61. doi: 10.1016/j.jhsa.2019.05.007

48. Kilgore KL, Anderson KD, Peckham PH. Neuroprosthesis for individuals with spinal cord injury. *Neurol Res*. (2020) 45:893–905. doi: 10.1080/01616412.2020.1798106

49. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. *Muscle Nerve*. (2005) 32:782–90. doi: 10.1002/mus.20428

50. Franke M, Vrabec T, Wainright J, Bhadra N, Bhadra N, Kilgore K. Combined KHFAC + DC nerve block without onset or reduced nerve conductivity after block. *J Neural Eng*. (2014) 11:056012. doi: 10.1088/1741-2560/11/5/056012

Glossary of Acronyms

FES	Functional electrical stimulation
FMA UE	Fugl–Meyer assessment of the upper extremity
mL	Milliliter
IRB	Institutional review board
ACT^{3D}	Arm coordination training 3D
SABD	Shoulder abduction
PSI	Pounds per square inch
FDS	Flexor digitorum superficialis
EDC	Extensor digitorum communis
μs	Microseconds
Hz	Hertz
ms	Milliseconds
API	Application programming interface
HPA	Hand pentagon area
mm^2	Millimeters squared
lbs	Pounds
LMER	Linear mixed effect regression
ANOVA	Analysis of variance
Vol	Volitional
LW	Limb weight
MVT	Maximum voluntary torque
EMG	Electromyography

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Attentional state-synchronous peripheral electrical stimulation during action observation induced distinct modulation of corticospinal plasticity after stroke

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Introduction: Brain computer interface-based action observation (BCI-AO) is a promising technique in detecting the user's cortical state of visual attention and providing feedback to assist rehabilitation. Peripheral nerve electrical stimulation (PES) is a conventional method used to enhance outcomes in upper extremity function by increasing activation in the motor cortex. In this study, we examined the effects of different pairings of peripheral nerve electrical stimulation (PES) during BCI-AO tasks and their impact on corticospinal plasticity.

Materials and methods: Our innovative BCI-AO interventions decoded user's attentive watching during task completion. This process involved providing rewarding visual cues while simultaneously activating afferent pathways through PES. Fifteen stroke patients were included in the analysis. All patients underwent a 15 min BCI-AO program under four different experimental conditions: BCI-AO without PES, BCI-AO with continuous PES, BCI-AO with triggered PES, and BCI-AO with reverse PES application. PES was applied at the ulnar nerve of the wrist at an intensity equivalent to 120% of the sensory threshold and a frequency of 50 Hz. The experiment was conducted randomly at least 3 days apart. To assess corticospinal and peripheral nerve excitability, we compared pre and post-task (post 0, post 20 min) parameters of motor evoked potential and F waves under the four conditions in the muscle of the affected hand.

Results: The findings indicated that corticospinal excitability in the affected hemisphere was higher when PES was synchronously applied with AO training, using BCI during a state of attentive watching. In contrast, there was no effect on corticospinal activation when PES was applied continuously or in the reverse manner. This paradigm promoted corticospinal plasticity for up to 20 min after task completion. Importantly, the effect was more evident in patients over 65 years of age.

Conclusion: The results showed that task-driven corticospinal plasticity was higher when PES was applied synchronously with a highly attentive brain state during the action observation task, compared to continuous or asynchronous

application. This study provides insight into how optimized BCI technologies dependent on brain state used in conjunction with other rehabilitation training could enhance treatment-induced neural plasticity.

KEYWORDS

brain computer interface, electrical stimulation therapy, action observation, cortical synchronization, cortical excitability, rehabilitation, stroke

1 Introduction

There are various sequelae of stroke, and disability of upper extremity motor function is one of the most common and persistent (Lai et al., 2002; Langhorne et al., 2011). Neuroplasticity is a term that describes the ability of the brain to create new neural connections, acquire additional functions, and adapt to compensate for neural damage (Murphy and Corbett, 2009). These processes play a crucial role in the recovery of upper extremity motor function after stroke. It is important to emphasize the significance of research that focuses on rehabilitation strategies to enhance brain plasticity. Various neuromodulation techniques have been clinically employed to enhance motor recovery by promoting neuroplasticity. These include non-invasive brain stimulation, neuromuscular electrical stimulation, paired associative stimulation, and application of the brain-computer interface (BCI) technique (Ting et al., 2021). However, individual treatment strategies do not induce sufficient neural plasticity for motor recovery. Consequently, various neurotechnologies have recently been incorporated into conventional rehabilitation techniques to improve their overall efficacy. The effectiveness of therapies for motor recovery can be enhanced by combining protocols based on various mechanisms, rather than utilizing each treatment individually. This approach promotes a more stable and synergistic motor recovery (Takeuchi and Izumi, 2015).

Rehabilitation strategies for patients with a stroke often integrate action observation (AO) based on the theory of mirror neuron system (MNS) activation to enhance motor cortical plasticity and improve upper extremity function (Franceschini et al., 2012; Tani et al., 2018; Mancuso et al., 2021). AO stimulates neural plasticity by engaging the MNS, which responds when individuals perform specific actions and observe the same motor actions (Fadiga et al., 1995, Rizzolatti et al., 2021). This paradigm has the advantage of being applicable even to severely paralyzed stroke patients, because it is not dependent on motor activity. However, in the conventional AO paradigm, it is difficult for patients affected by stroke to maintain prolonged attention during training session without feedback or rewards. Thus, it is difficult to estimate whether patients actively engage in AO training.

Brain-computer interfaces (BCI) have been developed to evaluate cortical potential and offer brain state-dependent feedback to aid in rehabilitation (Ting et al., 2021). The BCI technology has great potential in the field of neurorehabilitation, and can be applied alone or in combination with traditional rehabilitation techniques. As an example, a BCI-based AO game that provides real-time feedback to patients regarding their attention to a blinking action video through steady-state visual -evoked potentials (SSVEPs) was introduced (Lim and Ku, 2017). This strategy elicited greater MNS activation compared with the AO paradigm applied alone in the unaffected and affected hemispheres of patients with a history of chronic stroke (Choi et al., 2019).

Peripheral electrical stimulation (PES) promotes brain plasticity by generating afferents and increasing corticospinal excitability (Pascual-Leone et al., 1995, Everaert et al., 2010; Veldman et al., 2018). This process is associated with motor learning and hastens motor recovery in stroke patients (Stefan et al., 2000, Ward, 2005; Di Pino et al., 2014). PES is a widely used rehabilitation technique after stroke because it is easily accessible and applicable to severely paralyzed patients. The motor learning effects of AO are transient and need to be complemented by motor training to maintain and maximize their impact (Zhang et al., 2011; Larssen et al., 2021). In another study, the combined AO and PES paradigm induced corticospinal facilitation similar to that achieved through real motor training, resulting in enduring changes in brain plasticity (Bisio et al., 2015, 2017).

A previous study introduced the concept of attentional state-dependent PES during the AO paradigm using the BCI-SSVEPs protocol (Kim et al., 2022). The results indicated that the attentional state-dependent PES task was superior to AO alone or to a simple combination of AO and PES in facilitating corticospinal plasticity in both patients with stroke and in healthy individuals (Kim et al., 2022). Moreover, this paradigm is effective in enhancing sensorimotor cortical activation in the affected hemispheres of stroke patients (Lim et al., 2023). BCI interventions decode the user's attentive observation during the AO task, provide rewarding visual feedback and activate afferent pathways via electrical stimulation. Closed-loop stimulation paradigms of this nature seek to induce more synchronized patterns of neuronal activity enhancing Hebbian plasticity (Hebb, 1949).

However, it has been consistently demonstrated that simple combinations of various neurotechnologies do not always exhibit synergy in stroke rehabilitation (Takeuchi and Izumi, 2015; Coscia et al., 2019). From this perspective, how different PES pairings during BCI-AO tasks differentially impact corticospinal plasticity has not been fully explored in previous studies. Hence, the next step requires an in-depth exploration of the different pairings of PES during BCI-AO training that influence corticospinal neuroplasticity.

In this study, we explored four combinations of PES application during BCI-AO tasks (absence of PES, and continuous, synchronous, and asynchronous application). Consequently, our experiment aimed to assess how synchronous stimulation, aligned

with an individual's attentional state in the BCI-AO paradigm and combined with PES, affects corticospinal activation and neural plasticity after stroke. This investigation involved analyzing corticospinal excitability via transcranial magnetic stimulation (TMS) and quantifying mu suppression in electroencephalographic (EEG) activity.

2 Materials and methods

2.1 Participants

Patients enrolled in the study included (1) patients with mild to moderate upper extremity hemiplegia among patients with the first stroke diagnosed by radiological examination, (2) patients with chronic stroke at least 6 months after onset, (3) medically stable patients, and (4) patients with a stroke who were able to respond appropriately to verbal instructions. Patients were excluded if they had (1) contraindications for TMS, such as intracranial metal, pacemaker, or implant insertion; (2) mental disorders, such as depression and apraxia; (3) visual impairment or inability to communicate, (4) a history of seizures, and (5) absence of an MEP (motor evoked potential) response in the affected first dorsal interosseous (FDI) muscle. The Institutional Review Board of the university-affiliated hospitals approved the study protocol (EMCS 2022-07-012-002), and all participants provided written informed consent. Detailed clinical data of the patients with stroke and data on age and sex are provided in Table 1.

2.2 Experimental setup

We developed a video game using the BCI-AO paradigm, offering real-time visual cue feedback through the BCI. The patient's level of attentive watching was assessed by measuring EEG intensities in the beta and mu bands as well as SSVEPs evoked by a BCI-AO game featuring flashing action images. All patients were shown a video displaying repetitive grasping actions under four conditions. The details are described below and in Figure 1. The experiments were conducted in a randomized order, with intervals of at least 3 days between sessions to avoid potential carry-over effects (Figure 2).

The patients were instructed to perform each experiment while seated in a relaxed position in a comfortable chair without making any voluntary movement. This was confirmed by monitoring muscle activity throughout the experiment. The game implemented in this study included a video showing the movement of the hand and forearm holding a ball, and was individually executed by setting the direction of the arm in the game to the direction of the affected arm. The BCI-AO program was designed to provide rewarding visual feedback, highlighting the enlargement of the muscles in the hand and forearm based on the user's level of attentive watching. The video blinked at a frequency of 15 Hz to allow the classifier to detect the patient's SSVEP components in the EEG. The details are elaborated upon in the following sections.

2.2.1 Experimental conditions

In this study, the settings for the four conditions were determined by combining the PES and BCI-AO as follows and in Figure 1:

(1) In the BCI-AO without PES application (nPES condition), patients were instructed to observe the movement of the left or right (affected) hand and forearm holding the ball on the video screen. Patients received visual feedback whether their attentive watching was assessed by detector. However, they didn't provide PES during the task.
(2) In the BCI-AO with continuous PES application (cPES condition), patients followed the same BCI-AO paradigm as in the nPES condition. The difference was that continuous PES was applied while the video played on the screen, irrespective of whether patient's attentive watching was verified or not.
(3) In the BCI-AO with triggered PES application (tPES condition), the PES was turned on and off synchronously based on the patient's state of attentive watching. This allowed patients to receive visual feedback and synchronized PES simultaneously, with the PES application being dependent on attentive watching.
(4) In the BCI-AO with reverse PES application (rPES condition), the PES was operated in the opposite manner compared to the tPES condition. Specifically, the PES was turned off during periods of attentive watching and turned on during periods of low attentiveness. As a result, the participants were exposed to asynchronous PES, in which PES was applied in the opposite manner to tPES condition.

2.2.2 BCI-AO system

The BCI-AO paradigm was created by presenting a blinking video clip designed to evoke SSVEP patterns in the EEG of the patient while watching it. The video evokes SSVEP and stimulate brain activity in motor-related regions by providing appropriate visual feedback (forearm muscles in the AO video) to encourage users to watch videos of grasping movements according to the patient's attention. EEG data were obtained using DSI-24 with 19 electrodes (Wearable Sensing, San Diego, USA). The electrodes were positioned following the international 10–20 system. Data were collected at a frequency of 300 Hz, and the adequacy of the EEG signal quality was checked before each experiment.

Before each experimental session, a calibration session was carried out to collect data for designing an individual classifier. This session included a total of 15 trials over 3 min. Each trial involved a 6 s video of blinking actions followed by the display of a white cross pin on a black background for an additional 6 s.

The data were organized through a classifier design stage, which consisted of a classifier design and a Common Spatial Filter (CSF) design. CSFs were designed for alpha (8–13 Hz), beta (13–30 Hz), and SSVEP (14.5–15.5 Hz) bands, after which the CSFs were applied in the classifier design phase. The classifier was built using a Support Vector Machine (SVM) algorithm in the conformation of a linear kernel.

After designing of the classifier and CSF, the implementation of BCI-AO became feasible. The processing of EEG signal step for the runtime application consisted of applying band-pass filters and CSF to each feature, and then classifying the state according

TABLE 1 Clinical and demographic characteristics of the stroke patients included in the study.

Patients number	Sex	Age	Onset	Etiology	Site of lesion	mRS	FMA-UE	MMSE	MBI	MAS
1	F	55	2Y9M	Hemorrhage	Rt. BG (Subcortex)	3	28	28	100	G1
2	M	50	2Y4M	Hemorrhage	Lt. Thalamus (Subcortex)	1	64	28	89	G0
3	M	59	9Y	Infarction	Rt. MCA (Cortex & Subcortex)	1	64	29	100	G0
4	M	58	1Y	Hemorrhage	Rt. Thalamus (Subcortex)	1	60	27	92	G0
5	M	65	7Y	Hemorrhage	Lt. BG (Subcortex)	1	60	29	97	G0
6	M	64	6M	Hemorrhage	Rt. BG (Subcortex)	2	62	24	53	G0
7	F	70	1Y1M	Infarction	Rt. BG (Subcortex)	1	64	29	97	G0
8	M	67	10M	Hemorrhage	Lt. Thalamus (Subcortex)	2	66	26	97	G0
9	F	59	9M	Hemorrhage	Lt. Thalamus (Subcortex)	2	62	29	93	G1
10	M	65	1Y1M	Infarction	Lt. SC (Subcortex)	2	64	29	95	G0
11	M	79	9M	Infarction	Rt. MCA (Cortex & Subcortex)	1	64	29	98	G0
12	F	62	6M	Infarction	Lt. BG (Subcortex)	1	64	29	97	G0
13	M	68	6M	Hemorrhage	Rt. CR (Subcortex)	1	64	29	97	G0
14	M	73	7M	Infarction	Lt. SC (Subcortex)	1	63	29	97	G0
15	F	65	11M	Hemorrhage	Rt. BG (Subcortex)	3	39	29	91	G0

Rt, Right; Lt, Left; mRS, Modified Rankin Scale; EHI, Edinburgh Handedness Inventory; FMA-UE, Fugl-Meyer Assessment For Upper Extremity; MMSE, Mini-mental State Examination; MBI, Modified Barthel Index; MAS, Modified Ashworth Scale; BG, Basal ganglia; IC, Internal capsule; CR, Corona radiata; MCA, Middle cerebral artery; SC, Striatocapsular.

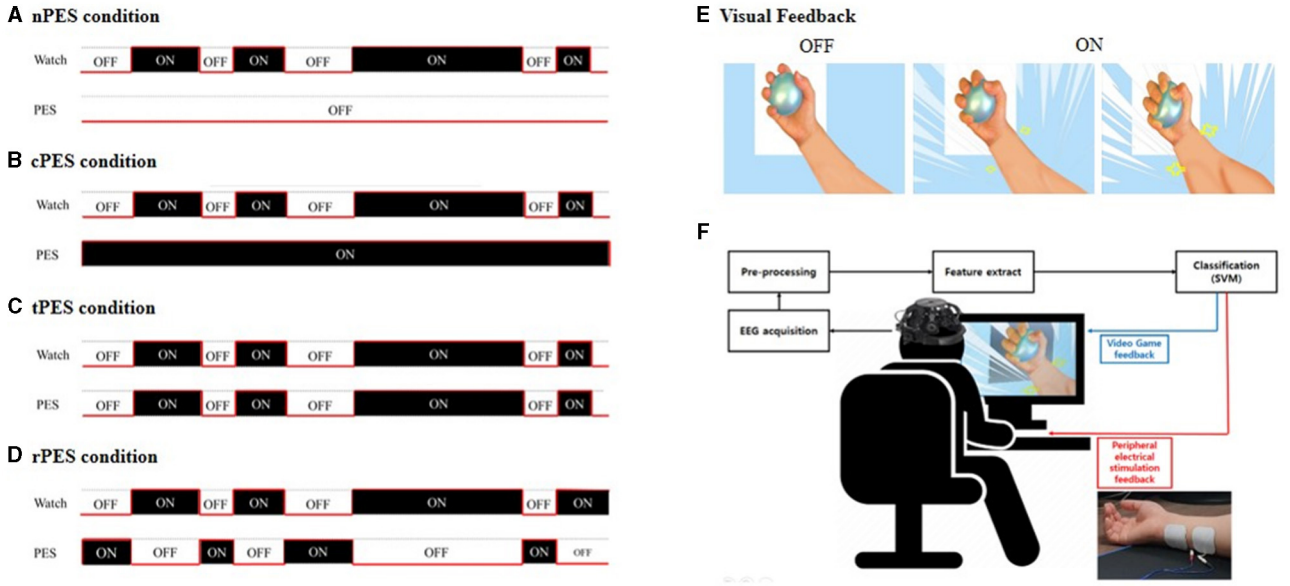

FIGURE 1
In the BCI-AO without PES application **(A)**, patients received visual feedback whether their attentive watching was assessed by detector without the application of PES. The BCI-AO with continuous PES application **(B)**, refers to a condition in which continuous PES was applied while the video played on the screen irrespective of whether patient's attentive watching was verified or not. In the BCI-AO with triggered PES application **(C)**, PES was turned on and off synchronously depending on whether the patient performed attentive watching or not. In the BCI-AO with reverse PES application **(D)**, PES application was operated in the opposite manner compared to the tPES condition. **(E)** Patients viewed a video with repetitive grasping actions. **(F)** The AO clip, modulated at 15 Hz, facilitated classifier identification of steady-state visually evoked potential components from EEG. The BCI-AO program was designed to provide rewarding visual feedback, highlighting the enlargement of muscles in the hand and forearm based on the level of attentive watching shown by the patient. AO, action observation; PES, peripheral electrical stimulation; BCI-AO, brain-computer interface-action observation; SVM, support vector machine; EEG, electroencephalogram.

to each feature using an SVM classifier. We performed AO on patients classified as attentive watching during all conditions and saved the results as EEG epochs with a window size of 1 s segmented at intervals of 0.1 s, allowing the BCI system to offer feedback at intervals of 0.1 s and then the classified state was applied to the PES trigger immediately which could be considered as real-time.

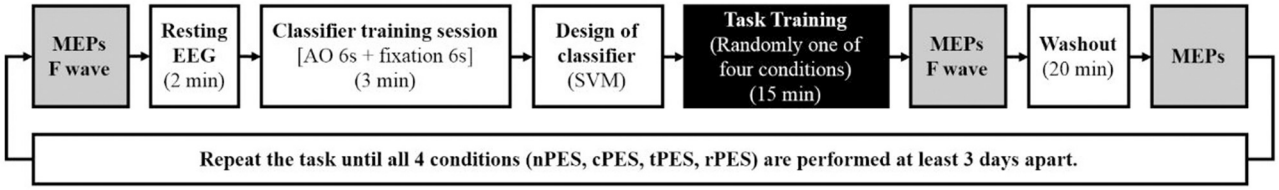

FIGURE 2
Experimental procedure and time points for measuring the latency and amplitude of MEPs and F wave latency. MEP parameters were assessed at three intervals: baseline (Pre), immediately after the task training (Post 0), and 20 min after completing each task (Post 20). The four tasks were conducted in a randomized order with intervals of at least 3-days.

In the runtime application, the BCI-AO measured the attentional ratio, defined as the degree of attentive watching during the running time. The average score was 56% ± 3.123, 58% ± 4.336, 60% ± 4.156, and 57% ± 2.563 during the nPES, cPES, tPES, and rPES conditions, respectively. The attention ratio was computed by expressing the time during which mu suppression was observed as a percentage of the total task time. EEG processing was performed using the OpenViBE software platform ver. 2.3.0 (INRIA, Rennes, France).

2.2.3 Peripheral nerve stimulation

PES was performed using a commercial system (Medel GmbH, Germany) with a single bipolar channel applied to the affected limb to inject a current (with a pulsed square waveform) into the right ulnar nerve. PES was delivered at 120% of the intensity of the sensory thresholds of stationary FDI muscles to the extent that muscle contraction did not occur, and at frequencies of 50 Hz and 1 ms pulse widths while patients were relaxed.

To avoid potential disturbances in the EEG signal by PES, a frequency of 50 Hz was selected for real-time EEG filtering in the BCI-AO program, which operates within the range of 0.1–50 Hz. The EEG signal was then filtered in three different bands (8–13 Hz, 13–30 Hz, and 14.5–15.5 Hz) to extract features for the real-time BCI program.

The stimulus intensity was set at 120% of the sensory threshold, defined as the lowest stimulus detected by the patient. The choice of intensity setting of the stimulus was based on the fact that PES above the motor threshold causes muscle spasms. Therefore, all the patients were able to tolerate this intensity of stimulation without complaining of muscle spasms or pain.

In each condition, the overall intensity of PES administered to the patients was expressed as the PES intensity (mA) for 15 min. The analysis revealed that the PES intensities under the cPES, tPES, and rPES conditions were 3,720, 2,153, and 1,674 mA, respectively.

2.3 Assessment

The time points for measuring the latency and amplitude of MEPs and F wave latency are illustrated in Figure 2. MEP parameters were assessed at three intervals: baseline (Pre), immediately after the task training (Post 0), and 20 min after completing each task (Post 20). F-wave latencies were evaluated at baseline (Pre) and immediately after the task training (Post 0). Additionally, we quantified mu suppression in EEG activity during each of the conditions.

2.3.1 Motor evoked potential

Motor induced potential (MEP) was achieved using Magstim 200² (The Magstim Company Limited, Whitland, UK) and D70² coils to measure cortical stimulation. Measurements of MEPs using MagStim were performed by a fully experienced physician in an electrical diagnostic laboratory. The coil orientation was applied to the mid-phase plane at a 45° posterior angle, and the hat featured hotspot points marked with the grid at 1 cm intervals to ensure a consistent stimulation area throughout the examination. The resting motor threshold (rMT) was determined as the minimum stimulation intensity with a MEP amplitude >50 μV recorded five times out of ten. The stimulation intensity was consistently set at 120% of the rMT and maintained throughout the experiment. Twenty MEPs were recorded with a stimulus interval of 5–6 s, and average peak-to-peak amplitude and latency were subsequently computed.

2.3.2 F-wave

To evaluate peripheral nerve excitability, the latency of the F-waves in the FDI muscle was measured by stimulating the ulnar nerves in the wrist using a Medelec Synergy electromyography machine (Natus Neurology Inc. USA) before and after each task. We maintained a temperature of 22°C in the laboratory to exclude temperature-dependent variations in the F response.

2.3.3 EEG analysis

To measure mu suppression during each condition, we extracted mu-band powers from the EEG data and the corresponding resting data, which were filtered between 4 and 30 Hz, applied an artifact subspace reconstruction filter to the filtered EEG data for artifact rejection, and then calculated mu suppression from the power spectrum density of the EEG using the following equation:

$$10 \times \log10\ (\text{mu\_power\_of\_task}/\text{mu\_power\_of\_rest}).$$

TABLE 2 Changes in MEP parameters among the four conditions.

Outcome	Time	nPES condition	cPES condition	tPES condition	rPES condition
Latency (ms)	Pre	22.735 (0.223)	22.793 (0.287)	22.864 (0.314)	22.930 (0.295)
	Post 0	22.289 (0.197)	22.100 (0.254)	21.990 (0.277)	22.383 (0.260)
	Post 20	22.340 (0.235)	22.188 (0.302)	22.124 (0.329)	22.495 (0.310)
Amplitude (μV)	Pre	441.581 (50.949)	412.843 (60.272)	380.570 (75.567)	407.349 (50.790)
	Post 0	537.802 (69.941)	630.647 (82.738)	742.088 (103.735)	555.911 (69.722)
	Post 20	484.981 (66.107)	574.948 (78.202)	648.695 (98.048)	532.051 (65.900)
F wave (ms)	Pre	26.850 (0.466)	26.730 (0.305)	26.950 (0.376)	26.797 (0.458)
	Post 0	26.797 (0.497)	26.730 (0.326)	26.943 (0.401)	26.747 (0.489)

All values are given as the estimated mean and standard error for each condition and three different time points: pre (before task), post 0 (after task), and post 20 (20 min after task). nPES, BCI-AO without PES application; cPES, BCI-AO with continuous PES application; tPES, BCI-AO with triggered PES application; rPES, BCI-AO with reverse PES application; AO, action observation; PES, peripheral electrical stimulation; BCI-AO, brain–computer interface action observation.

The left and right electrode positions were then reversed when necessary to match the data from the affected and unaffected sides of the patient.

2.4 Sample size

The main goal of this study was to evaluate the impact of four different conditions on corticospinal excitability in stroke patients. Sample size calculations were conducted using G Power 3.1.9.7 (Heinrich Heine University, Dusseldorf, Germany) for Windows. The determination of the sample size for repeated-measures ANOVA was made considering the primary endpoints. We analyzed four sets of conditions to identify differences in the MEP amplitudes between pre vs. post 0 and between pre vs. post 20 in stroke patients. We determined that a sample size of 15 patients was adequate for detecting an effect value of 0.26 (large effect size) (Ward, 2005). Additionally, the correlation among repeated measures of 0.7 was found to have a significance level of 0.05 (both sides) for a power of 90%. Consequently, we decided on a sample size of 15 patients and recruited 17 patients to account for potential dropouts.

2.5 Statistical analysis

Data are provided as estimated mean and standard error. Differences between measured values at baseline and after the tasks were calculated. The normality of continuous variables was assessed through the Kolmogorov–Smirnov test and the Shapiro-Wilk test. We applied the linear mixed-effects model to assess the impact of four conditions (nPES, cPES, tPES, and rPES), time (Pre, Post 0, Post 20), and the interaction between condition and time on MEP latencies and amplitudes. We applied the linear mixed model to analyze the impact of four conditions, time (Pre, Post 0) and the interaction between condition and time on the latency of the F wave. A three-way linear mixed model was employed to evaluate the effect of other variables such as age, sex, etiology, Modified Rankin Scale (mRS), Fugl-Meyer Assessment for Upper Extremity (FMA-UE), MMSE, Modified Ashworth Scale (MAS), as well as attentional ratio and intensity of PES during the tasks. When significant p-values were observed for variables in the three-way interaction, they were divided based on the median values, and a linear mixed model was employed. A repeated measures analysis of variance (ANOVA) was conducted to evaluate the differences in mu suppression among the four tasks on the C3/C4 and F3/F4 channels of the affected hemisphere in stroke patients. When significant differences were identified, *post-hoc* t-tests were conducted.

The results were defined as statistically significant if the p-value was <0.05, and trends were recognized if the interaction p-value was <0.15. All data were analyzed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA), and SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3 Results

3.1 Baseline characteristics

Twenty-eight patients with hemiplegic stroke were assessed, and all patients underwent a screening test to determine the measurability of MEP parameters. Eleven patients were excluded from the study because clear measurement of MEP parameters was not possible. In total, 17 patients were initially enrolled in the study. However, two patients dropped out due to side effects: one patient withdrew due to headaches during the study and the other due to eye fatigue that arose during the experiments. In the end, MEP results from 15 patients with stroke (10 men and five women) were analyzed. Their detailed clinical and demographic data are shown in Table 1. During EEG analysis, one more patient was excluded because mu-band powers could not be clearly recorded. Thus, the EEG analysis involved a total of 14 patients. The baseline MEP amplitude, MEP latency, and F-wave latency were not significantly different between the four conditions ($F_{3,84} = 0.23$, $p = 0.88$; $F_{3,84} = 0.34$, $p = 0.79$; $F_{3,42} = 0.37$, $p = 0.78$) (Supplementary Table).

3.2 Changes in MEP parameters after experiments

Table 2 and Figure 3 show the changes in MEP parameters among the four conditions in patients with stroke. There was a significant main effect of time (Pre, Post 0, Post 20; $F_{2,28}$

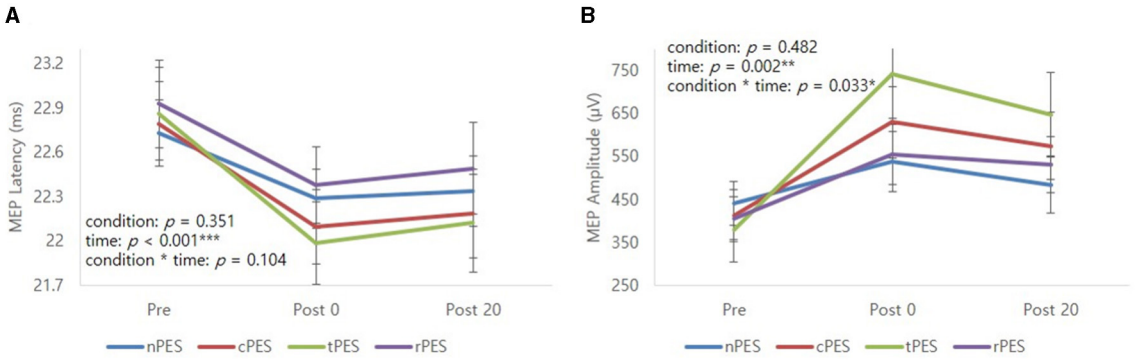

FIGURE 3
Mean profile graphs showed the significant main effect of time and a trend of condition × time interaction for MEP latency **(A)**, and significant main effect of time and condition × time interaction for MEP amplitude **(B)**. nPES condition (blue line), cPES condition (red line), tPES condition (yellowish green line), rPES condition (purple line). AO, action observation; MEP, motor evoked potential; nPES, BCI-AO without PES application; cPES, BCI-AO with continuous PES application; tPES, BCI-AO with triggered PES application; rPES, BCI-AO with reverse PES application; PES, peripheral electrical stimulation. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

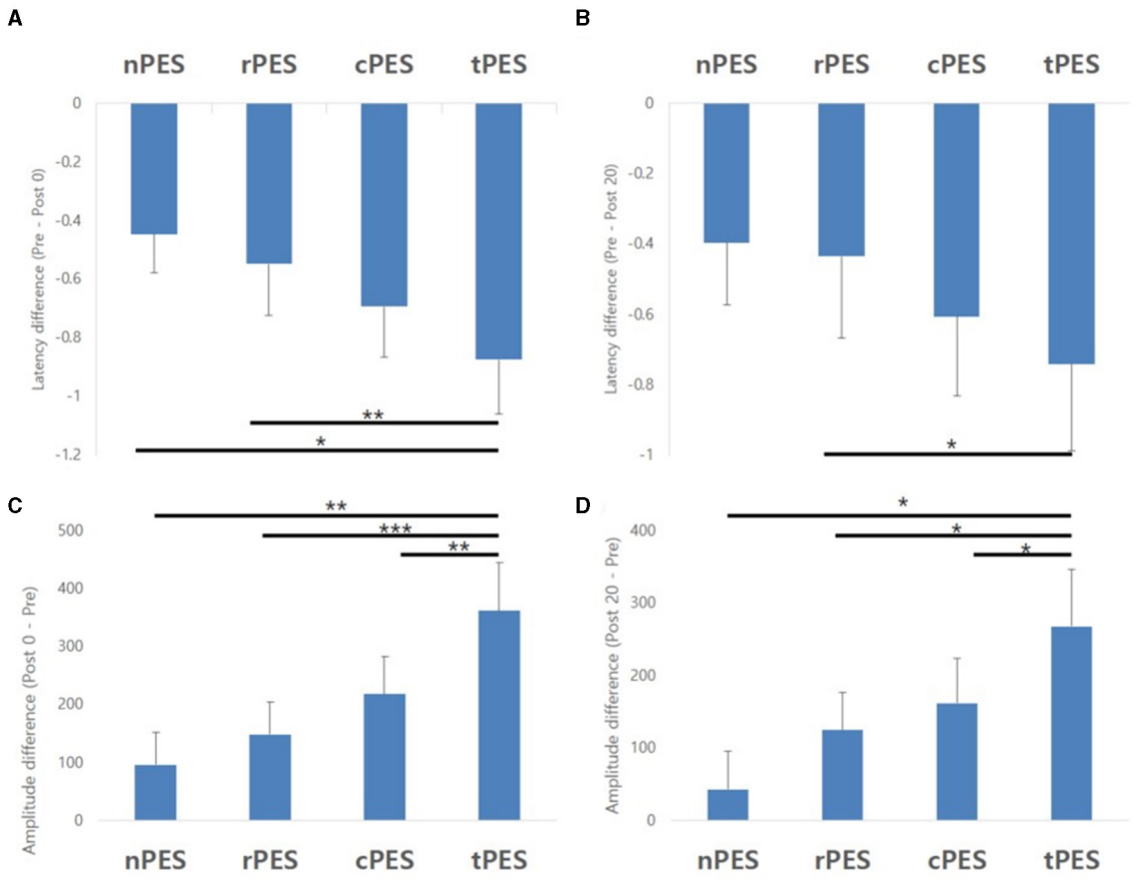

FIGURE 4
Results of the *post-hoc* analysis for MEP parameters. They showed a significant decrease in MEP latency between tPES vs. rPES condition and tPES vs. nPES condition **(A, B)**. A significant increase in MEP amplitude was observed between tPES and nPES condition, tPES and rPES condition, tPES and cPES condition **(C, D)**; MEP, motor evoked potentials, nPES, BCI-AO without PES application; cPES, BCI-AO with continuous PES application; tPES, BCI-AO with triggered PES application; rPES, BCI-AO with reverse PES application; AO, action observation; PES, peripheral electrical stimulation; BCI-AO, brain–computer interface-action observation. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

$= 9.93$, $p = 0.005$) and a trend in the interaction between condition and time ($F_{6,84} = 1.82$, $p = 0.1044$) on MEP latency. However, no significant effect of the condition was observed ($F_{3,42} = 1.12$, $p = 0.351$). *Post-hoc* t-tests revealed a significant reduction in MEP latency after the nPES, cPES, tPES, and rPES conditions compared to that at baseline (Pre vs. Post 0).

These differences in MEP latency persisted after 20 min, with no significant differences observed between Post 0 and Post 20 under any of the four conditions (Figure 3). The *post-hoc* *t*-tests further revealed a significant decrease in MEP latency between the tPES and rPES conditions (Pre-Post 0: $t = 2.89$, $p = 0.005$; Pre-Post 20: $t = 2.04$, $p = 0.045$), and between the tPES and nPES conditions (Pre-Post 0: $t = 2.55$, $p = 0.013$). However, there were no significant differences in the MEP latency between the nPES and cPES conditions, the nPES and rPES conditions, the cPES and tPES conditions, or the cPES and rPES conditions (Figure 4).

We observed a significant main effect of time ($F_{2,28} = 8.26$, $p = 0.002$) and an interaction between condition and time ($F_{6,84} = 2.43$, $p = 0.033$) on the MEP amplitude. *Post-hoc* analysis for time indicated a significant increase in MEP amplitude after the cPES, tPES, and rPES conditions compared to baseline (Pre vs. Post 0), with no significant increase after the nPES condition; however, the increase in MEP amplitude following the cPES, tPES, and rPES conditions remained significant for 20 min (Pre vs. Post 20), and no differences were found between Post 0 and Post 20 in the cPES, tPES, and rPES conditions (Figure 3). The *post-hoc* analysis on the interaction between condition and time revealed a significant increase in the MEP amplitude between the tPES and nPES conditions (Post 0: $t = 2.83$, $p = 0.006$; Post 20: $t = 2.54$, $p = 0.013$), tPES and rPES conditions (Post 0: $t = 3.57$, $p = 0.001$; Post 20: $t = 2.54$, $p = 0.013$), and tPES and cPES conditions (Post 0: $t = 2.69$, $p = 0.009$; Post 20: $t = 2.10$, $p = 0.039$). However, no significant differences were observed between nPES and cPES, nPES and rPES, and cPES and rPES conditions (Figure 4). The estimated mean difference in MEP amplitude after the task was highest between the nPES and tPES and rPES and tPES conditions (Table 3).

Time, condition, and the interaction between them did not exhibit any significant effects on the F-wave latency (see Supplementary Figure).

3.3 Effects of other variables in MEP parameter

The Mini-Mental State Examination (MMSE) showed a significant main effect on MEP latency ($F_{6,143} = 2.70$, $p = 0.016$). In patients with MMSE scores under 28, there was a significant effect of the interaction between condition and time on MEP latency ($F_{6,24} = 11.86$, $p < 0.001$). However, this was not seen in those with MMSE scores over 29 ($F_{6,54} = 1.72$, $p = 0.135$). There was no effect of sex ($F_{6,78} = 1.17$, $p = 0.333$), age ($F_{6,143} = 1.44$, $p = 0.202$), etiology ($F_{6,78} = 1.52$, $p = 0.183$), mRS ($F_{12,72} = 0.82$, $p = 0.629$), FMA-UE ($F_{6,143} = 0.32$, $p = 0.924$), MAS ($F_{6,78} = 1.77$, $p = 0.117$), the attentive ratio ($F_{6,142} = 0.57$, $p = 0.755$) or intensity of PES ($F_{4,103} = 0.60$, $p = 0.662$) on MEP latency.

Moreover, there was a significant main effect of age ($F_{6,143} = 3.53$, $p = 0.003$) on MEP amplitude. There was a significant effect of interaction between condition and time in patients aged ≥65 years ($F_{6,24} = 3.60$, $p = 0.006$), but not in those aged <64 years ($F_{6,36} = 1.61$, $p = 0.172$) on MEP amplitude. There was no effect of sex ($F_{6,78} = 1.05$, $p = 0.995$), etiology ($F_{6,78} = 2.16$, $p = 0.056$), mRS ($F_{12,72} = 1.82$, $p = 0.061$), FMA-UE ($F_{6,143} = 1.40$, $p = 0.219$), MMSE ($F_{6,143} = 1.80$, $p = 0.103$), MAS ($F_{6,78} = 1.29$, $p = 0.273$), attentional ratio ($F_{6,142} = 0.96$, $p = 0.452$), or PES intensity ($F_{4,103} = 1.31$, $p = 0.270$) on MEP amplitude.

3.4 Changes in mu suppression during the experiments

Figure 5A shows a topographical representation of mu suppression. Mu suppression of the affected hemisphere was strongest in the cPES and tPES conditions compared to the nPES and rPES conditions. In addition, when we assessed mu suppression in the motor cortex of the affected hemisphere (C3 or C4), there was no statistically significant difference between conditions (Figure 5B). Regarding mu suppression in the affected frontal area (F3 or F4), significant main effects were observed in the four conditions ($F_{3,39} = 6.272$, $p = 0.001$), with the most pronounced mu suppression observed in the cPES condition. The *post-hoc* analysis showed significantly stronger activation in the cPES and tPES conditions compared to the nPES and rPES conditions (cPES vs. nPES: $p = 0.013$; tPES vs. nPES: $p = 0.018$; cPES vs. rPES: $p = 0.003$; tPES vs. rPES: $p = 0.037$, Figure 5C).

3.5 Side effects during the experiments

After each experimental session, all patients were checked for the presence of any side effects, such as neck pain, dizziness, or headache. Two patients dropped out from the study due to side effects. One patient reported a headache, and the other reported eye fatigue. Most of the other patients completed the study without experiencing any discomfort.

4 Discussion

This study demonstrated that different PES pairings during BCI-AO task training can modulate corticospinal plasticity after a stroke. We found evidence that the corticospinal excitability in the affected hemisphere after a stroke was higher when PES was applied synchronously with AO training, dependent on a highly attentive brain state. Conversely, the effects of corticospinal activation were not significant when PES was applied continuously or in the reverse manner. Hence, the synchronous application of PES with attentional state AO training using BCI distinctly influenced the modulation of corticospinal plasticity, supporting our initial hypothesis. This paradigm continued to promote cortical plasticity for a short period after it was stopped.

It is well-known that AO promotes motor re-learning in patients with stroke by activating the MNS and motor cortex (Zhang et al., 2018). However, our study did not reveal a significant increase in MEP parameters after AO alone. This finding is consistent with that of a previous study (Kim et al., 2022) that suggested that the corticospinal plasticity induced by AO was insufficient in patients with chronic stroke. PES, known to stimulate the motor cortex through afferent stimulation during

TABLE 3 Estimated mean difference and *p*-value from the *post-hoc* analysis of MEP amplitude.

Condition	Pre vs. post 0		Pre vs. post 20		Post 0 vs. post 20	
nPES vs. cPES	121.582 (75.359)	0.1104	118.704 (71.287)	0.0996	−2.878 (65.303)	0.965
nPES vs. tPES	265.297 (93.583)	0.0057**	224.725 (88.527)	0.013*	−40.572 (81.096)	0.6182
nPES vs. rPES	52.341 (55.652)	0.3497	81.301 (52.645)	0.1263	28.960 (48.226)	0.5498
cPES vs. tPES	143.715 (53.380)	0.0086**	106.021 (50.496)	0.0388*	−37.694 (46.257)	0.4174
cPES vs. rPES	−69.241 (47.390)	0.1477	−37.403 (44.830)	0.4065	31.838 (41.067)	0.4403
tPES vs. rPES	−212.956 (59.733)	0.0006***	−143.424 (56.505)	0.013*	69.532 (51.762)	0.1828

All values are expressed as estimated mean and standard errors (pre: before task, post 0: after task, post 20:20 min after task). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. MEP, motor-evoked potentials; nPES, BCI-AO without PES application; cPES, BCI-AO with continuous PES application; tPES, BCI-AO with triggered PES application; rPES, BCI-AO with reverse PES application; AO, action observation; PES, peripheral electrical stimulation; BCI-AO, brain–computer interface action observation.

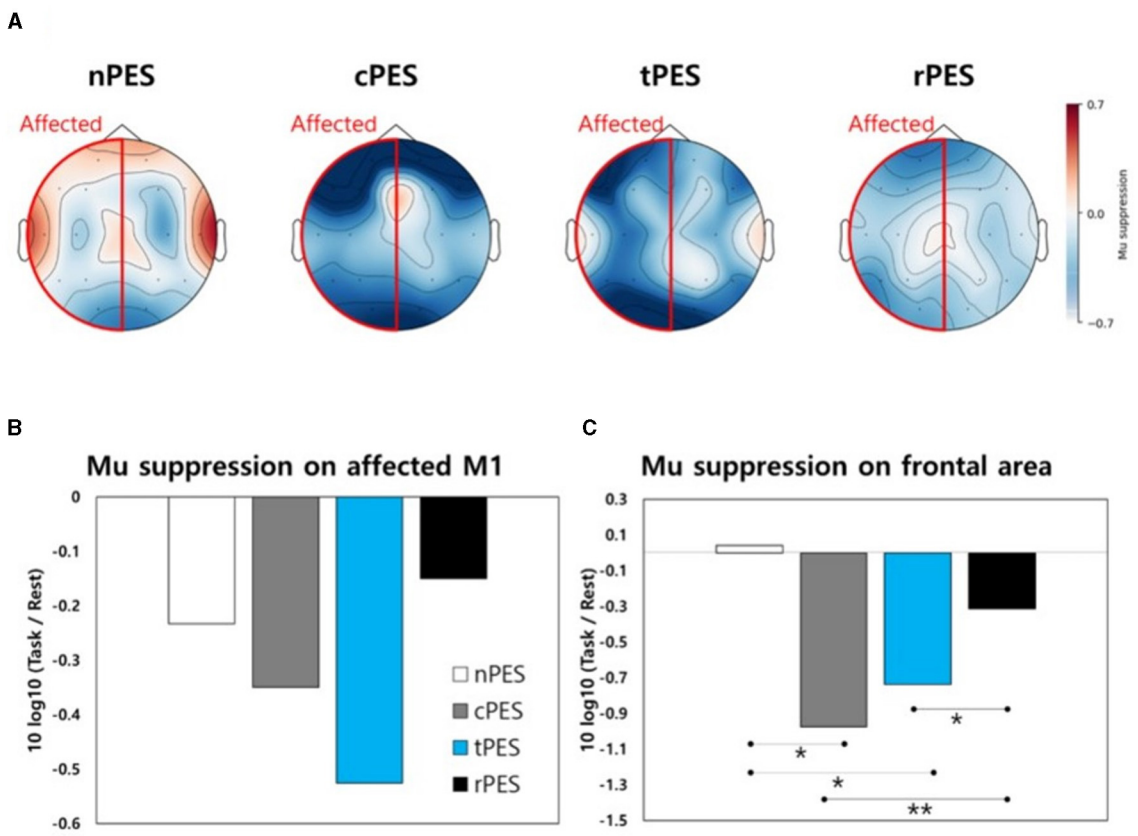

FIGURE 5
(A) Topographical representation of mu suppression in EEG during the four conditions. Mu suppression is observed in the motor area **(B)** and frontal area **(C)** of the affected hemisphere during the four conditions. nPES, BCI-AO without PES application; cPES, BCI-AO with continuous PES application; tPES, BCI-AO with triggered PES application; rPES, BCI-AO with reverse PES application; AO, action observation; PES, peripheral electrical stimulation; BCI-AO, brain–computer interface-action observation. *$p < 0.05$; **$p < 0.01$.

AO-induced activation, likely contributes to the induction of long-term potentiation (LTP)-like plasticity in a manner similar to overt movement execution (Bisio et al., 2017).

The paradigm that integrated a BCI video game with AO induced more significant mu suppression in the motor cortical area than AO alone in patients with stroke (Choi et al., 2019). Our BCI-AO paradigm is innovative and different from other BCI systems (Kim et al., 2016). In particular, it offers real-time rewarding visual feedback to aid patients to focus on the training and enhance their rehabilitation. Reward feedback strategies promote motor skill consolidation through motor network activation during training (Widmer et al., 2016). Motivation is an essential factor for active participation, and active patient engagement is crucial for the success of rehabilitation training in patients with stroke (Kusec et al., 2019). Thus, the BCI-AO paradigm can facilitate motor skill recovery by maintaining patient motivation.

In a previous study, the BCI-AO with PES paradigm was superior to AO with PES and AO alone in promoting corticospinal

plasticity in both healthy individuals and in patients with stroke (Kim et al., 2022). Moreover, the MNS can be successfully activated during electrical stimulation synchronized with AO using functional Near-Infrared Spectroscopy (Cui et al., 2023). Therefore, our finding of a significant increase in corticospinal excitability and central cortical activation in the EEG analysis following BCI-AO with the PES task is consistent with previous research. The synergistic application of neurorehabilitation therapies, each operating via distinct mechanisms, has the potential to enhance neural plasticity in patients with stroke (Takeuchi and Izumi, 2015). Thus, in this study, activation of the NMS induced by AO, activation of reward-learning attentional networks, and the peripheral nervous system may have enhanced corticospinal plasticity through associative plasticity beyond the motor cortex.

Furthermore, we investigated whether the timing of the BCI-defined stimulation and the pairing of highly attentive brain states with PES application could maximize corticospinal excitability. Importantly, our findings revealed that different PES pairings during BCI-AO training had distinct effects. This indicates that synchronous PES application during attentive watching was assisted by the BCI rather than by continuous PES application, reinforcing corticospinal plasticity. Conversely, there was a detrimental effect on corticospinal activation resulting from the inconsistency between the state of attentiveness of the brain and the application of PES. Thus, the rPES vs. nPES conditions showed no significant difference in corticospinal excitability. Corticospinal excitability was not affected by the overall state of attention (attentional ratio) or the PES intensity during each task. Although the overall intensity and duration of PES during the task was greater in the cPES condition than in the tPES condition, the increase in MEP amplitude was only significant in the tPES condition. These findings suggest that synchronous PES is crucial to a user's highly attentive brain state. In our novel BCI-AO paradigm dependent on brain state, the cortical state of attentiveness and PES have a stable and synergistic effect in the activation of the corticospinal system. Importantly, this paradigm sustained corticospinal activation for 20 min after task completion.

It has been suggested that simultaneous combinations of neurotechnologies for motor recovery are not always effective in patients with stroke (Coscia et al., 2019). Homeostatic plasticity might diminish the synergistic effects of simultaneous combinations (Takeuchi and Izumi, 2015). To maximize neural plasticity, closed-loop stimulation paradigms using BCI, which synchronize the stimulation of postsynaptic neurons with activity in presynaptic neurons, aim to engage more synergistic patterns of neuronal activity in the associative process (Mrachacz-Kersting et al., 2016). Thus, the plasticity effects induced by this paradigm are likely to translate more directly into functional gains compared to those from an open-loop paradigm (Ethier et al., 2015). Recent studies strongly support the hypothesis that timing-dependent, cue-based electrical stimulation enhances corticospinal neuroplasticity (Fu et al., 2021; Niazi et al., 2022). The results of an earlier study showed that PES application paired with EEG-defined movement intention enhanced MEPs (Niazi et al., 2012). More importantly, the change in corticospinal excitability was only observed when the PES was paired with cortical states corresponding to movement initiation, but not at the onset of muscle activation (Fu et al., 2021). When PES was paired with visual cue-based BCI interventions, there was a significantly increased MEP amplitude and exercise performance compared to PES application without visual cues (Niazi et al., 2022). Similarly, employing consistent coupling of repetitive TMS with the high-excitability state defined by the mu rhythm resulted in LTP in corticospinal excitability, whereas no significant change was observed when the coupling was to the low-excitability state or to a random mu rhythm phase (Zrenner et al., 2018).

In the present study, the latency of the ulnar nerve F-waves at the wrist showed no significant changes across the four conditions. This suggests that there were no notable changes at the peripheral or spinal levels after each task. This outcome aligns with those of a prior investigation wherein the application of PES alone did not induce modifications in F-wave responses (Ridding et al., 2000; Kaelin-Lang et al., 2002). Therefore, it is likely that the observed changes in MEP parameters after the task mainly originated from the cortex rather than from spinal or peripheral sources.

Whereas, participants aged $\geq$ 65 years showed significant differences in MEP amplitudes across the four conditions, those aged <64 years did not. This finding implies that corticospinal activation in older patients with stroke may be task-specific and more effective when stimulation dependent on the brain state is provided. Activity-dependent plasticity and LTP-like plasticity after motor learning are reduced in older individuals (Zimerman et al., 2013; Ghasemian-Shirvan et al., 2020). A previous study reported EEG findings indicating attention deficits during visual memory tasks in older people (Teng et al., 2018). In addition to the effect of aging, stroke induces structural and functional changes in the brain, resulting in decreased motor cortical activation. In a previous study, the integration of BCI-AO with the PES paradigm led to a shift in the brain activation pattern toward the central brain area (Lim et al., 2023). This paradigm induced more extensive utilization of the frontal and motor areas in stroke patients than the AO alone or the AO+PES paradigms. Therefore, older patients with stroke appear to require a training strategy that is dependent on the brain state to enhance attentiveness and cortical facilitation for motor recovery. Furthermore, patients with MMSE scores of <28 exhibited significant differences in MEP latency across the four conditions, unlike those with MEP scores of >29. Although we exclusively recruited patients with relatively good cognitive function (MMSE score >24), the results suggest that individuals with lower cognitive abilities may respond more effectively to stimulation that is dependent on brain state.

Cortical activation at the central site, as indicated by mu suppression, displayed some notable patterns during the four tasks according to the topographical analysis (Figure 5A). In the frontal area, the cPES and tPES conditions elicited stronger activation than the nPES and rPES conditions. However, these findings were not statistically significant in motor cortex. There are two potential explanations for the lack of statistically significant results for the motor cortex in the EEG analysis. First, the sample size may have been insufficient because it was calculated based on a previous TMS study following stroke (Mrachacz-Kersting et al., 2019). Secondly, the distinct spatial and temporal resolutions of the TMS and EEG methods may have influenced the results (Lapenta et al., 2018). In agreement with the TMS results, the rPES condition, in which

PES was applied in the opposite manner to tPES, revealed mu suppression patterns in the frontal area that were relatively similar to those observed in the absence of PES application (Figure 5C).

This study has some limitations. First, we only investigated short-term changes in corticospinal plasticity after training. Corticospinal activation lasted for 20 min after task completion, confirming that the present paradigm promoted cortical plasticity for a short period, even after it was stopped. In earlier studies, the repetitive application of BCI to detect the cortical state associated to motor intention in conjunction with electrical stimulation induced improvement in upper-extremity motor function after stroke (Biasiucci et al., 2018; Mrachacz-Kersting et al., 2019). Hence, further investigation of the impact of our novel paradigm on functional recovery after stroke is required. Second, we included relatively few patients with mild to moderate stroke impairment. As mentioned earlier, our paradigm has the advantage of being applicable even to severely paralyzed stroke patients, because it is not dependent on motor activity. Unfortunately, this study excluded patients with severe motor weakness, in whom MEPs in the affected hand muscles could not be elicited. Therefore, further research is necessary to investigate patients with severe paralysis using alternative brain imaging techniques. Third, we administered PES below the sensory threshold, at a frequency of 50 Hz. The intensity and frequency of stimulation can influence corticospinal excitability (Pitcher et al., 2003; Chipchase et al., 2011; Saito et al., 2013). Considering that the optimal PES settings may vary between different patients, future research is required to determine how to maximize the therapeutic effect in each individual case. Forth, this study employed an exploratory approach to analyze the results, considering the small sample size, so that there was a limitation in that no corrections were made for multiple comparisons.

5 Conclusion

This study demonstrated that different pairings of PES application during BCI-AO influenced the task-dependent corticospinal plasticity after stroke. We provided new insight indicating that corticospinal excitability in the affected hemisphere increased when PES was applied synchronously with an AO task using BCI during a state of high attention, compared to continuous or asynchronous PES application. This paradigm promoted corticospinal plasticity for up to 20 min after task completion. Importantly, this effect was more evident in patients over 65 years. The ideal neurorehabilitation treatment for elderly patients with stroke is likely to be multimodal, involving not only the incorporation of effective feedback to create a highly motivational environment but also the optimization of techniques that are dependent on the brain state for sufficient task-induced neural plasticity. This study extended these results by integrating BCI technologies dependent on the attentional state with other conventional rehabilitation training methods.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Institutional review board of Nowon Eulji Medical Center/Eulji University (2022-07-012-001). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CJ: Investigation, Writing—original draft, Methodology, Resources, Project administration. HL: Investigation, Methodology, Software, Writing—original draft, Resources, Visualization. JL: Investigation, Methodology, Writing—original draft, Resources. HL: Formal analysis, Writing—review & editing, Data curation. JK: Conceptualization, Data curation, Validation, Writing—review & editing, Formal analysis. YK: Conceptualization, Funding acquisition, Supervision, Validation, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1373589/full#supplementary-material

References

Biasiucci, A., Leeb, R., Iturrate, I., Perdikis, S., Al-Khodairy, A., Corbet, T., et al. (2018). Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. *Nat. Commun.* 9:2421. doi: 10.1038/s41467-018-04673-z

Bisio, A., Avanzino, L., Biggio, M., Ruggeri, P., and Bove, M. (2017). Motor training and the combination of action observation and peripheral nerve stimulation reciprocally interfere with the plastic changes induced in primary motor cortex excitability. *Neuroscience* 348, 33–40. doi: 10.1016/j.neuroscience.2017.02.018

Bisio, A., Avanzino, L., Gueugneau, N., Pozzo, T., Ruggeri, P., and Bove, M. (2015). Observing and perceiving: a combined approach to induce plasticity in human motor cortex. *Clin. Neurophysiol.* 126, 1212–1220. doi: 10.1016/j.clinph.2014.08.024

Chipchase, L. S., Schabrun, S. M., and Hodges, P. W. (2011). Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. *Clin. Neurophysiol.* 122, 456–463. doi: 10.1016/j.clinph.2010.07.025

Choi, H., Lim, H., Kim, J. W., Kang, Y. J., and Ku, J. (2019). Brain computer interface-based action observation game enhances mu suppression in patients with stroke. *Electronics* 8:1466. doi: 10.3390/electronics8121466

Coscia, M., Wessel, M. J., Chaudary, U., Millan, J. D. R., Micera, S., Guggisberg, A., et al. (2019). Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain* 142, 2182–2197. doi: 10.1093/brain/awz181

Cui, Y., Cong, F., Huang, F., Zeng, M., and Yan, R. (2023). Cortical activation of neuromuscular electrical stimulation synchronized mirror neuron rehabilitation strategies: an fNIRS study. *Front. Neurol.* 14:1232436. doi: 10.3389/fneur.2023.1232436

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., et al. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat. Rev. Neurol.* 10, 597–608. doi: 10.1038/nrneurol.2014.162

Ethier, C., Gallego, J. A., and Miller, L. E. (2015). Brain-controlled neuromuscular stimulation to drive neural plasticity and functional recovery. *Curr. Opin. Neurobiol.* 33, 95–102. doi: 10.1016/j.conb.2015.03.007

Everaert, D. G., Thompson, A. K., Chong, S. L., and Stein, R. B. (2010). Does functional electrical stimulation for foot drop strengthen corticospinal connections? *Neurorehabil. Neural Repair* 24, 168–177. doi: 10.1177/1545968309349939

Fadiga, L., Fogassi, L., Pavesi, G., and Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *J. Neurophysiol.* 73, 2608–2611. doi: 10.1152/jn.1995.73.6.2608

Franceschini, M., Ceravolo, M. G., Agosti, M., Cavallini, P., Bonassi, S., Dall'Armi, V., et al. (2012). Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial. *Neurorehabil. Neural Repair* 26, 456–462. doi: 10.1177/1545968311427406

Fu, L., Rocchi, L., Hannah, R., Xu, G., Rothwell, J. C., and Ibáñez, J. (2021). Corticospinal excitability modulation by pairing peripheral nerve stimulation with cortical states of movement initiation. *J. Physiol.* 599, 2471–2482. doi: 10.1113/JP278536

Ghasemian-Shirvan, E., Farnad, L., Mosayebi-Samani, M., Verstraelen, S., Meesen, R. L. J., Kuo, M. F., et al. (2020). Age-related differences of motor cortex plasticity in adults: a transcranial direct current stimulation study. *Brain Stimul.* 13, 1588–1599. doi: 10.1016/j.brs.2020.09.004

Hebb, D. O. (1949). *The Organization of Behavior; A Neuropsychological Theory*. Oxford: Wiley.

Kaelin-Lang, A., Luft, A. R., Sawaki, L., Burstein, A. H., Sohn, Y. H., and Cohen, L. G. (2002). Modulation of human corticomotor excitability by somatosensory input. *J. Physiol.* 540, 623–633. doi: 10.1113/jphysiol.2001.012801

Kim, M. G., Lim, H., Lee, H. S., Han, I. J., Ku, J., and Kang, Y. J. (2022). Brain-computer interface-based action observation combined with peripheral electrical stimulation enhances corticospinal excitability in healthy subjects and stroke patients. *J. Neural Eng.* 19:ac76e0. doi: 10.1088/1741-2552/ac76e0

Kim, T., Kim, S., and Lee, B. (2016). Effects of action observational training plus brain-computer interface-based functional electrical stimulation on paretic arm motor recovery in patient with stroke: a randomized controlled trial. *Occup. Ther. Int.* 23, 39–47. doi: 10.1002/oti.1403

Kusec, A., Velikonja, D., DeMatteo, C., and Harris, J. E. (2019). Motivation in rehabilitation and acquired brain injury: can theory help us understand it? *Disabil. Rehabil.* 41, 2343–2349. doi: 10.1080/09638288.2018.1467504

Lai, S. M., Studenski, S., Duncan, P. W., and Perera, S. (2002). Persisting consequences of stroke measured by the Stroke Impact Scale. *Stroke* 33, 1840–1844. doi: 10.1161/01.STR.0000019289.15440.F2

Langhorne, P., Bernhardt, J., and Kwakkel, G. (2011). Stroke rehabilitation. *Lancet* 377, 1693–1702. doi: 10.1016/S0140-6736(11)60325-5

Lapenta, O. M., Ferrari, E., Boggio, P. S., Fadiga, L., and D'Ausilio, A. (2018). Motor system recruitment during action observation: no correlation between mu-rhythm desynchronization and corticospinal excitability. *PLoS ONE* 13:e0207476. doi: 10.1371/journal.pone.0207476

Larssen, B. C., Ho, D. K., Kraeutner, S. N., and Hodges, N. J. (2021). Combining observation and physical practice: benefits of an interleaved schedule for visuomotor adaptation and motor memory consolidation. *Front. Hum. Neurosci.* 15:614452. doi: 10.3389/fnhum.2021.614452

Lim, H., Jeong, C. H., Kang, Y. J., and Ku, J. (2023). Attentional state-dependent peripheral electrical stimulation during action observation enhances cortical activations in stroke patients. *Cyberpsychol. Behav. Soc. Netw.* 26, 408–416. doi: 10.1089/cyber.2022.0176

Lim, H., and Ku, J. (2017). Flickering exercise video produces mirror neuron system (MNS) activation and steady state visually evoked potentials (SSVEPs). *Biomed. Eng. Lett.* 7, 281–286. doi: 10.1007/s13534-017-0035-2

Mancuso, M., Tondo, S. D., Costantini, E., Damora, A., Sale, P., and Abbruzzese, L. (2021). Action observation therapy for upper limb recovery in patients with stroke: a randomized controlled pilot study. *Brain Sci.* 11:290. doi: 10.3390/brainsci11030290

Mrachacz-Kersting, N., Jiang, N., Stevenson, A. J., Niazi, I. K., Kostic, V., Pavlovic, A., et al. (2016). Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface. *J. Neurophysiol.* 115, 1410–1421. doi: 10.1152/jn.00918.2015

Mrachacz-Kersting, N., Stevenson, A. J. T., Jørgensen, H. R. M., Severinsen, K. E., Aliakbaryhosseinabadi, S., Jiang, N., et al. (2019). Brain state-dependent stimulation boosts functional recovery following stroke. *Ann. Neurol.* 85, 84–95. doi: 10.1002/ana.25375

Murphy, T. H., and Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Nat. Rev. Neurosci.* 10, 861–872. doi: 10.1038/nrn2735

Niazi, I. K., Mrachacz-Kersting, N., Jiang, N., Dremstrup, K., and Farina, D. (2012). Peripheral electrical stimulation triggered by self-paced detection of motor intention enhances motor evoked potentials. *IEEE Trans. Neural Syst. Rehabil. Eng.* 20, 595–604. doi: 10.1109/TNSRE.2012.2194309

Niazi, I. K., Navid, M. S., Rashid, U., Amjad, I., Olsen, S., Haavik, H., et al. (2022). Associative cued asynchronous BCI induces cortical plasticity in stroke patients. *Ann. Clin. Transl. Neurol.* 9, 722–733. doi: 10.1002/acn3.51551

Pascual-Leone, A., Nguyet, D., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., and Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J. Neurophysiol.* 74, 1037–1045. doi: 10.1152/jn.1995.74.3.1037

Pitcher, J. B., Ridding, M. C., and Miles, T. S. (2003). Frequency-dependent, bi-directional plasticity in motor cortex of human adults. *Clin. Neurophysiol.* 114, 1265–1271. doi: 10.1016/S1388-2457(03)00092-0

Ridding, M. C., Brouwer, B., Miles, T. S., Pitcher, J. B., and Thompson, P. D. (2000). Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Exp. Brain Res.* 131, 135–143. doi: 10.1007/s002219900269

Rizzolatti, G., Fabbri-Destro, M., Nuara, A., Gatti, R., and Avanzini, P. (2021). The role of mirror mechanism in the recovery, maintenance, and acquisition of motor abilities. *Neurosci. Biobehav. Rev.* 127, 404–423. doi: 10.1016/j.neubiorev.2021.04.024

Saito, K., Yamaguchi, T., Yoshida, N., Tanabe, S., Kondo, K., and Sugawara, K. (2013). Combined effect of motor imagery and peripheral nerve electrical stimulation on the motor cortex. *Exp. Brain Res.* 227, 333–342. doi: 10.1007/s00221-013-3513-5

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., and Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 123, 572–584. doi: 10.1093/brain/123.3.572

Takeuchi, N., and Izumi, S. (2015). Combinations of stroke neurorehabilitation to facilitate motor recovery: perspectives on Hebbian plasticity and homeostatic metaplasticity. *Front. Hum. Neurosci.* 9:349. doi: 10.3389/fnhum.2015.00349

Tani, M., Ono, Y., Matsubara, M., Ohmatsu, S., Yukawa, Y., Kohno, M., et al. (2018). Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. *Neurosci. Res.* 133, 7–14. doi: 10.1016/j.neures.2017.10.002

Teng, C., Cheng, Y., Wang, C., Ren, Y., Xu, W., and Xu, J. (2018). Aging-related changes of EEG synchronization during a visual working memory task. *Cogn. Neurodyn.* 12, 561–568. doi: 10.1007/s11571-018-9500-6

Ting, W. K., Fadul, F. A., Fecteau, S., and Ethier, C. (2021). Neurostimulation for Stroke Rehabilitation. *Front. Neurosci.* 15:649459. doi: 10.3389/fnins.2021.649459

Veldman, M. P., Maurits, N. M., Zijdewind, I., Maffiuletti, N. A., van Middelkoop, S., Mizelle, J. C., et al. (2018). Somatosensory electrical stimulation improves skill acquisition, consolidation, and transfer by increasing sensorimotor activity and connectivity. *J. Neurophysiol.* 120, 281–290. doi: 10.1152/jn.00860.2017

Ward, N. S. (2005). Mechanisms underlying recovery of motor function after stroke. *Postgrad. Med. J.* 81, 510–514. doi: 10.1136/pgmj.2004.030809

Widmer, M., Ziegler, N., Held, J., Luft, A., and Lutz, K. (2016). Rewarding feedback promotes motor skill consolidation via striatal activity. *Prog. Brain Res.* 229, 303–323. doi: 10.1016/bs.pbr.2016.05.006

Zhang, J. J. Q., Fong, K. N. K., Welage, N., and Liu, K. P. Y. (2018). The activation of the mirror neuron system during action observation and action execution with mirror visual feedback in stroke: a systematic review. *Neural Plast.* 2018:2321045. doi: 10.1155/2018/2321045

Zhang, X., de Beukelaar, T. T., Possel, J., Olaerts, M., Swinnen, S. P., Woolley, D. G., et al. (2011). Movement observation improves early consolidation of motor memory. *J. Neurosci.* 31, 11515–11520. doi: 10.1523/JNEUROSCI.6759-10.2011

Zimerman, M., Nitsch, M., Giraux, P., Gerloff, C., Cohen, L. G., and Hummel, F. C. (2013). Neuroenhancement of the aging brain: restoring skill acquisition in old subjects. *Ann. Neurol.* 73, 10–15. doi: 10.1002/ana.23761

Zrenner, C., Desideri, D., Belardinelli, P., and Ziemann, U. (2018). Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimul.* 11, 374–389. doi: 10.1016/j.brs.2017.11.016

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Effects of a step-by-step inpatient rehabilitation program on self-care ability and quality of life in patients with acute cerebral infarction following intravascular stent implantation: a prospective cohort study

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Objective: This study aims to evaluate the influence of a step-by-step inpatient rehabilitation program (SIRP) on the self-care capability and quality of life of patients who have undergone intravascular stent implantation to treat large vessel occlusion during acute cerebral infarction (ACI).

Methods: This study included a cohort of 90 patients with ACI who received intravascular stent implantations at a tertiary hospital in the Third Affiliated Hospital of Anhui Medical University from January 2020 to February 2024. The patients were followed up for at least 3 months. Cohort grouping was based on the type of nursing care each patient received. The observation group participated in SIRP along with receiving routine nursing care, whereas the control group received only routine nursing care. Key outcome measures included the Barthel index, the National Institute of Health Stroke Scale (NIHSS) score, the incidence of complications, length of hospital stay, and 36-item short-form survey (SF-36) scores. These parameters were compared between the two groups.

Results: At the time of admission, there were no significant differences in demographic data, NIHSS score, Barthel index, or SF-36 scores between the observation and control groups (all $p > 0.05$). However, at 3 months postoperatively, the observation group showed significant improvements, with higher average scores in the Barthel index (62.49 ± 7.32 vs. 53.16 ± 4.37, $p < 0.001$) and SF-36 scores (502.33 ± 14.28 vs. 417.64 ± 9.65, $p < 0.001$). Additionally, this group had significantly lower NIHSS scores (3.38 ± 1.19 vs. 10.24 ± 2.10, $p < 0.001$), fewer complications (3 vs. 15, $p = 0.002$), and shorter hospital stays (12.40 ± 1.68 vs. 15.56 ± 1.87, $p < 0.001$).

Conclusion: Implementing SIRP notably enhanced self-care capabilities and overall quality of life, while also reducing complication rates and the length of hospital stays for patients with ACI who underwent intravascular stent implantation. This underscores the potential benefits of incorporating structured rehabilitation programs in the treatment and recovery processes of such patients.

KEYWORDS

self-care ability, quality of life, acute cerebral infarction, intravascular stent implantation, step-by-step inpatient rehabilitation

1 Introduction

Ischemic stroke, also known as acute cerebral infarction (ACI), is associated with significant morbidity, mortality, and disability rates, making it a leading cause of health issues and fatalities in the adult population worldwide (1). National stroke surveys indicate that the incidence, disability, and mortality rates of stroke stand at 0.25, 1.11, and 0.12%, respectively, highlighting the profound impact of ischemic stroke on the health and quality of life of individuals, as well as the substantial burden it imposes on families and society (2). Additionally, a previous study has shown that stroke can manifest as an initial symptom of certain hematological disorders or as a complication of such conditions (3). Accurate identification of underlying hematological diseases is crucial for the prompt and appropriate treatment of patients with stroke. In clinical practice, interventions such as intravenous thrombolysis, intra-arterial thrombectomy, and intravascular stent implantation are recognized as effective treatments for ischemic stroke (4). The therapeutic window for intravenous thrombolysis is restricted to 6 h, while arterial thrombectomy can be performed within a 24-h window, thus extending the opportunity for treatment (5). Intravascular stent implantation alleviates luminal stenosis by placing a stent that covers the torn section of the arterial intima, helps prevent thrombus formation, and effectively stops the progression of ischemic penumbra into full infarction or nerve cell necrosis (6).

Despite advancements in the diagnosis, management, and critical care for patients with ACI, stroke-related complications continue to significantly threaten patient survival and quality of life (7). Patients who have undergone intravascular stent implantation are particularly susceptible to complications such as intracranial hemorrhage, reperfusion injury, pneumonia, pressure ulcers, urinary tract infections, and other adverse events. These complications are often exacerbated by prolonged bed rest and compromised immunity, which can hinder recovery and lead to fatal outcomes (8). Consequently, providing high-quality, efficient, and standardized nursing care after intravascular stent implantation is crucial for optimizing patient outcomes.

The step-by-step inpatient rehabilitation program (SIRP) is a progressive training approach that aims to enhance specific skills or behaviors through gradual, continuous, and repetitive training sessions (9). SIRP is designed to increase the adaptability and resilience of the body, boost learning efficiency, and ultimately help restore near-normal functional capacity in patients (10). However, the effectiveness of SIRP on rehabilitation outcomes for patients with stroke after intravascular stent implantation has not been thoroughly investigated.

This study introduces a structured SIRP for patients with ACI who have undergone intravascular stent implantation. The program is divided into five phases and includes preoperative preparation, postoperative care, and long-term follow-up. It employs a collaborative nursing approach that involves physicians, nurses, patients, and family members. The hypothesis is that patients participating in this step-by-step program will show an improved quality of life after rehabilitation, up to 3 months, compared to those undergoing conventional rehabilitation. The study aims to evaluate the effectiveness of SIRP in enhancing rehabilitation outcomes and determine its advantages over routine inpatient rehabilitation in terms of improvements in self-care abilities, quality of life, complication rates, and length of hospital stays.

2 Patients and methods

2.1 Participants

This study is a prospective cohort investigation conducted at the Third Affiliated Hospital of Anhui Medical University. It included a total of 90 patients diagnosed with ACI who underwent interventional intravascular stent implantation treatment between January 2020 and February 2024. These patients were divided into observation and control groups based on different nursing patterns. All participants met the criteria specified in the 2018 edition of the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (11). The inclusion criteria were as follows: (i) patients within 24 h of symptom onset and deemed suitable for intravascular stent implantation; and (ii) informed consent provided by either the patients themselves or their representatives. The exclusion criteria included (i) severe cardiac, pulmonary, hepatic, and renal insufficiencies; and (ii) failure during the intraoperative intravascular stent implantation process. Initially, 106 patients were eligible; however, exclusions were made for five cases of surgical failure and 11 cases of postoperative mortality within 3 months [causes of death included sudden cardiac death ($n = 2$), multiorgan failure ($n = 2$), reinfarctions ($n = 2$), intracranial hemorrhage ($n = 3$), and other causes ($n = 2$); total mortality rate: 10.4%]. This resulted in a final cohort of 90 patients, with 45 in each group for analysis. The study was ethically approved by the Third Affiliated Hospital of Anhui Medical University (approval no. 2024-042-01).

2.2 Methods

2.2.1 Establishment of SIRP

The establishment of SIRP consisted of several distinct phases: Phase 1 began with the immediate admission of patients through a dedicated "green channel," where a specialized green channel nurse provided necessary examinations and preoperative care. In this phase, a specialized training group for patients with cerebral infarction was established, led by the department head and the head nurse, with the involvement of other medical staff. The team evaluated the motor function of each patient and developed a tailored rehabilitation training plan based on individual needs. Phase 2 focused on the creation of personalized training plans that aligned with the specific

conditions and rehabilitation goals of the patients. The plans included a variety of exercises such as limb positioning, passive and active movements, sitting and balance training, walking training, muscle strength enhancement, joint range of motion exercises, and balance ability training. Phase 3 was dedicated to training the families or caregivers of the patients on how to assist with daily living activities. Phase 4 involved evaluating the home rehabilitation environment of the patient and developing a corresponding plan to ensure a smooth transition before discharge. Phase 5 emphasized regular follow-up through telephone calls or home visits to monitor the rehabilitation progress of the patients, adjust training plans as needed, and provide ongoing support and encouragement to both patients and their families.

A previous study that employed SIRP for patients with breast cancer focused on psycho-oncological interventions, which included psychological interventions, relaxation techniques, educational sessions, and various types of activating physiotherapy (9). In contrast, SIRP in this study adopted a holistic nursing model that involved physicians, nurses, patients, and family members and included long-term follow-up. The control group received standard nursing care, which included assessments, monitoring, routine observations of conditions, nursing documentation, psychological support, and health education. Meanwhile, the observation group received SIRP care in addition to standard care. This group benefited from a dedicated team that provided comprehensive treatment and support, enhancing the overall care framework. This approach aims to integrate and optimize healthcare delivery for better patient outcomes.

2.3 Evaluation indicators

2.3.1 National Institute of Health Stroke Scale scores

The NIHSS scores were employed to evaluate the neurological deficits of the patients. A higher NIHSS score indicates more severe neurological impairments (12). The scale was validated in the Chinese population by Li et al. (13). The NIHSS includes various domains such as consciousness level, eye movements, muscle strength, sensation, coordination, language, and neglect, each scored on an ordinal scale. The total possible score ranges from 0 to 42, with higher scores indicating greater severity of the stroke.

2.3.2 Barthel index evaluation

The evaluation of self-care ability was conducted using the Barthel Index, which comprises 10 components including eating, grooming, and mobility, with a total possible score of 100 points. A higher score on the Barthel Index indicates better self-care ability (14). The Barthel index was translated into Chinese by Gao et al. (15).

2.3.3 Quality of life evaluation

The evaluation of quality of life is commonly conducted using the 36-item short-form survey (SF-36), an eight-dimensional, self-administered instrument designed to assess general health-related quality of life (HRQoL). The SF-36 includes eight domains: physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Scores for each domain range from 0 to 100, with higher scores indicating a better quality of life (16). The SF-36 scale was validated in Chinese by Ren et al. (17).

2.3.4 Other indicators

In addition to questionnaires, other important indicators, such as complication identification and length of hospital stay, are considered when evaluating patient outcomes. Complications are identified based on the occurrence of specific postoperative events, including intracranial hemorrhage, upper gastrointestinal bleeding, reperfusion injury, lower extremity deep vein thrombosis, pulmonary infection, and subcutaneous hematoma at the puncture site. The length of hospital stay is determined by the duration between the admission and discharge of a patient, providing additional insights into the overall impact and efficiency of the treatment process.

2.3.5 Statistical methods

Statistical analysis was performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY, United States). Data that followed a normal distribution were presented as mean ± standard deviation and compared between groups using the independent sample *t*-test. Data that followed a non-normal distribution were expressed as the median and interquartile range and analyzed using the Mann–Whitney U-test. Categorical data were presented as numbers (percentages) and analyzed using the chi-square test or Fisher's exact test, whichever is appropriate. A significance level of $p < 0.05$ was considered to be statistically significant.

3 Results

3.1 Comparative analysis of general characteristics between the two patient groups

Among the 90 patients included in this study, 63 (70.0%) were male and 27 (30.0%) were female. There was no significant difference in the onset time between the two groups (5.23 ± 0.67 h vs. 5.29 ± 0.71 h; $p = 0.671$). The average age was 66.02 ± 8.86 years in the control group and 63.84 ± 8.74 years in the observation group, with the difference not reaching statistical significance ($p > 0.05$). Additionally, other baseline characteristics showed no significant differences between the groups, as detailed in Table 1.

3.2 Comparison of NIHSS scores between the two patient groups

The initial comparison of NIHSS scores upon admission showed no statistically significant differences between the two groups ($p = 0.631$), as detailed in Table 2. However, following SIRP, there was a notable difference in outcomes. One week postoperatively, patients in the observation group had significantly lower NIHSS scores compared to those in the control group (5.69 ± 1.72 vs. 12.62 ± 2.26; $p < 0.001$). This trend continued at 1 month (4.80 ± 0.99 vs. 11.24 ± 1.96; $p < 0.001$) and 3 months postoperatively (3.38 ± 1.19 vs. 10.24 ± 2.10; $p < 0.001$), indicating a substantial improvement in the observation group over time.

TABLE 1 Comparison of general information between the two groups of patients.

	Observation group ($n = 45$)	Control group ($n = 45$)	t or χ^2 value	p value
Age (years, $x \pm s$)	63.84 ± 8.74	66.02 ± 8.86	−1.174	0.244
Gender (n, %)				
Male	31	32	0.053	0.818
Women	14	13		
Hypertension (n, %)	25	28	0.413	0.520
Diabetes mellitus (n, %)	10	8	0.278	0.598
Atrial fibrillation (n, %)	18	20	0.182	0.670
Time to onset (hours, $x \pm s$)	5.23 ± 0.67	5.29 ± 0.71	−0.427	0.671
Site of vascular occlusion (n, %)				
Middle cerebral artery	21	23	1.359	0.507
Internal carotid artery	15	17		
Vertebrobasilar system	9	5		

TABLE 2 Comparison of NIHSS scores between the two groups.

	NIHSS score (Points)			
	At the time of admission	1 week after surgery	1 month after surgery	3 months after surgery
Observation group ($n = 45$)	14.56 ± 2.19	5.69 ± 1.72	4.80 ± 0.99	3.38 ± 1.19
Control group ($n = 45$)	14.7 ± 2.18	12.62 ± 2.26	11.24 ± 1.96	10.24 ± 2.10
t value	−0.482	−16.392	−19.717	−19.064
p value	0.631	<0.001	<0.001	<0.001

3.3 Comparison of Barthel index between the two patient groups

Initially, there was no statistically significant difference in the Barthel index scores between the two patient groups upon admission ($p = 0.799$). However, following SIRP, significant differences emerged. Patients in the observation group showed significantly higher Barthel index scores compared to the control group at 1 week (34.96 ± 7.17 vs. 27.67 ± 5.04; $p < 0.001$), 1 month (53.93 ± 6.72 vs. 38.07 ± 4.93; $p < 0.001$), and 3 months postoperatively (62.49 ± 7.32 vs. 53.16 ± 4.37; $p < 0.001$). These outcomes are detailed in Table 3.

TABLE 3 Comparison of Barthel index between the two groups.

	Barthel index (Points)			
	At the time of admission	1 week after surgery	1 month after surgery	3 months after surgery
Observation group ($n = 45$)	22.09 ± 4.61	34.96 ± 7.17	53.93 ± 6.72	62.49 ± 7.32
Control group ($n = 45$)	22.36 ± 5.25	27.67 ± 5.04	38.07 ± 4.93	53.16 ± 4.37
t value	−0.256	5.580	12.764	7.343
p value	0.799	<0.001	<0.001	<0.001

TABLE 4 Comparison of SF-36 between the two groups at 3 months after surgery.

	Observation group ($n = 45$)	Control group ($n = 45$)	t value	p value
PF	65.26 ± 14.23	51.46 ± 12.28	7.286	<0.001
RP	60.40 ± 15.39	44.50 ± 10.69	8.049	<0.001
BP	61.38 ± 15.26	55.96 ± 18.42	4.368	0.003
GH	64.56 ± 14.99	56.38 ± 12.27	5.528	<0.001
VT	63.26 ± 14.44	52.16 ± 11.33	6.694	<0.001
SF	63.49 ± 12.19	49.87 ± 15.38	7.663	<0.001
RE	62.35 ± 13.28	51.02 ± 14.10	6.729	<0.001
MH	61.63 ± 15.58	56.38 ± 12.39	4.036	0.005
Total score	502.33 ± 14.28	417.64 ± 9.65	32.952	<0.001

PF, Physical functioning; RP, Physical problems; BP, Bodily pain; GH, General health; VT, Vitality; SF, Social functioning; RE, Role limitations due to emotional problems; and MH, Mental health.

3.4 Comparison of SF-36 between the two patient groups

Initially, there were no significant differences in the SF-36 scores and its components between the observation and the control group scores ($p > 0.05$). However, significant improvements were observed by the three-month mark. The overall SF-36 scores were notably higher in the observation group compared to the control group (502.33 ± 14.28 vs. 417.64 ± 9.65, $p < 0.001$). Similarly, all the SF-36 subscores in the observation group were significantly better than those in the control group (all $p < 0.05$). Detailed results are shown in Table 4 and Figure 1.

3.5 Comparison of complication rates and length of stay between the two patient groups

The control group experienced an average hospital stay of 15.56 ± 1.87 days, whereas the observation group had a shorter average

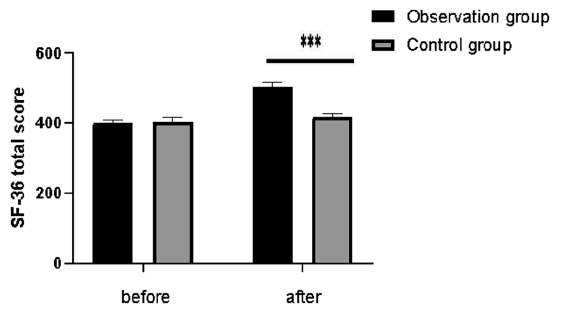

FIGURE 1
Comparison of SF-36 total score between the two groups. ***$p < 0.001$.

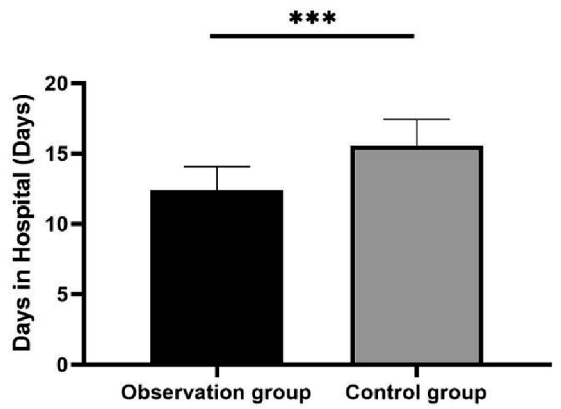

FIGURE 2
Comparison of hospital days between the two groups. ***$p < 0.001$.

stay of 12.40 ± 1.68 days, significantly reducing the length of the hospital stay ($p < 0.001$; Figure 2). Regarding complications, the control group reported three cases of gastrointestinal bleeding, four cases of intracranial hemorrhage, two cases of reperfusion injury, three cases of pulmonary infection, and three cases of subcutaneous hematoma. In contrast, the observation group had only one case each of gastrointestinal bleeding, intracranial hemorrhage, and subcutaneous hematoma. The incidence of complications was significantly lower in the observation group than in the control group ($p = 0.002$). These findings are detailed in Table 5.

4 Discussion

Ischemic stroke is characterized by its sudden onset and rapid progression, which demands immediate reperfusion of the occluded vessel. Mechanical intravascular stent implantation, which involves inserting a thrombus stent to remove the occlusion, is a commonly employed and effective approach for this purpose (18, 19). However, patients who undergo intravascular stent implantation are at a heightened risk for various complications, such as intracranial hemorrhage, reperfusion injury, and infections. These complications are often exacerbated by compromised immunity and prolonged immobilization, potentially hindering recovery and increasing the risk of mortality (20, 21). Vigilant and proactive monitoring by nursing staff after the procedure is crucial in preventing deterioration, enhancing the success of the procedure, facilitating patient recovery, and ultimately improving the quality of life (22).

Step-by-step inpatient rehabilitation program is progressive reinforcement training, which refers to the method of gradually adapting and strengthening a particular skill or behavior through continuous and repeated training. Its primary goal is to provide high-quality nursing services, ensuring that patients receive effective care (23). In this study, patients who received SIRP following intravascular stent implantation showed significantly lower NIHSS scores and higher Barthel index scores at 1 week, 1 month, and 3 months postoperatively compared to the control group. Additionally, SIRP significantly enhanced the quality of life for patients with ACI who underwent intravascular stent implantation, aligning with the findings from the previous studies (9).

Research by Chen et al. (24) on integrated emergency nursing for patients with ACI showed that this approach could effectively reduce triage time and improve neurological function. Similarly, this study found that the observation group, which received SIRP, had a significantly shorter hospital stay and improved quality of life compared to the control group. These outcomes suggest that SIRP not only helps reduce the length of hospital stay, thus lessening the economic burden on families but also significantly enhances the neurological recovery and self-care abilities of patients with ischemic stroke following intravascular stent implantation, thereby enhancing their overall quality of life.

Previous research has shown that the overall complication rate associated with intravascular stent implantation ranges between 5 and 20% (25). The occurrence of complications after such procedures is critical in determining both the length of hospital stays and patient outcomes. Styczen et al. (26) conducted a retrospective analysis on patients who underwent mechanical intravascular stent implantation at seven tertiary care centers from January 2013 to May 2020, revealing a 19% incidence of postoperative symptomatic intracranial hemorrhage. At our institution, the implementation of SIRP, a specialized postoperative care protocol, has been effective in mitigating blood pressure elevation caused by patient anxiety or emotional distress. Through vigilant postoperative monitoring, any abnormal blood pressure fluctuations are promptly identified and managed, reducing the likelihood of postoperative intracranial hemorrhage and reperfusion injury. The study demonstrated that the incidence of intracranial hemorrhage was significantly lower in the observation group at 2.2%, compared to 8.9% in the control group, and there were no instances of reperfusion injury in the observation group, in contrast to 4.4% in the control group. These findings highlight the significant role of SIRP in reducing postoperative complications.

A previous study has shown that the implementation of standardized perioperative care protocols significantly enhances patient outcomes for those undergoing mechanical intravascular stent implantation for ACI (27). At our institution, SIRP was developed to provide consistent nursing interventions for individuals undergoing intravascular stent implantation for ACI. This comprehensive protocol includes preoperative preparation, postoperative management, rehabilitation exercises, psychological support, management of complications, and continuity of care. Its goal is to offer comprehensive and standardized nursing services to patients undergoing this

TABLE 5 Comparison of complication rates between the two groups [Cases (*n*)].

	Gastrointestinal bleeding	Intracranial hemorrhage	Reperfusion injury	Pulmonary infection	Subcutaneous hematoma	Total
Observation group ($n=45$)	1	1	0	0	1	3
Control group ($n=45$)	3	4	2	3	3	15
χ^2						10.000
p						0.002

procedure. Despite the widespread adoption of intravascular stent implantation across various healthcare facilities, postoperative recovery outcomes often remain suboptimal due to the lack of standardized care practices. Thus, it is crucial to apply scientifically sound and effective care strategies to patients undergoing vascular recanalization procedures. Implementing these strategies will maximize the efficacy of this technology and improve patient recovery and outcomes (28, 29).

The study still has certain limitations, including potential bias in sample selection. Additionally, being a single-center clinical trial, it highlights the need for further validation through multi-center clinical studies. The relatively small sample size also highlights the necessity of expanding it in future studies to enhance the credibility of the results. The occurrence of five cases of surgical failure and 11 cases of postoperative mortality within 3 months further complicates the assessment of the effectiveness of SIRP. Considering the distinct pathophysiology, prognosis, and clinical characteristics of lacunar stroke compared to other types of cerebral infarcts (30), future research could beneficially explore the impact of SIRP on lacunar versus non-lacunar ischemic strokes. Additionally, examining the effects on other subtypes of ischemic strokes, such as atherothrombotic, cardioembolic, unusual, and essential infarcts, could provide more comprehensive insights.

In this study, we observed that the use of SIRP, compared to conventional care approaches, resulted in significant improvements in neurological function recovery, self-care abilities, complication rates, length of hospital stays, quality of life, and overall postoperative recovery in patients with ACI who underwent intravascular stent implantation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was ethically approved by the Third Affiliated Hospital of Anhui Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. NX: Conceptualization, Data curation, Investigation, Writing – original draft. JT: Data curation, Investigation, Writing – original draft. QC: Data curation, Investigation, Writing – original draft. QB: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Feske SK. Ischemic stroke. *Am J Med*. (2021) 134:1457–64. doi: 10.1016/j.amjmed.2021.07.027

2. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. (2017) 390:1151–210. doi: 10.1016/S0140-6736(17)32152-9

3. Westendorp WF, Dames C, Nederkoorn PJ, Meisel A. Immunodepression, infections, and functional outcome in ischemic stroke. *Stroke*. (2022) 53:1438–48. doi: 10.1161/STROKEAHA.122.038867

4. Paul S, Candelario-Jalil E. Emerging neuroprotective strategies for the treatment of ischemic stroke: an overview of clinical and preclinical studies. *Exp Neurol*. (2021) 335:113518. doi: 10.1016/j.expneurol.2020.113518

5. Rabinstein AA. Update on treatment of acute ischemic stroke. *Continuum*. (2020) 26:268–86. doi: 10.1212/CON.0000000000000840

6. Feng G, Gong Y. Correlation between selection of time window for acute cerebral infarction and efficacy of intravascular stent implantation. *J Healthcare Eng*. (2022) 2022:1–6. doi: 10.1155/2022/1357737

7. Junttola U, Lahtinen S, Liisanantti J, Vakkala M, Kaakinen T, Isokangas JM. Medical complications and outcome after endovascular therapy for acute ischemic stroke. *Acta Neurol Scand*. (2021) 144:623–31. doi: 10.1111/ane.13501

8. Sweid A, Head J, Tjoumakaris S, Xu V, Shivashankar K, Alexander TD, et al. Mechanical thrombectomy in distal vessels: revascularization rates, complications, and functional outcome. *World Neurosurg*. (2019) 130:e1098–104. doi: 10.1016/j.wneu.2019.07.098

9. Hartmann U, Muche R, Reuss-Borst M. Effects of a step-by-step inpatient rehabilitation programme on quality of life in breast cancer patients. A prospective randomised study. *Onkologie*. (2007) 30:177–82. doi: 10.1159/000099989

10. Gwak DW, Hwang JM. Step-by-step inpatient rehabilitation for critical illness after coronavirus disease 2019: a CARE-compliant case report. *Medicine (Baltimore)*. (2021) 100:e26317. doi: 10.1097/MD.0000000000026317

11. Chinese Society of Neurology, Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Zhonghua Shen Jing Ke Za Zhi*. (2018) 51:666–82. doi: 10.3760/cma.j.issn.1006-7876.2018.09.004

12. Rajashekar D, Wilms M, MacDonald ME, Schimert S, Hill MD, Demchuk A, et al. Lesion-symptom mapping with NIHSS sub-scores in ischemic stroke patients. *Stroke Vasc Neurol*. (2022) 7:124–31. doi: 10.1136/svn-2021-001091

13. Li H, Wong KS, Kay R. Relationship between the Oxfordshire community stroke project classification and vascular abnormalities in patients with predominantly intracranial atherosclerosis. *J Neurol Sci*. (2003) 207:65–9. doi: 10.1016/S0022-510X(02)00397-0

14. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for stroke rehabilitation. *J Clin Epidemiol*. (1989) 42:703–9. doi: 10.1016/0895-4356(89)90065-6

15. Gao Y, Wang Y, Li D, Zhao J, Dong Z, zhou J, et al. Disability assessment in stroke: relationship among the pictorial-based Longshi scale, the Barthel index, and the modified Rankin scale. *Clin Rehabil*. (2021) 35:606–13. doi: 10.1177/0269215520975922

16. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. *SAGE Open Med*. (2016) 4:2050312116671725. doi: 10.1177/2050312116671725

17. Ren XS, Amick B 3rd, Zhou L, Gandek B. Translation and psychometric evaluation of a Chinese version of the SF-36 health survey in the United States. *J Clin Epidemiol*. (1998) 51:1129–38. doi: 10.1016/S0895-4356(98)00104-8

18. Jadhav AP, Desai SM, Jovin TG. Indications for mechanical Thrombectomy for acute ischemic stroke: current guidelines and beyond. *Neurology*. (2021) 97:S126–36. doi: 10.1212/WNL.0000000000012801

19. Jolugbo P, Ariëns RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. *Stroke*. (2021) 52:1131–42. doi: 10.1161/STROKEAHA.120.032810

20. Watson CCL, Feria A, Chen CJ, Camacho A. Outcomes and complications of endovascular mechanical Thrombectomy in the treatment of acute posterior circulation occlusions: a systematic review. *World Neurosurg*. (2021) 145:35–44. doi: 10.1016/j.wneu.2020.08.221

21. Ganesh A, Fladt J, Singh N, Goyal M. Efficacy and safety of mechanical thrombectomy in acute stroke patients with pre-morbid disability. *Expert Rev Med Devices*. (2022) 19:641–8. doi: 10.1080/17434440.2022.2124109

22. Clare CS. Role of the nurse in acute stroke care. *Nurs Stand*. (2020) 35:68–75. doi: 10.7748/ns.2020.e11559

23. Ashley MJ, Gordon WA, Masel BE, Thomas PW, Connors SH. First do no harm: an opinion on bundled Care for Stroke Patients. *Arch Phys Med Rehabil*. (2019) 100:578–80. doi: 10.1016/j.apmr.2018.10.003

24. Chen Y, Mao Y, Chen L. Application effect of prehospital-hospital integrated emergency nursing in patients with acute cerebral infarction. *Biotechnol Genet Eng Rev*. (2023) 2023:1–13. doi: 10.1080/02648725.2023.2210954

25. Shapiro SZ, Sabacinski KA, Mantripragada K, Shah SS, Stein AA, Echeverry NB, et al. Access-site complications in mechanical Thrombectomy for acute ischemic stroke: a review of prospective trials. *AJNR Am J Neuroradiol*. (2020) 41:477–81. doi: 10.3174/ajnr.A6423

26. Styczen H, Fischer S, Yeo LL, Yong-Qiang Tan B, Maurer CJ, Berlis A, et al. Approaching the boundaries of endovascular treatment in acute ischemic stroke: multicenter experience with mechanical Thrombectomy in Vertebrobasilar artery branch occlusions. *Clin Neuroradiol*. (2021) 31:791–8. doi: 10.1007/s00062-020-00970-7

27. Wassélius J, Arnberg F, von Euler M, Wester P, Ullberg T. Endovascular thrombectomy for acute ischemic stroke. *J Intern Med*. (2022) 291:303–16. doi: 10.1111/joim.13425

28. Broocks G, Kemmling A, Faizy T, McDonough R, van Horn N, Bechstein M, et al. Effect of thrombectomy on oedema progression and clinical outcome in patients with a poor collateral profile. *Stroke Vasc Neurol*. (2021) 6:222–9. doi: 10.1136/svn-2020-000570

29. Wang M, Geng X, Dandu C, Patel R, Ding Y. Normobaric oxygen (NBO) therapy reduces cerebral ischemia/reperfusion injury through inhibition of early autophagy. *Evid Based Complement Alternat Med*. (2021) 2021:1–11. doi: 10.1155/2021/7041290

30. Rudilosso S, Rodríguez-Vázquez A, Urra X, Arboix A. The potential impact of neuroimaging and translational research on the clinical management of lacunar stroke. *Int J Mol Sci*. (2022) 23:1497. doi: 10.3390/ijms23031497

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The effect of mobile application-based technology on post-stroke aphasia: a systematic review

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Background: Enhancing speech-language therapy remains the most effective strategy for improving post-stroke aphasia, However, conventional face-to-face interventions often lack the necessary therapeutic intensity. In recent years, mobile application-based speech-language therapy has emerged progressively, offering new opportunities for independent rehabilitation among aphasic patients. This review aims to evaluate the impact of mobile application-based interventions on post-stroke aphasic.

Methods: By conducting a systematic search across five databases (PubMed, Web of Science, EMBASE, CINAHL, and Scopus), we identified and included studies that investigated the utilization of mobile application-based technologies (such as computers, iPads, etc.) for treating post-stroke aphasia.

Results: This study included 15 research investigations, including 10 randomized controlled trials (RCTs), four self-controlled studies and one cross-over experimental design study. Among these, eight studies demonstrated the efficacy of mobile application-based therapy in enhancing overall language functionality for post-stroke aphasia patients, three studies highlighted its potential for improving communication skills, three studies observed its positive impact on spontaneous speech expression. Moreover, four studies indicated its effectiveness in enhancing naming abilities, two studies underscored the positive influence of mobile application-based interventions on the quality of life for individuals with aphasia. Six studies noted that speech improvement effects were maintained during the follow-up period.

Conclusion: The results of this review demonstrate the potential of mobile application-based interventions for improving speech-language function in individuals with aphasia. However, further high-quality research is needed to establish their effects across different domains and to delve into the comparative advantages of various treatment approaches.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=405248

KEYWORDS

mobile application, aphasia, speech and language therapy, post-stroke, systematic review

1 Introduction

Aphasia arising post-stroke is an acquired communication disorder characterized by impairment in linguistic abilities. It stems from varying degrees of damage to the language center of the brain (usually located in the left hemisphere), which affects oral expression, reading ability, writing ability, language comprehension, and even cognitive and computational functions (1, 2). After an initial ischemic stroke, ~30% of patients may manifest symptoms of aphasia (3). Studies reveal that during the year following a stroke, ~43% of individuals with aphasia still confront ongoing communication challenges (4). Aphasia significantly hinders daily life functioning, subsequently reducing quality of life and potentially leading to issues such as depression (5–8).

In recent years, an increasing number of studies have focused on the use of mobile applications, such as computers and tablets, to enhance the expressive language skills of individuals with aphasia (9, 10). For example, Zhou et al. (11) found that a 14-day, 30-min-a-day computer-based training session resulted in more significant speech improvements compared to traditional treatments. Mobile application-based therapy is gaining attention as a means of remote delivery (12). One potential advantage of this treatment modality is its potential for increased cost-effectiveness, reduced therapist burden, and enhanced patient satisfaction and treatment adherence (13).

Three systematic review studies have already explored the impacts of various innovative technologies on aphasia, and their consistent findings suggest that innovative technologies hold promise in improving language functions among individuals with aphasia (14–16). However, the systematic reviews conducted by Lavoie et al. (14) and Russo et al. (16) focused only on the impact of a specific technology on language performance in a particular domain for people with aphasia and the literature included was limited to studies conducted prior to 2017. Additionally, the review by Repetto et al. covered literature from only three databases (15). Hence, the objective of this present systematic review is to comprehensively explore the impact of mobile application-based speech-language therapy (SLT) on language functional performance across multiple domains in individuals with aphasia.

2 Methods

2.1 Search strategy

This systematic review strictly follows the guidelines outlined by the PRISMA framework. The systematic review has been registered in the PROSPERO-International Prospective Register of Systematic Reviews (CRD42023405248). The search timeframe spans from the inception of databases to August 15, 2023. We conducted searches in five major databases (PubMed, Web of Science, EMBASE, CINAHL, and Scopus). To ensure search accuracy, we employed PubMed MeSH terms including "stroke," "aphasia," and "computer" to identify relevant keywords for retrieval. In the search process, Boolean operators were utilized to combine these keywords, aiming to capture a comprehensive range of literature (see Supplementary Table S1 for the search formula).

2.2 Study selection

Inclusion criteria were determined according to the PICOS principles (include participant, intervention, control group, outcomes and study): (1) Study design: English language, randomized controlled trial, self-controlled trial, and crossover design trial; (2) Study participant: individuals ≥18 years of age with stroke, confirmed by medical imaging diagnosis, and diagnosed by speech-language pathologists according to the diagnostic criteria of the Aphasia Scale (e.g., the Western Aphasia Battery of Tests); (3) Intervention method: mobile application technology, including, but not limited to, application interventions on devices such as PCs, iPads, tablets, and cell phones. If mobile application technology is used in combination with other treatments, the control group needs to adopt the same method. (4) Control group: the control group included no intervention (waiting group), therapist intervention alone, or computer-based pseudo-intervention; (5) The outcome measures include language functioning outcomes such as overall language function (assessed by the Overall Language Scale), functional communication skills (assessed by the Functional Communication Scale), spontaneous language functioning (assessed by picture description tasks, etc.), and naming ability (assessed by the Naming Scale). In addition, attention will also be paid to outcomes such as quality of life related to aphasia.

2.3 Literature screening procedures

Literature screened in the database will be imported into EndNote software. Two researchers will screen the titles and abstracts of the literature based on predetermined inclusion criteria. During the screening process, if disagreement arises between the two researchers, a third researcher will be asked to participate in order to jointly decide whether to include or exclude the literature. After the initial screening, the full-text screening stage was carried out. During the full-text screening process, evaluations are also made based on pre-set criteria. After the screening is complete, a reference search will be performed for the included literature to manually search for relevant literature that may meet the requirements.

2.4 Data extraction

The researchers will create data extraction tables to record the information from each included study, which will be populated into Tables 1, 2. Extracted details will include author, publication year, study type, sample size, type of aphasia, age, gender, duration of condition, intervention setting, severity of aphasia, intervention method, frequency and duration of intervention, description of control group, outcome measures, and results. Two researchers will carry out the data extraction process, and in case of any discrepancies, the opinion of a third researcher will be sought. Given the significant variations in intervention content, outcome assessment, and study designs across different studies, conducting a meta-analysis would not be appropriate.

TABLE 1 Characteristics of randomized controlled trials.

References	Sample size	Age (year)	Sex (female) (%)	Post-stroke duration (d/m/y)	Type of aphasia	Severity of aphasia (mean ± SD)	Intervention address	Intervention	Session, duration	Control	Follow up	Outcome measures	PEDro score
Braley et al. (17)	32 IG: 17 CG: 15	IG 58.9 ± 10 CG 62.4 ± 9.9	43.75%	IG 53 ± 56 (m) CG 38.1 ± 32 (m)	Broca's:10 Anomic:10 Conduction:6 Wernicke's:4 Transcortical Motor:2	WAB-AQ IG: 61.62 ± 24.28 CG: 66.02 ± 19.08	Home	iPad-based therapy	at least 30min/day,5 days a week for 10 weeks	Paper workbooks	2 weeks	WAB-R-AQ; WAB-R-LQ; WAB-R-CQ; SAQOL-39.	7
Cherney (18)	25 IG: 11 CG: 14	IG 56.6 ± 9.2 CG 61.1 ± 14.8	36%	IG 66.7 ± 71.5 (m) CG 41.3 ± 45.7 (m)	NA	WAB-AQ IG: 62 ± 19.9 CG:47.3 ± 27.9	Not clear	Computer-based therapy	1 h/session, 2–3 times a week, 24 times in total	Waitlist	NA	WAB; Discourse words/min; Discourse CIUs/min.	6
Elhakeem et al. (19)	50 IG: 25 CG: 25	IG 57.04 ± 10.88 CG 58.80 ± 11.58	20%	NA	Broca's:24% Anomic:2% Transcortical motor: 18% Transcortical mixed: 24% Global: 32%	BADE 0.8 ± 0.58	Clinic	Computer-based therapy	60 min/session,48 sessions over 6 months	Traditional speech and language therapy	NA	BADE	8
Kesav et al. (20)	20 IG: 11 CG: 9	IG 56.27 ± 11.62 CG 48.67 ± 11.83	30%	IG 31.2 ± 31 (d) CG 29.3 ± 30 (d)	Broca(50%) Wernicke(25%) Anomic(15%) Transcortical sensory aphasia(10%)	WAB-AQ IG: 32.4 ± 25.8 CG:45.1 ± 28.4	NA	Computer-based therapy combined with traditional therapy	120 min/session, 3 session a week for 4 weeks	Traditional speech and language therapy	8 weeks	WAB	6
Palmer et al. (21)	33 IG: 16 CG: 17	IG 69.5 ± 12.2 CG 66.2 ± 12.3	36.4%	IG 6.2 (y) CG 6.6 (y)	Fluent: 6 Non fluent: 25 Global: 2	Mild: 20 Moderate: 9 Severe: 4	Home	Computer word finding training	at least 20 min 3 days a week for 5 months	Usual care	3month	The change in word retrieval ability	5

(Continued)

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TABLE 1 (Continued)

References	Sample size	Age (year)	Sex (female) (%)	Post-stroke duration (d/m/y)	Type of aphasia	Severity of aphasia (mean ± SD)	Intervention address	Intervention	Session, duration	Control	Follow up	Outcome measures	PEDro score
Palmer et al. (22)	169 IG: 83 CG: 71	IG 64.9 ± 13.0 CG 63.8 ± 13.1	39%	IG 2.9 ± 2.9 (m) CG 3.6 ± 4.8 (m)	Non-fluent: 61 Fluent: 10 Mixed non-fluent: 31 Anomic: 52	Severity of word finding difficulty Mild: 44% Moderate: 30% Severe: 26%	Home	Computer word finding training combined with usual care	20–30min/session, 7 sessions a week for 6 month	Paper-based puzzle book activities and usual care	6month	Picture naming test of 100 personally relevant words; functional communication ability; COAST	8
Spaccavento et al. (23)	22 IG: 13 CG: 9	IG 57.38 ± 9.23 CG 64.11 ± 15.04	27%	IG 25.92 ± 25.99 (d) CG 20 ± 10.66 (d)	Global: 9 Broca: 8 Wernicke's: 1 Transcortical sensory: 2 Anomic: 2	Severe Aphasia: 12 Moderate Aphasia: 10	Clinic	Computer-based therapy	50min/session, 5 days a week for 8 weeks	Traditional therapist-mediated treatment	NA	AAT: FOQ-A: QLQA	6
Doesborgh et al. (24)	18 IG: 8 CG: 10	IG 62 ± 9 CG 65 ± 12	50%	>11 (m)	NA	NA	Clinic	Computer-based therapy	30–40min a session, 2–3 sessions a week for 8 weeks	No treatment	NA	BNT; ANELT-A	6
Katz and Wertz (25)	40 IG: 21 CG: 19	IG 61.6 ± 10 CG 64.4 ± 6	20%	IG 6.2 ± 5.2 (y) CG 5.4 ± 4.6 (y)	NA	WAB-AQ IG:68.9 ± 24.3 CG:72.2 ± 24.8	clinic	Reading Treatment Software	3 hours a week, for 26 weeks	Computer stimulation	NA	PICA; WAB-AQ	4
Cherney et al. (26)	32 IG: 19 CG: 13	IG 58.27 ± 18.55 CG 55.19 ± 11.46	40.6%	IG 39.75 ± 40.76 (m) CG 60.97 ± 30.19 (m)	Fluent: 18 Non-fluent:14	WAB-AQ IG: 59.21 ± 18.07 CG: 62.76 ± 16.81	Home	Computer-based treatment	90 minutes a day, six days a week for six weeks	Computer game, Bejeweled 2©	6 weeks	WAB-LQ	5

IG Intervention group; CG Control group; m, months; d, days; y, years; WAB, Western Aphasia Battery; R, Revised; AQ, Aphasia Quotient; CQ, Cortical Quotients; LQ, Language Quotients; SAQOL, Stroke and Aphasia Quality of Life Scale; CIU, correct information units; BADE, Boston Diagnostic Aphasia Examination; COAST, Communication Outcomes After Stroke questionnaire; AAT, Aachener Aphasia Test; FOQ-A, Italian Version of Functional Outcome Questionnaire for Aphasia; QLQA, Quality of Life Questionnaire for Aphasics; BNT, Boston Naming Test; ANELT-A, Amsterdam Nijmegen Everyday Language Test; PICA, The Porch Index of Communicative Ability; CETI, Communicative Effectiveness Index; ASHA-FACS, Functional Assessment of Communication Skills for Adults; CAT, Comprehensive Aphasia Test; CTPD, Cookie Theft Picture Description.

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TABLE 2 Characteristics of quasi-experimental studies.

References	Study design	Sample size	Age (year)	Sex (female) (%)	Post-stroke duration (d/m/y)	Type of aphasia	Severity of aphasia	Intervention address	Intervention	Session, duration	control	Follow up	Outcome measures
Archibald et al. (27)	Self-controlled study	8	71 ± 11.1	25%	48.3 ± 53.27 (m)	Broca's:2 Anomic:3 Conduction:2 Global:1	WAB-AQ 60.29 ± 33.37	Home/clinic	Computer-based therapy	At least 1 hour/week, 15 weeks	NA	NA	WAB; CETI; ASHA-FACS
Choi et al. (28)	Self-controlled study	8	50.75 ± 8.3	50%	29.8 ± 25 (m)	Broca's:2 Wernicke's:3 mixed transcortical:1 anomic:1 Global:1	K-WAB-AQ 49.6 ± 26.38	Home	Ipad-based therapy	The number of treatments is not clear, 4 weeks	NA	One month	K-WAB-AQ
Zettin et al. (29)	Self-controlled study	7	46 ± 7.7	57%	49.7 ± 35.7 (m)	Non fluent: 7	WAB-AQ 42.1 ± 16.1	Home/clinic	Computer-based therapy	90 min per day, 5days a week for 6weeks.	NA	NA	WAB; BNT; picture description task
Kurland et al. (30)	Self-controlled study	21	66 ± 8.4	38%	29.3 ± 37.1 (m)	NA	Mild:8 Moderate:9 Severe:4	Home	Tablet-Based Home Practice	At least 20 min, 5–6 days per week, for 6 months	NA	4 months	Percent accuracy on naming.
Stark and Warburton (31)	Cross-over study	7	63.6 ± 13.88	37.5%	36.2 ± 25 (m)	NA	NA	Home	Self-delivered iPad speech therapy	20 min a session, 7 days per week, for 4 weeks	Computer game, Bejeweled©	6 month	CAT; content unit production and rate of speech on the CTPD.

IG, Intervention group; CG, Control group; m, months; d, days; y, years; WAB, Western Aphasia Battery; R, Revised; AQ, Aphasia Quotient; CQ, Cortical Quotients; LQ, Language Quotients; SAQOL, Stroke and Aphasia Quality of Life Scale; CIU, correct information units; BADE, Boston Diagnostic Aphasia Examination; COAST, Communication Outcomes After Stroke questionnaire; AAT, Aachener Aphasia Test; FOQ-A, Italian Version of Functional Outcome Questionnaire for Aphasia; QLQA, Quality of Life Questionnaire for Aphasics; BNT, Boston Naming Test; ANELT-A, Amsterdam Nijmegen Everyday Language Test; PICA, The Porch Index of Communicative Ability; CETI, Communicative Effectiveness Index; ASHA-FACS, Functional Assessment of Communication Skills for Adults; CAT, Comprehensive Aphasia Test; CTPD, Cookie Theft Picture Description.

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2.5 Quality assessment

The Cochrane bias risk tool will be employed to analyze the risk of bias in the included randomized controlled trials (See content 1 in the Additional file for detailed judging details) (32). Evaluation of Six Bias Domains: Selection bias, Performance bias, Detection bias, Attrition bias, Reporting bias, and Other potential sources of bias. If <1 domain is assessed as high risk (-), the study is considered as low risk. If one or two domains are assessed as high risk (-) or unclear (?), the study is considered as medium risk. If more than two domains are assessed as high risk (-) or unclear (?), the study is considered as high risk (33). The quality of the included literature strictly followed the PEDro scale, which consists of 11 entries out of 10 points. Studies with a total score of ≥7 points will be classified as high quality, those with scores between 5 and 6 points as moderate quality, and those with scores ≤4 points as low quality. Assessment of Quasi-Experimental Studies Using the TREND (Transparent Reporting of Evaluations with Non-randomized Designs) Checklist (34, 35). This checklist comprises 22 items assessing the quality of titles and abstracts, introduction, methods, results, and discussion sections across five domains. The assessment will be carried out by two reviewers, and if consensus cannot be reached between them, a third reviewer will make the final decision.

3 Results

3.1 Study selection

After the initial search, a total of 1,391 documents were obtained. Through manual searching of the reference lists of the included literature, two additional papers were additionally identified. Subsequently, a full-text review of this literature was conducted, and a total of 89 studies met the review criteria. Ultimately, 10 randomized controlled trials, four self-controlled trail and one cross-over trial design study met the inclusion criteria for this study. The flow chart for literature screening is shown in Figure 1.

3.2 Quality of the studies

Ten randomized controlled trial studies were assessed for risk of bias and evaluated qualitatively. The results of the risk of bias analysis indicated that five studies performed random sequence generation, three studies described a hidden random allocation scheme, no studies blinded subjects and trial personnel due to the specificity of the trial intervention, six studies reported blinding the outcome assessor, and four studies demonstrated a low risk of attrition bias. Comparing the methodology of each study, only four studies had low reporting bias. Figures 2 and 3 depict total risk of bias plots for all randomized controlled trials, with one study at low risk and the remaining nine studies judged to be at high risk. By qualitative evaluation, three studies were of high quality, six studies were of moderate quality, and one study was of poor quality (details see Supplementary Table S2). Determining the quality of quasi-experimental studies is challenging, as evidenced by significant score disparities obtained using the TREND checklist. Evaluation using the TREND checklist revealed that included quasi-experimental studies performed well in aspects such as Title and Abstract (all studies met criteria), Background (all met criteria), Participants (eligibility criteria for participants), Intervention, Unit of Assignment, and Unit of Analysis. However, they showed poor performance in reporting results (patient registration and screening reports, adverse events, data analysis, follow-up, etc.) and discussion (see Supplementary Table S3).

3.3 Study characteristics

The characteristics of the 10 included randomized controlled studies are listed in Table 1. The sample size ranged from 18 to 169 individuals and covered a total of 441 subjects. The experimental group containing 224 subjects and the control group containing 217 subjects. In addition, 34.27% of the subjects were female, while the mean duration of stroke varied between 25 days and 6 years. The daily duration of the intervention varied between 20 min and 2 h, the intervention period varied from 4 weeks to 6 months, and the follow-up period was from 2 weeks to 6 months. Table 2 gives the characteristics of the four self-controlled studies and one cross-over experimental design study.

3.4 Characteristics of intervention component

3.4.1 Single-component interventions

Eight studies used a single component of program intervention, focusing on 1–2 aspects of language. Of these, 3 studies used a method in which a person with aphasia watched an in-computer speech therapist read sentences and follow along (18, 26, 29). Four studies used interventions that targeted naming functions (21, 22, 24, 30). For example, Palmer et al. (22) designed a computer program containing 100 words related to the subject and had participants perform word-finding training. One other study focused on intervention methods in reading (25).

3.4.2 Multi-component interventions

Seven studies used therapeutic procedures oriented toward multiple aspects of language (17, 19, 20, 23, 27, 28, 31). These treatments include auditory comprehension, reading comprehension, repetition, naming, and writing et al. These treatments address various aspects of language comprehension, naming, repetition, and spontaneous language.

3.5 General overview of technology

These studies primarily employed two types of technology: computers (in a total of 11 studies) and tablet devices (in a total of four studies). Compared to traditional face-to-face therapist-led interventions, computer and tablet-based interventions offer the advantage of structured difficulty

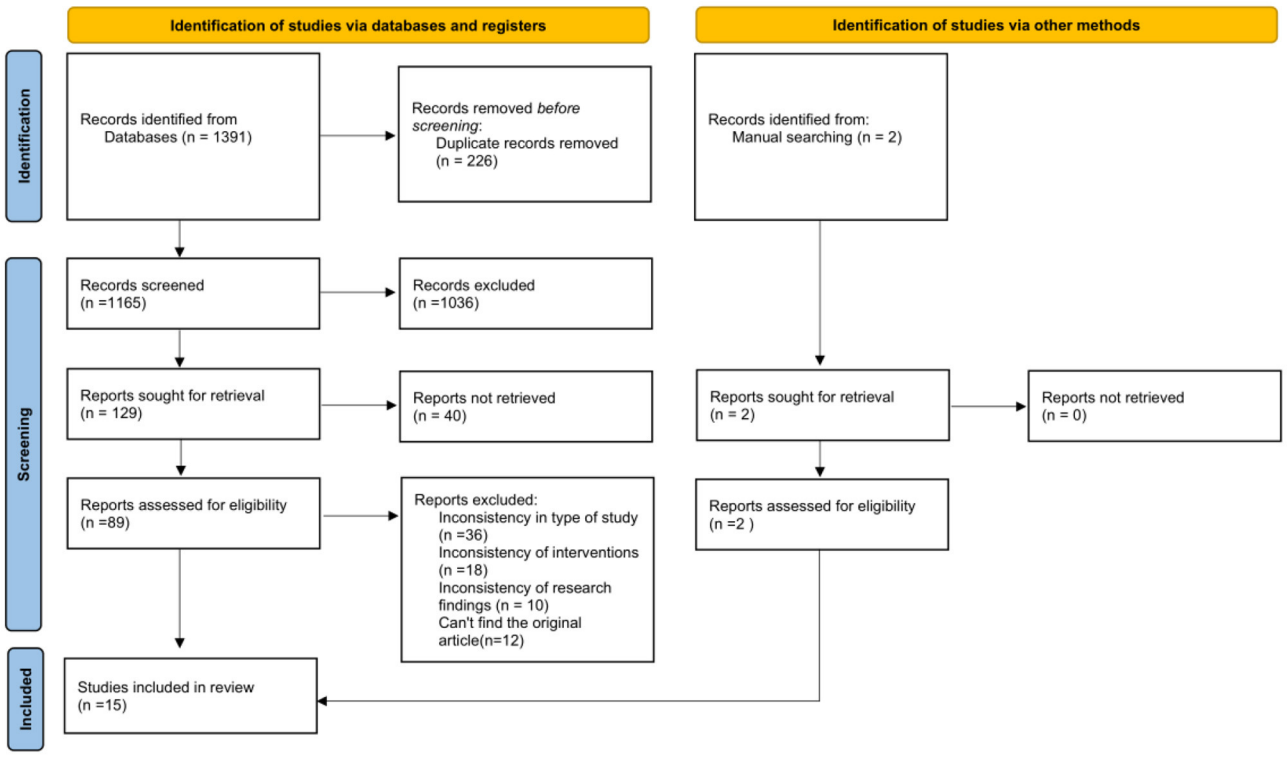

FIGURE 1
PRISMA flow chart.

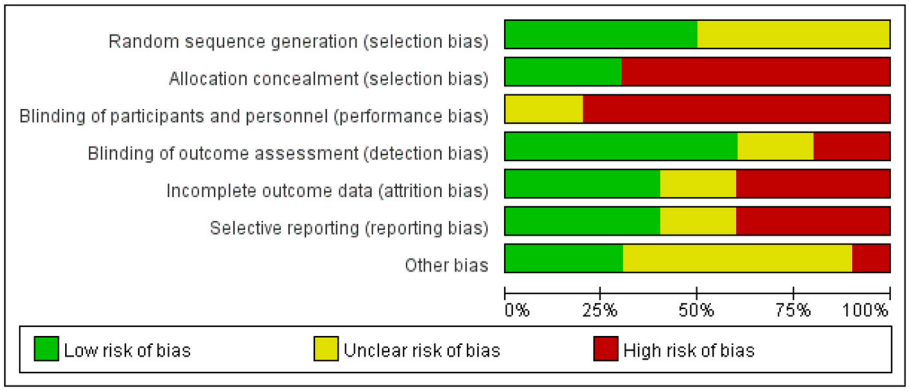

FIGURE 2
Risk of bias graph.

progression and the ability to adjust difficulty levels based on participants' training performance. In this regard, 8 studies provided detailed descriptions of the difficulty levels within their treatment programs. Furthermore, computer- and tablet-based therapy programs typically provide only a single type of feedback. In this regard, only six studies have reported how computers provide feedback on the training performance of patients with aphasia, usually by providing feedback on how well the patient answered questions correctly. A detailed description of the content of the intervention can be found in the Supplementary Table S5.

3.6 Effects of interventions

3.6.1 Overall language function

A total of 10 studies assessed the effect of intervention components on overall speech function improvement. Measurement tools used included the WAB, the AAT, and the BADE. Detailed results of the included literature (see Supplementary Table S4).

Eight of these 10 studies found that mobile application-based intervention content was effective in improving the overall speech performance of individuals with aphasia. The intervention

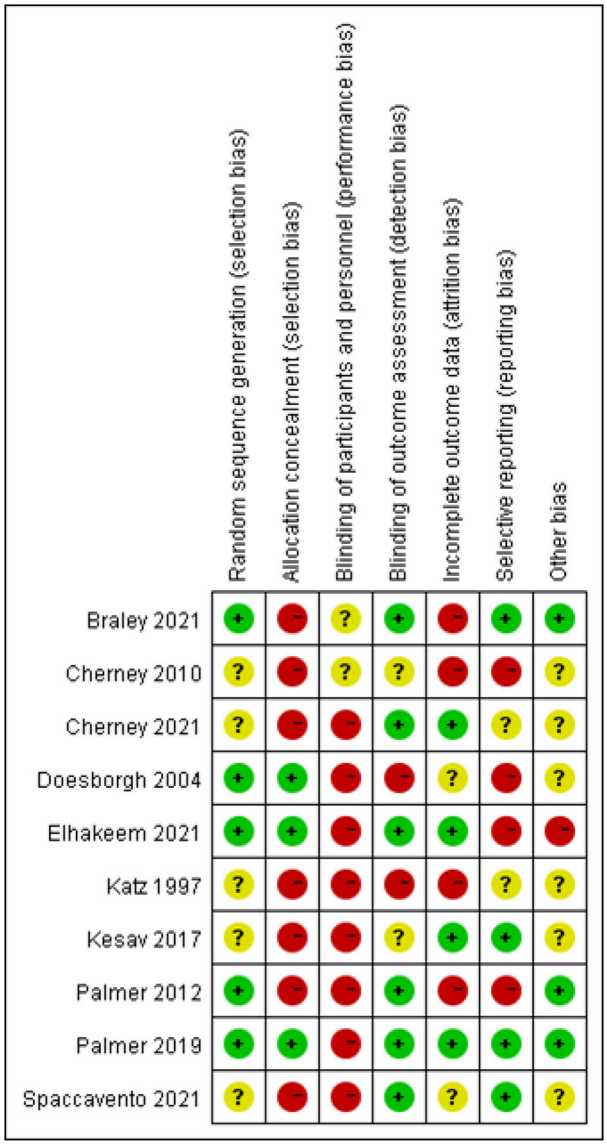

FIGURE 3
Risk of bias summary. + indicates low risk, - indicates high risk, ? indicates unclear risk of bias.

methods used in these studies varied, with four of the studies utilizing a multi-component intervention approach. Additionally, four studies used a single-component intervention. Among these four studies, three studies utilized computer-based therapy with the imitation of a language therapist for reading tasks (18, 26, 29). One study used a reading function-specific approach (25). Of these eight studies, two found that the mobile application-based treatment was superior to the control group, with improvements in post-intervention language performance showing significant differences between groups. Katz and Wertz (25) reported a significant increase in WAB-AQ scores ($p < 0.008$) for computer-based reading software training compared to an active control group (computer stimulation). Braley et al. (17) found a significant improvement in WAB-R-AQ scores ($p < 0.05$) for 10 weeks of iPad-based SLT compared to home practice booklet training. Among these eight studies, four studies observed significant differences in overall language performance within the experimental group before and after treatment. However, no significant differences were observed when comparing between the experimental and control groups.

Of these 10 studies, two found that the intervention component of the experimental group failed to significantly improve language performance in aphasic patients. In one of these studies, although a significant difference between groups was found, the control group (using a traditional therapist intervention) showed a more significant improvement.

3.6.2 Functional communication skills

Five studies assessed the impact of mobile application-based intervention methods on functional communication skills. The assessment instruments used were highly variable and included The Functional Assessment of Communication Skills for Adults, functional communication ability (using the activity scale of the Therapy Outcome Measures), Functional Outcome Questionnaire for Aphasia (FOQ-A), The Porch Index of Communicative Ability(PICA), Amsterdam Nijmegen Everyday Language Test (ANELT).

Of the five studies, two noted that functional communication skills improved after the intervention but were not significantly different from the control group, one used a blank control and the intervention was a single-content intervention (naming training), and one used a negative control and the intervention used was a multi-component intervention.

One study found that the experimental group's communication skills improved significantly after the intervention, with a significant difference between the groups (25). The two studies found no significant improvement in the experimental group's communication skills after the intervention, which used a multi-component intervention approach and a single-component intervention (word find).

3.6.3 Spontaneous language

Three studies evaluated the impact of a mobile application-based intervention approach on spontaneous language production ability. In terms of evaluation, all of these studies used methods that described pictures and counted the number and frequency of words produced. Two of the studies used a non-randomized controlled study design and showed a significant increase in the number and frequency of words produced by people with aphasia after the intervention (29, 31). One other study used a randomized controlled trial design and found an increase in the number and frequency of words produced in the computer-based intervention group compared to the wait-for-treatment group, but there was no significant difference between the two groups (18).

3.6.4 Naming ability

Five studies evaluated the effects of mobile application-based interventions on naming ability. Four studies found significant improvements in naming ability in individuals with aphasia following mobile application-based interventions. Two of these studies found significant differences in naming ability between

groups using a single-component intervention method (word finding training). Two self-controlled studies found significant improvements in naming ability after the intervention. One RCT found no significant differences in naming ability between the experimental group and a blank control group after computer-based cued naming training.

3.6.5 Quality of life

Three studies assessed the impact of mobile application-based interventions on quality of life. Two studies noted significant improvements in quality of life after the intervention, but there were no significant differences between groups compared to the control group, and one study found no significant improvement in quality of life after the intervention.

3.6.6 Maintaining the effect

Eight studies explored the effects of mobile application-based interventions on the maintenance of efficacy, with two self-controlled studies and one crossover pilot study reporting the ability to maintain improvements in WAB-AQ ($p=0.206$), naming ability, and expressive ability in spontaneous speech in patients with aphasia after the time of follow-up (1, 4, and 6 months, respectively) (28, 30, 31). Three randomized controlled studies have found that WAB, naming ability in patients with aphasia was found to maintain its improvement at 6 weeks, 3 months, and 6 months of follow-up (21, 22, 26).

4 Discussions

Interventions based on mobile applications have gained increasing popularity for individuals with aphasia, primarily utilizing computers and tablets. These electronic devices have become integral to people's lives and have also brought convenience to rehabilitation therapy. Among the studies included, 66% allowed aphasic patients to use software for training at home, while therapist involvement during clinic-based training was primarily focused on addressing technical issues rather than guiding the therapy process. This underscores the potential for individuals with aphasia to engage in speech-language therapy either independently or with minimal assistance. A systematic review of 10 randomized controlled trials, four pre-post controlled studies, and one crossover trial indicates a high risk of bias. Heterogeneity of applications, varied outcome measures, differing intervention intensities, variations in aphasia onset times and severity, result in diverse study outcomes. This makes it challenging to assess and conduct meta-analyses across studies (36). Most of the studies had selection bias, all randomized controlled trials used random allocation, while five of them did not specify the exact method of randomization (18, 20, 23, 25, 26), leading to uncertain risks, and 70% of studies did not conceal allocation. There were no studies describing blinding of subjects, thus introducing performance bias. Monitoring bias had a better performance with 8 studies reporting assessor blinding, but 2 did not describe blinding procedures (18, 25). The five non-randomized controlled studies showed significant bias, lacking random allocation (27–31). Furthermore, according to the TREND report, none of the 5 studies described blinding. Thus, overall high bias across all studies is unfavorable for determining the effectiveness of mobile application-based speech-language therapy. However, overall, mobile application-based SLT holds significant promise and potential for improving the performance of individuals with aphasia.

The results of the study revealed that eight studies indicated the effectiveness of mobile application-based speech-language therapy (SLT) in improving the overall language functioning of individuals with aphasia. Of these, four studies showed no significant difference in improvement between the intervention and control groups. Mobile application-based therapy shows promise in enhancing language function; however, it is uncertain whether it is superior to the effects of traditional therapy. There were inconsistent results from five studies regarding whether mobile application-based therapy could produce transferable effects in terms of communicative and expressive language skills.

Four of the 10 RCTs compared mobile application-based speech-language therapy with Speech therapist (ST)-mediated therapy (19–21, 23). These studies aimed to explore whether computer-based interventions were comparable or potentially superior to face-to-face ST interventions. Among these, 3 studies found that computer-based interventions had outcomes for aphasic patients that were either better than or non-inferior to those of ST-mediated treatment. However, a study by Kesav et al. (20) reported that a regimen of three sessions per week for 60 min of ST treatment was more effective than a schedule of three sessions per week for 120 min of computer-based treatment. This discrepancy could potentially be attributed to the relative unfamiliarity of the included aphasic patients with computer programs (20). The study by Kesav et al. (20) did not provide detailed descriptions of the feedback mechanisms and patient compliance related to computer-based treatment. Personalized therapy and feedback are crucial factors for enhancing treatment efficacy (37). However, in our study, only 40% of the reports mentioned the feedback methods used in mobile application-based interventions, and these feedback mechanisms typically displayed errors made by patients during training. This type of feedback is relatively limited compared to the feedback provided by ST. Future research could explore whether more diverse feedback methods might have an impact on treatment outcomes.

Treatments that can be delivered at home can reduce the financial burden on patients and provide a higher intensity of treatment. Several studies have emphasized the need for intensive treatment programs for aphasia (38, 39). According to a network meta-analysis, the greatest gains in overall language proficiency were associated with >20 h of SLT (40). Breitenstein et al. observed that engaging in ≥ 10 h of intensive speech-language therapy per week for 3 weeks effectively improved communication skills in patients with chronic aphasia (41). Clearly, delivering therapy through mobile applications enables patients to achieve higher treatment intensity while participating in independent treatment. However, among the studies we included, only one managed to reach a treatment intensity of ≥ 10 h per week. Cherney et al. (26) founded that engaging in computer-based language imitation therapy six times per week, with each session lasting 90 min,

effectively enhanced the overall language abilities of the patients. However, the training effects did not show significant differences when compared to the control group. This could potentially be attributed to the fact that the control group utilized computer games designed for memory and attention training. Training focused on cognitive functions might also lead to improvements in language abilities among individuals with aphasia (42). Therefore, it remains uncertain whether intensive, application-based SLT effectively enhances language function in individuals with aphasia. Additionally, application-based interventions offer a cost-effective supplemental approach that can address the limitations of high-intensity, in-clinic speech therapy for individuals who face challenges in accessing such treatment (43).

From the studies we included, the interventions can be divided into two main types: single-component interventions and multi-component interventions. Single-component interventions primarily focus on naming abilities. For instance, Palmer et al. (22) found that computer-based word retrieval training effectively improved naming abilities in individuals with aphasia, but did not significantly enhance their communicative skills. This might be attributed to the narrow focus of the training content. In contrast, Spaccavento et al. (23) employed a computer-based multi-component intervention, which resulted in significant improvements in the communicative abilities of aphasic patients post-treatment. However, as there have been no studies directly comparing the effectiveness of these two types of interventions, we cannot conclude whether there is a difference in the improvement effects between single-component and multi-component interventions. Additionally, the extent to which training effects can transfer to other functional aspects requires further investigation. Similar to findings in studies related to post-stroke motor function, where motor training improved motor skills but had limited effects on overall quality of life and daily functioning, it remains important to determine the potential for transfer effects in aphasia interventions (44, 45). In conclusion, further research is needed to delve into the differences in improvement effects between single-component and multi-component interventions, in order to better inform the application of mobile application-based speech-language therapy in clinical practice.

5 Limitation

The sample sizes of the included studies were generally small, ranging from 7 to 169 individuals, with ~66% of the studies having a sample size of <30 individuals. This small sample size may be related to the difficulty of recruiting people with aphasia. However, smaller sample sizes may affect the assessment of treatment effects. In addition, there was variability in the duration of post-stroke in aphasia patients in the included studies, with ~73% of the studies including patients with chronic aphasia, so there is uncertainty about the benefit of treatment for patients with different stages of aphasia. Another challenge was the wide variation in the intervention components used in the included studies, which made it difficult to compare and synthesize the findings. Finally, only eight studies explored the effect of mobile application-based intervention methods on the maintenance of efficacy, with follow-up times ranging from 2 weeks to 6 months, with an average of approximately 12 weeks. However, this follow-up period may be too short to effectively assess whether intervention approaches are able to maintain language functioning in people with aphasia over an extended period of time.

6 Recommendations for research

With regard to the many shortcomings and deficiencies of CSLT research, based on these studies, future researchers can develop a more rigorous and standardized procedure to validate the significance of CSLT beyond traditional face-to-face speech therapy. In this procedure, several aspects need consideration: the types and severity of aphasia; the optimal treatment stages of aphasia; maintenance therapy in chronic phases; the best monitoring of naming, perception, communication performance, social participation, and wellbeing; the definition of appropriate control groups; the efficacy and maintenance of intensified therapy; and the management of patient attention and feedback control interference. It is worth noting that the cost-effectiveness of CSLT is not publicly available and requires separate investigation.

7 Conclusion

The findings of this systematic review suggest that mobile application-based interventions for aphasia hold promise in improving overall language function. However, uncertainties remain regarding the improvement in functional communication abilities and whether gains in naming abilities can transfer to untrained objects. The efficacy of single-component interventions cannot be directly compared to multi-component interventions. Nonetheless, overall, mobile application-based interventions show positive prospects for enhancing speech-language function in aphasia.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number (s) can be found in the article/Supplementary material.

Author contributions

ZJ: Writing – original draft, Software, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. MH: Writing – review & editing, Supervision, Investigation. CZ: Writing – review & editing, Supervision, Software, Investigation. XC: Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1405209/full#supplementary-material

References

1. Benghanem S, Rosso C, Arbizu C, Moulton E, Dormont D, Leger A, et al. Aphasia outcome: the interactions between initial severity, lesion size and location. *J Neurol.* (2019) 266:1303–9. doi: 10.1007/s00415-019-09259-3

2. Lazar RM, Boehme AK. Aphasia as a predictor of stroke outcome. *Curr Neurol Neurosci Rep.* (2017) 17:83. doi: 10.1007/s11910-017-0797-z

3. Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke.* (2006) 37:1379–84. doi: 10.1161/01.STR.0000221815.64093.8c

4. Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M. Aphasia in acute stroke and relation to outcome. *J Intern Med.* (2001) 249:413–22. doi: 10.1046/j.1365-2796.2001.00812.x

5. Hilari K, Byng S. Health-related quality of life in people with severe aphasia. *Int J Lang Commun Disorders.* (2009) 44:193–205. doi: 10.1080/13682820802008820

6. Darrigrand B, Dutheil S, Michelet V, Rereau S, Rousseaux M, Mazaux JM. Communication impairment and activity limitation in stroke patients with severe aphasia. *Disabil Rehabil.* (2011) 33:1169–78. doi: 10.3109/09638288.2010.524271

7. Ashaie SA, Hurwitz R, Cherney LR. Depression and subthreshold depression in stroke-related aphasia. *Arch Phys Med Rehabil.* (2019) 100:1294–9. doi: 10.1016/j.apmr.2019.01.024

8. Rombough RE, Howse EL, Bartfay WJ. Caregiver strain and caregiver burden of primary caregivers of stroke survivors with and without aphasia. *Rehabil Nurs.* (2006) 31:199–209. doi: 10.1002/j.2048-7940.2006.tb00136.x

9. Cook R, Davidson P, Martin R. Computerised speech and language therapy can help people with aphasia find words following a stroke. *BMJ.* (2020) 368:m520. doi: 10.1136/bmj.m520

10. Flöel A. Computerised speech and language therapy in post-stroke aphasia. *The Lancet Neurology.* (2019) 18:806–7. doi: 10.1016/S1474-4422(19)30199-1

11. Zhou QM, Lu X, Zhang Y, Sun ZH, Li JN, Zhu ZD. Telerehabilitation combined speech-language and cognitive training effectively promoted recovery in aphasia patients. *Front Psychol.* (2018) 9:2312. doi: 10.3389/fpsyg.2018.02312

12. Gerber SM, Schütz N, Uslu AS, Schmidt N, Röthlisberger C, Wyss P, et al. Therapist-guided tablet-based telerehabilitation for patients with aphasia: proof-of-concept and usability study. *JMIR Rehab Assist Technol.* (2019) 6:e13163. doi: 10.2196/13163

13. Mallet K, Shamloul R, Pugliese M, Power E, Corbett D, Hatcher S, et al. RecoverNow: A patient perspective on the delivery of mobile tablet-based stroke rehabilitation in the acute care setting. *Int J Stroke.* (2019) 14:174–9. doi: 10.1177/1747493018790031

14. Lavoie M, Macoir J, Bier N. Effectiveness of technologies in the treatment of post-stroke anomia: a systematic review. *J Commun Disord.* (2017) 65:43–53. doi: 10.1016/j.jcomdis.2017.01.001

15. Repetto C, Paolillo MP, Tuena C, Bellinzona F, Riva G. Innovative technology-based interventions in aphasia rehabilitation: a systematic review. *Aphasiology.* (2021) 35:1623–46. doi: 10.1080/02687038.2020.1819957

16. Russo MJ, Prodan V, Meda NN, Carcavallo L, Muracioli A, Sabe L, et al. High-technology augmentative communication for adults with post-stroke aphasia: a systematic review. *Expert Rev Med Devices.* (2017) 14:355–70. doi: 10.1080/17434440.2017.1324291

17. Braley M, Pierce JS, Saxena S, De Oliveira E, Taraboanta L, Anantha V, et al. A virtual, randomized, control trial of a digital therapeutic for speech, language, and cognitive intervention in post-stroke persons with aphasia. *Front Neurol.* (2021) 12:626780. doi: 10.3389/fneur.2021.626780

18. Cherney LR. Oral reading for language in aphasia (ORLA): evaluating the efficacy of computer-delivered therapy in chronic nonfluent aphasia. *Top Stroke Rehabil.* (2010) 17:423–31. doi: 10.1310/tsr1706-423

19. Elhakeem ES, Saeed S, Elsalakawy RNA, Elmaghraby RM, Ashmawy G. Post-stroke aphasia rehabilitation using computer-based Arabic software program: a randomized controlled trial. *Egyptian J Otolaryngol.* (2021) 37:144. doi: 10.1186/s43163-021-00144-3

20. Kesav P, Vrinda SL, Sukumaran S, Sarma PS, Sylaja PN. Effectiveness of speech language therapy either alone or with add-on computer-based language therapy software (Malayalam version) for early post stroke aphasia: a feasibility study. *J Neurol Sci.* (2017) 380:137–41. doi: 10.1016/j.jns.2017.07.010

21. Palmer R, Enderby P, Cooper C, Latimer N, Julious S, Paterson G, et al. Computer therapy compared with usual care for people with long-standing aphasia poststroke a pilot randomized controlled trial. *Stroke.* (2012) 43:1904–11. doi: 10.1161/STROKEAHA.112.650671

22. Palmer R, Dimairo M, Cooper C, Enderby P, Brady M, Bowen A, et al. Self-managed, computerised speech and language therapy for patients with chronic aphasia post-stroke compared with usual care or attention control (Big CACTUS): a multicentre, single-blinded, randomised controlled trial. *The Lancet Neurol.* (2019) 18:821–33. doi: 10.1016/S1474-4422(19)30192-9

23. Spaccavento S, Falcone R, Cellamare F, Picciola E, Glueckauf RL. Effects of computer-based therapy versus therapist-mediated therapy in stroke-related aphasia: Pilot non-inferiority study. *J Commun Disord.* (2021) 94:106158. doi: 10.1016/j.jcomdis.2021.106158

24. Doesborgh S, van de Sandt-Koenderman M, Dippel D, van Harskamp F, Koudstaal P, Visch-Brink E. Cues on request: the efficacy of multicue, a computer program for wordfinding therapy. *Aphasiology.* (2004) 18:213–22. doi: 10.1080/02687030344000580

25. Katz RC, Wertz RT. The efficacy of computer-provided reading treatment for chronic aphasic adults. *J Speech Lang Hear Res.* (1997) 40:493–507. doi: 10.1044/jslhr.4003.493

26. Cherney LR, Lee JB, Kim KA, van Vuuren S. Web-based oral reading for language in aphasia (Web ORLA(®)): a pilot randomized control trial. *Clin Rehabil.* (2021) 35:976–87. doi: 10.1177/0269215520988475

27. Archibald LM, Orange JB, Jamieson DJ. Implementation of computer-based language therapy in aphasia. *Ther Adv Neurol Disord.* (2009) 2:299–311. doi: 10.1177/1756285609336548

28. Choi YH, Park HK, Paik NJ, A. Telerehabilitation approach for chronic aphasia following stroke. *Telemed J E Health.* (2016) 22:434–40. doi: 10.1089/tmj.2015.0138

29. Zettin M, Leopizzi M, Galetto V. How does language change after an intensive treatment on imitation? *Neuropsychol Rehabil.* (2019) 29:1332–58. doi: 10.1080/09602011.2017.1406861

30. Kurland J, Liu A, Stokes P. Effects of a tablet-based home practice program with telepractice on treatment outcomes in chronic aphasia. *J Speech Lang Hear Res.* (2018) 61:1140–56. doi: 10.1044/2018_JSLHR-L-17-0277

31. Stark BC, Warburton EA. Improved language in chronic aphasia after self-delivered iPad speech therapy. *Neuropsychol Rehabil.* (2018) 28:818–31. doi: 10.1080/09602011.2016.1146150

32. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* (2011) 343:d5928. doi: 10.1136/bmj.d5928

33. Winters M, Eskes M, Weir A, Moen MH, Backx FJ, Bakker EW. Treatment of medial tibial stress syndrome: a systematic review. *Sports Med.* (2013) 43:1315–33. doi: 10.1007/s40279-013-0087-0

34. Des Jarlais DC, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Pub Health.* (2004) 94:361–6. doi: 10.2105/AJPH.94.3.361

35. Vlahov D. Transparent reporting of evaluations with nonrandomized designs (TREND). *J Urban Health.* (2004) 81:163–4. doi: 10.1093/jurban/jth099

36. Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH. Stem cell injections in knee osteoarthritis: a systematic review of the literature. *Br J Sports Med.* (2017) 51:1125–33. doi: 10.1136/bjsports-2016-096793

37. Burke J, Palmer R, Harrison M. What are the factors that may influence the implementation of self-managed computer therapy for people with long term aphasia following stroke? A qualitative study of speech and language therapists' experiences in the Big CACTUS trial. *Disability and rehabilitation.* (2022) 44:3577–89. doi: 10.1080/09638288.2020.1871519

38. Worrall L, Foster A. Does intensity matter in aphasia rehabilitation? *Lancet.* (2017) 389:1494–5. doi: 10.1016/S0140-6736(17)30546-9

39. Pierce JE, O'Halloran R, Menahemi-Falkov M, Togher L, Rose ML. Comparing higher and lower weekly treatment intensity for chronic aphasia: a systematic review and meta-analysis. *Neuropsychol Rehabil.* (2021) 31:1289–313. doi: 10.1080/09602011.2020.1768127

40. Dosage, intensity, and frequency of language therapy for aphasia: a systematic review-based, individual participant data network meta-analysis. *Stroke.* (2022) 53:956–67. doi: 10.1161/STROKEAHA.121.035216

41. Breitenstein C, Grewe T, Flöel A, Ziegler W, Springer L, Martus P, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet.* (2017) 389:1528–38. doi: 10.1016/S0140-6736(17)30067-3

42. Nikravesh M, Aghajanzadeh M, Maroufizadeh S, Saffarian A, Jafari Z. Working memory training in post-stroke aphasia: near and far transfer effects. *J Commun Disord.* (2021) 89:106077. doi: 10.1016/j.jcomdis.2020.106077

43. Latimer NR, Bhadhuri A, Alshreef A, Palmer R, Cross E, Dimairo M, et al. Self-managed, computerised word finding therapy as an add-on to usual care for chronic aphasia post-stroke: an economic evaluation. *Clin Rehabil.* (2021) 35:703–17. doi: 10.1177/0269215520975348

44. Yeh TT, Chang KC, Wu CY. The active ingredient of cognitive restoration: a multicenter randomized controlled trial of sequential combination of aerobic exercise and computer-based cognitive training in stroke survivors with cognitive decline. *Arch Phys Med Rehabil.* (2019) 100:821–7. doi: 10.1016/j.apmr.2018.12.020

45. Miranda CS, Oliveira TP, Gouvêa JXM, Perez DB, Marques AP, Piemonte MEP. Balance training in virtual reality promotes performance improvement but not transfer to postural control in people with chronic stroke. *Games Health J.* (2019) 8:294–300. doi: 10.1089/g4h.2018.0075

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Repetitive transcranial magnetic stimulation in central post-stroke pain: a meta-analysis and systematic review of randomized controlled trials

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Background: The rehabilitation of central post-stroke pain (CPSP) is a complex clinical challenge, and repetitive transcranial magnetic stimulation (rTMS) has been widely applied in the research of neurofunctional recovery following stroke. However, there is currently no reliable evidence-based medicine supporting the efficacy of rTMS in central post-stroke pain. This review aims to evaluate the effects of rTMS on central post-stroke pain.

Methods: Following the PRISMA guidelines, we conducted searches on PubMed, Cochrane Library, Embase, Web of Science, CNKI, and Wan Fang Data Knowledge Service Platform. We searched for randomized controlled trials (RCTs) investigating the use of rTMS in treating central post-stroke pain, and conducted screening based on inclusion and exclusion criteria. Characteristics of the included RCTs were extracted. The heterogeneity of the trials was assessed using the I2 statistic. Meta-analysis was performed using Stata 17 software. Bias risk and methodological quality were evaluated using the Cochrane RoB 2 tool and the Pedro scale.

Results: A total of six randomized controlled trials involving 288 patients met our inclusion criteria. In our analysis, rTMS was more effective in treating patients with CPSP compared to the placebo group (SMD=-1.15, 95% CI: −1.69, −0.61, $P < 0.001$). Furthermore, results from subgroup analysis indicated no statistically significant difference in the improvement of pain for durations exceeding 6 months when comparing rTMS to conventional treatment (SMD=-0.80, 95% CI: −1.63, 0.03, $P = 0.059$).

Conclusion: TMS can alleviate pain in CPSP patients and improve their motor function, but its effects on depression, anxiety, and MEP-latency are not significant.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, CRD42024497530.

KEYWORDS

central pain, central post-stroke pain, repetitive transcranial magnetic stimulation, meta, meta-analysis, systematic reviews

1 Introduction

Stroke is one of the diseases with high global incidence, disability rates, and mortality rates (Zhang et al., 2020). Despite comprehensive rehabilitation treatments, most stroke patients experience varying degrees of recovery in motor and sensory functions. However, some patients still suffer from persistent pain on the affected side of the body after a stroke. This pain, occurring after a stroke and associated with the damaged area while excluding other causes, is referred to as CPSP (Radiansyah and Hadi, 2023). Although the onset time of CPSP may be related to the severity and progression of the condition, more than half of the cases manifest within the initial months following a stroke (Klit et al., 2009; Osama et al., 2018; Vukojevic et al., 2018). The incidence rate ranges from 1% to 35% (Dub and Mercier, 2011; Hansen et al., 2012). Many patients may experience various forms of pain concurrently with sensory abnormalities, such as searing, pressing, pulsating, or freezing sensations, numbness, and decreased sensation (Kumar, 2009; Klit et al., 2011). CPSP significantly impacts the sleep, emotions, and overall quality of life for stroke patients, hindering the implementation of effective rehabilitation treatments. The pathogenesis of CPSP is not fully understood, and its treatment remains challenging. Currently, the primary approach involves medications for neuropathic pain. Existing evidence suggests that even with the use of high-dose medications, pain relief is often difficult to achieve for the majority of CPSP patients (Scuteri et al., 2020; Singh et al., 2020; Choi et al., 2021; Mohanan et al., 2023). Additionally, these medications are associated with various side effects (Banerjee et al., 2013; Kim, 2014) and may lead to drug dependence (Kumar and Soni, 2009).

rTMS provides a non-invasive, painless method for studying and treating neuropathic pain states (Lefaucheur, 2016). By applying a magnetic field to the cerebral cortex, it induces electric currents, influencing neural electrical activity. This, in turn, regulates cerebral blood flow and neurotransmitter expression to alleviate pain. Currently, it is recommended by relevant treatment guidelines for various pain conditions (Winstein et al., 2016; Lefaucheur et al., 2020). In addition to its impact on the target area, the synaptic effects produced by rTMS contribute to its distal therapeutic effects (Hallett et al., 2017), but there is no uniform standard for therapeutic parameters in the treatment of CPSP using rTMS. Diverse treatment parameters, including stimulation frequency, target site, and duration of therapy, yield varying analgesic effects. Traditionally, low-frequency (LF) rTMS, defined as stimulation below 1 Hz, has been shown to reduce cortical excitability, whereas high-frequency (HF) rTMS, with frequencies above 1 Hz, exerts the opposite effect (Cruccu et al., 2007; Bai et al., 2022). Previous studies investigating the analgesic effects of rTMS on PSP have discovered that HF-rTMS (5–20 Hz) can effectively alleviate PSP-related pain (Pazzaglia et al., 2018). Compared to single and short-term interventions, multiple sessions and longer durations of intervention have been found to produce superior analgesic outcomes (Hosomi et al., 2013; Ramger et al., 2019).

The meta-analytic review conducted by McDonnell and Stinear (2017) indicated that, in stroke patients, the M1 of the non-affected hemisphere did not exhibit heightened activation during both active muscle contraction and rest, as evidenced by the absence of significant disparities in the parameters of aMT (active motor threshold), rMT (resting motor threshold), and MEPs (motor evoked potentials) when compared to those of healthy controls. This finding suggests that directly enhancing the excitability of the affected M1 may confer greater therapeutic benefits than indirectly suppressing the excitability of the unaffected M1 in facilitating motor recovery following stroke. Numerous previous studies have also discovered that LF-rTMS and continuous theta-burst stimulation (cTBS) not only suppress the amplitude of MEPs in the stimulated M1, but also enhance the MEP amplitude in the non-stimulated M1 (Di Lazzaro et al., 2011; Boddington and Reynolds, 2017). The increased cortical excitability within the unstimulated M1 may be associated with an elevated intrinsic excitability of excitatory interneurons responsible for glutamatergic non-NMDA receptor activity (Heide et al., 2006).

In studies utilizing a rat model of thalamic pain, it has been observed that neuronal structural damage occurs in the lesion area following cerebral hemorrhage or infarction, leading to increased neural excitability. Such alterations may precipitate a range of clinical manifestations, including limb pain and motor functional impairments (An et al., 2019). Other animal experiments have also demonstrated that CPSP reduces the functional connectivity between the VPL and S1/S2 (primary and secondary somatosensory cortices), responsible for perceiving pain location, intensity, and duration, while enhancing connectivity between the thalamus (involved in attention, cognitive abilities) and amygdala (associated with emotional aspects of pain assessment) (Sweet et al., 1971), rTMS can alleviate this abnormal connectivity (Gruart and Delgado-García, 1994).

In recent years, some reviews have summarized the impact of rTMS on pain (Pan et al., 2022; Cheng et al., 2023; Mohanan et al., 2023; Radiansyah and Hadi, 2023), suggesting that rTMS may have a beneficial effect in alleviating pain. However, some reviews primarily focus on exploring the mechanisms and concentrate on conditions such as fibromyalgia, postherpetic neuralgia, malignant neuropathic pain. There is limited analysis in these reviews regarding the clinical evidence of rTMS in treating CPSP. The effectiveness of rTMS for CPSP has not yet received sufficient support from evidence-based medicine. Therefore, to establish the relationship between rTMS and the relief of CPSP, we conducted a systematic review and meta-analysis of published randomized controlled trials. This meta-analysis aims to provide the latest evidence for the use of transcranial magnetic stimulation in the treatment of CPSP.

2 Methods

This study has been registered in PROSPERO with registration number CRD42023480458. Simultaneously, we will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to conduct and report the current systematic review and meta-analysis.

2.1 Eligibility criteria

2.1.1 Study inclusion criteria

Participants: Individuals with a confirmed first-time stroke, whether ischemic or hemorrhagic, as verified by computed tomography (CT) or magnetic resonance imaging (MRI).

Confirmed CPSP Diagnosis: Participants must have a confirmed diagnosis of CPSP (Hansen et al., 2012; Scholz et al., 2019), exhibiting persistent or intermittent pain characterized by sensations of burning, throbbing, compression, or freezing (Klit et al., 2009).

Exclusion of Other Causes: Participants with CPSP excluding cases attributed to other diseases causing central neuropathic pain.

Intervention: Subjects undergoing rTMS as an intervention.

Comparison: The control group should receive either sham stimulation or conventional rehabilitation treatment. The specific interventions in the conventional rehabilitation treatment must be consistent with those in the intervention group.

Study Design: Randomized controlled trials with a crossover or parallel design.

2.1.2 Exclusion criteria

Reviews, conference papers, animal studies, retrospective studies, case-control studies, and self-controlled studies will be excluded. Randomized controlled trials that do not report pain score-related outcomes will also be excluded.

2.2 Search strategy

We conducted searches in PubMed, Embase, Cochrane Library, Web of Science (WOS), Chinese National Knowledge Infrastructure (CNKI), and Wan Fang Data Knowledge Service Platform for relevant studies published until December 30, 2023. Additionally, manual searches of references in included studies and relevant reviews were performed to identify additional trials. Detailed search strategies and exclusion criteria can be found in Supplementary material.

2.3 Study selection

The search records obtained through the search strategy were imported into Endnote 21 to remove duplicate records. The first screening was conducted by reviewing titles and abstracts, followed by a full-text reading to determine the final inclusion of studies. Two reviewers (YL and QH) independently conducted the literature search and screening process. Any discrepancies between the two reviewers were resolved through discussion. If a consensus could not be reached, a third reviewer (FYZ) made the final decision.

2.4 Data extraction

Two reviewers independently conducted data extraction using a predefined standardized form. Extracted information included author and publication year, stroke onset time, sample size, participant demographics (age and gender), intervention details, relevant parameters, outcome indicators, and more. In cases where the original research data could not be obtained from the article, the corresponding author of the original study was contacted for the required information. After independent extraction, cross-checking was performed, and any discrepancies were resolved by the third reviewer (FYZ).

2.5 Assessment of risk of bias

The Cochrane RoB 2 tool was employed to assess the risk of bias in the included studies. The assessment covered five aspects of the study's overall risk of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For each randomized controlled trial (RCT), two reviewers (YL and QH) independently assessed each involved item as high risk, some concerns, or low risk. Discrepancies were resolved through verification. Additionally, the methodological quality was assessed using the Pedro scale. Any disagreements were consulted with a third reviewer (FYZ).

2.6 Outcome indicators

Primary outcome measures include Visual Analog Scale (VAS) or Numeric Rating Scale (NRS). Secondary outcome measures encompass McGill Pain Questionnaire (MPQ), Hamilton Rating Scale for Depression (HADM), Hamilton Anxiety Scale (HAMA), Motor Evoked Potential Latency (MEP-latency), and Fugl-Meyer Assessment for Upper Extremity (FMA-UE).

2.7 Data synthesis and statistical analysis

Statistical analysis was performed using Stata 17 software. Continuous data were expressed as standardized mean difference (SMD) with a 95% confidence interval (CI). In cases of substantial heterogeneity ($I^2 \geq 50\%$ or $P < 0.05$), a random-effects model was applied, and subgroup analyses were conducted to explore the sources of heterogeneity. Otherwise, a fixed-effects model was used. If $I^2 \geq 75\%$, indicating "considerable heterogeneity," sensitivity analysis was performed to assess result stability. A significance level of $P < 0.05$ was considered statistically significant for all analyses.

When multiple outcome measures were used in a study, the primary outcome measure reported in the article was prioritized for analysis.

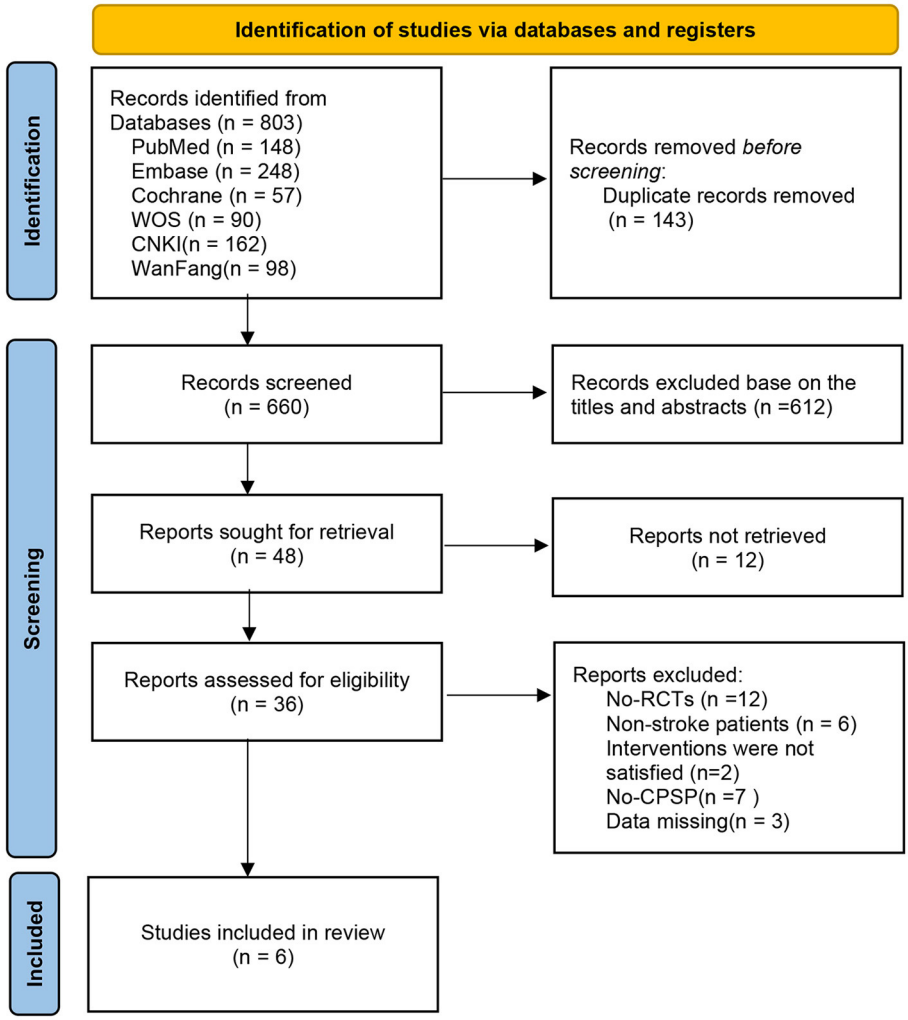

FIGURE 1
The screening flowchart.

3 Result

3.1 Results on literature search and selection

We retrieved a total of 803 relevant articles from six databases, and after removing duplicates (143 articles), we evaluated them through title, abstract, and full-text reading. Finally, six eligible studies were included. A detailed flowchart is provided in Figure 1.

3.2 Characteristics of included study

This study included a total of six RCTs, comprising two English-language papers (De Oliveira et al., 2014; Zhao C.-G. et al., 2021) and four Chinese-language papers (Sun et al., 2019; Chen et al., 2020; Zhao Y. Y. et al., 2021; Jiang et al., 2022). The studies were published between 2014 and 2022, involving a total of 288 participants. Among them, 144 patients received rTMS combined with conventional rehabilitation training, while the remaining 144 patients underwent conventional rehabilitation training or sham stimulation. In the five studies (De Oliveira et al., 2014; Sun et al., 2019; Chen et al., 2020; Zhao C.-G. et al., 2021; Jiang et al., 2022) using sham stimulation combined with conventional rehabilitation training, four studies (De Oliveira et al., 2014; Sun et al., 2019; Zhao C.-G. et al., 2021; Jiang et al., 2022) employed a sham coil with no effective stimulation, and one study (Chen et al., 2020) used a method perpendicular to the surface of the skull for sham stimulation. Two studies (De Oliveira et al., 2014; Zhao Y. Y. et al., 2021) had a stroke duration >6 months, while the other four studies (Sun et al., 2019; Chen et al., 2020; Zhao C.-G. et al., 2021; Jiang et al., 2022) had a duration <6 months. All studies assessed pain in patients, with 5 studies using VAS as the primary outcome measure. The study by Zhao C.-G. et al. (2021) used NRS. Three studies (Sun et al., 2019; Zhao C.-G. et al., 2021; Jiang et al., 2022) reported results for MEP-latency, and two studies (Chen et al., 2020; Zhao C.-G. et al., 2021) reported results for FMA-UE. The studies by Zhao C.-G. et al. (2021) and De Oliveira et al. (2014) reported results for MPQ, HAM-A, and HAM-D. For detailed characteristics, refer to Table 1.

TABLE 1 Characteristics of the randomized controlled studies.

References	Study design	Year	Sample size (T, C)	Age [mean (SD)] (T, C)	Gender (male/female) (T, C)	Duration of stroke (T/C)	Type of stroke (H:I) (T, C)	Intervention (T, C)	Coil type	Site	Treatment characteristics	Treatment time	Outcome indicator
Jiang et al. (2022)	RCT	2022	32/32	61.56±6.36, 60.13±7.87	19/13, 17/15	33.25±7.66 d, 32.81±6.29 d	/	rTMS+CT, sham+CT	Figure-eight coil (MagPro R30 stimulator, Tonica Company, Denmark)	Ipsilesional M1	10 Hz, 80% RMT, 1500 pulses	8 weeks, 2 days per week	VAS, MEP
Zhao C.-G. et al. (2021)	RCT	2021	19,19	50.16±11.34, 48.95±11.51	/	12.21±5.61 m,10.63 ±5.77 m	/	rTMS+CT, sham+CT	Figure-eight coil (CCY-1 stimulator, Yiruide Medical Equipment Company, China)	Ipsilesional M1	10 Hz, 80% RMT, 1500 pulses	3 weeks, 6 days per week	NRS, SF-MPQ-2, MEP, HAM-A HAM-D
Zhao Y. Y. et al. (2021)	RCT	2021	41/42	52.03±14.22, 52.11±14.28	25/16, 27/15	2.13±0.51 m, 2.16±0.52 m	20/21, 22/20	rTMS+CT, CT	Figure-eight coil (CCY-1 stimulator, Yiruide Medical Equipment Company, China)	Ipsilesional M1	10 Hz, 90% RMT, 1000 pulses	4 weeks, 7 days per week	VAS, FMA-UE
Chen et al. (2020)	RCT	2020	20/20	51.5±17.0, 55.1±18.8	14/6, 11/9	1.9±2.1m, 1.6±1.5 m	10/10, 11/9	rTMS+CT, sham+CT	Figure-eight coil (Yiruide Medical Equipment Company, China)	Ipsilesional M1	10 Hz, 90% RMT, 1500 pulses	2 weeks, 7 days per week	VAS, FMA-UE
Sun et al. (2019)	RCT	2019	20/20	48.1±8.5, 50.1±7.7	15/5, 12/8	6.0±1.5 d, 7.0±1.1 d	8/12, 10/10	rTMS+CT, sham+CT	Figure-eight coil (CCY-1 stimulator, Yiruide Medical Equipment Company, China)	Ipsilesional M1	10 Hz, 80% RMT, 1500 pulses	4 weeks, 6 days per week	VAS, MEP
De Oliveira et al. (2014)	RCT	2014	12, 11	55.0±9.67, 57.8±11.86	5/7, 6/6	64.1 ± 49.2 m, 50.1 ± 28.0 m	4/8, 2/9	rTMS+CT, sham+CT	Figure-eight coil (MagPROX100 machine Magventure Tonika Elektronic, Farum, Denmark)	Left DLPFC/PMC	10 Hz, 120% RMT, 1250 pulses	2 weeks, 5 days per week	VAS, MPQ, HAM-D, HAM-A

HADM, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; T, Treatment Group; C, Control Group; rTMS, Repetitive Transcranial Magnetic Stimulation; RCT, Randomized Controlled Trial; VAS, M1, motor cortical area; MEP, Motor-Evoked Potential; RMT, Resting Motor Threshold; NRS, Numeric rating scale; SF-MPQ-2, Short-form McGill Pain Questionnaire-2; MPQ-2, McGill Pain Questionnaire; VAS, visual analog scale; CT, conventional therapy; d, day; m, month; FMA-UE, Fugl-Meyer Assessment Upper Extremity Scale; /, no information.

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FIGURE 2
Risk of Bias of RCTs.

3.3 Risk of bias

We assessed the risk of bias in the six RCTs using Cochrane RoB 2.0. One study was rated as high risk, one study had some concerns, and the remaining four studies were assessed as low risk. Simultaneously, using the Pedro scale, four studies scored ≥7 points, indicating high-quality research. Two studies scored 6 points, categorizing them as medium-quality studies (Moseley et al., 2020; Meng et al., 2023). The specific bias risks are detailed in Figure 2, Table 2.

3.4 Results of the meta-analysis

Primary Outcome: Six studies reported pain scores. The overall pooled Standardized Mean Difference (SMD) using a random-effects model showed that rTMS significantly reduced patients' pain scores compared to the control group (SMD = −1.15, 95% CI: −1.69, −0.61, $P < 0.001$). However, there was substantial heterogeneity ($I^2 = 71.5\%$, $P < 0.001$). Subgroup analysis for the duration less than 6 months revealed a significant reduction in pain scores with rTMS (SMD = −1.31, 95% CI: −2.01, −0.60, $P < 0.001$). In contrast, for the subgroup with a duration >6 months, the analysis showed no significant effect of rTMS on improving patients' pain (SMD = −0.80, 95% CI: −1.63, 0.03, $P = 0.059$). Detailed results are shown in Figure 3.

Three studies reported MEP-latency. The meta-analysis indicated no statistically significant difference between the rTMS group and the control group (SMD = −0.99, 95% CI:−2.05, 0.07, $P = 0.066$), but with high heterogeneity ($I^2 = 88.2\%$, $P < 0.001$) (Figure 4A). Two studies reported FMA-UE. The meta-analysis demonstrated a statistically significant difference in improving FMA-UE scores between the rTMS group and the control group (WMD = 13.13, 95% CI: 10.03, 16.22, $P < 0.001$) with low heterogeneity ($I^2 = 0\%$, $P = 0.328$) (Figure 4B). Two studies reported MPQ. Using a random-effects model, the meta-analysis revealed no statistically significant difference in improving patients' MPQ scores between the rTMS group and the control group (SMD = −0.08, 95% CI: −1.65, 1.49, $P = 0.921$), but with high heterogeneity ($I^2 = 88.2\%$, $P = 0.004$) (Figure 4C).

TABLE 2 PEDro scores of the included studies.

References	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Participants blinded	Therapists blinded	Assessors blinded	Adequate follow-up	No missing data or intention to treat analysis	Between-groups comparisons	Point estimates and variability	Total score (/10)
Jiang et al. (2022)	Yes	1	0	1	1	1	1	1	1	1	1	6
Zhao C.-G. et al. (2021)	Yes	1	1	1	1	0	1	1	1	1	1	6
Zhao Y. Y. et al. (2021)	Yes	1	0	1	0	0	0	1	1	1	1	6
Chen et al. (2020)	Yes	1	0	1	0	0	0	1	1	1	1	6
Sun et al. (2019)	Yes	1	0	1	0	0	0	1	1	1	1	6
De Oliveira et al. (2014)	Yes	1	0	1	1	0	1	1	1	1	1	8

1 = Yes, 0 = No.

Two studies reported HAM-A. The meta-analysis showed no statistically significant difference in reducing patients' HAM-A scores between the rTMS group and the control group (WMD = −0.49, 95% CI: −1.06, 0.08, $P = 0.095$) with low heterogeneity ($I^2 = 0\%$, $P = 0.834$) (Figure 4D). Two studies reported HAM-D. The meta-analysis indicated no statistically significant difference in improving patients' HAM-D scores between the rTMS group and the control group (WMD = 0.95, 95% CI: 0.23, 1.65, $P = 0.010$) with high heterogeneity ($I^2 = 62.9\%$, $P = 0.101$) (Figure 4E).

3.5 Sensitivity analysis and publication bias

We conducted a sensitivity analysis on the meta-analysis results of the primary outcomes (effect = −1.19, CI: −1.45, −0.93), Indicating that the results are stable. The results of Egger test were P=0.585>0.05, suggesting no significant publication bias (Figures 5, 6).

4 Discussion

Our meta-analysis results integrated quantitative data from pain, anxiety, and depression rating scales, as well as FMA-UE and MEP-latency assessments in CPSP patients treated with rTMS. The data analysis revealed a significant efficacy of rTMS in alleviating pain and enhancing upper limb motor function in CPSP patients. Nevertheless, there was no statistically significant improvement noted in the patients' anxiety and depression levels, and MEP-latency remained unaffected.

The pain inhibitory mechanisms in CPSP patients may be dysregulated. The presence of post-stroke lesions results in decreased excitability of the affected hemisphere's M1, leading to reduced neural output, including interhemispheric inhibition (IHI) from the unaffected hemisphere to M1. This results in a relative increase in excitability of the contralateral hemisphere's M1 and increased neural output, thereby shifting IHI from the contralateral hemisphere's M1 to the affected hemisphere's M1, inhibiting the excitability of the affected hemisphere's M1 (Gerges et al., 2022). A recent study found that rTMS induces an increase in IHI from the affected hemisphere to the contralateral hemisphere, thereby alleviating pain (Alhassani et al., 2019). Thus, LF-rTMS over the unaffected hemisphere may reduce inhibition of the affected hemisphere. Conversely, HF-rTMS over the affected hemisphere increases inhibition of the unaffected hemisphere, normalizing cortical excitability and ultimately achieving pain relief.

Numerous clinical trials have established that a reduction in gamma-aminobutyric acid GABAergic neurotransmission within the central nervous system is a principal etiology of persistent neuropathic pain (Yang et al., 2019; Lanza et al., 2020). It is widely posited that corticosterogenic inhibition within the M1, known as intracortical inhibition (ICI), mirrors the activity of interneurons. Both ICI and intracortical facilitation (ICF) are considered potential indicators of GABAergic inhibitory interneuron function, particularly in relation to GABAergic processes. Prior investigations have demonstrated

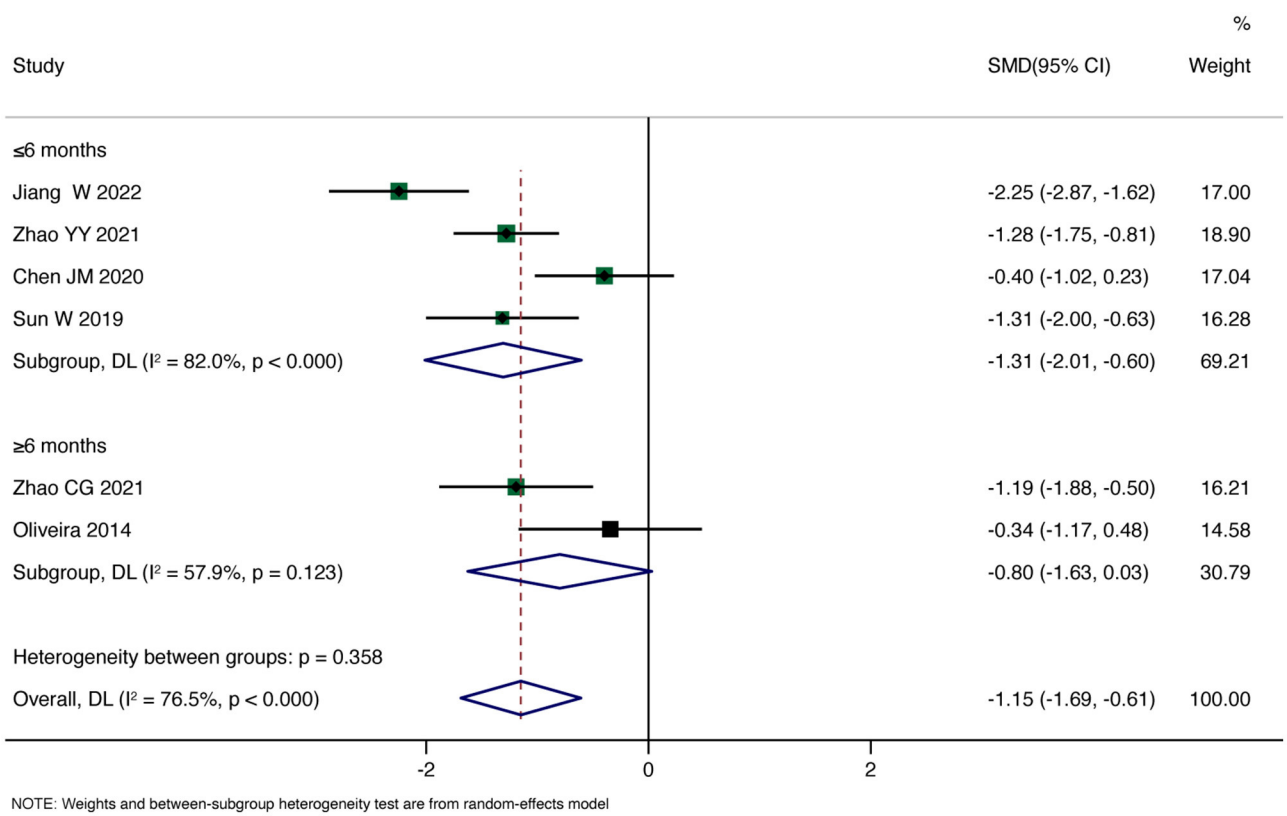


FIGURE 3
Forest plot for pain.

that high-frequency rTMS can enhance ICI and ICF, with these alterations being correlated with pain alleviation in patients with CPSP (Hosomi et al., 2013). Consequently, rTMS may exert its analgesic effect on CPSP through a mechanism that involves the augmentation of GABAergic neuronal transmission (Pan et al., 2022).

rTMS may be mechanistically analogous to Motor Cortex Stimulation (MCS), as indicated by findings from MCS research. These investigations propose that MCS could directly modulate regions of the brain involved in the affective processing of pain, and/or indirectly initiate mechanisms enhancing the activity of inhibitory pathways in the dorsal horn (Leung et al., 2009), Additionally, rTMS might mitigate pain by augmenting perfusion to the afflicted area. Evidence indicates a relative decrease in Cerebral Blood Flow (CBF) in chronic pain conditions, with PET studies revealing that rTMS application targeting the M1 significantly elevates CBF in individuals with neuropathic pain (Jin et al., 2015; Quesada et al., 2018). Recent studies have reported the potential of rTMS in alleviating neuropathic pain in conditions such as post-spinal cord injury, post-trigeminal nerve surgery pain, and burning mouth syndrome (Ma et al., 2015; Gatzinsky et al., 2021; Isagulyan et al., 2023). The M1 has been suggested as an effective target for pain relief (O'Brien et al., 2016), and functional neuroimaging studies indicate that rTMS applied to the pre-motor cortex (PMC)/Dorsolateral Prefrontal Cortex (DLPFC) can provide robust and lasting analgesic effects, improving the condition of patients with severe depression (Ciampi Andrade et al., 2014; Che et al., 2021; Zhu et al., 2022). While previous research predominantly associated CPSP with thalamic damage, recent studies propose that vascular damage in any part of the central nervous system can lead to CPSP (Flaster et al., 2013; Cheng et al., 2023). This shift in understanding may be attributed to post-stroke abnormalities in pathways such as the corticospinal tract, thalamocortical tract, spinothalamic tract, and posterior limb of the internal capsule, ultimately resulting in abnormal neural excitations associated with pain (De Oliveira et al., 2012; Osama et al., 2018).

In clinical settings, the pharmacological management of CPSP typically involves the trial of various medications until pain relief is achieved, often requiring combinations of multiple drugs. Initial therapy for neuropathic pain typically involves tricyclic antidepressants, such as amitriptyline (75 mg/day), which effectively reduces pain in CPSP patients (Kremer et al., 2016; Obata, 2017). Adverse effects, including fatigue and dry mouth, are commonly reported, particularly with plasma concentrations exceeding 300 nmol/L (Dworkin et al., 2007). Anticonvulsant drugs, such as gabapentin and pregabalin, are known for their efficacy in both peripheral and central neuropathic pain by reducing neuronal hyperexcitability. Pregabalin has shown significant therapeutic benefits in pain intensity for central neuropathic pain patients, with common adverse effects including nausea, somnolence, cognitive decline, and dizziness (Vranken et al., 2008). Lamotrigine

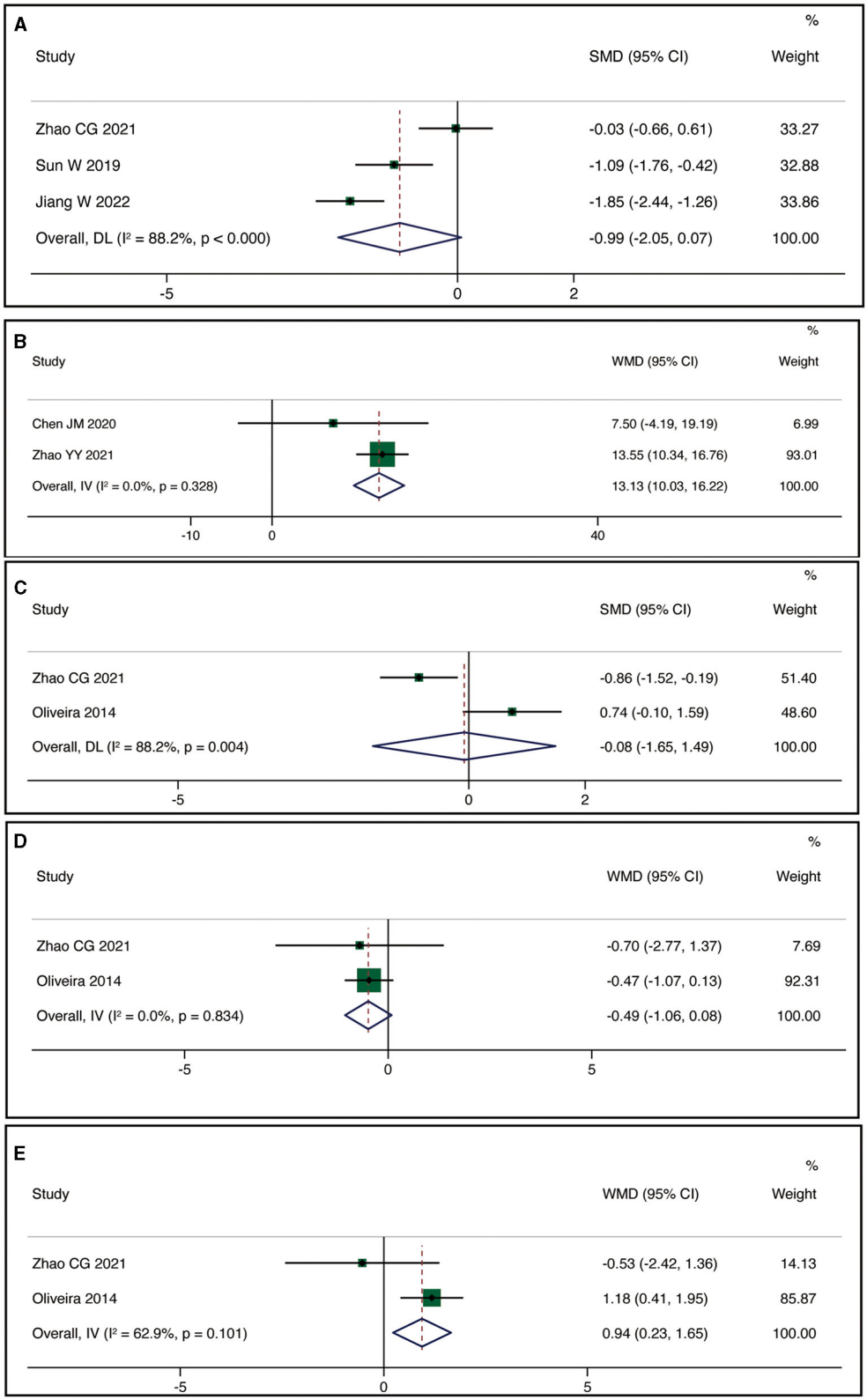


FIGURE 4
Forest plot for MEP-latency **(A)**, FMA-UE **(B)**, MPQ **(C)**, HAM-A **(D)**, HAM-D **(E)**.

has been found to be well-tolerated and beneficial for pain relief in CPSP patients (Dworkin et al., 2007; Rollo et al., 2023).

Studies have indicated that in the treatment of CPSP, transcranial magnetic TMS with a frequency >5 Hz is more effective than low-frequency stimulation. This effectiveness may

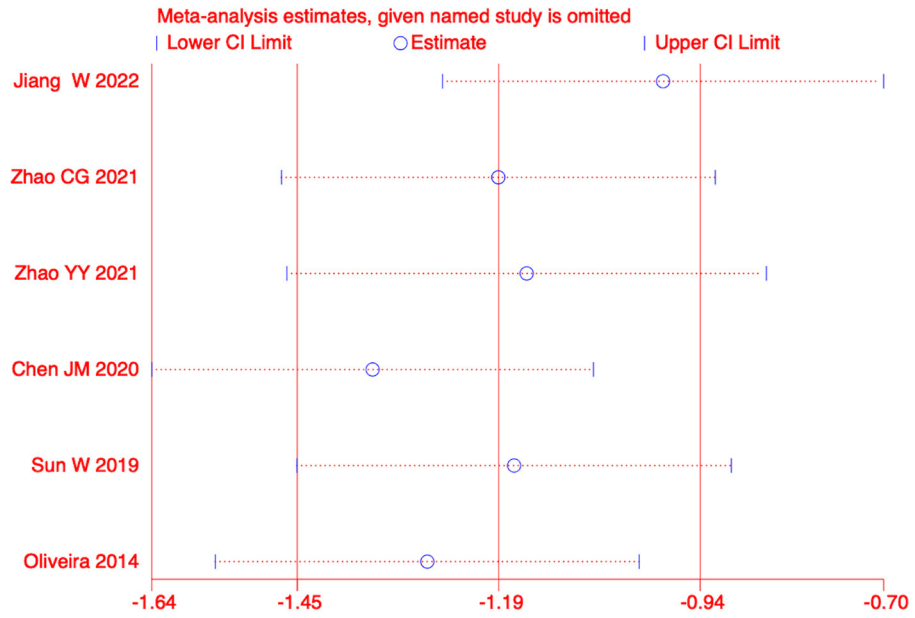
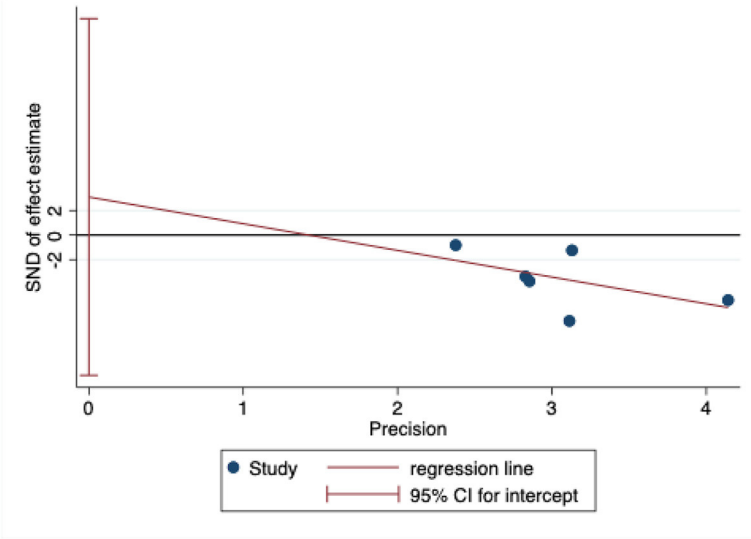


FIGURE 5
Sensitivity analysis of pain.



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Number of studies = 6 Root MSE = 2.21

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-2.173851	1.676274	-1.30	0.264	-6.827935	2.480232
bias	3.103408	5.231322	0.59	0.585	-11.42107	17.62789

Test of H0: no small-study effects P = 0.585

FIGURE 6
Egger test of pain.

be attributed to the ability of high-frequency stimulation to restore the excitability of the abnormal cortex (Khedr et al., 2005; Kobayashi et al., 2015). Alhassani et al. (2019) discovered that the affected M1 on the contralateral side inhibits the unaffected M1. Therefore, high-frequency rTMS to the damaged hemisphere increases inhibition of the unaffected hemisphere, normalizing cortical excitability, and producing pain relief. Although the mechanisms underlying the analgesic effects of rTMS on M1 are not fully understood, they likely involve several factors. Firstly, rTMS can alter cortical excitability, and existing evidence suggests that the pain relief associated with rTMS in post-stroke pain is often accompanied by the restoration of cortical excitability abnormalities (Hosomi et al., 2013). Secondly, rTMS induces neuroplastic changes in the brain by mediating the up-down regulatory mechanism of cortical-spinal inhibition, ultimately leading to increased secretion of brain-derived neurotrophic factor (BDNF) (Zhao C.-G. et al., 2021). This process also influences the structural and functional connections of brain regions involved in pain processing and modulation (Dall'Agnol et al., 2014; Pan et al., 2022). Subgroup analysis in this study revealed that patients with CPSP lasting more than 6 months showed no significant relief in pain compared to the control group. This suggests that the mechanisms of pain in patients with a longer duration of illness may be more complex and require further research for clarification.

5 Limitations

Several limitations should be acknowledged in our study. Firstly, this meta-analysis is based on a limited pool of six randomized controlled trials (RCTs), each with a sample size <100. This small sample size may potentially exaggerate the treatment effects. Secondly, only two studies reported measurements of depression and anxiety. Caution should be exercised in interpreting these results due to the limited data available. The efficacy differences between different stimulation sites (M1 vs. DLPFC) were not analyzed in our study due to the insufficient number of included studies. Future research may benefit from comparing the effects of different intervention sites (M1 vs. DLPFC) on CPSP patients. Moreover, multicenter, randomized controlled, double-blind trials with diverse stimulation protocols are warranted in clinical practice. These trials would facilitate longitudinal and cross-sectional comparisons between different stimulation parameters to determine the optimal stimulation protocol.

6 Conclusion

Our systematic review and meta-analysis of rTMS for the treatment of CPSP indicate that rTMS may be effective in alleviating pain and potentially improving motor function in CPSP patients. However, its efficacy for depression, anxiety, and MEP-latency remains inconclusive.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YL: Data curation, Writing – original draft, Writing – review & editing. RM: Methodology, Supervision, Writing – review & editing. HZ: Software, Writing – review & editing. QH: Conceptualization, Writing – original draft, Writing – review & editing. SY: Resources, Software, Validation, Writing – original draft, Writing – review & editing. FZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1367649/full#supplementary-material

References

Alhassani, G., Liston, M. B., and Schabrun, S. M. (2019). Interhemispheric inhibition is reduced in response to acute muscle pain: a cross-sectional study using transcranial magnetic stimulation. *J. Pain* 20, 1091–1099. doi: 10.1016/j.jpain.2019.03.007

An, J.-X., Shi, W.-R., Zhang, J.-F., Qian, X.-Y., Fang, Q.-W., Wang, Y., et al. (2019). A new rat model of thalamic pain produced by administration of cobra venom to the unilateral ventral posterolateral nucleus. *Pain Physician* 22, E635–e647. doi: 10.36076/ppj/2019.22.E635

Bai, Z., Zhang, J., and Fong, K. N. K. (2022). Effects of transcranial magnetic stimulation in modulating cortical excitability in patients with stroke: a systematic review and meta-analysis. *J. Neuroeng. Rehabil.* 19, 24. doi: 10.1186/s12984-022-00999-4

Banerjee, M., Pal, S., Bhattacharya, B., Ghosh, B., Mondal, S., and Basu, J. (2013). A comparative study of efficacy and safety of gabapentin versus amitriptyline as coanalgesics in patients receiving opioid analgesics for neuropathic pain in malignancy. *Indian J. Pharmacol.* 45, 334–338. doi: 10.4103/0253-7613.115000

Boddington, L. J., and Reynolds, J. N. J. (2017). Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimul.* 10, 214–222. doi: 10.1016/j.brs.2017.01.006

Che, X., Cash, R. F. H., Luo, X., Luo, H., Lu, X., Xu, F., et al. (2021). High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: a systematic review and meta-analysis. *Brain Stimul.* 14, 1135–1146. doi: 10.1016/j.brs.2021.07.004

Chen, J. M., Koguchi, K., Okada, K., Hosomi, M., Ueguchi, T., Kida, I., et al. (2020). The effect of repeated transcranial magnetic stimulation on the perception threshold in patients with cen-tral post- stroke pain. Chinese Journal of Rehabilitation Medicine, 35, 820–824.+842.

Cheng, Y., Wu, B., Huang, J., and Chen, Y. (2023). Research progress on the mechanisms of central post-stroke pain: a review. *Cell. Mol. Neurobiol.* 43, 3083–3098. doi: 10.1007/s10571-023-01360-6

Choi, H. R., Aktas, A., and Bottros, M. M. (2021). Pharmacotherapy to manage central post-stroke pain. *CNS Drugs* 35, 151–160. doi: 10.1007/s40263-021-00791-3

Ciampi Andrade, D., Mhalla, A., Adam, F., Texeira, M. J., and Bouhassira, D. (2014). Repetitive transcranial magnetic stimulation induced analgesia depends on N-methyl-D-aspartate glutamate receptors. *Pain* 155, 598–605. doi: 10.1016/j.pain.2013.12.022

Cruccu, G., Aziz, T. Z., Garcia-Larrea, L., Hansson, P., Jensen, T. S., Lefaucheur, J.-P., et al. (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur. J. Neurol.* 14, 952–970. doi: 10.1111/j.1468-1331.2007.01916.x

Dall'Agnol, L., Medeiros, L. F., Torres, I. L. S., Deitos, A., Brietzke, A., Laste, G., et al. (2014). Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. *J Pain* 15, 845–855. doi: 10.1016/j.jpain.2014.05.001

De Oliveira, R. A., de Andrade DC, Machado, A. G., and Teixeira, M. J. (2012). Central poststroke pain: somatosensory abnormalities and the presence of associated myofascial pain syndrome. *BMC Neurol.* 12:89. doi: 10.1186/1471-2377-12-89

De Oliveira, R. A., de Andrade, D. C., Mendonça, M., Barros, R., Luvisoto, T., Myczkowski, M. L., et al. (2014). Repetitive transcranial magnetic stimulation of the left premotor/dorsolateral prefrontal cortex does not have analgesic effect on central poststroke pain. *J. Pain* 15, 1271–1281. doi: 10.1016/j.jpain.2014.09.009

Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., et al. (2011). Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. *J. Neurophysiol.* 105, 2150–2156. doi: 10.1152/jn.00781.2010

Dub,é, J. A., and Mercier, C. (2011). Effect of pain and pain expectation on primary motor cortex excitability. *Clin. Neurophysiol.* 122, 2318–2323. doi: 10.1016/j.clinph.2011.03.026

Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., et al. (2007). Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132, 237–251. doi: 10.1016/j.pain.2007.08.033

Flaster, M., Meresh, E., Rao, M., and Biller, J. (2013). Central poststroke pain: current diagnosis and treatment. *Top. Stroke Rehabil.* 20, 116–123. doi: 10.1310/tsr2002-116

Gatzinsky, K., Bergh, C., Liljegren, A., Silander, H., Samuelsson, J., Svanberg, T., et al. (2021). Repetitive transcranial magnetic stimulation of the primary motor cortex in management of chronic neuropathic pain: a systematic review. *Scand J. Pain* 21, 8–21. doi: 10.1515/sjpain-2020-0054

Gerges, A. N. H., Hordacre, B., Di Pietro, F., Moseley, G. L., and Berryman, C. (2022). Do adults with stroke have altered interhemispheric inhibition? A systematic review with meta-analysis. *J. Stroke Cerebrovasc. Dis.* 31:106494. doi: 10.1016/j.jstrokecerebrovasdis.2022.106494

Gruart, A., and Delgado-García, J. M. (1994). Discharge of identified deep cerebellar nuclei neurons related to eye blinks in the alert cat. *Neuroscience* 61, 665–681. doi: 10.1016/0306-4522(94)90443-X

Hallett, M., Di Iorio, R., Rossini, P. M., Park, J. E., Chen, R., Celnik, P., et al. (2017). Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. *Clin. Neurophysiol.* 128, 2125–2139. doi: 10.1016/j.clinph.2017.08.007

Hansen, A. P., Marcussen, N. S., Klit, H., Andersen, G., Finnerup, N. B., and Jensen, T. S. (2012). Pain following stroke: a prospective study. *Eur. J. Pain* 16, 1128–1136. doi: 10.1002/j.1532-2149.2012.00123.x

Heide, G., Witte, O. W., and Ziemann, U. (2006). Physiology of modulation of motor cortex excitability by low-frequency suprathreshold repetitive transcranial magnetic stimulation. *Exp. Brain Res.* 171, 26–34. doi: 10.1007/s00221-005-0262-0

Hosomi, K., Kishima, H., Oshino, S., Hirata, M., Tani, N., Maruo, T., et al. (2013). Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain. *Pain* 154, 1352–1357. doi: 10.1016/j.pain.2013.04.017

Isagulyan, E., Tkachenko, V., Semenov, D., Asriyants, S., Dorokhov, E., Makashova, E., et al. (2023). The effectiveness of various types of electrical stimulation of the spinal cord for chronic pain in patients with postherpetic neuralgia: a literature review. *Pain Res. Manag.* 2023:6015680. doi: 10.1155/2023/6015680

Jiang, W., Yuan, L., Tang, X., Zhang, D., and Wang, S. (2022). Clinical study of high-frequency repetitive transcranial magnetic stimulation regularly and intermittently in the treatment of central pain after thalamic infarction. *Chin. J. Brain Dis. Rehabil.* 12, 269–273. doi: 10.3877/cma.j.issn.2095-123X.2022.05.003

Jin, Y., Xing, G., Li, G., Wang, A., Feng, S., Tang, Q., et al. (2015). High frequency repetitive transcranial magnetic stimulation therapy for chronic neuropathic pain: a meta-analysis. *Pain Physician* 18, E1029–E1046. doi: 10.36076/ppj.2015/18/E1029

Khedr, E. M., Kotb, H., Kamel, N. F., Ahmed, M. A., Sadek, R., and Rothwell, J. C. (2005). Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J. Neurol. Neurosurg. Psychiatr.* 76, 833–838. doi: 10.1136/jnnp.2004.055806

Kim, J. S. (2014). Pharmacological management of central post-stroke pain: a practical guide. *CNS Drugs* 28, 787–797. doi: 10.1007/s40263-014-0194-y

Klit, H., Finnerup, N. B., Andersen, G., and Jensen, T. S. (2011). Central poststroke pain: a population-based study. *Pain* 152, 818–824. doi: 10.1016/j.pain.2010.12.030

Klit, H., Finnerup, N. B., and Jensen, T. S. (2009). Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol.* 8, 857–868. doi: 10.1016/S1474-4422(09)70176-0

Kobayashi, M., Fujimaki, T., Mihara, B., and Ohira, T. (2015). Repetitive transcranial magnetic stimulation once a week induces sustainable long-term relief of central poststroke pain. *Neuromodulation* 18, 249–254. doi: 10.1111/ner.12301

Kremer, M., Salvat, E., Muller, A., Yalcin, I., and Barrot, M. (2016). Antidepressants and gabapentinoids in neuropathic pain: mechanistic insights. *Neuroscience* 338, 183–206. doi: 10.1016/j.neuroscience.2016.06.057

Kumar, B. (2009). Central poststroke pain: a review of pathophysiology and treatment. *Anesth. Analg.* 108, 1645–1657. doi: 10.1213/ane.0b013e31819d644c

Kumar, G., and Soni, C. R. (2009). Central post-stroke pain: current evidence. *J. Neurol. Sci.* 284, 10–17. doi: 10.1016/j.jns.2009.04.030

Lanza, G., Aric,ò, D., Lanuzza, B., Cosentino, F. I. I., Tripodi, M., Giardina, F., et al. (2020). Facilitatory/inhibitory intracortical imbalance in REM sleep behavior disorder: early electrophysiological marker of neurodegeneration? *Sleep* 43:zsz242. doi: 10.1093/sleep/zsz242

Lefaucheur, J. P. (2016). Cortical neurostimulation for neuropathic pain: state of the art and perspectives. *Pain* 157, S81–s89. doi: 10.1097/j.pain.0000000000000401

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., et al. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin. Neurophysiol.* 131, 474–528. doi: 10.1016/j.clinph.2019.11.002

Leung, A., Donohue, M., Xu, R., Lee, R., Lefaucheur, J.-P., Khedr, E. M., et al. (2009). rTMS for suppressing neuropathic pain: a meta-analysis. *J. Pain* 10, 1205–1216. doi: 10.1016/j.jpain.2009.03.010

Ma, S.-M., Ni, J.-X., Li, X.-Y., Yang, L.-Q., Guo, Y.-N., and Tang, Y.-Z. (2015). High-frequency repetitive transcranial magnetic stimulation reduces pain in postherpetic neuralgia. *Pain Med.* 16, 2162–2170. doi: 10.1111/pme.12832

McDonnell, M. N., and Stinear, C. M. (2017). TMS measures of motor cortex function after stroke: a meta-analysis. *Brain Stimul.* 10, 721–734. doi: 10.1016/j.brs.2017.03.008

Meng, L., Liang, Q., Yuan, J., Li, S., Ge, Y., Yang, J., et al. (2023). Vestibular rehabilitation therapy on balance and gait in patients after stroke: a systematic review and meta-analysis. *BMC Med.* 21, 322. doi: 10.1186/s12916-023-03029-9

Mohanan, A. T., Nithya, S., Nomier, Y., Hassan, D. A., Jali, A. M., Qadri, M., et al. (2023). Stroke-induced central pain: overview of the mechanisms, management, and emerging targets of central post-stroke pain. *Pharmaceuticals (Basel)* 16:1103. doi: 10.3390/ph16081103

Moseley, A. M., Elkins, M. R., Van der Wees, P. J., and Pinheiro, M. B. (2020). Using research to guide practice: the physiotherapy evidence database (PEDro). *Braz. J. Phys. Ther.* 24, 384–391. doi: 10.1016/j.bjpt.2019.11.002

Obata, H. (2017). Analgesic Mechanisms of Antidepressants for Neuropathic Pain. *Int. J. Mol. Sci.* 18:2483. doi: 10.3390/ijms18112483

O'Brien, A. T., Amorim, R., Rushmore, R. J., Eden, U., Afifi, L., Dipietro, L., et al. (2016). Motor cortex neurostimulation technologies for chronic post-stroke pain: implications of tissue damage on stimulation currents. *Front. Hum. Neurosci.* 10:545. doi: 10.3389/fnhum.2016.00545

Osama, A., Hagar, A. A., Elkholy, S., Negm, M., El-Razek, R. A., and Orabi, M. (2018). Central post-stroke pain: predictors and relationship with magnetic resonance imaging and somatosensory evoked potentials. *Egypt J. Neurol Psychiatr Neurosurg* 54:40. doi: 10.1186/s41983-018-0041-z

Pan, L. J., Zhu, H., Zhang, X., and Wang, X. (2022). The mechanism and effect of repetitive transcranial magnetic stimulation for post-stroke pain. *Front. Mol. Neurosci.* 15, 1091402. doi: 10.3389/fnmol.2022.1091402

Pazzaglia, C., Vollono, C., Testani, E., Coraci, D., Granata, G., Padua, L., et al. (2018). Low-frequency rTMS of the primary motor area does not modify the response of the cerebral cortex to phasic nociceptive stimuli. *Front. Neurosci.* 12, 878. doi: 10.3389/fnins.2018.00878

Quesada, C., Pommier, B., Fauchon, C., Bradley, C., Créac'h, C., Vassal, F., et al. (2018). Robot-guided neuronavigated repetitive transcranial magnetic stimulation (rTMS) in Central Neuropathic Pain. *Arch. Phys. Med. Rehabil.* 99, 2203–2215.e1. doi: 10.1016/j.apmr.2018.04.013

Radiansyah, R. S., and Hadi, D. W. (2023). Repetitive transcranial magnetic stimulation in central post-stroke pain: current status and future perspective. *Korean J. Pain* 36, 408–424. doi: 10.3344/kjp.23220

Ramger, B. C., Bader, K. A., Davies, S. P., Stewart, D. A., Ledbetter, L. S., Simon, C. B., et al. (2019). Effects of non-invasive brain stimulation on clinical pain intensity and experimental pain sensitivity among individuals with central post-stroke pain: a systematic review. *J. Pain Res.* 12, 3319–3329. doi: 10.2147/JPR.S216081

Rollo, E., Romozzi, M., Vollono, C., Calabresi, P., Geppetti, P., and Iannone, L. F. (2023). Antiseizure medications for the prophylaxis of migraine during the anti- CGRP drugs era. *Curr. Neuropharmacol.* 21, 1767–1785. doi: 10.2174/1570159X21666221228095256

Scholz, J., Finnerup, N. B., Attal, N., Aziz, Q., Baron, R., Bennett, M. I., et al. (2019). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain* 160, 53–59. doi: 10.1097/j.pain.0000000000001365

Scuteri, D., Mantovani, E., Tamburin, S., Sandrini, G., Corasaniti, M. T., Bagetta, G., et al. (2020). Opioids in post-stroke pain: a systematic review and meta-analysis. *Front. Pharmacol.* 11, 587050. doi: 10.3389/fphar.2020.587050

Singh, V. K., Shetty, Y. C., Salins, N., and Jain, P. (2020). Prescription pattern of drugs used for neuropathic pain and adherence to NeuPSIG guidelines in cancer. *Indian J. Palliat. Care* 26, 13–18. doi: 10.4103/IJPC.IJPC_172_19

Sun, W., Zhao, C. G., Yuan, H., and Mu, X. (2019). Transcranial magnetic stimulation relieves pain and improves cortical excitability after stroke. *Chin. J. Rehabil. Med.* 41, 252–256. doi: 10.3760/cma.j.issn.0254-1424.2019.04.003

Sweet, L. C., Anderson, J. A., Callies, Q. C., and Jr, E. O. C. (1971). Hypersensitivity pneumonitis related to a home furnace humidfier. *J. Allergy Clin. Immunol.* 48, 171–178. doi: 10.1016/0091-6749(71)90013-3

Vranken, J. H., Dijkgraaf, M. G. W., Kruis, M. R., van der Vegt, M. H., Hollmann, M. W., and Heesen, M. (2008). Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 136, 150–157. doi: 10.1016/j.pain.2007.06.033

Vukojevic, Z., Dominovic Kovacevic, A., Peric, S., Grgic, S., Bjelica, B., Basta, I., et al. (2018). Frequency and features of the central poststroke pain. *J. Neurol. Sci.* 391, 100–103. doi: 10.1016/j.jns.2018.06.004

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., et al. (2016). Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 47, e98–e169. doi: 10.1161/STR.0000000000000098

Yang, L., Liu, X., Yao, K., Sun, Y., Jiang, F., Yan, H., et al. (2019). HCN channel antagonist ZD7288 ameliorates neuropathic pain and associated depression. *Brain Res.* 1717, 204–213. doi: 10.1016/j.brainres.2019.03.036

Zhang, T., Zhao, J., Li, X., Bai, Y., Wang, B., Qu, Y., et al. (2020). Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of stroke rehabilitation. *Stroke Vasc. Neurol.* 5, 250–259. doi: 10.1136/svn-2019-000321

Zhao, C. G., Sun, W., Ju, F., Jiang, S., Wang, H., Sun, X. L., et al. (2021). Correction to: analgesic effects of navigated repetitive transcranial magnetic stimulation in patients with acute central poststroke pain. *Pain Ther* 10, 1101–1103. doi: 10.1007/s40122-021-00270-z

Zhao, Y. Y., Wu, S., Liu, S., and Li, X. W. (2021). Analysis of clinical efficacy of rTMS in the treatment of central poststroke pain. *Reflexol. Rehabil. Med.* 2, 134–136.

Zhu, Y., Li, D., Zhou, Y., Hu, Y., Xu, Z., Lei, L., et al. (2022). Systematic review and meta-analysis of high-frequency rTMS over the dorsolateral prefrontal cortex.on chronic pain and chronic-pain-accompanied depression. *ACS Chem. Neurosci.* 13, 2547–2556. doi: 10.1021/acschemneuro.2c00395

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Global research hotspots and trends in constraint-induced movement therapy in rehabilitation over the past 30 years: a bibliometric and visualization study

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Background: Stroke is a cerebrovascular disease with high prevalence and mortality, and upper limb hemiparesis is a major factor limiting functional recovery in stroke patients. Improvement of motor function in stroke patients through various forms of constraint-induced movement therapy (CITM) has been recognized as safe and effective in recent years. This research field lacks a comprehensive systematic and clear vein combing analysis, analyzing the literature research of CIMT in the field of rehabilitation in the past three decades, summarizing the research hotspots and cutting-edge trends in this field, in an effort to offer ideas and references for subsequent researchers.

Methods: Relevant literature on CIMT in rehabilitation was collected from 1996 to 2024 within the Web of Science database's core dataset by using CiteSpace6.1, VOSviewer1.6.18, R-bibliometrix4.6.1, Pajek5.16, Scimago Graphica 1.0.26 software for visualization and analysis.

Results: There were 970 papers in all United States was ranked first with 401 papers. Alabama Univ was ranked first for institutions with 53 papers. Neurorehabilitation and Neural Repair was ranked first for journals with 78 papers, and Taub E was ranked first for author publications with 64 papers. Research keywords were CIMT, stroke rehabilitation, upper extremity function, lower extremity gait balance, randomized controlled trials, physical therapy techniques (transcranial magnetic stimulation and sensory amplitude electrical stimulation), primary motor cortex plasticity, lateral dominance (spatial behaviors), cerebral vascular accidents, activities of daily living, hand function, disability, functional restoration, bimanual training, aphasia, acquired invalidity, type A Botulinum toxin and joystick riding toys.

Conclusion: The current state of research shows that CIMT still has a vast potential for development in the field of rehabilitation research. The research hotspots are the clinical efficacy of CIMT combined with other therapies (botulinum toxin type A, transcranial direct current stimulation, virtual reality, mirror therapy, robotic-assisted) to enhance the functionality of upper limb hemiparesis in stroke patients, the mechanism of CIMT to improve the plasticity of the motor cortex through electrophysiological and imaging methods, and

improvement of lower limb gait balance function in stroke patients and aphasia applications, the optimal intervention time and dose, and exploration of CIMT in new settings such as robot-assisted, telemedicine, and home rehabilitation.

KEYWORDS

CIMT, constraint-induced movement therapy, stroke, exercise rehabilitation, Citespace, bibliometrics

1 Introduction

Strokes are the second leading cause of death globally and the third leading cause of disability (1). It is estimated that strokes result in 5.5 million deaths each year, with up to 50% of survivors experiencing long-term disability (2). Around 65% of patients are unable to use their affected hand for daily activities 6 months post-stroke, and up to 35% of individuals with lower limb paralysis do not fully regain their physical abilities (3), and upper extremity hemiparesis is a major limiting factor in functional recovery. When stroke patients fail to effectively use their affected upper extremity, they may develop 'learned nonuse, 'where they rely on their unaffected side for daily tasks (4). Constraint-induced movement therapy (CIMT) can enhance upper extremity function by addressing learned disuse and leveraging use-dependent neuroplasticity (5). CIMT comprises reinforcement training, shaping training, 'transfer kits' to facilitate the application of treatment benefits to daily activities, and discouragement of compensatory strategies (6, 7). During the 2 weeks of the program, the less affected upper extremity is immobilized in a sling, and 90% of waking hours (including time spent receiving direct treatment) are spent wearing a splint, glove, or cast, while the more severe upper extremity receives 6 h of treatment per day following a routine procedure (8, 9). Each session includes shaping and targeted, task-specific exercises that increase in difficulty as function or performance improves. Traditional CIMT is most effective for individuals with specific criteria, including a minimum of 10° of wrist and thumb extension, extension of at least 2 other fingers in the most impaired upper extremity, and the ability to stand and transfer independently (8, 10). Challenges have been reported by both patients and therapists in implementing this approach in clinical settings (11), leading to the development of distributed or modified forms of CIMT (dCIMT/mCIMT). These modified forms reduce the duration of each training session (0.5–3 h/session) and daily time commitment (5–9 h/day), extending the overall duration of treatment (3–10 weeks). Evidence suggests that both mCIMT and dCIMT improve motor function in affected limbs (12–14). In addition to improving post-stroke hemiparesis, CIMT also addresses related issues such as unilateral neglect (15, 16) and aphasia (6). CIMT has shown effectiveness in treating Parkinson's patients (17), children with cerebral palsy (18), and improving fine and gross motor skills, daily living abilities, and cognitive function in the upper limbs. Furthermore, CIMT has shown promise in improving conditions related to peripheral nerve diseases, such as brachial plexus nerve injury (19, 20) and finger dystonia (21).

Over the past three decades, clinical studies on CIMT/mCIMT to enhance stroke patients' quality of life and function have significantly advanced. Although the efficacy of CIMT/mCIMT has reached a consensus, the mechanism of its action remains unclear. Further research is needed to verify issues such as the intensity of training, timing of intervention, and duration of treatment efficacy. The treatment of stroke and other mental illnesses faces new opportunities and challenges due to the development of new ideas and technologies. Investigating CIMT research trends and hotspots in the rehabilitation sector is crucial, yet there is a lack of corresponding bibliometric studies in this field. Therefore, this study aims to analyze hotspots, frontiers, and development trajectories to provide a fresh perspective for a comprehensive understanding of the area and offer researchers valuable references and support.

2 Methodology

2.1 Search strategy and data retrieval

Bibliometric research is a quantitative analysis of scientific literature. Gathered data from Web of Science in "plain text," including "complete records and references." Collected data (500 records per file) was exported, renamed "download," and input into Citespace software. Citespace software visualizes scientific literature, generating maps to understand patterns. Drew visualization maps by selecting specific node types, aiding comprehension of scientific literature patterns. Supplementary Table S1 provides detailed information on the search strategy. The selection of the literature for this study was done using the following inclusion and exclusion standards: The literature met the following requirements: (i) it was published between January 1, 1996, and January 1, 2024; (ii) it was written in English; (iii) it was an article or review; (iv) it did not place restrictions on the species or organisms it studied; and (v) duplicates were eliminated from the analysis of the publications to guarantee the dataset's uniqueness. Since the data in the publications contained no personally identifiable information about the patients, ethical approval was not necessary. In Figure 1, the relevant workflow diagram is displayed.

2.2 Literature screening

Independently, two evaluators perused the literature. The article's title and abstract served as the basis for the first screening. Next, the inclusion and exclusion criteria were used to determine which papers should be included or excluded. If there was any doubt, a third assessor, who possessed veto power, read the entire document and made the final decision.

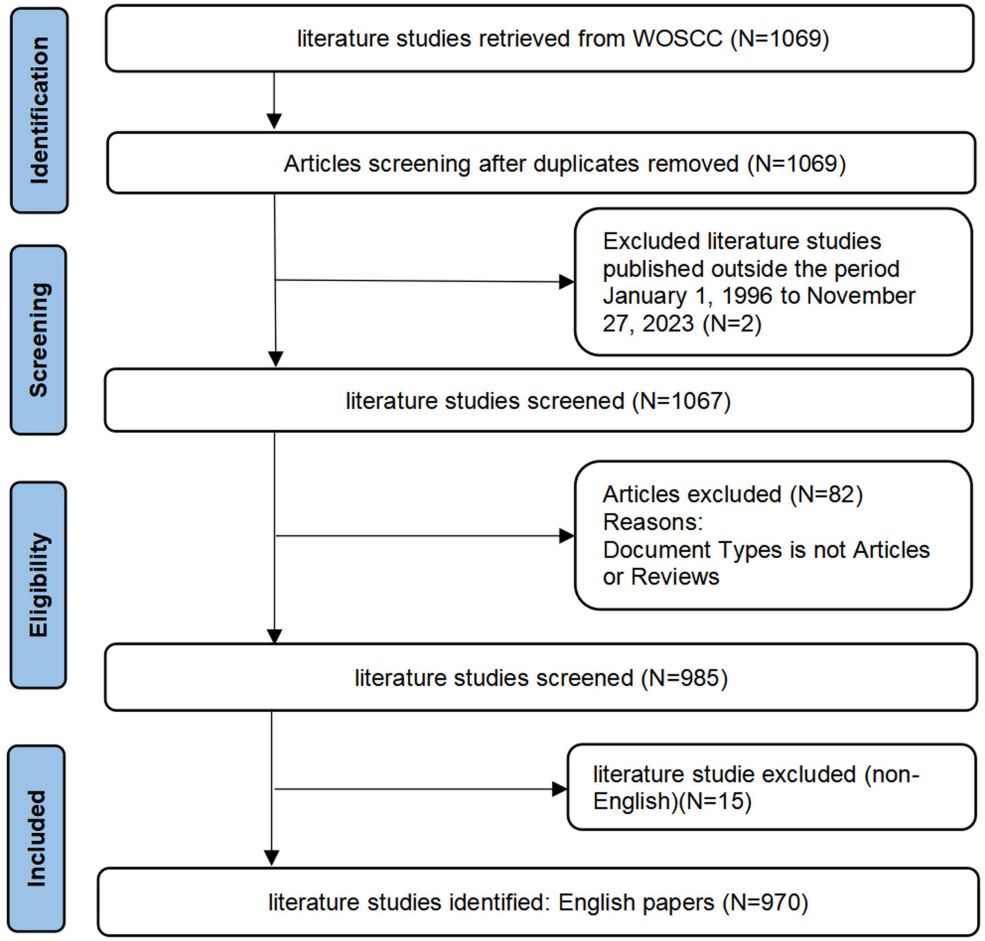


FIGURE 1
Workflow diagram.

2.3 Methods of statistical analysis

A number of tools, including CiteSpace version 6.1.R6, R-Studio based R-bibliometrix version 4.6.1, Pajek version 5.16, Scimago Graphica version 1.0.26, and VOSviewer version 1.6.18, were used in our bibliometric analysis research.

CiteSpace version 6.1.R6 (Drexel University, Philadelphia, PA) is a software tool developed by Prof. Chen C. It excels in identifying research hotspots and trends within the academic field by analyzing citation relationships and evolutionary trends in the literature, which allows for the discovery of key research themes and widely cited papers. In this study, we do a visual analysis using CiteSpace that covers several features, including journal citations, reference analysis, country and institutional distribution, and keyword and citation bursts. The network structure has been simplified and key aspects have been highlighted by selecting "Pruning sliced networks" and "Pathfinder," and the filtering criteria has been set to "Top N," the threshold is set to 50, and the time scale is set to 1 year. See Supplementary Table S2 for details.

VOSviewer version 1.6.18 (Leiden University, Leiden, the Netherlands) is a visualization software developed by Prof. Van Eck and Prof. Waltman, which focuses on co-word relationships between the literature and the analysis of co-word frequencies. It can help researchers to discover common themes and concepts in the literature and to construct co-occurrence network diagrams for visualization. Analyzing the co-occurrence frequency and temporal information of keywords in the literature reveals the evolution process of research topics and the development trend of keywords and helps researchers understand the development dynamics of academic fields (22). In this work, VOSviewer was utilized to investigate keyword co-occurrence and coverage networks as well as to analyze and display the distribution of nations, institutions, authors, and co-cited authors. The detailed parameters were: the keyword inclusion criterion was a minimum number of occurrences of 5, the association strength method was chosen for the normalization process, the cluster resolution and minimum cluster size were both 1 and merge small clusters were checked, the minimum strength of cluster links was 0, and the maximum number of links was 1,000, as detailed in Supplementary Table S3.

R-Studio-based R-bibliometrics version 4.6.1, Pajek version 5.16, and Scimago Graphics version 1.0.26 are powerful tools for multi-modal and multi-dimensional geo-visualization. In this study, it was used to highlight the inter-cooperative network relationships between different countries or regions.

3 Results

3.1 Characteristics and trends in the volume of publications

By searching the core database of Web of Science, a total of 1,069 CIMT in the field of rehabilitation research-related literature was retrieved, excluding the literature publication time not from January 1, 1996, to January 01, 2024, 2 literature, then excluding the literature type for non-article and review of 82 literature, and finally excluding non-English literature 15, and finally 970 literatures were included, as shown in Figure 1. Of them, 796 comprised 82.1% of original research publications, while 174 reviewed papers made up 17.9%. The total citation frequency was 46,987 times, and the average citation frequency per paper was 48.44 times. The annual publishing volume across several nations is displayed in Figure 2A. From 1996 to 2024, the quantity of research articles in the topic of rehabilitation in CIMT remained rather consistent, showing remarkable expansion in 2006 as the number of publications rose by 38.2% over the year before, the annual number of publications was maintained at around 48 and peaked at 60 in 2009. In general, the top three countries for research in the sector continue to be the US, China, and Canada. China has able to surpass the US as the leading nation in terms of yearly publications from 2023. The U.S. has the highest share in terms of total publications, with a tendency to be overtaken by China in terms of annual publications. Through an investigation of polynomial fits between the number of publications and the year of publication, we found a significant correlation (for total papers, articles, reviews, and RCTs, the coefficients of determination (R2) were 0.8601, 0.8472, 0.7629, and 0.7331, in that order). We predicted that the number of

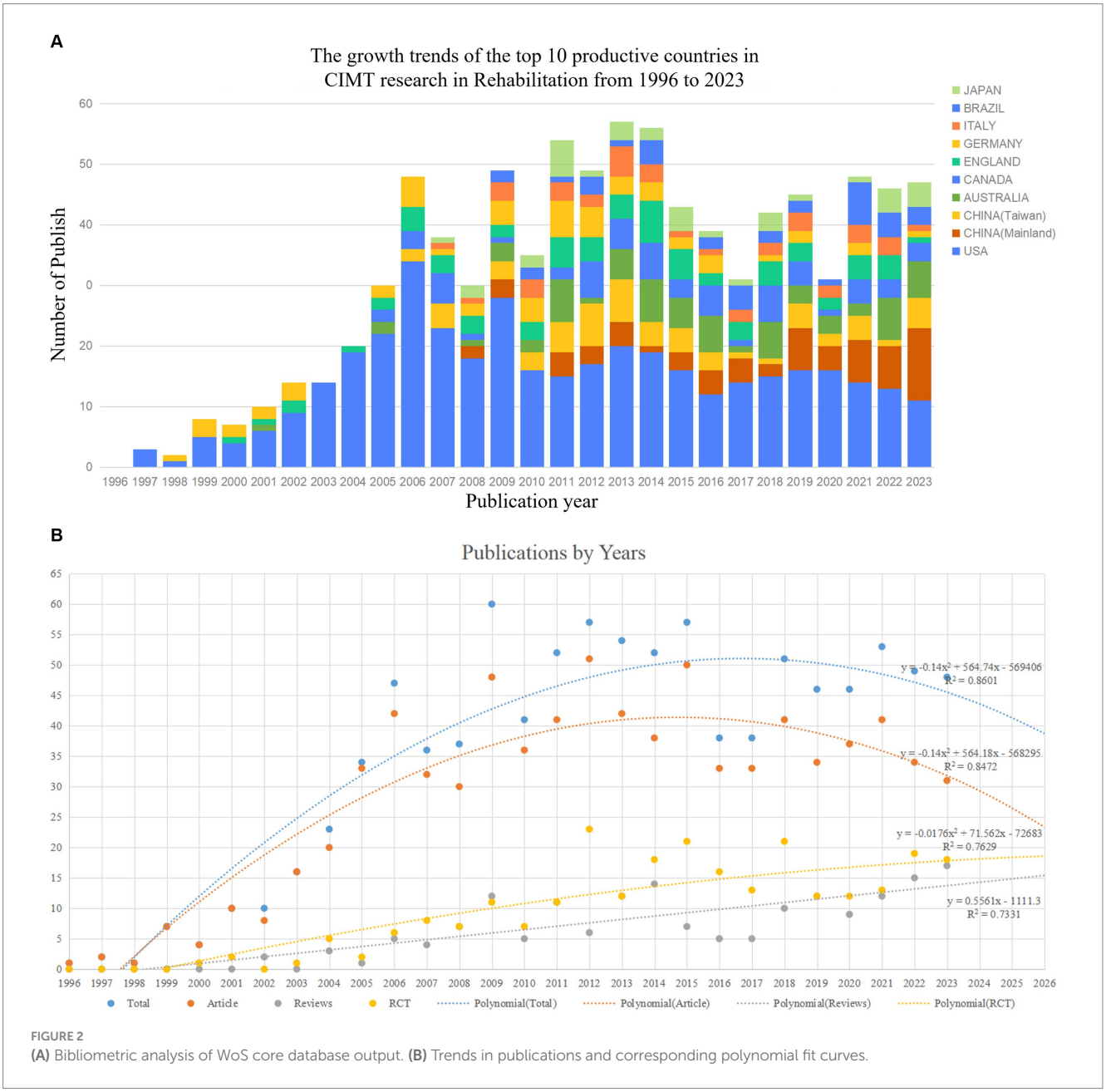


FIGURE 2
(A) Bibliometric analysis of WoS core database output. **(B)** Trends in publications and corresponding polynomial fit curves.

publications in 2026 would reach about 39, including about 23 original articles, 16 reviews, and 19 RCTs, as shown in Figure 2B. However, it can be observed that there is still a relative lack of high-quality RCT studies despite the increasing number of publications year by year.

3.2 Countries or regions collaboration analysis

The resultant graphic includes 58 nations or areas in total, of which 10 have at least 30 articles. The data pertaining to the top 10 nations in terms of publications is displayed in Table 1. In the filled Figure 3, the larger percentage of the country area represents more articles sent, the color is darker, which represents a stronger cooperation relationship, the thickness of the lines indicates the intensity of the link, while the connecting lines show the level of collaboration. Therefore, it can be inferred that the United States (401 articles or 41.34%) is the most active country, followed by China (125 articles or 12.89%, which can be categorized into 66 articles or 6.80% in Mainland China and 59 articles or 6.08% in Taiwan, China) and Australia (66 articles or 6.80%). These three nations are the biggest contributors to the area, with a combined total of publications that account for 61% of all publications. In terms of total citation rate (TC), total link strength (TLS), and H-index, the US leads the world, while the United Kingdom leads in average citations per publication (ACPP). The TLS indicates the level of partnerships between researchers, while the H-index is frequently employed to gauge academic influence.

3.3 Research institution collaboration analysis

In the realm of rehabilitation, 1,377 institutions released studies connected to CIMT, of which 28 institutions had ≥10 publications. Table 2 displays data on the top ten institutions based on the quantity of publications, and 36.39% of the total number of articles came from the top 10 universities with the most publications. Figure 4 illustrates the international collaborations between the 95 institutions that have collaborated on at least five publications. It is noteworthy that the University of Alabama Birmingham (United States) performed most prominently with 53 publications or 5.46% of all publications, followed by Emory Univ (United States) (49 publications, 5.05%) and Natl Taiwan Univ (China) (40 publications, 4.12%). It is noteworthy that among universities, Emory University has the greatest TC and TLS. University Florida and University Alabama Birmingham had the greatest ACPP and H-index, respectively. Chang Gung University, Emory University, and University of Alabama in Birmingham are three universities that have improved their research partnerships with a few other universities.

TABLE 1 Top 10 countries with high impact of CIMT research in the field of rehabilitation.

Country	NP	TC	ACPP	TLS	H-index
United States	401 (41.34%)	26,010	64.86	6,566	77
China (Mainland)	66 (6.80%)	938	14.21	1,196	17
Australia	66 (6.80%)	5,146	77.97	1,606	23
Canada	66 (6.80%)	2,816	42.67	1,246	24
England	61 (6.29%)	6,928	113.57	1,461	30
China (Taiwan)	59 (6.08%)	1746	29.59	1,474	26
Germany	57 (5.88%)	5,804	101.82	1782	30
Italy	40 (4.12%)	1,439	35.98	1,126	15
Brazil	36 (3.71%)	792	22.00	839	14
Japan	36 (3.71%)	656	18.22	547	11

NP, number of publications; TC, total citation; TLS, total link strength; ACPP, average citations per publication.

3.4 High-impact authors collaboration analysis

Of the 3,444 authors included in the graphic map, 91 had ≥5 publications. Table 3 displays the information of the top ten academics in regards to quantity of publications and citations. Three of the most prominent researchers of the CIMT in the field of rehabilitation, i.e., Taub E, Lin K, and Uswatte G, with 64 (6.60%), 43 (4.43%) and 40 (4.12%) publications, respectively, are very active and influential authors. TC, ACPP, H-index, and TLS of Taub E, University of Alabama, United States were ranked top. The top three authors of CIMT with regard to of co-citation frequency in the field of rehabilitation were Taub E. (1806), Wolf SL. (976), and Page S. J. (818), according to the author co-citation study carried out by VOSviewer. The network of co-cited author relationships is depicted in Figure 5, with each node's size according to how frequently it has been mentioned. Various colors show various clusters, which comprise 196 authors with a citation frequency of 30 or more. The connection and thickness between the nodes, respectively, reflect the co-citation relationship and its strength.

3.5 High-impact journals collaboration analysis

The 261 journals that contained the 970 documents that were retrieved had the highest number of publications across the top three journals: Archives of Physical Medicine and Rehabilitation (63 articles with 1,275 total citations and 20.24 average citations), Neurorehabilitation and Neural Repair (78 articles with 1,392 total citations and an average of 17.85 citations), and Physical Therapy (33 articles with 411 total citations and 12.45 average citations). The top three journals in this field of research with high H-index and top three H-index are Archives of Physical Medicine and Rehabilitation (40), Neurorehabilitation and Neural Repair (37), and Stroke (25). There is a good amount of research in the relevant domains, as indicated by the Q1 and Q2 classifications assigned to all 10 journals. The fact that these 10 journals originated from Europe and the United States suggests that they have played a crucial role in advancing scholarship in the field, and according to the VOSviewer-generated journal co-citation analysis, the top three co-cited journals were Stroke (3,871 times), Archives of Physical Medicine and Rehabilitation (3,511 times), and Neurorehabilitation and Neural Repair (2,654 times). Table 4 and Figure 6A show the network of co-cited journal relationships, which includes 75 journals with a citation frequency of

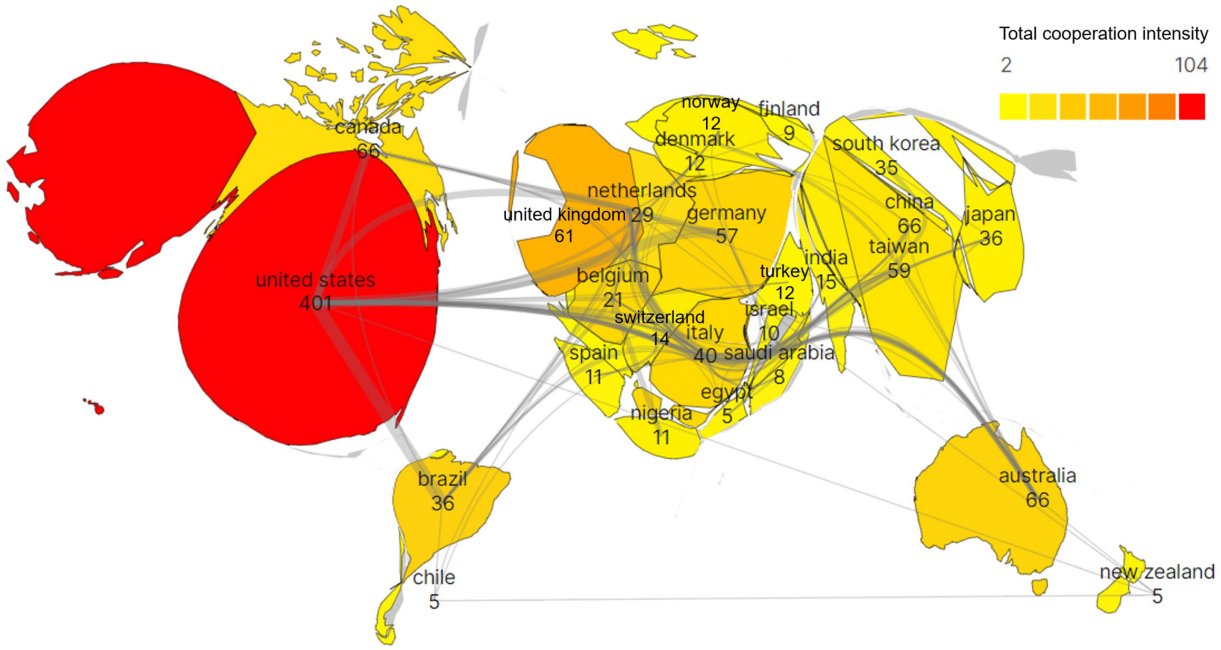


FIGURE 3
Populated chart of CIMT's bibliometric analysis of country collaborations in the field of rehabilitation.

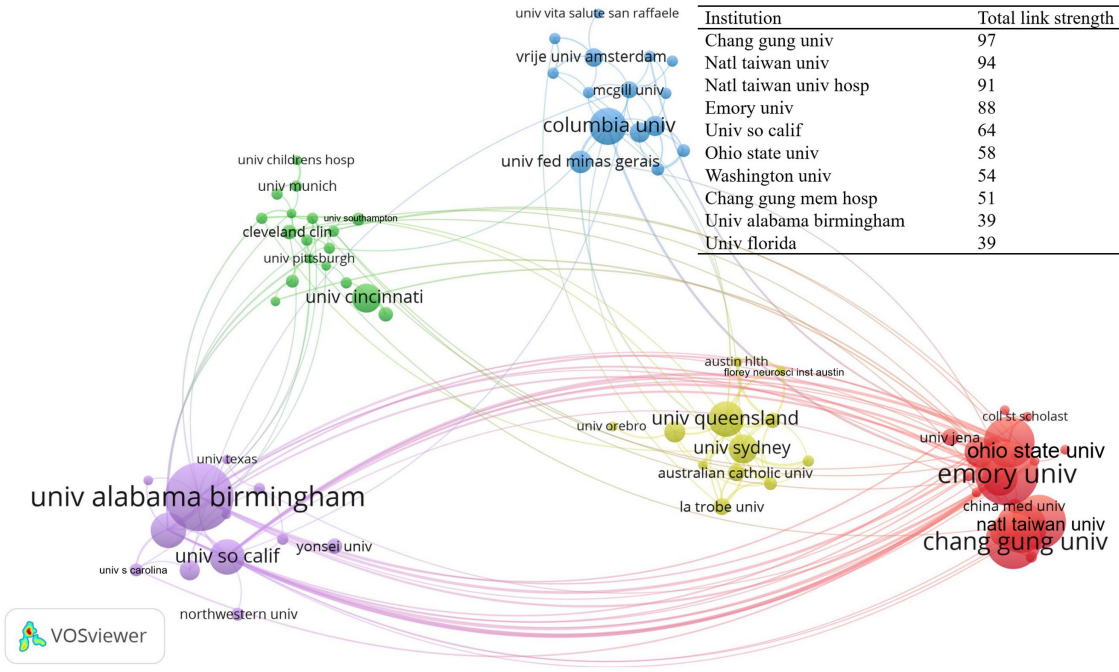
TABLE 2 CIMT top 10 high impact institutions in the field of rehabilitation.

Institution	NP	TC	ACPP	TLS	H-index	Location
Alabama Univ	53 (5.46%)	4,537	85.60	2,161	39	United States
Emory Univ	49 (5.05%)	5,438	110.98	2,576	29	United States
Natl Taiwan Univ	40 (4.12%)	1,335	33.38	1,603	22	China (Taiwan)
Chang Gung Univ	40 (4.12%)	1,468	36.70	1,625	23	China (Taiwan)
Natl Taiwan Univ Hosp	37 (3.81%)	1,305	35.27	1,485	20	China (Taiwan)
Ohio State Univ	37 (3.81%)	3,226	87.19	1736	30	United States
Columbia Univ	25 (2.58%)	1988	79.52	938	11	United States
Univ Florida	24 (2.47%)	3,306	137.75	990	16	United States
Univ Queensland	24 (2.47%)	1,387	57.79	873	15	Australia
Univ So Calif	24 (2.47%)	3,236	134.83	1,517	22	United States

100 or more times. Presently, journals publishing publications in this field of study have a significant impact. The double graph overlay's colored pathways connecting journal clusters show the citation linkages between the citing and cited journals. The colored paths indicate that studies published in NEUROLOGY, SPORTS, OPHTHALMOLOGY journals usually cite studies published in SPORTS, REHABILITATION, SPORT and PSYCHOLOGY, EDUCATION, SOCIAL. Figure 6B provides further details regarding the typical citing and referenced journals in each cluster. For example, the most representative journals in the Physical Education/Rehabilitation/Sports cluster are Archives of Physical Medicine and Rehabilitation, Neurorehabilitation and Neural Repair, Clinical Rehabilitation, and Physical Therapy. The journals most represented in the Psychology/Education/Sociology group are Stroke, Developmental Medicine and Child Neurology, and Neurology.

4 Keyword visualization and analysis

When it comes to examining research trends and summarizing research hotspots, keyword analysis is crucial. Using the keyword time view produced by VOSviewer, each vertical bar in Figure 7A represents a cluster, and the circle represents the keyword, with a larger circle indicating a higher frequency of occurrence of the term. The connecting lines show the connections between terms, and the skewed yellow node color represents the years from far to near. The keywords with high centrality and frequency in Table 5 represent the research hotspots in that period of time. The keyword co-occurrence clustering map in this field is shown in Figure 7B. Thirteen clusters in all were created using the conventional log-likelihood rate (LLR) technique, and via analysis of the keyword clusters, it was shown that the homogeneity of the study improved with increasing degree of



Institution	Total link strength	Citations
Chang gung univ	97	1468
Natl taiwan univ	94	1335
Natl taiwan univ hosp	91	1305
Emory univ	88	5438
Univ so calif	64	3236
Ohio state univ	58	3226
Washington univ	54	4249
Chang gung mem hosp	51	551
Univ alabama birmingham	39	4357
Univ florida	39	3306

FIGURE 4
CIMT's intensity of collaboration across agencies in the rehabilitation field, http://tinyurl.com/ynp5b7fb.

TABLE 3 CIMT's top 10 high impact authors in the field of rehabilitation.

Author	NP	TC	ACPP	TLS	H-index	Institution
Taub E	64 (6.60%)	2,629	41.08	132	39	University of Alabama
Uswatte G	43 (4.43%)	1,512	35.16	121	29	University of Alabama
Wolf SL	40 (4.12%)	1,233	30.83	69	28	Emory University
Lin KC	31 (3.20%)	582	18.77	73	22	Natl Taiwan Univ
Wu CY	29 (2.99%)	592	20.41	75	22	Chang Gung Univ
Page SJ	29 (2.99%)	656	22.62	16	19	University of Cincinnati
Morris DM	26 (2.68%)	195	7.50	45	10	University of Alabama
Mark VW	22 (2.27%)	363	16.50	61	16	University of Alabama
Blanton S	20 (2.06%)	438	21.90	54	14	Emory University
Levine P	19 (1.96%)	612	32.21	24	17	University of Cincinnati

aggregation (23). The biggest cluster is denoted by #0, and so on. The cluster number is inversely proportionate to the cluster size. Keyword co-occurrence and cluster analysis yielded activities of daily living, physical therapy techniques, hand function, motor therapy, primary motor cortex, gait, disability, functional recovery, occupational therapy, stroke rehabilitation, upper extremity, motor cortex plasticity, and lateral dominance as the current research hotspots. Figure 7C Timeline view of CIMT's keywords in the field of rehabilitation, it can be concluded that research hotspots such as #0 activities of daily living, #2 hand function, #5 gait, and #6 disability have been continuing to this day and will remain so. Furthermore, as Figure 7D illustrates, the top 20 terms with the strongest burst were chosen by extending the burst period to 2 years. The symbol "Strength" in the graphic denotes the burst's size, while "Begin" and "End" signify its start and end times, respectively. The time interval is represented by the blue line, while the burst's length is shown by the red line. By analyzing the burst words, we may investigate this field's projected development tendencies and hotspots for study, especially when analyzing the keywords with the duration of the burst time up to now, which is of important reference value and guidance significance. The most frequent mutation intensity is "forced use" (15.84), followed by "physical rehabilitation" (11.09), and the third one is "learned nonuse" (10.09). learned nonuse" (10.47). The most frequent words were "motor function," "people," "transcranial direct current stimulation," "transcranial current stimulation," "physical rehabilitation," and "learned nonuse" (10.47). "motor function," "people," "transcranial direct current stimulation," "systematic review," and "individual" have all persisted so far, and are probably going to stay hot.

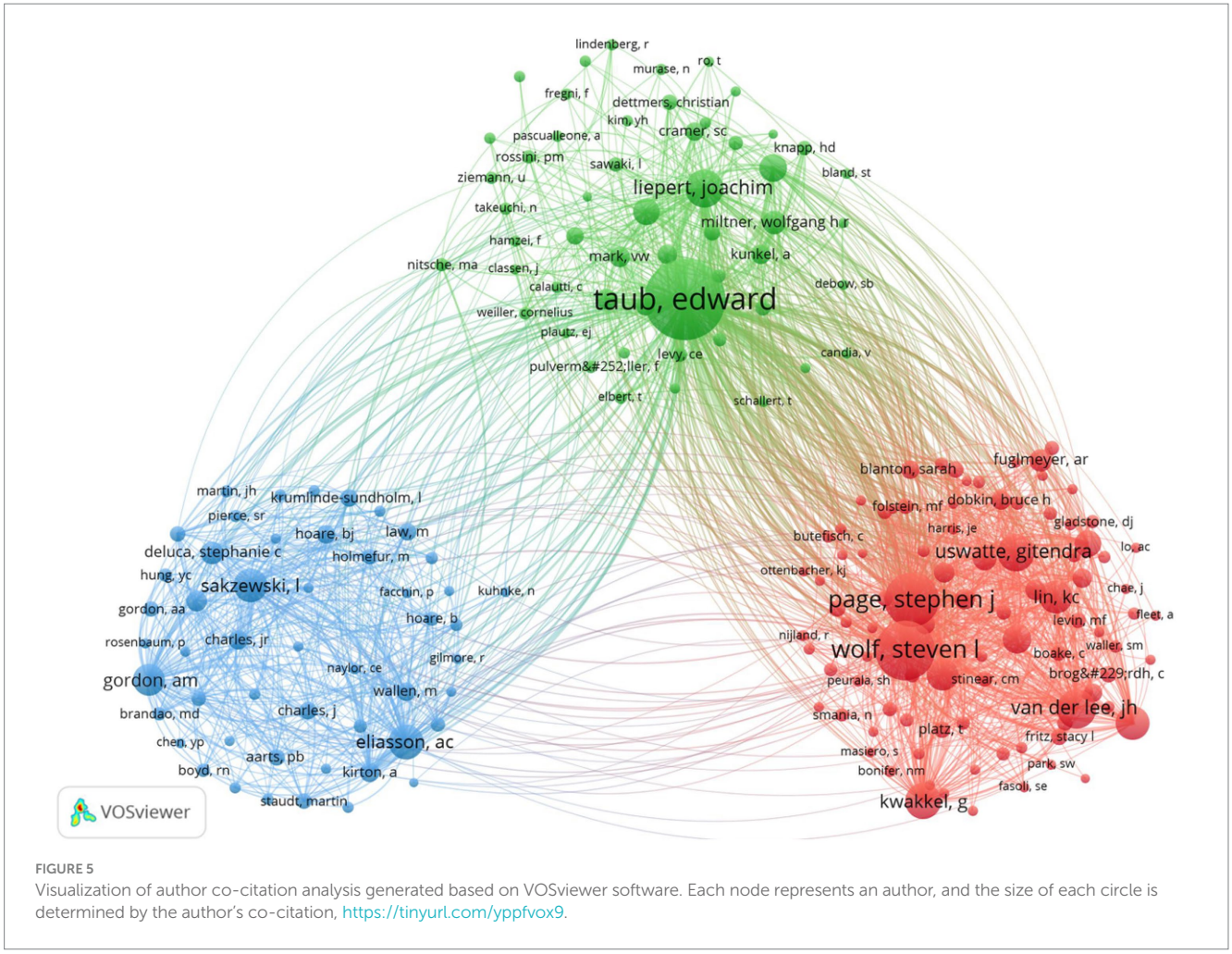


FIGURE 5
Visualization of author co-citation analysis generated based on VOSviewer software. Each node represents an author, and the size of each circle is determined by the author's co-citation, https://tinyurl.com/yppfvox9.

TABLE 4 Status of CIMT high volume journals in the field of rehabilitation.

Journal	NP	TC	ACPP	TLS	H-index	IF (2023)	JCR (2023)
Neurorehabilitation and Neural Repair	78	1,392	17.85	1,309	37	4.1	Q1
Archives of Physical Medicine and Rehabilitation	63	1,275	20.24	1,228	40	4.3	Q1
Physical Therapy	33	411	12.45	563	21	3.8	Q1
Neurorehabilitation	33	244	7.39	486	14	2	Q2
Clinical Rehabilitation	33	481	14.58	687	18	3	Q1
Stroke	31	1,332	42.97	1,001	25	8.4	Q1
Topics in Stroke Rehabilitation	27	184	6.81	359	16	2.2	Q2
American Journal of Occupational Therapy	27	166	6.15	366	13	2.9	Q1
Disability and Rehabilitation	21	111	5.29	255	13	2.2	Q2
Frontiers in Neurology	20	31	1.55	251	8	3.4	Q2

5 Visual analysis of key literature

Top 10 most cited literatures are displayed in Table 6. Through examining and evaluating highly cited publications, the areas of interest in research can be revealed. Concurrently, it is possible to identify the areas of research concentration and the development path of CIMT in the field of rehabilitation. The top 10 cited frequency-ranked literature in this field all study stroke, which makes it clear that CIMT for stroke is an enduring research hotspot in this field. In light of the categorization of research methods, they fall into two categories: clinical trials and Meta-analysis. The 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, and 10th cited frequency items are clinical studies, and the 9th cited frequency item is Meta-analysis. Among them, the cited frequency items 1, 2, 4, 6, 7, 8, and 10 studies used randomized

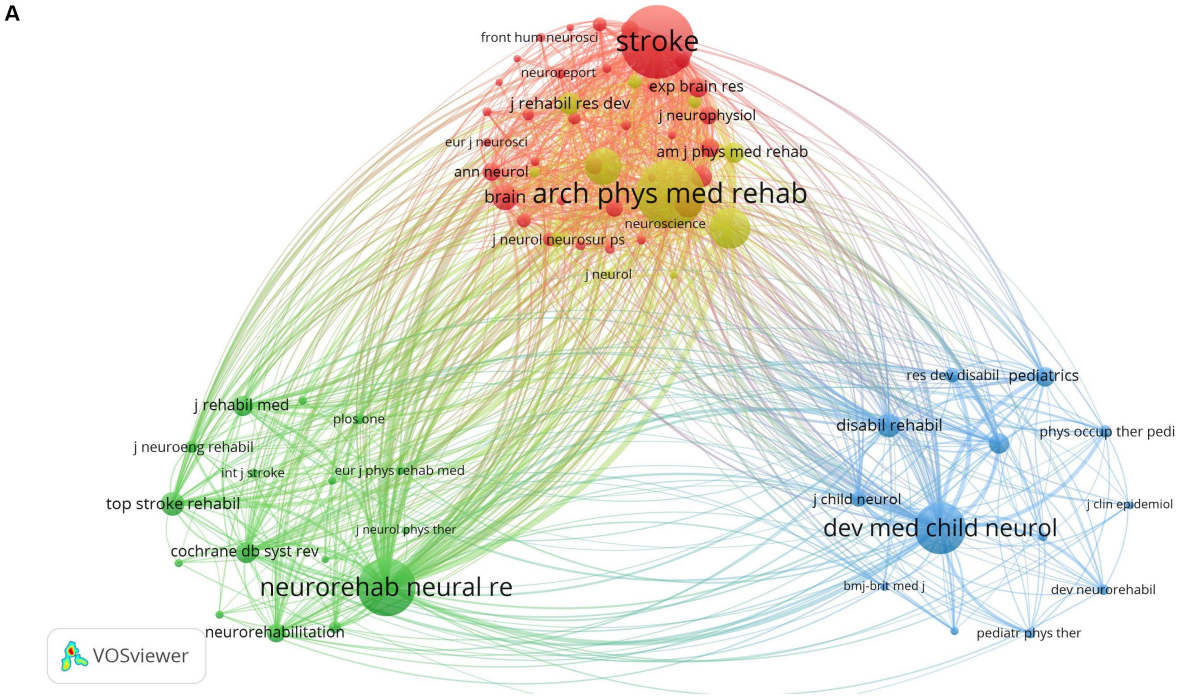


FIGURE 6
(A) Visualization of journal co-citation analysis generated based on VOSviewer software, https://tinyurl.com/yord8ryt. **(B)** CIMT double plot overlay of citing and cited journals in the field of rehabilitation. Cited journals are on the left, cited journals are on the right, and the connecting lines represent citations.

controlled study methods, and the cited frequency items 3 and 5 used non-randomized controlled study methods. The Fugl-Meyer Assessment of Motor Recovery (FMA), the Stroke Impact Scale (SIS), the Wolf Motor Function Test (WMFT), the Motor Activity Log (MAL), the Action Research Arm Test (ARAT), and the Upper Extremity Function Rating Scale were used as testing indexes in the majority of the studies to evaluate the efficacy of the therapy. This was done by comparing changes in the ratings of the visual analogical rating scales over a predetermined period of time. Every clinical study's findings demonstrated that 2-week CIMT/mCIMT had a better effect on the prognosis of stroke, and the visual analogical rating scale values were significantly different before and after treatment.

Subfields that reflect important research hotspots can be shown using cluster analysis based on co-cited literature (24). Twenty clusters in all were created with the traditional LLR technique. Literature clustering can identify the sub-topic directions of the hot research in the field, with the biggest cluster denoted by #0 and the rest by analogy, with the cluster number being inversely proportionate to the cluster size, as shown in Figure 8A. The hot areas of research are stroke, cerebral palsy, lower limb balance, bimanual training, multiple sclerosis, aphasia, physical therapy (transcranial magnetic stimulation), plasticity, sensory amplitude electrical stimulation, learned non-use, motor reinforcement, spatial behavior, botulinum toxin type A, upper limb function (machine learning), joystick ride-on toys (new

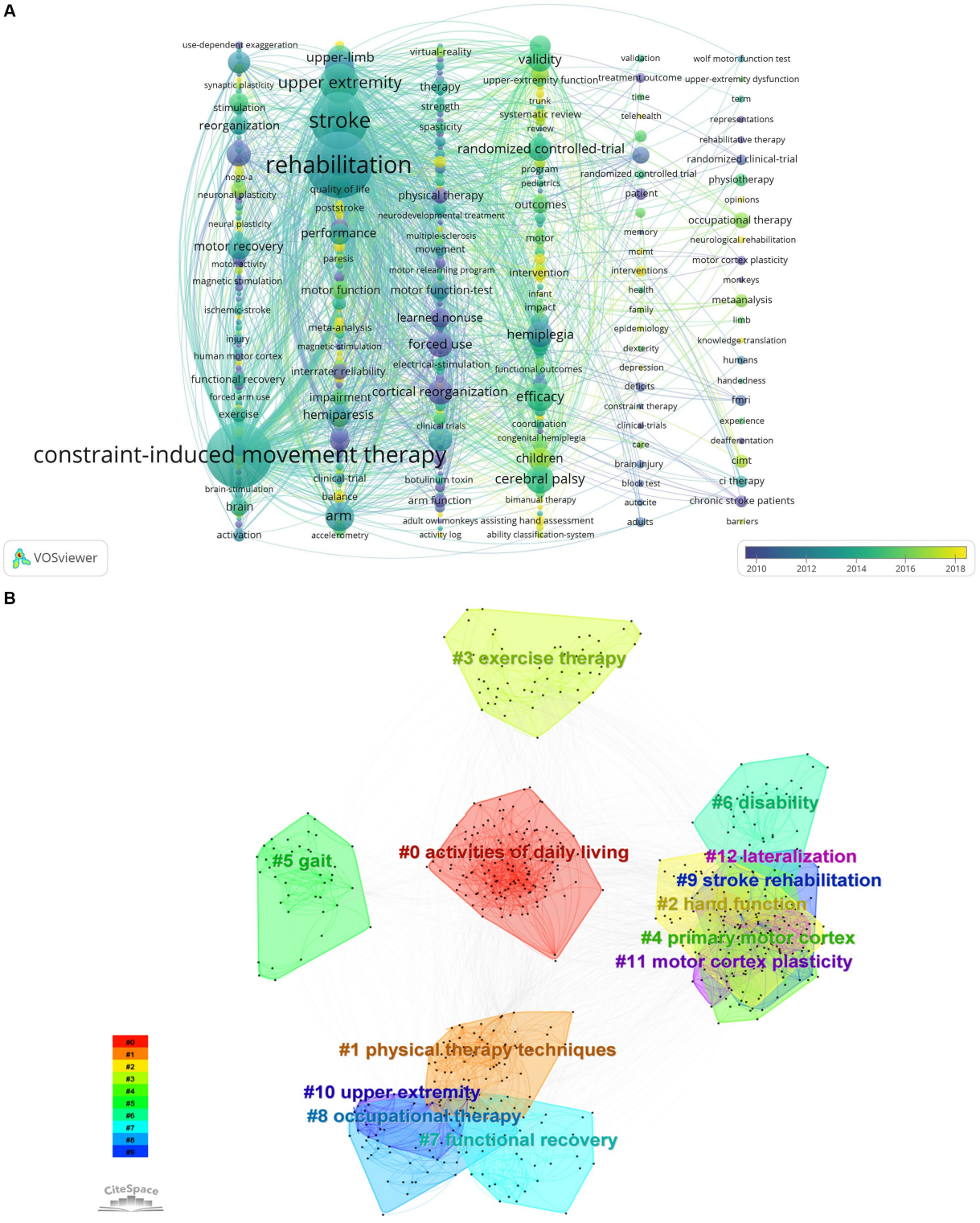


FIGURE 7 (Continued)

technology in rehabilitation), CIMT, disability, monitoring, positron emission tomography, exercise rehabilitation. Figure 8B Timeline view of key CIMT literature in Rehabilitation shows that the research trends in this area are lower extremity balance, upper extremity function (machine learning), and joystick riding toys (new technologies in rehabilitation), judging from the brighter color of the clusters. Furthermore, as Figure 8C illustrates, the emerging citations highlight important works that are often cited throughout time, highlighting hotspots and patterns. Out of the 25 emerging citations that the Web of Science database reviewed and found to have the greatest frequency of co-cited literature, the one with the highest mutation intensity was the EXCITE randomized clinical trial using

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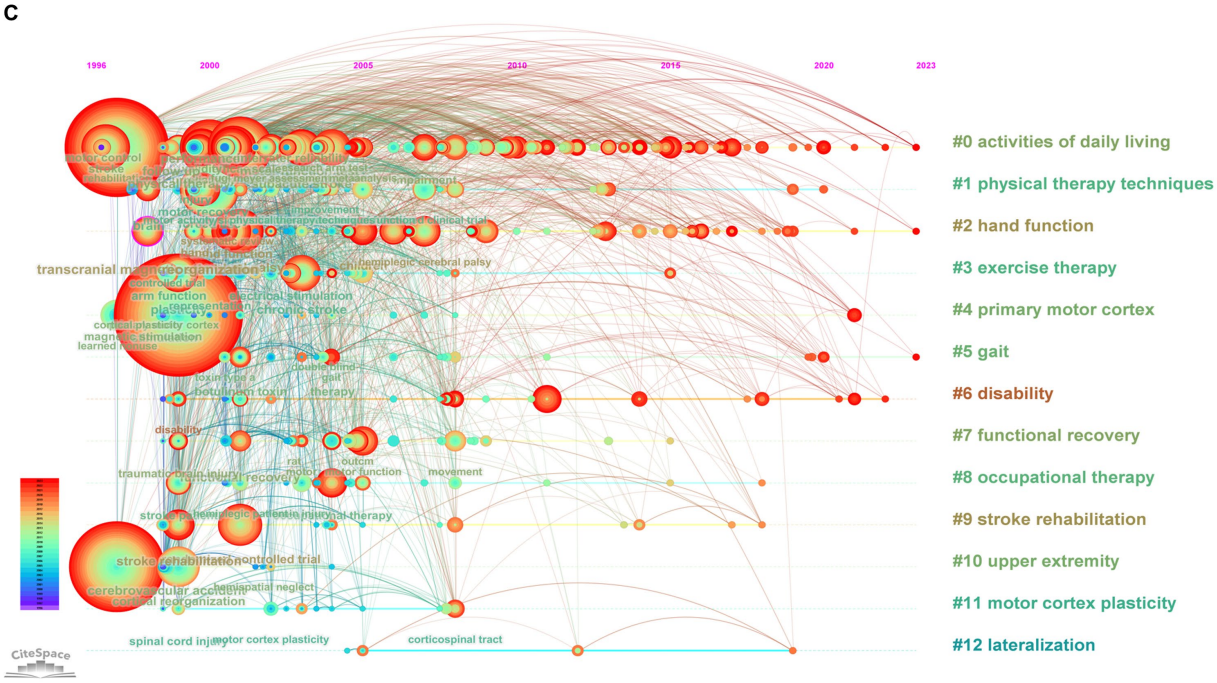

D

Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1996 - 2023
learned nonuse	1997	10.47	**1997**	2006	
cerebrovascular accident	1999	7.23	**1999**	2006	
physical therapy	1999	5.24	**1999**	2006	
arm function	1999	4.7	**1999**	2009	
motor activity	1999	3.66	**1999**	2005	
treatment outcome	2000	4.7	**2000**	2006	
representation	2000	3.78	**2000**	2008	
forced use	2000	15.84	**2001**	2007	
physical rehabilitation	2001	11.09	**2001**	2007	
patient	2001	4.25	**2001**	2008	
cortical reorganization	1999	5.85	**2003**	2012	
randomized trial	2009	4.51	**2009**	2014	
motor control	1997	4.52	**2012**	2017	
motor function	2005	4.21	**2012**	2023	
congenital hemiparesis	2009	5.66	**2013**	2021	
metaanalysis	2005	4.43	**2014**	2020	
people	2016	3.94	**2016**	2023	
transcranial direct current stimulation	2016	3.83	**2016**	2023	
systematic review	2001	5.5	**2017**	2023	
individual	2017	5.01	**2017**	2023	

FIGURE 7
(A) Keyword time view of CIMT in rehabilitation based on VOSviewer, http://tinyurl.com/ysc66zbg. **(B)** Citespce-based keyword co-occurrence clustering of CIMT in the field of rehabilitation. **(C)** Timeline view of CIMT keywords in the field of rehabilitation. **(D)** Keyword bursting map for CIMT in the field of rehabilitation.

CIMT to treat 222 patients 3–9 months after ischemic stroke, published by Wolf SL in 2006, which resulted in a significant improvement in hand-arm motor function (WMFT, MAL) that lasted for at least 1 year (50.66) (8); followed by the first demonstration by Liepert in 2000 that long-term changes in brain function correlate with treatment-induced improvements in motor rehabilitation after neurological injury. Following chronic phase stroke patients' CIMT therapy, the afflicted hemisphere's muscle output area significantly expanded, and recruitment from nearby brain areas was improved. It even lasted until 6 months when the size of motor cortical areas in both hemispheres was almost the same (23.98) (25); in third place, Miltner WHR's 1999 publication replicating in Germany the results of the US laboratory CIMT to improve WMFT and MAL in chronic stroke patients, demonstrating the general applicability of the intervention (22.96) (26).

TABLE 5 CIMT's high-frequency keywords and centrality in the field of rehabilitation top 10.

Keyword	Frequency	Keyword	Centrality
Constraint-induced movement therapy	618	Transcranial magnetic stimulation	0.11
Rehabilitation	438	Functional recovery	0.1
Upper extremity	372	Cerebral palsy	0.09
Upper extremity function	195	Cerebrovascular accident	0.09
Reliability	170	Chronic stroke	0.08
Cerebral palsy	145	Reorganization	0.08
Forced use	144	Asymmetry	0.08
Stroke	120	Motor function test	0.07
Efficacy	116	Stroke rehabilitation	0.07
Randomized controlled trial	109	Brain	0.07

6 Discussion

To comprehensively review the literature on constraint-induced movement therapy (CIMT) in the realm of rehabilitation research over the past three decades, this study employs a bibliometric approach. Through visual knowledge mapping, the study delineates the field's knowledge structure and growth trajectory from various perspectives. The results of the study reveal a significant level of interest among rehabilitation researchers in CIMT. When categorized by research topics, the most prominent area of research is the utilization of CIMT in stroke patients, which constitutes 80.2% of the literature analyzed. Additionally, CIMT applications in cerebral palsy and Parkinson's disease account for 19.28 and 0.52% of the literature, respectively, while no studies on CIMT application in peripheral neurological disorders were found.

The average year of publishing for academic articles is particularly early in the United States, Germany, the United Kingdom, and Canada, as they are leading research nations. These countries have significantly contributed to the early study of this field, establishing a solid knowledge base for further research. In contrast, China, the second largest producer of research articles, only began to make relevant contributions in 2006. However, China has recently accelerated its development in this field, showing a consistent increase in publications. It is important to note that research trends vary across regions due to different national policies. Taiwan, China has been an

TABLE 6 CIMT's top 10 cited literature frequency rankings in the field of rehabilitation.

Author, Year	Frequency	Title	Journal (IF)	H-index	JCR
Wolf SL, 2006	114	Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial	Journal of the American Medical Association (120.7)	622	Q1
Page SJ, 2004	49	Efficacy of modified constraint-induced movement therapy in chronic stroke: a single-blinded randomized controlled trial	Archives of physical medicine and rehabilitation (4.3)	169	Q1
Liepert J, 2000	49	Treatment-induced cortical reorganization after stroke in humans	Stroke (6.157)	292	Q1
Taub E, 2006	47	A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke	Stroke (6.157)	292	Q1
Miltner WHR, 1999	45	Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication	Stroke (6.157)	292	Q1
Wittenberg GF, 2003	42	Constraint-induced therapy in stroke: magnetic-stimulation motor maps and cerebral activation	Neurorehabilitation and neural repair (4.2)	92	Q2
van der Lee JH, 2004	41	Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients	Stroke (6.157)	292	Q1
Page SJ, 2005	41	Modified constraint-induced therapy in acute stroke: a randomized controlled pilot study	Neurorehabilitation and neural repair (4.2)	92	Q2
Kwakkel G, 2015	40	Constraint-induced movement therapy after stroke	Lancet Neurology (48)	259	Q1
Sterr A, 2002	40	Longer versus shorter daily constraint-induced movement therapy of chronic hemiparesis: an exploratory study	Archives of physical medicine and rehabilitation (4.3)	169	Q1

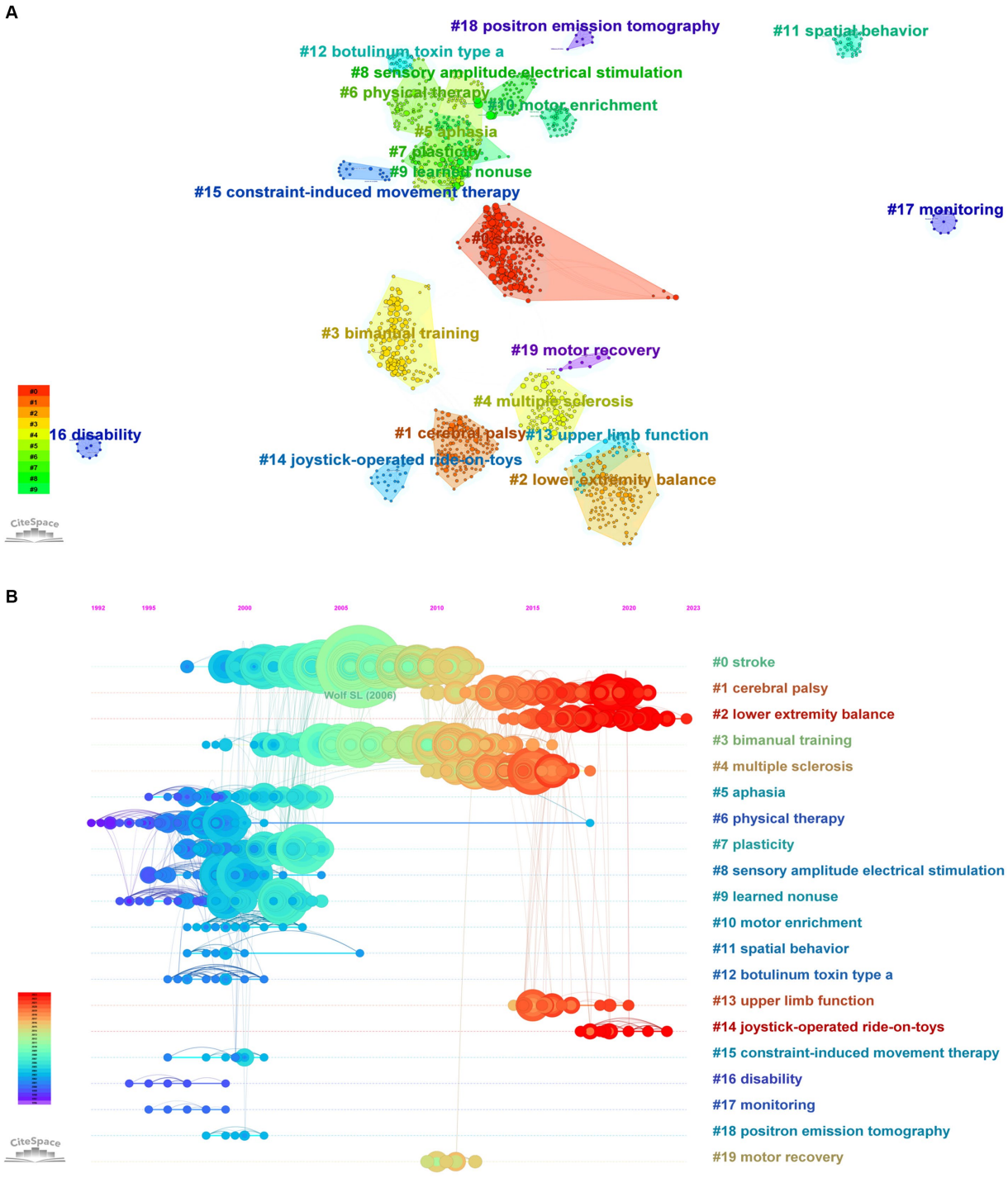

FIGURE 8 (Continued)

early research region in this field, with an annual publication volume of around 3 articles. Mainland China started later but has shown a faster growth rate. In 2023, its growth rate reached 58%, surpassing the US in terms of publication numbers for the first time. However, mainland China's research output ranks in the bottom 1 of the top 10 countries/regions, indicating that the overall research quality of China's publications is low and fails to achieve wide dissemination in the field. This highlights the importance of focusing not only on the quantity but also on the quality of research output when aiming for academic prestige and influence in a specific research area. The United States exhibits the highest TLS, demonstrated by its strong research collaborations with Australia and the United Kingdom. The partnership between North America and Europe is notably stronger than its relationships with Asia and Africa. Despite ranking fifth in publishing volume, the United Kingdom boasts the highest ACPP, signifying widespread recognition and citation of its academic research. Notably, North America and Europe collectively represent 50% of the top 10 countries/regions with the highest publication

C

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1996 - 2023
Miltner WHR, 1999, STROKE, V30, P586, DOI 10.1161/01.STR.30.3.586, DOI	1999	22.96	1999	2004	
Kunkel A, 1999, ARCH PHYS MED REHAB, V80, P624, DOI 10.1016/S0003-9993(99)90163-6, DOI	1999	16.79	1999	2004	
Liepert J, 2000, STROKE, V31, P1210, DOI 10.1161/01.STR.31.6.1210, DOI	2000	23.98	2000	2005	
Taub E, 1999, J REHABIL RES DEV, V36, P237	1999	17.9	2000	2004	
van der Lee JH, 1999, STROKE, V30, P2369, DOI 10.1161/01.STR.30.11.2369, DOI	1999	16.31	2000	2004	
Morris DM, 2001, ARCH PHYS MED REHAB, V82, P750, DOI 10.1053/apmr.2001.23183, DOI	2001	16.7	2003	2006	
Wolf SL, 2001, STROKE, V32, P1635, DOI 10.1161/01.STR.32.7.1635, DOI	2001	14.31	2003	2006	
Wittenberg GF, 2003, NEUROREHAB NEURAL RE, V17, P48, DOI 10.1177/0888439002250456, DOI	2003	20.04	2004	2008	
Sterr A, 2002, ARCH PHYS MED REHAB, V83, P1374, DOI 10.1053/apmr.2002.35108, DOI	2002	19.24	2004	2007	
Winstein CJ, 2003, NEUROREHAB NEURAL RE, V17, P137, DOI 10.1177/0888439003255511, DOI	2003	18.11	2004	2008	
Page SJ, 2004, ARCH PHYS MED REHAB, V85, P14, DOI 10.1016/S0003-9993(03)00481-7, DOI	2004	21.57	2005	2009	
van der Lee JH, 2004, STROKE, V35, P1410, DOI 10.1161/01.STR.0000126900.24964.7e, DOI	2004	18.02	2005	2009	
Taub E, 2006, STROKE, V37, P1045, DOI 10.1161/01.STR.0000206463.66461.97, DOI	2006	17.85	2006	2011	
Page SJ, 2005, NEUROREHAB NEURAL RE, V19, P27, DOI 10.1177/1545968304272701, DOI	2005	17.44	2006	2010	
Uswatte G, 2005, STROKE, V36, P2493, DOI 10.1161/01.STR.0000185928.90848.2e, DOI	2005	16.15	2006	2010	
Dettmers C, 2005, ARCH PHYS MED REHAB, V86, P204, DOI 10.1016/j.apmr.2004.05.007, DOI	2005	14.44	2006	2010	
Wolf SL, 2006, JAMA-J AM MED ASSOC, V296, P2095, DOI 10.1001/jama.296.17.2095, DOI	2006	50.66	2007	2011	
Charles JR, 2006, DEV MED CHILD NEUROL, V48, P635, DOI 10.1017/S0012162206001356, DOI	2006	15.73	2007	2011	
Uswatte G, 2006, NEUROLOGY, V67, P1189, DOI 10.1212/01.wnl.0000238164.90657.c2, DOI	2006	15.29	2007	2011	
Boake C, 2007, NEUROREHAB NEURAL RE, V21, P14, DOI 10.1177/1545968306291858, DOI	2007	14.86	2008	2012	
Dromerick AW, 2009, NEUROLOGY, V73, P195, DOI 10.1212/WNL.0b013e3181ab2b27, DOI	2009	15.09	2010	2014	
Aarts PB, 2010, NEUROREHAB NEURAL RE, V24, P509, DOI 10.1177/1545968309359767, DOI	2010	16.09	2011	2015	
Sakzewski L, 2011, DEV MED CHILD NEUROL, V53, P313, DOI 10.1111/j.1469-8749.2010.03859.x, DOI	2011	15.31	2012	2016	
Gordon AM, 2011, NEUROREHAB NEURAL RE, V25, P692, DOI 10.1177/1545968311402508, DOI	2011	14.17	2013	2016	
Kwakkel G, 2015, LANCET NEUROL, V14, P224, DOI 10.1016/S1474-4422(14)70160-7, DOI	2015	21.55	2016	2020	

FIGURE 8
(A) Clustering of CIMT co-cited literature in the field of rehabilitation. **(B)** Timeline View of CIMT's Key Literature in Rehabilitation. **(C)** CIMT in Rehabilitation Key Literature Breakout Chart.

numbers, while 30% are located in East Asia, highlighting these regions as key centers of study in this field.

University of Alabama Birmingham has solidified its position as a leading institution in the field, with notable publications. One such study conducted in Germany replicated a US laboratory experiment using CIMT to enhance upper limb function (WMFT, MAL) in chronic stroke patients, showing lasting improvements up to a 6-month follow-up (26). Emory University stands out for its high TLS and strong collaboration with other institutions. A significant study involving 222 patients 3–9 months post-ischemic stroke demonstrated long-term improvements in arm motor function (WMFT, MAL) through CIMT treatment, which was the first application of a prospective multicenter (EXCITE) randomized controlled clinical trial to confirm the Positive efficacy of CIMT in the treatment of subacute stroke (8). Despite fewer publications, University of Florida ranks highly in academic impact, as evidenced by a study involving 127 patients with upper extremity injuries post-stroke. The study compared CIMT, robotic-assisted treatment, and usual care, showing that robotic-assisted treatment did not significantly improve motor function (FMA, WMFT) after 12 weeks, but did show better results compared to standard care after 36 weeks, highlighting the effectiveness of CIMT in chronic stroke treatment (27). Although China National Taiwan University ranked third in research paper production, but its Average Citation Per Paper (ACPP) was relatively low, suggesting a need for further improvement in research quality. Enhancing collaboration and communication with other leading research groups is crucial. Additionally, it is noteworthy that the average publication year of National Taiwan University's papers is relatively recent, with a primary focus on comparative clinical efficacy studies of mCIMT.

In the realm of academic publications, among the top 10 writers, respectively, among which Taub E from Alabama Univ, United States, holds the top spot in TC, ACPP, H-index, and TLS in addition to being the most prolific author in the area, His highly cited articles provide evidence that CIMT is effective in improving chronic (>1 year) (26) or subacute (3–9 months) (8) upper extremity function in stroke patients, with long-term benefits. Furthermore, CIMT has been shown to enhance muscle output in the affected hemisphere of chronic stroke patients, leading to increased muscle output and recruitment in adjacent brain regions (28). Even when sustained for up to 6 months, motor cortical areas in both hemispheres can be nearly identical in size (25). This was the first time that CIMT was proposed and demonstrated. This is the first suggestion and illustration that CIMT can enhance the brain's motor cortex's plasticity in individuals with chronic stroke. Recent research has explored the efficacy of CIMT in improving motor function in paralyzed lower limbs post-stroke (29, 30), as well as its potential applications in other neurological conditions such as multiple sclerosis (31, 32) and cerebral palsy (33). Taub E's top ranking in TLS reflects his collaborative efforts with scholars like Uswatte G, Morris DM, Wolf SL, Mark VW, and Miltner WHR from the University of Alabama. In addition, Uswatte G from Alabama University, United States, who ranked second in terms of number of publications, TC, ACPP, H-index, and TLS, is the top-ranked researcher in total link strength. Uswatte G's research focused on evaluating the accuracy of accelerometry based on CIMT

in tracking actual arm movement in subacute stroke patients (34, 35). Notably, Bai YL from Fudan University, representing mainland China, has conducted research on the molecular mechanisms of CIMT to enhance neurological and motor functions in stroke patients. He communicated closely with Ce L and Hu J. This research has focused on areas such as ipsilateral corticospinal tracts (36), sensory-motor cortex and hippocampal synapses (37), phosphorylated extracellularly regulated protein kinase (38), AMPA receptor-dependent synapses in the ipsilateral hemisphere (39), and inhibition of extracellular traps of neutrophils in the ischemic cortex (40). In Taiwan, Lin KC from Natl Taiwan Univ, along with Wu CY and Chen CL, has concentrated on improving motor performance, daily functioning, and quality of life in chronic stroke patients through mCIMT, dCIMT, and constraint-induced therapy with trunk restraints (CIT-TR) in clinical randomized controlled studies (41–43).

Neurorehabilitation and Neural Repair is the most influential journal in the field. Among the most frequently cited papers on a clinical trial of CIMT in chronic stroke patients with aphasia, which showed that CIMT improved several standardized clinical tests, self-ratings, and the effectiveness of communication in patients' daily lives (44). Stroke is a top-ranked ACPP journal and a Q1 journal with the highest IF. One of its high-profile papers was the first to demonstrate that long-term changes in brain function are associated with improved motor rehabilitation after treatment-induced neurological injury (25). The Q1 journals with the highest IF and H indices are Stroke and Archives of Physical Medicine and Rehabilitation, respectively. This suggests that the articles that have appeared in these two reputable journals have a high academic reference value. You may give these incredibly productive journals priority when submitting research to get published in this subject, and when searching for related literature, you can prefer the proceedings of these highly cited journals.

Highly cited literature often signifies impactful research, with a substantial academic influence, providing insights into key areas of focus within a particular field (45). Therefore, examining the most referenced literature can provide early insights into research trends and directions in the field. The top ten cited works primarily fall into two categories: comparative clinical efficacy studies of CIMT/mCIMT for enhancing upper limb function in stroke patients, and investigations into the molecular mechanisms underlying the efficacy of CIMT in improving upper limb function in stroke patients. Among the comparative clinical efficacy studies of conventional CIMT, an earlier study was that of Miltner et al. who replicated the results of US laboratory CIMT to improve WMFT and MAL in patients with chronic stroke in Germany, demonstrating the general applicability of the intervention (26). Following closely behind, Sterr et al. found that a 6-h CIMT training protocol was more effective than a 3-h protocol in improving motor function (WMFT, MAL) in chronic stroke patients (46). Taub et al. also reported that CIMT significantly improved arm motor deficits (WMFT, MAL) in patients with mild to moderate chronic stroke (47). Notably, Wolf et al. reported the first application of the prospective multicenter, large sample size (EXCITE) randomized controlled clinical trial to confirm the positive efficacy of CIMT in the treatment of subacute stroke (8). CIMT significantly improved arm motor function (WMFT, MAL) in 222 patients 3–9 months after ischemic stroke and persisted for at least 1 year (8). In addition, Peurala et al. in a meta-analysis that included 27 randomized controlled trial studies, found that 60–72 h of CIMT exercises over a two-week period produced better mobility. And only 30 h of CIMT exercises in 3 weeks showed improvement (48).

In a comparative study of the clinical efficacy of mCIMT, the most frequently cited is Page et al. conducted a mCIMT 3 times/week for 10 weeks, with the less affected arm being restricted 5 days/week for 5 h, and the findings that mCIMT improved the function of the more affected arm in chronic stroke patients and the use, further confirming that repetitive, task-specific exercises are critical for regaining function, whereas the intensity of the exercise program is less important (49). For acute stroke patients, Page et al. found that mCIMT improved the use of the affected arm, MAL, Fugl-Meyer, and ARAT, and the ability of the patient to perform valuable activities again, compared with the efficacy of conventional rehabilitation for the treatment of upper extremity hemiparesis in acute stroke patients less than 14 days post-stroke (50). In addition, a review published by Kwakkel et al. describes the current evidence regarding, original CIMT and mCIMT. The beneficial effects of the original and mCIMT types on motor function, arm-hand activity, and self-reported arm-hand function in daily life, immediately after treatment, and at long-term follow-up were summarized (51). Of note, the optimal timing, dose, and training intensity of CIMT/mCIMT interventions in acute and chronic stroke patients are not yet defined.

Among the studies on the molecular mechanisms of CIMT efficacy, Liepert J and Bauder H (2000) were the first to propose and demonstrate that CIMT improves plasticity in the motor cortex of the brain in chronic stroke patients. Their 12-day CIMT intervention with 13 chronic stroke patients compared the cortical motor output areas of the hand muscles on both sides before and after treatment to evaluate the reorganization of the motor cortex following effective rehabilitation therapy in stroke patients. The results showed a significant enlargement of the muscle output area in the affected hemisphere and increased recruitment from neighboring brain regions in chronic stroke patients. These changes were observed to persist for up to 6 months, with the size of motor cortical areas in both hemispheres becoming nearly identical (25). Additionally, Wittenberg et al. utilized transcranial magnetic stimulation to map the motor cortex and positron emission tomography to assess changes in motor task-related activation as a result of CIMT intervention. Their findings indicated that CIMT treatment led to a significant decrease in brain activation during the motor task, along with an expansion of the motor map in the affected hemisphere. This suggests an enhanced capacity of the upper motor neurons to generate movement (52). The underlying mechanisms driving both the CIMT/mCIMT are still poorly understood, but results from kinesiological studies suggest that improvements are largely based on post-stroke adaptation through learning to optimize the use of intact end-effector for some autonomous motor control of wrist and finger extensor muscles (51). These influential publications have made a substantial academic contribution and have been instrumental in pushing the field forward. Continued analysis of these publications will enhance our comprehension of the present state and future trajectory of the field, ultimately bolstering our research capabilities and the quality of our research outcomes.

In recent years, there have been several studies comparing CIMT to other therapies, for example, to proprioceptive-based training (13), compared to an unconstrained task-oriented training group (53), CIMT has been shown to improve motor function and ADLs and can be used in combination with other therapies. For example, in

combination with virtual reality training (54) and botulinum toxin A injections (55), visual biofeedback training (56), combined with mirror therapy (57), which resulted in better improvements in upper limb motor function, ADLs, grasping and pad-pinch function. It can be assumed that CIMT, in combination with other treatments, produces additional results. This suggests that we need to choose the most appropriate treatment for the patient based on their condition and needs. It is noteworthy that the use of trunk surrogate methods may hinder the upper extremity's long-term functional rehabilitation. CIMT can be augmented with trunk restraints. It has been demonstrated that in terms of upper extremity motor function, ADLs, and use of the hemiplegic upper extremity, CIMT in conjunction with trunk restraint is much better than CIMT alone (12, 58). Enhancing upper limb motor performance may also be possible by combining CIMT with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) (59–61). A major field of study is robot-based rehabilitation, which offers precision control and real-time patient monitoring to achieve effective rehabilitation. A research comparing CIMT with robot-assisted treatment shown that while both enhanced patient performance, there was no discernible change in motor function across the groups (62). Nevertheless, compared to robot-assisted therapy alone, studies that combined CI therapy with robot-assisted therapy demonstrated a decrease in compensatory trunk movements during activities and a greater improvement in motor function and ADLs (63, 64). In the aftermath of the new coronavirus era, home rehabilitation and telemedicine have become hot study issues. Studies have shown that CIMT in conjunction with telemedicine and home rehabilitation using a gaming approach can have efficacy comparable to clinic-based rehabilitation (65, 66). For stroke patients who require long-term rehabilitation, it is particularly practical and effective.

CIMT for the lower extremities in stroke patients is a modification of the original CIMT for the upper extremit (30). In lower extremity CIMT, the number of exercise tasks, rather than the duration of the exercises, might be crucial to the functional recovery process. As a result, using the mCIMT, which prioritizes repeat count over length, could be more practical (67). Numerous studies have demonstrated that CIMT considerably enhances patients' walking speed, lower limb motor function, and balance (68). In addition, treatments for aphasia should also incorporate behavioral and communicative correlates of interactions throughout therapy, as well as a thorough training program tailored to the individual's communication requirements and abilities. These principles have been adopted by new treatments (6). CIMT can be used to treat acute post-stroke aphasia (69) and to improve chronic aphasia (>1 year) (70). The benefits derived from it may persist long after treatment has ended (71). In addition, CIMT may improve depressive symptoms (72) and unilateral spatial neglect (16). Impairment of hand function is a major dysfunction in children with cerebral palsy, and children often tend to use the healthy side more in daily life, leading to "learned disuse." CIMT and mCIMT are equally useful for improving spasticity and cerebral palsy children's upper limb motor function, with benefits lasting long (14, 33, 73).

Keywords and key literature co-occurrence and clustering analyses showed that CIMT, stroke rehabilitation, upper limb function (machine learning), lower limb gait balance, randomized controlled trials, physical therapy techniques (transcranial magnetic stimulation and sensory amplitude electrical stimulation), primary motor cortex plasticity, lateral dominance (spatial behavior), cerebrovascular accidents, activities of daily living, hand function, disability, functional restoration, cerebral palsy, bilateral arm training, aphasia, learned disuse, botulinum toxin type A, and joystick riding toys (new technologies in rehabilitation) are the main research hotspot keywords in this field. The clustering timeline graphs of keywords and key literature can be observed that the clustering labels of #0 activities of daily living, #2 hand function, #5 gait, #6 disability, and #2 lower extremity balance, #13 upper extremity function, and #14 joystick riding toys, respectively, are still evolving, which to a certain extent reflects the current research hotspots. Research hotspots that have received a lot of attention over time are known as burst keywords. Keywords that have exploded in the field in recent years include motor function, human, transcranial direct current stimulation, and systematic review. These research hotspots offer insightful information for next studies in addition to reflecting present trends. Specifically the main research hotspots are the clinical efficacy of CIMT combined with other therapies (transcranial direct current stimulation, botulinum toxin type a, virtual reality, mirror therapy, and robotic assistance) to improve the function of upper extremity hemiparesis in patients with stroke, the mechanism of CIMT to improve the plasticity of the motor cortex through electrophysiological and imaging methods, and improvement of lower limb gait balance function in stroke patients and aphasia applications. In the future, we can further delve into the optimal intervention time and dosage of CIMT for different stages of stroke and the exploratory application of CIMT in new environments, such as robotic-assisted, telemedicine, and home-based rehabilitation, with the goals of enhancing the effectiveness of the rehabilitation program and offering practical assistance for the stroke rehabilitation industry.

6.1 Limitations of the study

This research may have missed excellent literature from other databases in the area or in other languages because it only included studies of literature in the English language from the WOS database's core dataset. It also has certain limitations when it comes to literature retrieval. That being said, it is crucial to stress that the WoSCC database is generally accepted as the most extensively used database for bibliometric research (74–76).

7 Conclusion

This work offers a fresh viewpoint for a rapid comprehension of CIMT in rehabilitation as it is the first bibliometric and visualisation analysis of CIMT in rehabilitation research during the previous 30 years from many angles. The current state of research suggests that CIMT in rehabilitation research still has vast potential for growth. The most influential countries, institutions, journals, and authors are the United States, Alabama Univ, Neurorehabilitation and Neural Repair, and Taub E. The research hotspot keywords are CIMT, stroke rehabilitation, upper extremity function (machine learning), lower extremity gait balance, randomized controlled trials, physical therapy techniques (transcranial magnetic stimulation and sensory amplitude electrical stimulation), primary motor cortex plasticity, lateral dominance (spatial behavior), cerebrovascular accidents, activities of daily living, hand function, disability, functional restoration, bimanual training, aphasia, learned disuse, botulinum toxin type A, and joystick ride-on toys (new rehabilitation technology). These hot keywords reflect, to some

extent, the development trend and cutting-edge research direction of the field. However, CIMT still faces many opportunities and challenges in rehabilitation research, including the clinical efficacy of CIMT combined with other therapies (botulinum toxin type A, transcranial direct current stimulation, virtual reality, mirror therapy, robotic-assisted) to enhance the functionality of upper limb hemiparesis in stroke patients, the investigation of the mechanism of CIMT to improve motor cortex plasticity through electrophysiological and imaging methods, and improvement of lower limb gait balance function in stroke patients and aphasia applications. Meanwhile, future studies should focus on an in-depth exploration of the optimal intervention time and dose of CIMT for different stages of stroke CIMT in new environments such as robot-assisted, telemedicine, and home rehabilitation. Overall, this research offers a comprehensive and well-structured overview of the extensive and intricate literature on CIMT in the field of rehabilitation. It is given in the form of a knowledge map. This facilitates the comprehension of the discipline's history and future prospects by academics, hence promoting further scholarly investigation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JX: Conceptualization, Software, Writing – original draft, Writing – review & editing. MC: Formal analysis, Writing – review & editing. XW: Investigation, Writing – review & editing. ZC: Funding acquisition, Supervision, Writing – review & editing. YW: Funding acquisition, Supervision, Writing – review & editing. XL: Funding acquisition, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1375855/full#supplementary-material

References

1. Collaborators GS. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Donkor ES. Stroke in the 21(st) century: a snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat*. (2018) 2018:3238165. doi: 10.1155/2018/3238165

3. Han P, Zhang W, Kang L, Ma Y, Fu L, Jia L, et al. Clinical evidence of exercise benefits for stroke. *Adv Exp Med Biol*. (2017) 1000:131–51. doi: 10.1007/978-981-10-4304-8_9

4. Bonifer NM, Anderson KM, Arciniegas DB. Constraint-induced movement therapy after stroke: efficacy for patients with minimal upper-extremity motor ability. *Arch Phys Med Rehabil*. (2005) 86:1867–73. doi: 10.1016/j.apmr.2005.04.002

5. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation--a clinical review. *J Rehabil Res Dev*. (1999) 36:237–51.

6. Rose ML, Nickels L, Copland D, Togher L, Godecke E, Meinzer M, et al. Results of the COMPARE trial of constraint-induced or multimodality aphasia therapy compared with usual care in chronic post-stroke aphasia. *J Neurol Neurosurg Psychiatry*. (2022) 93:573–81. doi: 10.1136/jnnp-2021-328422

7. Morris DM, Taub E, Mark VW. Constraint-induced movement therapy: characterizing the intervention protocol. *Eura Medicophys*. (2006) 42:257–68. doi: 10.2478/hacq-2013-0010

8. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke. *JAMA*. (2006) 296:2095–104. doi: 10.1001/jama.296.17.2095

9. Kunkel A, Kopp B, Müller G, Villringer K, Villringer A, Taub E, et al. Constraint-induced movement therapy for motor recovery in chronic stroke patients. *Arch Phys Med Rehabil*. (1999) 80:624–8. doi: 10.1016/S0003-9993(99)90163-6

10. Wolf SL, Thompson PA, Winstein CJ, Miller JP, Blanton SR, Nichols-Larsen DS, et al. The EXCITE stroke trial: comparing early and delayed constraint-induced movement therapy. *Stroke*. (2010) 41:2309–15. doi: 10.1161/STROKEAHA.110.588723

11. Viana R, Teasell R. Barriers to the implementation of constraint-induced movement therapy into practice. *Top Stroke Rehabil*. (2012) 19:104–14. doi: 10.1310/tsr1902-104

12. Bang DH, Shin WS, Choi HS. Effects of modified constraint-induced movement therapy with trunk restraint in early stroke patients: a single-blinded, randomized, controlled, pilot trial. *NeuroRehabilitation*. (2018) 42:29–35. doi: 10.3233/NRE-172176

13. Alaca N, Öcal NM. Proprioceptive based training or modified constraint-induced movement therapy on upper extremity motor functions in chronic stroke patients: a randomized controlled study. *NeuroRehabilitation*. (2022) 51:271–82. doi: 10.3233/NRE-220009

14. Wang TN, Liang KJ, Liu YC, Shieh JY, Chen HL. Effects of intensive versus distributed constraint-induced movement therapy for children with unilateral cerebral palsy: a quasi-randomized trial. *Neurorehabil Neural Repair*. (2023) 37:109–18. doi: 10.1177/15459683231162330

15. Wu CY, Wang TN, Chen YT, Lin KC, Chen YA, Li HT, et al. Effects of constraint-induced therapy combined with eye patching on functional outcomes and movement kinematics in poststroke neglect. *Am J Occup Ther*. (2013) 67:236–45. doi: 10.5014/ajot.2013.006486

16. Taub E, Mark VW, Uswatte G. Implications of CI therapy for visual deficit training. *Front Integr Neurosci*. (2014) 8:78. doi: 10.3389/fnint.2014.00078

17. Lee KS, Lee WH, Hwang S. Modified constraint-induced movement therapy improves fine and gross motor performance of the upper limb in Parkinson disease. *Am J Phys Med Rehabil*. (2011) 90:380–6. doi: 10.1097/PHM.0b013e31820b15cd

18. Geerdink Y, Aarts P, Geurts AC. Motor learning curve and long-term effectiveness of modified constraint-induced movement therapy in children with unilateral cerebral palsy: a randomized controlled trial. *Res Dev Disabil*. (2013) 34:923–31. doi: 10.1016/j.ridd.2012.11.011

19. Rostami HR, Khayatzadeh MM, Yarmohammadi N. Feasibility of the modified constraint-induced movement therapy in patients with median and ulnar nerve injuries: a single-subject A-B-A design. *Clin Rehabil*. (2015) 29:277–84. doi: 10.1177/0269215514542357

20. Rostami HR, Akbarfahimi M, Hassani MA, Akbarinia AR, Samani S. Occupation-based intervention versus rote exercise in modified constraint-induced movement therapy for patients with median and ulnar nerve injuries: a randomized controlled trial. *Clin Rehabil*. (2017) 31:1087–97. doi: 10.1177/0269215516672276

21. Candia V, Schäfer T, Taub E, Rau H, Altenmüller E, Rockstroh B, et al. Sensory motor retuning: a behavioral treatment for focal hand dystonia of pianists and guitarists. *Arch Phys Med Rehabil*. (2002) 83:1342–8. doi: 10.1053/apmr.2002.35094

22. Chen C, Song M. Visualizing a field of research: a methodology of systematic scientometric reviews. *PLoS One*. (2019) 14:e0223994. doi: 10.1371/journal.pone.0223994

23. Sabe M, Pillinger T, Kaiser S, Chen C, Taipale H, Tanskanen A, et al. Half a century of research on antipsychotics and schizophrenia: a scientometric study of hotspots, nodes, bursts, and trends. *Neurosci Biobehav Rev*. (2022) 136:104608. doi: 10.1016/j.neubiorev.2022.104608

24. Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. *AMIA Annu Symp Proc*. (2005) 2005:724–8.

25. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke*. (2000) 31:1210–6. doi: 10.1161/01.STR.31.6.1210

26. Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. *Stroke*. (1999) 30:586–92. doi: 10.1161/01.STR.30.3.586

27. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*. (2010) 362:1772–83. doi: 10.1056/NEJMoa0911341

28. Liepert J, Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett*. (1998) 250:5–8. doi: 10.1016/S0304-3940(98)00386-3

29. Dos AS, Morris DM, Taub E. Constraint-induced movement therapy for improving motor function of the paretic lower extremity after stroke. *Am J Phys Med Rehabil*. (2020) 99:e75–8. doi: 10.1097/PHM.0000000000001249

30. Dos AS, Morris D, Taub E. Constraint-induced movement therapy for lower extremity function: describing the LE-CIMT protocol. *Phys Ther*. (2020) 100:698–707. doi: 10.1093/ptj/pzz191

31. Barghi A, Allendorfer JB, Taub E, Womble B, Hicks JM, Uswatte G, et al. Phase II randomized controlled trial of constraint-induced movement therapy in multiple sclerosis. Part 2: effect on white matter integrity. *J. Neurol. Rehabil.* (2018) 32:233–41. doi: 10.1177/1545968317753073

32. Mark VW, Taub E, Uswatte G, Morris DM, Cutter GR, Adams TL, et al. Phase II randomized controlled trial of constraint-induced movement therapy in multiple sclerosis. Part 1: effects on real-world function. *Neurorehabil Neural Repair*. (2018) 32:223–32. doi: 10.1177/1545968318761050

33. Taub E, Ramey SL, DeLuca S, Echols K. Efficacy of constraint-induced movement therapy for children with cerebral palsy with asymmetric motor impairment. *Pediatrics*. (2004) 113:305–12. doi: 10.1542/peds.113.2.305

34. Uswatte G, Giuliani C, Winstein C, Zeringue A, Hobbs L, Wolf SL. Validity of accelerometry for monitoring real-world arm activity in patients with subacute stroke: evidence from the extremity constraint-induced therapy evaluation trial. *Arch Phys Med Rehabil*. (2006) 87:1340–5. doi: 10.1016/j.apmr.2006.06.006

35. Uswatte G, Foo WL, Olmstead H, Lopez K, Holand A, Simms LB. Ambulatory monitoring of arm movement using accelerometry: an objective measure of upper-extremity rehabilitation in persons with chronic stroke. *Arch Phys Med Rehabil*. (2005) 86:1498–501. doi: 10.1016/j.apmr.2005.01.010

36. Hu J, Li C, Hua Y, Zhang B, Gao BY, Liu PL, et al. Constrained-induced movement therapy promotes motor function recovery by enhancing the remodeling of ipsilesional corticospinal tract in rats after stroke. *Brain Res*. (2019) 1708:27–35. doi: 10.1016/j.brainres.2018.11.011

37. Hu J, Li C, Hua Y, Liu P, Gao B, Wang Y, et al. Constraint-induced movement therapy improves functional recovery after ischemic stroke and its impacts on synaptic plasticity in sensorimotor cortex and hippocampus. *Brain Res Bull*. (2020) 160:8–23. doi: 10.1016/j.brainresbull.2020.04.006

38. Zhang B, He Q, Li YY, Li C, Bai YL, Hu YS, et al. Constraint-induced movement therapy promotes motor function recovery and downregulates phosphorylated extracellular regulated protein kinase expression in ischemic brain tissue of rats. *Neural Regen Res*. (2015) 10:2004–10. doi: 10.4103/1673-5374.172319

39. Hu J, Liu PL, Hua Y, Gao BY, Wang YY, Bai YL, et al. Constraint-induced movement therapy enhances AMPA receptor-dependent synaptic plasticity in the ipsilateral hemisphere following ischemic stroke. *Neural Regen Res*. (2021) 16:319–24. doi: 10.4103/1673-5374.290900

40. Li C, Hu J, Xing Y, Han J, Zhang A, Zhang Y, et al. Constraint-induced movement therapy alleviates motor impairment by inhibiting the accumulation of neutrophil extracellular traps in ischemic cortex. *Neurobiol Dis*. (2023) 179:106064. doi: 10.1016/j.nbd.2023.106064

41. Wu CY, Chen CL, Tsai WC, Lin KC, Chou SH. A randomized controlled trial of modified constraint-induced movement therapy for elderly stroke survivors: changes in motor impairment, daily functioning, and quality of life. *Arch Phys Med Rehabil*. (2007) 88:273–8. doi: 10.1016/j.apmr.2006.11.021

42. Wu CY, Chen YA, Lin KC, Chao CP, Chen YT. Constraint-induced therapy with trunk restraint for improving functional outcomes and trunk-arm control after stroke: a randomized controlled trial. *Phys Ther*. (2012) 92:483–92. doi: 10.2522/ptj.20110213

43. Wu CY, Chuang LL, Lin KC, Chen HC, Tsay PK. Randomized trial of distributed constraint-induced therapy versus bilateral arm training for the rehabilitation of upper-limb motor control and function after stroke. *Neurorehabil Neural Repair*. (2011) 25:130–9. doi: 10.1177/1545968310380686

44. Pulvermüller F, Neininger B, Elbert T, Mohr B, Rockstroh B, Koebbel P, et al. Constraint-induced therapy of chronic aphasia after stroke. *Stroke*. (2001) 32:1621–6. doi: 10.1161/01.STR.32.7.1621

45. Li R, Wang Y, Zhao Z, Li X, Liu Z. A bibliometric analysis based on web of science from 2012 to 2021: current situation, hot spots, and global trends of medullary thyroid carcinoma. *Front Oncol*. (2023) 13:1119915. doi: 10.3389/fonc.2023.1119915

46. Sterr A, Elbert T, Berthold I, Kölbel S, Rockstroh B, Taub E. Longer versus shorter daily constraint-induced movement therapy of chronic hemiparesis: an exploratory study. *Arch Phys Med Rehabil*. (2002) 83:1374–7. doi: 10.1053/apmr.2002.35108

47. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. *Stroke*. (2006) 37:1045–9. doi: 10.1161/01.STR.0000206463.66461.97

48. Peurala SH, Kantanen MP, Sjögren T, Paltamaa J, Karhula M, Heinonen A. Effectiveness of constraint-induced movement therapy on activity and participation after stroke: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil*. (2012) 26:209–23. doi: 10.1177/0269215511420306

49. Page SJ, Sisto S, Levine P, McGrath RE. Efficacy of modified constraint-induced movement therapy in chronic stroke: a single-blinded randomized controlled trial. *Arch Phys Med Rehabil*. (2004) 85:14–8. doi: 10.1016/S0003-9993(03)00481-7

50. Page SJ, Levine P, Leonard AC. Modified constraint-induced therapy in acute stroke: a randomized controlled pilot study. *Neurorehabil Neural Repair*. (2005) 19:27–32. doi: 10.1177/1545968304272701

51. Kwakkel G, Veerbeek JM, van Wegen EEH, Wolf SL. Constraint-induced movement therapy after stroke. *Lancet Neurol*. (2015) 14:224–34. doi: 10.1016/S1474-4422(14)70160-7

52. Wittenberg GF, Chen R, Ishii K, Bushara KO, Taub E, Gerber LH, et al. Constraint-induced therapy in stroke: magnetic-stimulation motor maps and cerebral activation. *Neurorehabil Neural Repair*. (2003) 17:48–57. doi: 10.1177/0888439002250456

53. Wang D, Li L, Pan H, Huang L, Sun X, He C, et al. Comparison of the effects of constraint-induced movement therapy and unconstraint exercise on oxidative stress and limb function – a study on human patients and rats with cerebral infarction. *Brain Sci*. (2022) 13:4. doi: 10.3390/brainsci13010004

54. Ji EK, Lee SH. Effects of virtual reality training with modified constraint-induced movement therapy on upper extremity function in acute stage stroke: a preliminary study. *J Phys Ther Sci*. (2016) 28:3168–72. doi: 10.1589/jpts.28.3168

55. Nasb M, Shah S, Chen H, Youssef AS, Li Z, Dayoub L, et al. Constraint-induced movement therapy combined with botulinum toxin for post-stroke spasticity: a systematic review and Meta-analysis. *Cureus*. (2021) 13:e17645. doi: 10.7759/cureus.17645

56. Seok H, Lee SY, Kim J, Yeo J, Kang H. Can short-term constraint-induced movement therapy combined with visual biofeedback training improve hemiplegic upper limb function of subacute stroke patients? *Ann Rehabil Med*. (2016) 40:998–1009. doi: 10.5535/arm.2016.40.6.998

57. Yoon JA, Koo BI, Shin MJ, Shin YB, Ko HY, Shin YI. Effect of constraint-induced movement therapy and mirror therapy for patients with subacute stroke. *Ann Rehabil Med*. (2014) 38:458–66. doi: 10.5535/arm.2014.38.4.458

58. Bang DH. Effect of modified constraint-induced movement therapy combined with auditory feedback for trunk control on upper extremity in subacute stroke patients with moderate impairment: randomized controlled pilot trial. *J Stroke Cerebrovasc Dis*. (2016) 25:1606–12. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.030

59. Figlewski K, Blicher JU, Mortensen J, Severinsen KE, Nielsen JF, Andersen H. Transcranial direct current stimulation potentiates improvements in functional ability in patients with chronic stroke receiving constraint-induced movement therapy. *Stroke*. (2017) 48:229–32. doi: 10.1161/STROKEAHA.116.014988

60. Rocha S, Silva E, Foerster Á, Wiesiolek C, Chagas AP, Machado G, et al. The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Disabil Rehabil*. (2016) 38:653–60. doi: 10.3109/09638288.2015.1055382

61. Abo M, Kakuda W, Momosaki R, Harashima H, Kojima M, Watanabe S, et al. Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: the NEURO-VERIFY study. *Int J Stroke*. (2014) 9:607–12. doi: 10.1111/ijs.12100

62. Terranova TT, Simis M, Santos A, Alfieri FM, Imamura M, Fregni F, et al. Robot-assisted therapy and constraint-induced movement therapy for motor recovery in stroke: results from a randomized clinical trial. *Front Neurorobot*. (2021) 15:684019. doi: 10.3389/fnbot.2021.684019

63. Simis M, Thibaut A, Imamura M, Battistella LR, Fregni F. Neurophysiological biomarkers of motor improvement from constraint-induced movement therapy and robot-assisted therapy in participants with stroke. *Front Hum Neurosci*. (2023) 17:1188806. doi: 10.3389/fnhum.2023.1188806

64. Hsieh YW, Lin KC, Horng YS, Wu CY, Wu TC, Ku FL. Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: a randomized controlled trial. *J Neurol*. (2014) 261:1037–45. doi: 10.1007/s00415-014-7345-4

65. Barzel A, Ketels G, Stark A, Tetzlaff B, Daubmann A, Wegscheider K, et al. Home-based constraint-induced movement therapy for patients with upper limb dysfunction after stroke (HOMECIMT): a cluster-randomised, controlled trial. *Lancet Neurol*. (2015) 14:893–902. doi: 10.1016/S1474-4422(15)00147-7

66. Gauthier LV, Nichols-Larsen DS, Uswatte G, Strahl N, Simeo M, Proffitt R, et al. Video game rehabilitation for outpatient stroke (VIGoROUS): a multi-site randomized controlled trial of in-home, self-managed, upper-extremity therapy. *EClinicalMedicine*. (2022) 43:101239. doi: 10.1016/j.eclinm.2021.101239

67. Abdullahi A, Aliyu NU, Useh U, Abba MA, Akindele MO, Truijen S, et al. Comparing two different modes of task practice during lower limb constraint-induced movement therapy in people with stroke: a randomized clinical trial. *Neural Plast*. (2021) 2021:6664058. doi: 10.1155/2021/6664058

68. Marklund I, Sefastsson A, Fure B, Klässbo M, Liv P, Stålnacke BM, et al. Lower-extremity constraint-induced movement therapy improved motor function, mobility, and walking after stroke. *Eur J Phys Rehabil Med*. (2023) 59:136–44. doi: 10.23736/S1973-9087.23.07683-9

69. Sickert A, Anders LC, Münte TF, Sailer M. Constraint-induced aphasia therapy following sub-acute stroke: a single-blind, randomised clinical trial of a modified therapy schedule. *J Neurol Neurosurg Psychiatry*. (2014) 85:51–5. doi: 10.1136/jnnp-2012-304297

70. Szaflarski JP, Ball AL, Vannest J, Dietz AR, Allendorfer JB, Martin AN, et al. Constraint-induced aphasia therapy for treatment of chronic post-stroke aphasia: a randomized, blinded, controlled pilot trial. *Med Sci Monit*. (2015) 21:2861–9. doi: 10.12659/MSM.894291

71. Doppelbauer L, Mohr B, Dreyer FR, Stahl B, Büscher V, Pulvermüller F. Long-term stability of short-term intensive language-action therapy in chronic aphasia: a 1-2 year follow-up study. *Neurorehabil Neural Repair*. (2021) 35:861–70. doi: 10.1177/15459683211029235

72. Stahl B, Millrose S, Denzler P, Lucchese G, Jacobi F, Flöel A. Intensive Social interaction for treatment of Poststroke depression in subacute aphasia: the CONNECT trial. *Stroke*. (2022) 53:3530–7. doi: 10.1161/STROKEAHA.122.039995

73. Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. *Pediatrics*. (2014) 133:e175–204. doi: 10.1542/peds.2013-0675

74. Wang J, Zhao W, Zhang Z, Liu X, Xie T, Wang L, et al. A journey of challenges and victories: a bibliometric worldview of nanomedicine since the 21st century. *Adv Mater*. (2023) 36:e2308915. doi: 10.1002/adma.202308915

75. Wang C, Zhang Y, Zhang Y, Li B. A bibliometric analysis of gastric cancer liver metastases: advances in mechanisms of occurrence and treatment options. *Int J Surg*. (2024) 110:2288–99. doi: 10.1097/JS9.0000000000001068

76. Li P, Sheng L, Ye Y, Wang JS, Geng S, Ning D, et al. Allergenicity of alternative proteins: research hotspots, new findings, evaluation strategies, regulatory status, and future trends: a bibliometric analysis. *Crit Rev Food Sci Nutr*. (2024):1–12. doi: 10.1080/10408398.2023.2299748

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Transcutaneous vagus nerve stimulation: a bibliometric study on current research hotspots and status

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Background: Transcutaneous Vagal Nerve Stimulation (tVNS) has been used as a promising noninvasive neuromodulation technique for the treatment of various systems.The aim of this study was to analyze the research hotspots and future directions of tVNS in the 21st century by using bibliometric methods.

Methods: The study object was the literature related to tVNS from the Web of Science database from 2000 to May 2024. In order to measure and analyze the number of literature issuance, institutions, authors, countries, keywords, co-citations, and journals of publication, we used VOSviewer, Citespace, Bibliometrix R-package, and Scimago Graphica software. A narrative review of the current research content of tVNS was conducted to gain a better understanding of the current state of the field.

Results: A total of 569 papers were included in the study. The results show that from 2000 to 2024, the number of publications shows an increasing trend year by year, involving a total of 326 research institutions. The United States, China, and Germany are the major research centers. The study identified 399 keywords, which roughly formed 11 natural clusters, revealing that the current hotspots of related research are mainly reflected in 3 areas: intervention efficacy on nervous system diseases, mechanism of action of tVNS, and stimulation mode of tVNS. The top 10 most cited references focus on research into the mechanism of action of tVNS.

Conclusion: The efficacy and safety of tVNS have been confirmed in previous studies, but a standardized tVNS treatment protocol has not yet been developed, and most clinical studies have small sample sizes and lack multicenter and multidisciplinary collaboration. Currently, tVNS is used in the treatment of neurological diseases, psychiatric diseases, cardiovascular diseases, and some autoimmune diseases. It is expected that future research in this field will continue to focus on the application of tVNS in central nervous system diseases and the exploration of related mechanisms, and at the same time, with the rise of non-invasive neuromodulation technology, the application of tVNS in other diseases also has great potential for development.

KEYWORDS

bibliometrics, transcutaneous vagal nerve stimulation, non-invasive neuromodulation, current state of research, hot trends, visual analysis, Citespace

1 Introduction

The Vagus nerve is the 10th pair of cerebral nerves, originating from the nucleus of suspicion and the dorsal nucleus of the vagus nerve, which is widely distributed in the pharynx, ear, and internal organs. The vagus nerve fibers are composed of 20% efferent fibers and 80% afferent fibers, which can transmit sensory information to the central nervous system. It is the longest and most widely distributed cerebral nerve in the human body and belongs to the category of parasympathetic nervous system. It exerts a significant regulatory influence on the human body's nervous system, respiratory system, circulatory system, and digestive system (Skandalakis et al., 1993; Berthoud and Neuhuber, 2000). As early as the 19th century, American neurologist James Corning first proposed the application of vagus nerve stimulation (VNS) to treat epilepsy (Lanska, 2002). Subsequently, based on VNS, further attempts were made to use Transcutaneous Vagal Nerve Stimulation (tVNS) to intervene in epilepsy, but the above therapies were not popularized due to the lack of a complete theoretical framework and controversy throughout the therapeutic efficacy. Since the 20th century, with the improvement of relevant basic research and revision of the conceptual framework, VNS and tVNS therapies have re-entered the public's view, and become one of the important neuromodulation therapies in the field of neuroscience (Ventureyra, 2000; Lanska, 2002).

tVNS is a non-invasive neuromodulation technology that affects relevant pathways of the central nervous system through non-invasive stimulation of the vagus nerve branches distributed in the skin sensory zone. It exerts anti-inflammatory, anti-oxidative stress, modulation of cortical excitability and neuroplasticity, regulation of endocrine and the Brain-Gut-Microbiome Axis (BGMA; Colzato and Beste, 2020; Bonaz, 2023; Kumaria and Ashkan, 2023). In addition tVNS may play a role in regulating circulatory control, maintaining arterial pressure, and mediating the vasodilatory component of the cardiovascular reflexes through the oxygen-conserving reflexes, which ultimately serve as neuroprotection. This is related to its involvement in the trigeminal cardiac reflex (TCR; Schaller et al., 2009; Nöthen et al., 2010). Previous studies have demonstrated that tVNS can effectively improve neuropsychiatric disorders, such as headache, epilepsy, stroke, and depression, to some extent (Schindler and Burish, 2022). It can also be used to treat circulatory disorders, such as heart failure and atrial fibrillation (Geng et al., 2022), and digestive disorders, such as inflammatory bowel disease (Gu and Li, 2020). The efficacy and safety of this treatment have been well documented. Therefore it is worthwhile to promote its clinical application.

Bibliometrics employs mathematical and statistical techniques to qualitatively and quantitatively analyze literature characteristics, revealing knowledge structures, research trends, and hotspots in a given field (Luo, 1994). VOSviewer, Citespace, Bibliometrix R-package, and Scimago Graphica have powerful visualization and data analysis capabilities and are now widely used in bibliometric analysis (Zeng et al., 2023). This study employs bibliometrics to analyze collaborative network analysis and keyword analysis of relevant literature on tVNS in the 21st century. We present an overview of the current state of research in this field, identify key research topics, and suggest future research directions (Broadly, this includes mechanistic studies of tVNS, standardization of stimulation parameters and efficacy in neurological disorders.). This analysis is a reference for subsequent research endeavors and the formulation of relevant diagnosis and treatment plans in this field.

2 Materials and methods

2.1 Search strategy and data collection

A computerized search was conducted on Web of Science for literature pertaining to tVNS from 2000 to May 25, 2024, using the English search strategy outlined in Supplementary Table 1. The search was limited to the 'Web of Science Core Collection,' resulting in the retrieval of 914 English articles. These articles were manually screened based on predefined inclusion and exclusion criteria, with 569 articles meeting the inclusion criteria.

2.1.1 Inclusion criteria

·Publicly available journal literature related to tVNS (excluding invasive vagus nerve stimulation), with the type of "Article" and a few high relevance 'Review'. The studies included in this article for analysis were selected from the literature on the basis of their relevance to the topic under discussion. They comprise clinical trials, animal experiments, and case studies. The objective is to elucidate the clinical efficacy or mechanism of action associated with taVNS.

2.1.2 Exclusion criteria

- Excluded duplicates and literature lacking complete information or relevance to the topic.
- Excluded document types such as conference papers, books, book chapters, newspapers, news, and conference reviews.
- No restrictions were imposed based on geography or language; however, documents with incomplete information and duplicate publications were excluded.

2.2 Data processing flow and parameter setting

The scientometric analysis in this study utilized various tools: CiteSpace software (version 6.1.6), VOSviewer (version 1.6.19), Bibliometrix R-package, and Scimago Graphica (version 1.0.38). Literature from Web of Science was exported in Refworks format, processed through CiteSpace software, and converted to _xxx.txt format for compatibility. The following steps were conducted:

1. CiteSpace 6.1.6 was used for de-duplication, resulting in 569 documents.
2. Manual data merging resolved discrepancies in country names and author variations.
3. Microsoft Excel 2013 facilitated the mapping annual publication trends and the categorization of keywords, authors, institutions, and countries.
4. CiteSpace 6.1.6 was used for data conversion and analysis, with parameters set for a time frame from 2002 to 2024, and specific criteria for node selection and threshold settings. Keyword emergence graphs were plotted with Burstness- γ (0.8) for comprehensive mapping.

5. VOSviewer 1.6.19 was employed for author collaboration network visualization, using Refworks text format with a co-occurrence minimum frequency of 5.
6. Scimago Graphica 1.0.38 was utilized to analyze and visualize publication distribution across different regions and countries.
7. Bibliometrix R-package was applied to summarize cited literature and journal distribution information.

3 Results

3.1 Analysis of trends in publications

The annual publications (Figure 1) serve as an indicator of the field's development. tVNS-related research has exhibited progressive growth since the 21st century. From 2000 to 2012, the average annual publications were low (1/year), indicating an embryonic stage. Between 2012 and 2019, a slow but steady increase occurred, averaging 19 publications/year. Since 2019, the average annual number of publications has grown rapidly. The 5-year growth rate reaches 33.7% and peaks in 2023 (112 articles). Exponential regression analysis reveals a positive correlation (y = 3E-221e0.2533x, R2 = 0.9204), suggesting sustained research interest in the future.

3.2 Author collaboration analysis

To ensure data analysis accuracy, we examined raw data using Microsoft Excel 2013. Name variants for the same author were manually merged for precision. Results revealed 569 publications involving 2,655 authors in this study. The top contributors were from the Department of Functional Research, Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, particularly Peijing Rong, with 52 publications. Supplementary Table 2 displays the top 10 authors and their affiliations. Following Price's law, authors with more than 5 publications are considered core contributors (Ninkov et al., 2022). According to the search results, there are 106 core authors in this study. Utilizing VOSviewer software for author density mapping (Figure 2), a network of author collaborations with 106 nodes was generated. After removing isolated points, 18 clusters emerged, suggesting a network of authors led by Peijing Rong, Liebler Eric, Badran Bashar W, Burger Andreas, and others, forming the research team.

3.3 Analysis of institutional cooperation

Citespace is used to analyze the collaborating institutions. This study encompasses 326 institutions cited in the literature (Figure 3), resulting in 682 connections among them. The network density of institutional collaboration stands at 0.0126, indicating a relatively dispersed collaboration among institutions. It is evident that research institutions, primarily in the medical schools, predominate, forming collaborative groups centered around institutions such as China Acad Chinese Med Sci, Harvard Med Sch, Leiden Univ, and Med Univ South Carolina, with China Acad Chinese Med Sci leading in publication output (60 papers). Due to geographical and academic factors, collaboration between Chinese institutions and those in Europe and America remains relatively limited. A tightly woven mesh of collaborative relationships has yet to emerge.

3.4 Analysis of country cooperation

Scimago Graphica is used to make a national collaboration analysis. This study engaged researchers from 52 countries. Table 1 highlights the top 10 countries by publication count, led by the United States ($n = 172$), followed by China ($n = 169$) and Germany ($n = 131$). The U.S. holds the highest total citations at 5115. In Figure 4, the collaboration network among countries/regions is depicted, with circle color indicating collaboration strength, and the circle size denoting the number of articles. According to a comprehensive analysis, the United States is recognized as a significant contributor to international cooperation, with the highest number of articles issued

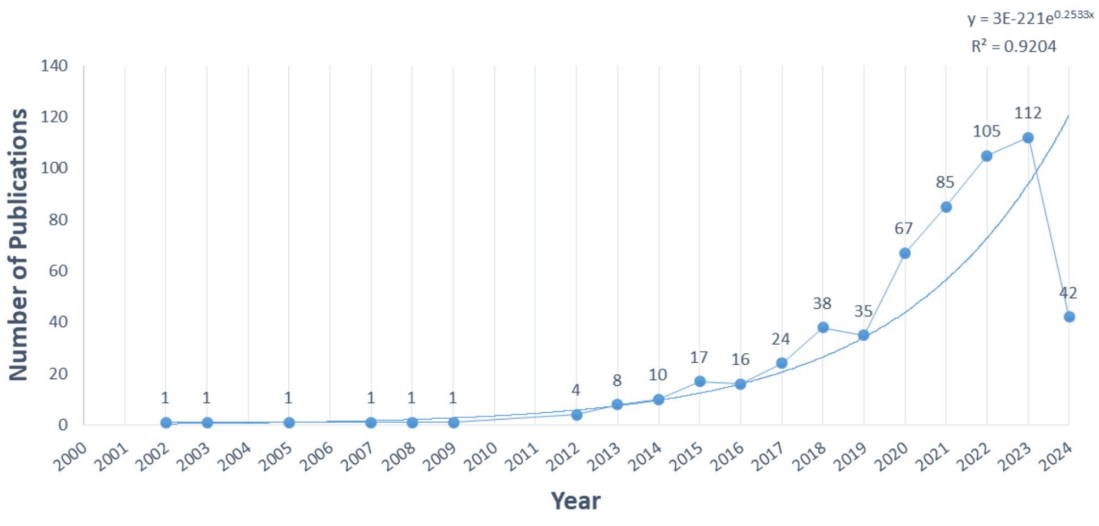


FIGURE 1
The trend of the annual published articles of tVNS from 2000 to 2024.

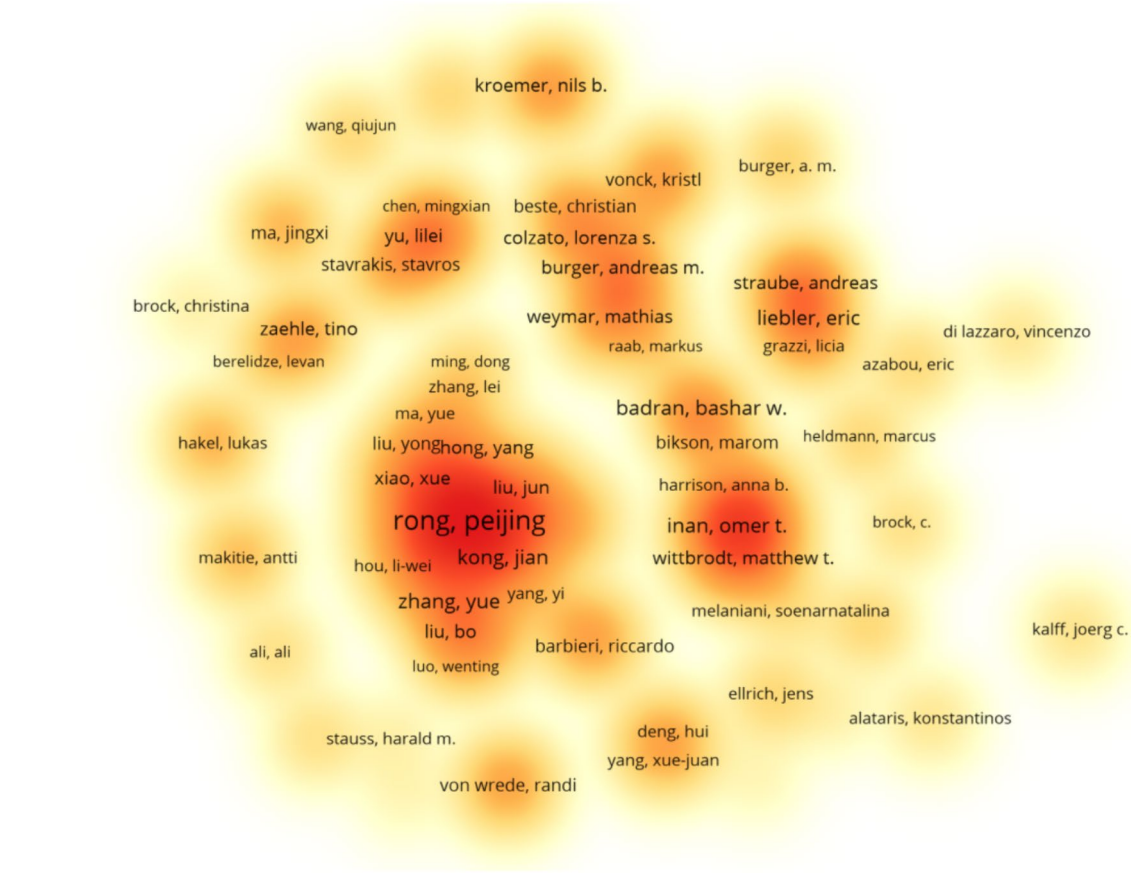


FIGURE 2
Occurrence of authors. The closer the color of the area is to red, the higher the density of authors in the area, and the scale denoting the number of documents.

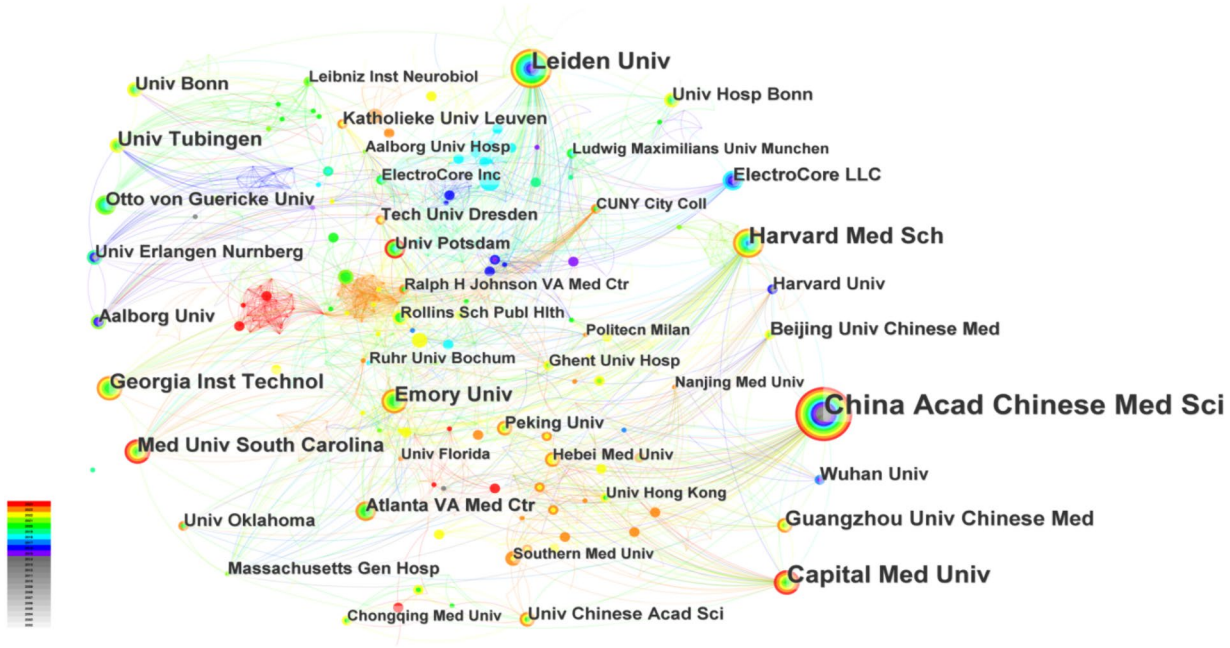


FIGURE 3
Occurrence of institutions. The thickness of the line indicating collaboration strength, and the circle size denoting the number of articles.

and the total number of citations. Furthermore, the United States has established a close cooperation with China, the United Kingdom, Germany, Italy, and other nations.

3.5 Keyword visualization and analysis

3.5.1 Co-occurrence analysis

The article's keywords have been condensed to effectively summarize the core research content. The presence of high-frequency keywords may indicate a hot research direction. As depicted in Figure 5A, the keywords have been visualized and analyzed using Citespace. The total number of keywords is 399, with 2,504 links, and a network density of 0.0315, which suggests a high literature density. Table 2 presents the top 10 keywords, excluding low-information words such as 'therapy', 'efficacy', and 'vagus nerve'. The keywords can be broadly categorized into the mechanism of action, stimulation mode, therapeutic diseases, and other categories. Currently, the mechanisms of action related to tVNS include activation of the noradrenergic neural pathway originating from the blue spot and the cholinergic anti-inflammatory pathway (CAP), among others (Urbin et al., 2021; Agarwal et al., 2024). The stimulation modes included transcutaneous vagus nerve electrical stimulation, transcutaneous vagus nerve magnetic stimulation and so on (Zhang et al., 2023).

TABLE 1 The top 10 countries in tVNS research.

Rank	Number of publications/ article	Citations	Country
1	172	5,115	United States
2	169	2,894	China
3	131	4,967	Germany
4	43	1,526	United Kingdom
5	39	1,317	Netherlands
6	37	815	Italy
7	33	790	Belgium
8	17	1,363	Denmark
9	17	259	Spain
10	17	209	France

3.5.2 Cluster analysis

The keyword clustering analysis (Figure 5B) can show a highly condensed keyword clustering plate. To a certain extent, it reflects the knowledge structure and research hotspots in this field, which is conducive to grasping the research direction (Huifeng, 2017). The K-clustering algorithm, utilizing the LLR approach, was employed to cluster the keywords associated with tVNS. A total of 11 clustering results were obtained for the keywords in this study. The clustering module value, Modularity $Q = 0.3969 > 0.3$, indicates the presence of a significant clustering structure. The silhouette value, Silhouette $(S) = 0.7285 > 0.7$. This indicates that the clustering results are highly convincing and can reflect the research hotspots in this field to a significant extent (Yue et al., 2015). The overlapping and interlacing

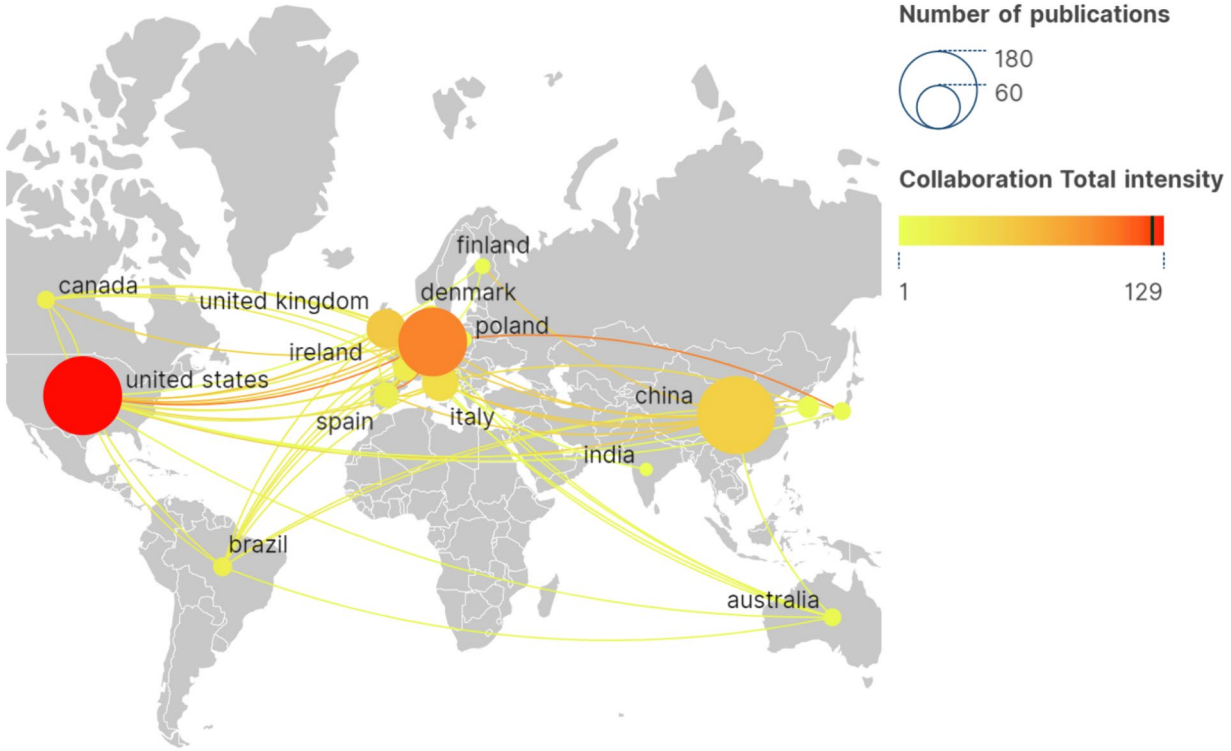
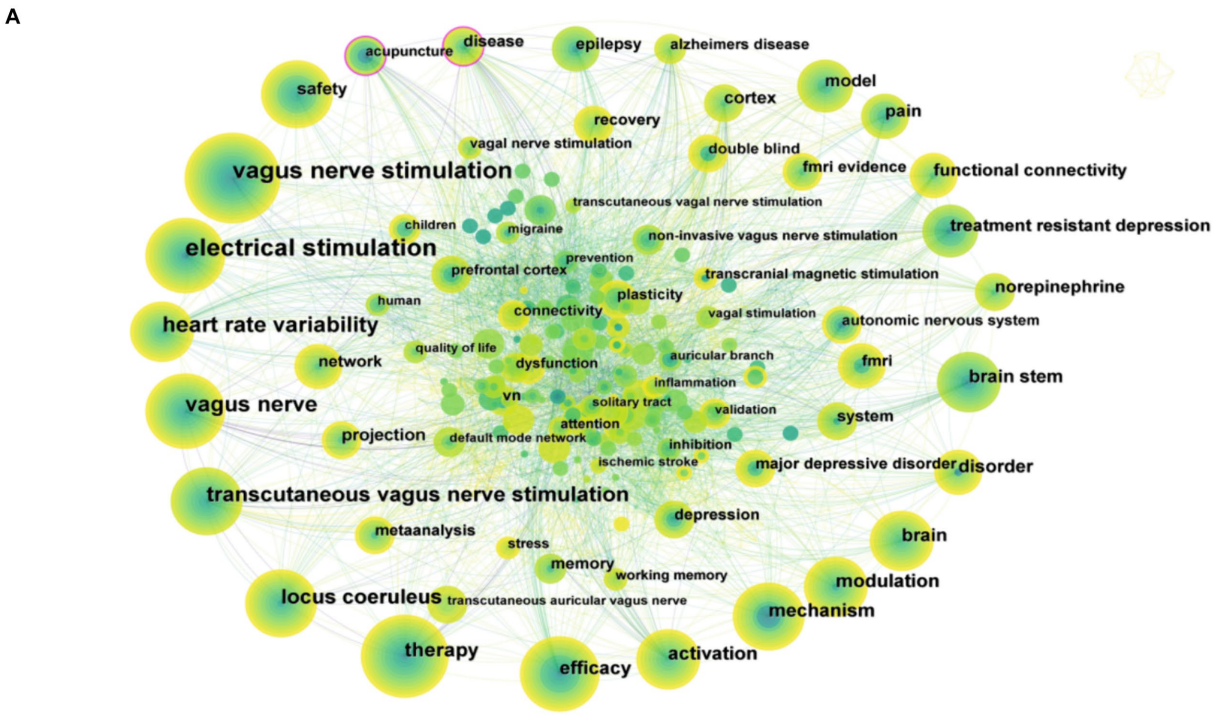


FIGURE 4
International collaborative network for geovisualization. The circle color indicating collaboration strength, and the circle size denoting the number of articles.



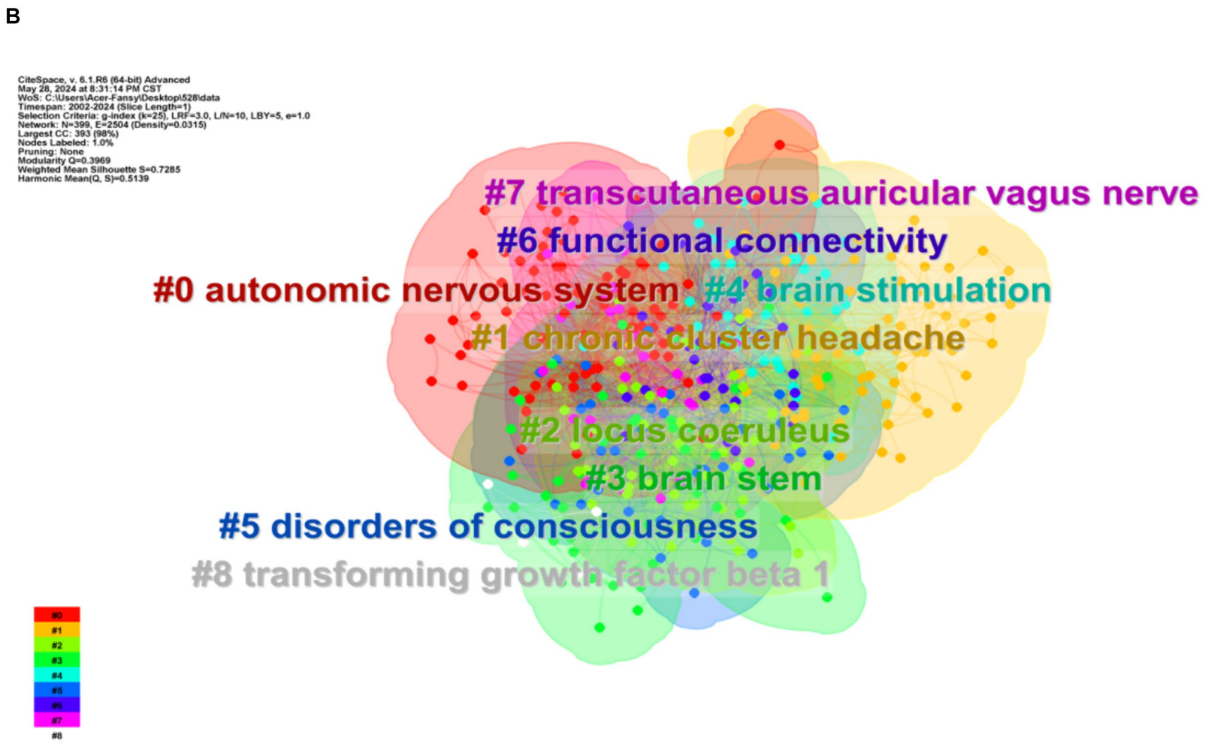


FIGURE 5 (Continued)

between the clusters indicate that the clusters are more closely linked to each other. Table 3 presents the top nine keyword clusters. Clusters #4 and #7 reveals different tVNS stimulation methods, in which transcutaneous auricular vagus nerve stimulation (taVNS) has been the subject of considerable research interest. Clusters #1 and #5 illustrate the advantageous diseases that can be treated with tVNS intervention, with a primary focus on the treatment of neurological disorders. The clusters #0, #2, #3, #6, and #8 demonstrate the mechanism of action of tVNS. This indicates that the regulation of the autonomic nervous system, the functional connectivity between

C

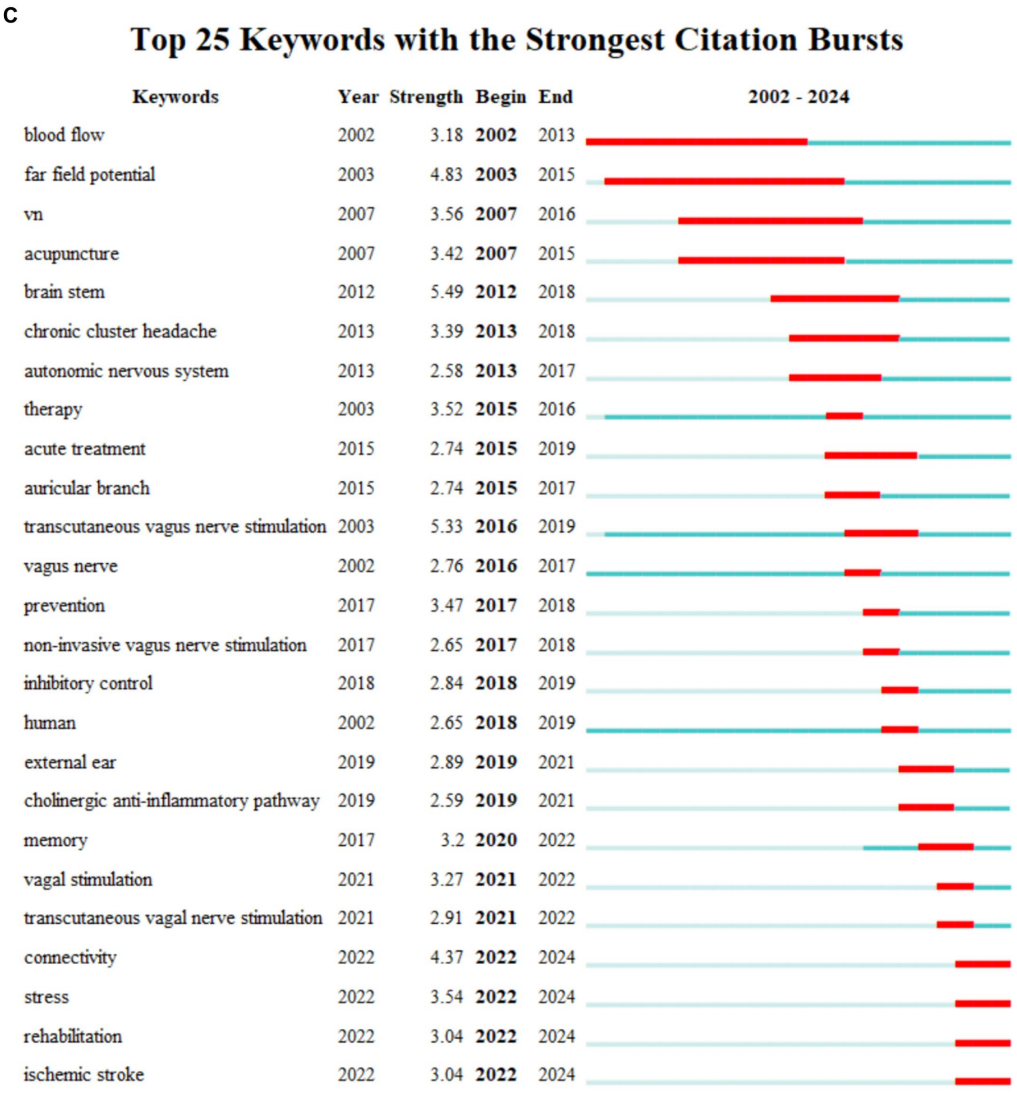


FIGURE 5
(A) Keywords occurrence. The thickness of the line indicating collaboration strength, and the circle size denoting the number of articles. **(B)** Keyword clustering. The color of the region represent cluster. The size of the area represents the number of keywords that are included. **(C)** Top 25 keywords with the strongest citation bursts.

TABLE 2 Keyword frequency and center value in tVNS research.

Rank	Literature volume/article	Centrality	Keywords
1	141	0.12	Electrical stimulation
2	80	0.08	Heart rate variability
3	66	0.07	Locus coeruleus
4	43	0.13	Activation
5	38	0.09	Mechanism
6	38	0.09	Brain stem
7	35	0.02	Disorder
8	32	0.06	Treatment resistant depression
9	29	0.02	Norepinephrine
10	28	0.02	Pain

various brain regions, and the CAP pathway associated with the locus coeruleus in the brainstem are the current research focus.

3.5.3 Keyword with citation bursts analysis

Figure 5C illustrates the emergence of keywords that are used more frequently or suddenly appear during the development of the field. This analysis provides insight into the research process over time and the historical span of the literature. The Citespace software was utilized to identify 25 emergent words in the included literature. Previous research has mainly concentrated on investigating the therapeutic effects of tVNS, which involves assessing its effectiveness through measures such as "blood flow" and vagus nerve sensory evoked potentials. After 2010, the research direction of the field gradually shifted toward clinical trials of tVNS for different diseases, including cluster headache, stroke. In recent years, there has been an increase in studies on the stimulation mode and mechanism of action related to tVNS. Furthermore, the exploration of the

TABLE 3 Keyword clustering in tVNS research.

Cluster ID	Size	Silhouette	Year	Term label
0	73	0.743	2016	Autonomic nervous system
1	72	0.73	2016	Chronic cluster headache
2	57	0.659	2018	Locus coeruleus
3	48	0.683	2016	Brain stem
4	38	0.809	2014	Brain stimulation
5	36	0.673	2019	Disorders of consciousness
6	36	0.713	2018	Functional connectivity
7	27	0.838	2015	Transcutaneous auricular vagus nerve
8	6	0.976	2015	Transforming growth factor beta 1

anti-inflammatory mechanism in tVNS has become a focus of research and future research in this area will be more intensive.

3.6 Analysis of co-cited literature

The analysis of the characteristics of the co-cited literature is beneficial in understanding the current research hotspots and frontiers in this field, as well as exploring future research directions (Zhilong et al., 2023). The Bibliometrix R-package was employed to analyze the number of citations of related literature published in this field between 2000 and 2024. Table 4 presents the 10 most highly cited articles, all of which have been cited more than 100 times. This indicates that these articles have high academic and reference values and are widely recognized. "Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans," published by Frangos in 2015, was ranked first (cited 396 times). Employing Citespace for co-cited literature clustering revealed the top 10 clusters (Figure 6A; Q = 0.6897, S = 0.8802), suggesting high clustering confidence. The integration of the clustering outcomes with the timeline (Figure 6B) reveals recent research directions in the fields of stroke (#3), noradrenaline (#2), and stress (#0).

3.7 Analysis of journals

According to the statistical analysis conducted using the Bibliometrix R-package, Table 5 presents the top 10 journals with the highest number of publications in the field of tVNS. Among these journals, 'BRAIN STIMULATION' (IF = 7.70, Q1) stands out with 44 papers related to tVNS. The article has received a considerable number of citations, totaling 2,441, which highlights its significant influence in this research domain.

Using Citespace software for dual-map overlay journal network analysis, the dual-map overlay function demonstrates the knowledge flow between citing and cited journals (Figure 7), revealing a scientific hybrid model of the global journal map in this field (Wei et al., 2022). After Z-score correction, the results indicate that MOLECULAR/BIOLOGY/GENETICS/PSYCHOLOGY/EDUCATION/SOCIOLOGY serves as the primary citation pathways in cited journals. It forms the main theoretical and technical basis for research with limited interdisciplinary studies and the strongest correlations (Chen et al., 2024). Among citing journals, NEUROLOGY/SPORTS/OPHTHALMOLOGY represent the top three citation pathways, indicating high citation frequency and relevance in these disciplines' research. When these disciplines are used as source journals, molecular biology, biology, and genetics are the most frequently cited clusters with a Z-score of 4.00. This suggests a strong interconnection and high citation rates between these fields.

4 Discussion

In this study, we visualize and analyze the number of publications, authors, countries, institutions, references, and published journals of tVNS-related literature. Furthermore, we conducted a comprehensive and systematic review of the latest research directions based on the findings of the visualization analysis, with the aim of providing a detailed account of the advancements made in the field of tVNS.

4.1 Analysis of the current status of tVNS research

According to the data, the annual publication volume has been steadily increasing since the 21st century, with a peak in 2021–2023. It is reasonable to assume that there will be continued potential for development in this area in the future. Upon analyzing the number of author publications and their collaboration network, it appears that Peijing Rong and her team have published a significant number of works in this field. A recent study has investigated the effects of taVNS on gastric motility injury and autonomic mechanisms (Zhu et al., 2023). Furthermore, they have investigated the regulatory effects of taVNS on brain networks and neural activities in patients with mild, moderate, and severe depression (Ma et al., 2023). It is worth noting that the United States and China had the highest number of publications. The United States plays a leading role in tVNS research, as demonstrated by its extensive academic collaborations with other nations. From an institutional perspective, three of the top 10 institutions are located in China, which is consistent with the distribution of publications by country. However, cross-regional collaboration is limited and may hinder global research exchange and integration. Highly cited publications often indicate the research field's theme (Jiang et al., 2023). This study provides a summary of the 10 most frequently cited publications since the 21st century, which mainly focus on the mechanism of action and clinical application of tVNS. The article published in BRAIN STIMULATION has been cited most frequently. It demonstrates that the central projection of the ear branch of the vagus nerve is consistent with the classical central vagal projection and can act in a non-invasive manner through the outer ear (Frangos et al., 2015). According to the distribution of journals, BRAIN

TABLE 4 The top 10 references in tVNS research.

Rank	Author	Year	Title	Total citations	TC per year
1	Frangos E	2015	Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans	396	39.60
2	Clancy JA	2014	Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity	275	25.00
3	Kraus T	2007	BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation	274	15.22
4	Yakunina N	2017	Optimization of Transcutaneous Vagus Nerve Stimulation Using Functional MRI	237	29.63
5	Fang JL	2016	Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder	212	23.56
6	Kraus T	2013	CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - a pilot study	196	16.33
7	Dietrich S	2008	A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI	185	10.88
8	Stefan H	2012	Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial	171	13.15
9	Silberstein SD	2016	Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study	171	19.00
10	Straube A	2015	Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial	168	16.80

STIMULATION and FRONTIERS IN NEUROSCIENCE have the highest number of articles and citations in this field. This indicates that there is significant potential for further development of tVNS research in neuroscience.

4.2 Content analysis of tVNS research

The objective of this study is to examine the prevalent research areas of tVNS. Keywords are brief summaries of literature content that facilitate in-depth exploration of research hotspots and development trends (Wang et al., 2023). Based on keyword and citation clustering themes, which are divided into three relevant aspects of tVNS research content, including tVNS mechanisms of action, stimulation patterns, and clinical applications. The following is an in-depth discussion of the keywords that appear more frequently in the results of this bibliometric study, as well as the results achieved by representative research teams in the field. Moreover, this study also investigates the safety of tVNS applications.

4.2.1 Mechanism of action of tVNS (keyword clusters #0, #2, #3, #6, #8)

Keyword clusters #0, #2, #3, #6, #8 are relevant with the mechanism of tVNS. The findings of our study indicate that the investigation of anti-inflammatory mechanisms, functional connectivity in brain regions and locus coeruleus-norepinephrine (LC-NE) system represents a current area of interest.

1. Anti-inflammatory mechanism

The vagus nerve is a major component of the neuroendocrine-immune axis, participating in the regulation of neural, behavioral, and endocrine responses. As the frontline of innate defense against infections/inflammations in the body, it helps maintain internal homeostasis (Johnston and Webster, 2009). The anti-inflammatory pathways of tVNS mainly include CAP, the splenic sympathetic anti-inflammatory pathway, and the hypothalamic–pituitary–adrenal (HPA) axis anti-inflammatory pathway (Yan et al., 2024).

① CAP anti-inflammatory mechanism

The result of keyword with citation bursts analysis showed that 'cholinergic anti-inflammatory pathway' appears in large numbers during 2019–2021. CAP refers to the excitation of the vagus nerve by external stimulation, leading to the production of the anti-inflammatory neurotransmitter acetylcholine (ACh) at the vagus nerve endings, which activates alpha-7 nicotinic acetylcholine receptors (α7nAChR) on monocytes and macrophages (Hongxian et al., 2023). This further activates the nuclear factor kappa B (NF-κB) signaling pathway and the Janus kinase 2/signal transducers and activators of transcription 3 (JAK2/STAT3) pathway within the cells, suppressing the production of cytokines such as IL-1β and TNF-α, ultimately exerting anti-inflammatory effects (Wang et al., 2003). Previous animal studies have suggested that by enhancing CAP, tVNS can counteract colon cancer induced by 1,2-dimethylhydrazine (DMH). The research results showed that applying tVNS could restore DMH-induced mitochondrial apoptosis. At the protein and mRNA levels, tVNS can activate CAP by upregulating the expression of α7nAChR, downregulating nuclear factor kappa B p65 (NFκBp65) in activated B cells, and enhancing the expression of tissue necrosis factor-alpha and high mobility group box-1 (Rawat et al., 2019). Aranow et al. (2021) conducted a 12-day randomized controlled study and concluded that taVNS significantly improves inflammatory musculoskeletal pain and fatigue in patients with systemic lupus erythematosus. The mechanism of action may involve the activation of the CAP, leading to a reduction in plasma levels of substance P in subjects. This suggests that plasma substance P may be more sensitive to the biological response of taVNS than cytokines, which is a worthy area for further exploration. In an ischemic stroke model, taVNS is believed to modulate brain ischemia/reperfusion (I/R) injury, axonal

FIGURE 6
(A) Clustering map of cited literature. The color of the region represent cluster. The size of the area represents the number of keywords that are included. **(B)** Timeline chart of cited literature.

plasticity, and vascular regeneration, thereby improving neuro-motor function. Its molecular mechanism involves taVNS activating the CAP pathway, thereby activating downstream PPAR-γ (expressed mainly in neurons and astrocytes) nuclear transcription factors to promote the expression and secretion of brain-derived neurotrophic factors (BDNF) and vascular endothelial growth factors (Li, 2020).

② HPA axis

The HPA axis is one of the crucial neuroendocrine axes in the human body. Stimulation of the vagus nerve, on the one hand, can reduce peripheral inflammatory responses by activating the HPA axis (Kaniusas et al., 2019). According to the anatomy of the vagus nerve, peripheral inflammatory factors including interleukin (IL)-1, IL-6, and TNFα can transmit information to the nucleus of the solitary tract (NTS) through vagal afferent fibers, activating neurons located in the A2 noradrenergic group and projecting information to the paraventricular nucleus of the hypothalamus (PVH). This pathway can activate neurons producing corticotropin-releasing factor (CRF) in this area, stimulating the hypothalamus to release corticotropin-releasing hormone via the HPA axis, ultimately leading to adrenal release of glucocorticoids, thereby reducing peripheral inflammation

TABLE 5 The top 10 journals in tVNS research.

Rank	Journals	Documents	h_index	Total citation	IF, JCR [2022]
1	Brain Stimulation	44	22	2,441	7.7,Q1
2	Frontiers in Neuroscience	28	9	249	4.3,Q3
3	Scientific Reports	18	9	226	4.6,Q2
4	Frontiers in Neurology	16	6	143	3.4,Q3
5	Autonomic Neuroscience-Basic & Clinical	14	8	196	2.7,Q4
6	Neuromodulation	14	8	392	2.8,Q3
7	Frontiers in Human Neuroscience	14	6	195	2.9,Q3
8	Plos one	10	8	220	3.72,Q2
9	Brain Sciences	10	6	74	3.3,Q3
10	Journal of Headache and Pain	9	9	493	7.4,Q1

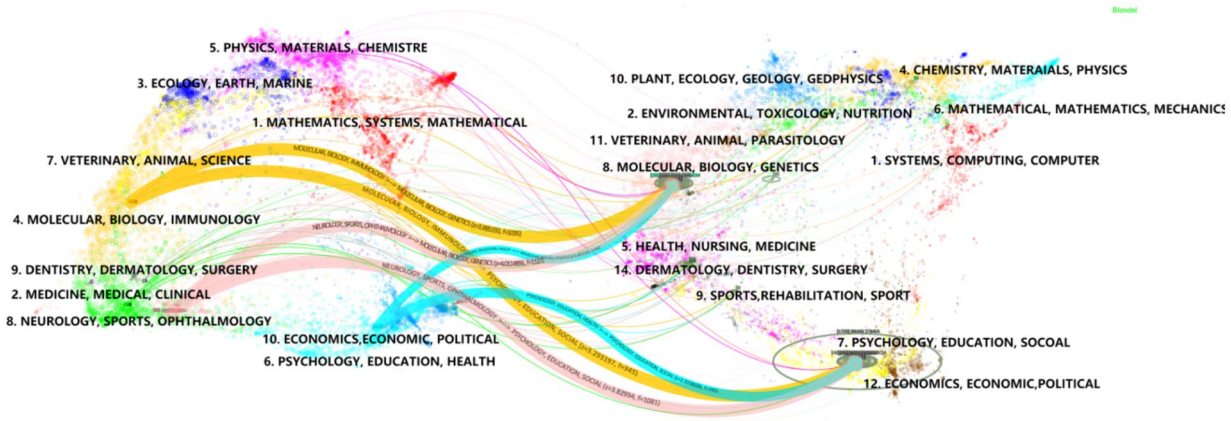


FIGURE 7
A dual-map overlay of the journals on tVNS research. The map of cited journals is superimposed on top of the map of citing journals, with the former being the iterative map and the latter being the base map. The labels represent the disciplines covered by the journals, and the colored paths represent citation relationships.

(Bonaz et al., 2016). In terms of anti-inflammatory effects, taVNS shares similar physiological effects with VNS. Studies have shown that taVNS can reduce pro-inflammatory cytokines, modulate lung injury, and alleviate acute respiratory distress syndrome caused by COVID-19 by activating the HPA anti-inflammatory pathway and the CAP (Kaniusas et al., 2020). On the other hand, the HPA axis is the primary stress response system in the human body and is closely associated with the pathophysiology of depression. Long-term stress, including psychological and physiological stress as well as other stimulation, can lead to HPA axis hyperactivity, resulting in abnormal secretion of plasma cortisol (CORT) and adrenocorticotropic hormone (ACTH), thereby inducing depressive-like behavior (Liyanarachchi et al., 2017). Previous animal studies have shown that taVNS can improve depressive states in rats by inhibiting excessive activity of the HPA axis (Hou et al., 2022). Recent clinical research has found that tVNS can upregulate salivary cortisol levels and decrease salivary flow rate in temporal lobe epilepsy patients, improving epilepsy symptoms by suppressing excessive activation of the HPA axis and the autonomic nervous system (Doerr et al., 2023). The study by Li et al. (2020) demonstrated that 20 Hz taVNS is an effective treatment for depressive-like behavior and downregulates the excessive activity of the HPA axis.

③ Splanchnic sympathetic anti-inflammatory pathway

The stimulation of the vagus nerve has been demonstrated to activate splanchnic sympathetic anti-inflammatory pathways and to inhibit the secretion of pro-inflammatory factors in splanchnic macrophages (Kaniusas et al., 2019). Studies have shown that taVNS may inhibit peripheral inflammatory responses, reduce the release of the chemokine CXCL1, and ameliorate lipopolysaccharide (LPS)-induced depressive-like behaviors in rats by activating the splenic α7n Ach R/JAK2/STAT3 signaling pathway (Yu et al., 2023). However, the splanchnic sympathetic anti-inflammatory pathway has been questioned by some researchers. Martelli et al. (2014) demonstrated that plasma levels of the key inflammatory mediator tumor necrosis factor-alpha (TNFα) in rats injected intravenously with lipopolysaccharide were not affected by previous bilateral cervical vagotomy. However, the level of TNFα was increased by about 5-fold after severing visceral sympathetic nerves. This suggested that the inflammatory response after LPS immune attack is not reduced by reflex activation of the splanchnic sympathetic anti-inflammatory pathway by the vagus nerve. Instead, its anti-inflammatory mechanism may be related to splanchnic nerve activity driven by the conventional sympathetic pathway via the visceral nerve. However, the

above-mentioned anti-inflammatory mechanisms are mostly derived from invasive VNS, and in a recent systematic review, the results suggest that VNS is only beneficial in acute inflammatory events. The current evidence is insufficient to confirm the claim that VNS affects human inflammatory cytokines (Schiweck et al., 2024). Therefore, further high-quality research is needed to substantiate the anti-inflammatory mechanisms of tVNS in the future.

2. Functional Connectivity and Neuroplasticity

The term "functional connectivity" emerged as a topic term in the keyword cluster with high silhouette values (0.713). tVNS has been demonstrated to optimize brain plasticity, enhancing functional connectivity between brain regions and modulating neurotransmitter and neurotrophic factor secretion (Brambilla-Pisoni et al., 2022). Recent studies have demonstrated that tVNS can enhance functional connectivity between parietal and temporal lobe regions and that it can induce heightened activity in various brain regions among patients with mild cognitive impairment (MCI). Among these patients, the cingulate gyrus may be a particularly promising target for tVNS-based MCI regulation (Chunlei, 2023). The functional impairment of the thalamocortical connectivity network is considered the basis of migraine pathophysiology. The findings of Zhang et al. (2021) confirm that taVNS may alleviate migraines by increasing connectivity between the motor-related subregions of the thalamus and the pregenual anterior cingulate cortex/medial prefrontal cortex while reducing connectivity between the occipital cortex-related thalamic subregion and the central posterior cingulate/precuneus. It is well established that the dynamic equilibrium between excitability and inhibition (E/I balance) is crucial for the development and sustenance of typical cerebral functionality and plasticity (He et al., 2018). VNS has been demonstrated to enhance the imbalance between excitability and inhibition in the brain (Ooi et al., 2023). For instance, previous studies demonstrated that taVNS enhanced the activity of the cortical GABA system and inhibited the release of the excitatory neurotransmitter glutamate (Chen et al., 2016; van Midden et al., 2023). This may be one of the result that VNS can influence the progression of disorders such as epilepsy, stroke, and depression (Di Lazzaro et al., 2004; Bajbouj et al., 2007; Wang et al., 2023). Moreover, research indicates that taVNS may also be an effective treatment for migraines by activating the descending pathways of the locus coeruleus and the dorsal raphe nucleus. These pathways are responsible for the synthesis and release of norepinephrine and serotonin, respectively, which are key neurotransmitters involved in central pain modulation (Hao Han et al., 2023). Baig et al. (2022) demonstrated that prolonged tVNS intervention is associated with increased PPAR-γ, BDNF, and growth differentiation factor 11 in stroke models. These findings suggest that tVNS may promote angiogenesis and neurogenesis, and modulate neuroplasticity, thereby alleviating vascular and neurological impairments linked to stroke.

3. LC-NE system

Keyword cluster #2 "locus coeruleus," #3 "brain stem" and "norepinephrine" indicate that the mechanism of action of tVNS is related to the LC-NE system. The LC in the brainstem is one of the main sources of NE in the brain. Previous studies have shown that stimulation of the vagus nerve affects the LC-NE system, thereby exerting a therapeutic effect on depression, chronic pain, post-traumatic stress disorder, neurodegenerative diseases, as well as cognitive decline in aging (Kaczmarczyk et al., 2017; Fischer et al., 2018; Zhang et al., 2019; Garcia et al., 2021). Zhang et al. (2019) showed that taVNS at 1 HZ reduced the fMRI signal of LC and enhanced the resting-state functional connectivity between LC and temporoparietal junction, amygdala, hippocampus/parahippocampus, and the left secondary somatosensory cortex, thus modulating the vagal pathway and pain-modulating network to alleviate migraine symptoms in patients with migraine. Additionally, evidence indicates that taVNS may facilitate associative memory and situational memory, while also eliminating fear memory by activating the LC-NE pathway (Hansen, 2018). Furthermore, it has been demonstrated to enhance mood and to promote attention, memory, and cognitive control-factors affected by long COVID (Colzato et al., 2023).

4.2.2 tVNS stimulation patterns (keyword cluster #7)

Keyword cluster #7 (taVNS) is one of the tVNS stimulation patterns. tVNS stimulation modes can be classified into three broad categories: taVNS, transcutaneous cervical vagal nerve stimulation (tcVNS), and transcutaneous vagal nerve magnetic stimulation. These categories are based on the different stimulation sites and modes. Concerning stimulation parameters, it is worth noting that there is no uniform standard. Previous studies have shown that the stimulation frequency is mostly 25 Hz, and the stimulation intensity is often adjusted according to the sensitivity threshold. Pulse widths of 0.2 ms and 0.5 ms are predominant (Yap et al., 2020). However, due to the large variation in stimulation protocols across studies, it may be difficult to determine the optimal stimulation parameters. Therefore, it is suggested that closed-loop controlled tVNS may provide greater clinical benefits.

At present taVNS is widely used as a neuromodulation modality. The most in-depth research is conducted by Prof. Rong Peijing's team. According to anatomical studies the auricular branch is the only branch of the vagus nerve that reaches the body surface (Butt et al., 2020). taVNS is a promising technique that combines vagus nerve stimulation with Chinese medicine auricular acupoint therapy. The technique aims to regulate bodily functions and treat disease through non-invasive electrical stimulation of skin receptor sites distributed by the auditory branch of the vagus nerve in the outer ear (Wang et al., 2021). According to Jiakai et al. (2023) taVNS and VNS share a common anatomical basis and mechanism of action. The indications and efficacy of VNS and taVNS were also compared and the results indicated that their clinical efficacy was comparable. taVNS has the potential to expand the applications of VNS to include heart failure diabetes mellitus and neurological disorders. However further clinical studies are needed to confirm the efficacy of taVNS.

The research team led by Brock C. is engaged in studies pertaining to tcVNS (Drewes et al., 2021; Kornum et al., 2024). tcVNS is a therapeutic approach that targets the vagus nerve near the carotid artery through transcutaneous electrical stimulation. It is based on the concept of the "carotid bifurcation," which was initially developed by American neurologist James L. Corning (Farmer et al., 2020). tcVNS was originally developed for the treatment of epilepsy. Its function is to stimulate the branches of the cervical nerve near the carotid artery, which reduces the heart rate (HR) and subsequently decreases blood flow to the brain. As research progressed, tcVNS has gained FDA approval for the management of migraines and cluster headaches (Nesbitt et al., 2015). A multitude of studies have indicated its efficacy

in the intervention of cardiovascular diseases, acute ischemic brain disorders, and psychiatric conditions (Ay et al., 2016; Brock et al., 2017; Gazi et al., 2022). In a randomized double-blind controlled trial, Gurel et al. (2020) demonstrated that tcVNS can regulate the autonomic nervous system, cardiovascular, and vascular indices in patients with post-traumatic stress disorder. This treatment reduced sympathetic arousal and improved recovery from traumatic stress. In a study by Moazzami et al. (2023), the levels of gastrin, a biomarker of stress, were measured in response to various stressful stimulation. The results demonstrated that tcVNS can reduce gastrin levels and modulate hormonal and autonomic responses to stress, thereby treating psychiatric disorders.

Transcutaneous vagus nerve magnetic stimulation is an intervention that combines vagus nerve stimulation with repetitive transcranial magnetic stimulation (rTMS; Lin et al., 2018). This innovative approach addresses some limitations of tVNS, including attenuation of current upon entering the body, difficulty in stimulating deep tissues and nerves, and excessively high current intensity, which can lead to adverse events such as pain, skin reddening, and itching (Redgrave et al., 2018). Previous studies have shown that rTMS can activate the auricular branch of the vagus nerve to improve swallowing function in stroke patients (Lin et al., 2018) and patients' level of consciousness (Wang et al., 2022). Furthermore, Zhang et al. (2023) demonstrated through a single-arm study that transcutaneous cervical vagus nerve magnetic stimulation can effectively enhance cognitive function in patients with traumatic brain injury-related cognitive impairment, offering a safe and feasible treatment option. However, the currently available evidence is insufficient to demonstrate the efficacy and mechanisms of action of transcutaneous vagus nerve magnetic stimulation. Therefore, further clinical and basic research of the highest quality is required to provide more definitive evidence on this topic.

As research on non-invasive neurostimulation techniques progresses, researchers propose the concept of closed-loop transcutaneous auricular vagus nerve stimulation (CL-taVNS), an automated taVNS system regulated by biofeedback signals such as behavioral changes, respiratory variations, and brain activity (Cook et al., 2020). The CL-taVNS system primarily consists of biological signal sensors (identifiers) and taVNS stimulators integrated with remote control solutions (Kaniusas et al., 2019). It aims to adapt more sensitively to dynamically detectable changes in the clinical setting, thus providing personalized taVNS protocols to enhance therapeutic efficacy. Current forms of CL-taVNS include movement-activated auricular vagus nerve stimulation (MAAVNS) and respiratory-gated auricular vagus nerve afferent stimulation (RAVANS). MAAVNS has been applied in neonatal neurorehabilitation (Badran et al., 2020) and adult upper limb rehabilitation. RAVANS have been previously utilized in intervention studies for the treatment of pain (Garcia et al., 2017) and hypertension (Stowell et al., 2019). Moreover, in the future, electroencephalogram signals, electrocardiogram signals, and subcutaneous fluid signals may also be considered as potential triggers for taVNS in specific patients (Yu et al., 2021). Nevertheless, given the limited sample sizes and the paucity of research currently available, the efficacy and safety of these approaches remain uncertain. It is conceivable that this will become a prospective avenue of development for non-invasive neuromodulation techniques in the future.

4.2.3 tVNS advantageous diseases (keyword clusters #1 and #5)

4.2.3.1 Diseases of the nervous system

Keyword clusters #1 and #5 showed the parts of tVNS advantageous diseases. Currently, there is significant attention being given to tVNS intervention in neurological disorders, including migraines, Parkinson's disease, Alzheimer's disease, epilepsy, and stroke. Prof. Liebler Eric's team delves into the efficacy of tVNS intervention in cluster headaches and related mechanisms (Diener et al., 2019). The findings of their study indicated that tVNS was an efficacious intervention for the acute and prophylactic treatment of migraine headaches (Grazzi et al., 2017; Goadsby et al., 2018). According to a meta-analysis, tVNS has significantly increased the responder rate by at least 50% in migraine patients. Low-frequency taVNS has been found to reduce the number of migraine days significantly. Furthermore tcVNS is considered safe and well-tolerated (Song et al., 2023). A four-week clinical trial conducted by Zhang et al. (2021) demonstrated that taVNS could relieve headache symptoms and modulate thalamocortical circuits in migraine patients. These findings suggest a potential therapeutic target for this population. Research has shown that tVNS affects the cortical areas responsible for controlling trigeminal pain. Additionally, taVNS (1 Hz) significantly alters the activity and connectivity of the central vagal pathway and brain regions associated with the pain modulatory system. These findings may provide insight into the neural mechanisms of taVNS for treating migraines (Zhang et al., 2019).

In our analysis the terms "memory" and "Alzheimer's disease" emerged as key concepts with high frequency. AD is a neurodegenerative disease commonly observed in the elderly population. It is characterized by the formation of neuroinflammatory plaques made up of amyloid β-protein (Aβ) and neurofibrillary tangles made up of hyperphosphorylated tau proteins. AD is characterized by atrophy in various regions of the brain including the hippocampus and internal olfactory cortex. Neuromodulation techniques are being investigated as a potential treatment for AD (Duyu and Wei, 2019). One such technique is tVNS which has demonstrated encouraging outcomes in animal studies. In particular tVNS has been shown to alter the morphology of microglia in aged AD model animals such as APP/PS1 mice from a neurodestructive phenotype to a neuroprotective phenotype. This has the potential to slow down the progression of the disease (Kaczmarczyk et al., 2017). Recent studies have shown that 40 Hz taVNS may inhibit hippocampal P2X7R/NLRP3/Caspase-1 signaling and potentially improve spatial learning and memory in APP/PS1 mice (Yu et al., 2023). However further clinical research is needed to determine the effectiveness of tVNS in treating AD.

The keyword co-occurrence analysis revealed that the term "Parkinson's disease" appeared 18 times, which suggests that tVNS may be an effective therapy for Parkinson's disease (PD). Previous evidence suggests that tVNS may have beneficial therapeutic effects on both motor and non-motor symptoms in PD. It has been proposed that tVNS could potentially improve several objective gait parameters, such as stride length, speed, and frequency (Marano et al., 2022). In a study conducted by Zhang et al. (2023), the effects of tVNS (20 Hz) on gait disturbances in PD patients were investigated. The results demonstrated that tVNS was an effective intervention for alleviating gait disturbances and remodeling sensorimotor integration. Lench

et al. (2023) also conducted a study that affirmed the safety and feasibility of multiple sessions of taVNS in intervening PD. Furthermore, the involvement of the vagus nerve in regulating the onset and progression of PD has prompted researchers to propose tVNS as a potential treatment for autonomic dysfunction in PD (Ko, 2021).

The keyword "epilepsy" is referenced with greater frequency. Among the 10 most frequently cited documents are studies on tVNS for epilepsy (Stefan et al., 2012). VNS has previously been used to manage refractory epilepsy (Penry and Dean, 1990), but due to safety and tolerability concerns associated with implantable VNS, tVNS has emerged as a potential alternative therapy (Ben-Menachem et al., 2015). In a large randomized controlled study, Yang et al. (2023) investigated the effectiveness and safety of tVNS in patients with epilepsy. The study showed a significant reduction in seizure frequency after the intervention, and no serious adverse events were observed. These findings suggest that tVNS may be a safe and effective treatment option for epilepsy. In a study conducted by von Wrede et al. (2022), the effects of taVNS on brain network function in various types of epilepsy were investigated. The study found that taVNS produced immediate and significant improvements in network robustness. However, it is worth noting that the lasting effects of taVNS differed significantly across types of epilepsy. While the focal epilepsy group experienced enhanced robustness, the generalized epilepsy group experienced a reduction in robustness. The fluctuating stability of the network could potentially be linked to the magnitude of the susceptibility to perturbation induced by taVNS in different types of epilepsy.

The results of the top 25 Keywords with the Strongest Citation Bursts indicate that "stroke" is a more popular research topic in the period from 2022 to 2024. The team led by Schaller demonstrated that tVNS can enhance limb and memory function in patients with ischemic stroke by increasing central noradrenergic activity (Sternberg and Schaller, 2020). Furthermore, tVNS has been demonstrated to markedly enhance upper limb motor function, cognitive, and dysphagia in stroke patients (Yuan et al., 2019; Colombo et al., 2023). The mechanism of action may be related to various factors, some acute effects including the reduction of infarct size, improvement of neurological deficits, regulation of blood–brain barrier permeability and inhibition of neuroinflammation. Longer term effects of tVNS in stroke that may mediate neuroplasticity include microglial polarization, angiogenesis and neurogenesis (Baig et al., 2022, 2023). It has been confirmed that tVNS intervention is both effective and safe in treating nervous system diseases. However, the mechanism of action is still not fully understood and requires further exploration in the future.

4.2.3.2 Mental illness

The research team led by Prof. Peijing Rong has dedicated the past few years to investigating the efficacy and mechanism of tVNS in treating depression (Sun et al., 2024). In 1997 and 2005, respectively, the FDA approved the use of cervical VNS for refractory depression that does not respond to pharmacological treatments (Cristancho et al., 2011). In 2016, Rong et al. (2016) conducted a non-randomized controlled pilot study to explore the effects of taVNS on MDD. After 12 weeks of intervention, it was observed that the taVNS group showed a more significant improvement in their symptoms compared to the control group after 4 weeks of treatment. This improvement was mainly observed in terms of changes in Hamilton scores, as well as response and remission rates in the fourth week. A recent study further investigated the effects of prolonged longitudinal taVNS on the modulation of functional connectivity in striatal subregions of MDD patients. According to the study, prolonged longitudinal taVNS was found to affect the resting-state functional connectivity in the striatum with the prefrontal cortex, occipital cortex, and temporal cortex. It was also found that this effect was associated with symptom improvement (Zhang et al., 2022). Furthermore, Wang et al. (2021) conducted an experimental study utilizing CUMS rats as a model, which demonstrated that taVNS may exert antidepressant effects by modulating the hippocampal α7nAchR/NF-κB signaling pathway.

4.2.3.3 Diseases of the circulatory system

The second most frequent keyword is "heart rate variability," which indicates that tVNS has been met with considerable enthusiasm in the field of cardiovascular disease. Current studies have shown that tVNS is effective in improving heart rate variability and maintaining the balance of the autonomic nervous system (Geng et al., 2022). In a study conducted by Clancy et al. (2014), the effects of tVNS on autonomic function were investigated in 48 healthy participants. The results demonstrated that tVNS enhanced heart rate variability and reduced sympathetic outflow, which has significant implications for the clinical management of disorders with elevated sympathetic activity, such as heart failure. Central blood pressure is considered to be the main indicator of left ventricular (LV) afterload, so lowering central blood pressure can reduce LV afterload and prevent heart failure decompensation. One study showed that tVNS in the left external auditory canal can significantly reduce central blood pressure in elderly patients with acute heart failure (AHF), reduce cardiac afterload, and thus improve cardiac function in patients with AHF (Nagai et al., 2023).

tVNS has also been shown to be effective in arrhythmias and myocardial infarction. Previously, it has been suggested that low levels of tVNS may exert anti-fibrillation effects by prolonging the effective refractory period of atrial and pulmonary vein myocardium, inhibiting activation of the atrioventricular ganglionic plexus, decreasing stellate ganglionic neural activity, and decreasing sympathetic ganglion cells in the sympathetic left stellate ganglion (Li et al., 2015). Dalgleish et al. (2021) have further demonstrated that occipital artery decompression in combination with taVNS increases cardiac parasympathetic tone on the one hand and prolongs atrial conduction time on the other hand, which has a positive effect on ventricular rate control during auricular fibrillation. There is also evidence that taVNS may ameliorate cardiac ischemia/reperfusion injury by mediating the dynamic balance between pro-inflammatory and anti-inflammatory responses in cardiac macrophages (Chung et al., 2020). This suggests that tVNS may play a beneficial role in improving cardiac function and regulating cardiac rhythm.

4.2.3.4 Diseases of the digestive system

Citation clusters #4 (postoperative ileus) and #8 (electrogastrogram) appear with greater frequency. It is evident that aside from circulatory system and neuropsychiatric diseases, tVNS also impacts the development of digestive system diseases. Studies indicate tVNS may be an effective treatment for gastrointestinal discomfort in PD (Kaut et al., 2019). Steidel et al. (2021) demonstrated tVNS's ability to enhance gastric motility in healthy individuals,

particularly with high-frequency stimulation. Furthermore, tVNS has demonstrated efficacy in alleviating constipation and abdominal discomfort in patients with irritable bowel syndrome. This effect may be mediated by autoimmune mechanisms such as activation of the CPA, inhibition of the 5-HT pathway, and improvement of rectal sensation (Shi et al., 2021). Additionally, tVNS has been observed to have a combined effect on visceral hypersensitivity, delayed gastric emptying, and depression-like behavior in iodoacetamide (IA)-treated rats. These effects are likely linked to anti-inflammatory activation, improvement of duodenal mucosal integrity, enhanced vagal efferent activity, and down-regulation of HPA axis hyperactivation (Hou et al., 2023). Moreover, Müller et al. (2022) demonstrated that tVNS enhanced gastro-brain coupling via the NTS-midbrain pathway, thereby substantiating the capacity of vagal signaling to effectively modulate brain-digestive organ communication and the beneficial impact of vagal modulation in digestive disorders.

4.2.4 tVNS safety

While tVNS is widely recognized as a promising replacement therapy for VNS in clinical practice due to its non-invasiveness and effectiveness, researchers remain concerned about its safety. The results of the keyword co-occurrence analysis also showed that keyword "safety" appeared frequently. The underlying cause of its safety concerns may be linked to the TCR (Chowdhury et al., 2014). Previous studies has demonstrated that when the trigeminal nerve is stimulated, excitation is conveyed to the vagus nerve via the common fiber ganglion, resulting in an enhancement of vagal excitability and subsequent cardiovascular effects, including an increase in heart rate and blood pressure (Meuwly et al., 2017). It is generally believed that tVNS is mostly applied to the left ear, as stimulation of the right side is more likely to induce bradycardia since the efferent vagal fibers on the right side regulate heart rate (Keute et al., 2018). It is worth noting that tcVNS tends to stimulate peripheral non-vagal nerves. Similar to invasive VNS, it can be challenging for tcVNS to selectively stimulate VN fibers percutaneously. Consequently, current products are likely to stimulate afferent and efferent fibers indiscriminately. Some have questioned the safety of this modality due to the possibility of stimulating motor efferent nerves that innervate the sinus node, which could lead to arrhythmias, conduction block, and other adverse effects (AEs; Simon and Blake, 2017). However, analyzing relevant clinical studies in recent years, the incidence of AEs associated with tVNS was low. A recent meta-analysis evaluated the possible AEs of taVNS and their incidence. The study found that the most common AEs reported were earache, headache, tingling, dizziness, skin redness, and fatigue. However, the results showed no significant difference in the risk or intensity of AEs between the taVNS group and the control group, suggesting that taVNS is a safe treatment option (Kim et al., 2022). It has been shown that tVNS can produce therapeutic effects similar to those of VNS but with a higher level of safety. Additionally, tVNS is effective in treating refractory epilepsy, particularly in pediatric cases (Rong et al., 2014). Clinical studies have evaluated the efficacy and safety of tVNS in treating acute stroke. The studies have shown that both tcVNS and taVNS are safe and effective in treating acute ischemic or hemorrhagic stroke (Arsava et al., 2022; Li et al., 2022). Additionally, tVNS is safe in treating acute/chronic headaches, depression, gastrointestinal disorders, and Novel coronavirus pneumonia (Goadsby et al., 2018; Kaczmarczyk et al., 2021; Tornero et al., 2022; Alam and Chen, 2023). It is suggested that tVNS may be comparatively safer than VNS. However, it is important to note that the current studies have mostly included small sample sizes and short follow-up times. Therefore, it is recommended that more large clinical studies be conducted in the future to validate the safety of tVNS further.

5 Conclusion and outlook

This bibliometric study reveals the global publication trends and dynamics of tVNS in the 21st century.The results show that the research fever in the field of tVNS is generally on the rise. The study systematically clarifies the development of this research field and comprehensively analyzes the current hot research topics related to tVNS, including mechanism of action, stimulation mode, advantage diseases, and safety. This will help to grasp the future development direction of tVNS.

The current tVNS research field still faces some challenges. Firstly, the mechanism of tVNS mainly focuses on exploring the anti-inflammatory pathway, and its central and peripheral anti-inflammatory effects have been verified by some clinical and basic experiments, but the relevant research is still insufficient. There is a relative lack of research on the application and mechanism of tVNS in acute and chronic inflammation of various respiratory and digestive diseases.

Secondly, It is well known that VN has been confirmed as a crucial mediator of bidirectional communication between the gut and the brain (Bonaz et al., 2018). Consequently, the brain-gut axis may also be a mechanism of action of tVNS. Although there are fewer related studies, this may be one of the future research directions.

Thirdly, the current research is somewhat arbitrary in its selection of tVNS treatment sites and stimulation parameters. Previous studies indicated that different diseases may respond differently to specific stimulation parameters. The use of tVNS for the treatment of epilepsy and depression involves the application of a range of stimulation frequencies (20–30 Hz), pulse widths (up to 500 μs), and stimulation on-times (30–90 s) followed by off-times (5 min). The optimal parameters for the modulation of cognition require the use of much higher current stimulations, typically up to 8 mA (Vargas-Caballero et al., 2022). In contrast, Yu et al. (2023) demonstrated that 40-Hz taVNS enhanced spatial learning and memory in APP/PS1 mice. The findings of Badran et al. (2019) indicate that the 500 μs pulse width is the most biologically active. In terms of frequency, 25 Hz has proven to be an effective frequency. Nevertheless, further studies are required in the future in order to establish standardized tVNS stimulation protocols for different diseases.

Finally, there is still a lack of evidence regarding the longer-term efficacy and safety of tVNS, In the future, more clinical studies with large samples and long-term follow-up are needed to validate.

It is predicted that tVNS research will continue to focus on the effects of tVNS on neuropsychiatric diseases in the next few years and explore its mechanism of action in depth. It is also expected to strengthen the combination with ECG, EEG, and other technical means to form a closed-loop automated stimulation, to take advantage of its precise neuromodulation. In addition, the combination of tVNS with other non-invasive neuromodulation techniques (e.g., TMS) may be a potential direction for future research.

This study is subject to certain limitations. Firstly, only the WOS database was used as the source of literature analysis. Secondly, as there was less tVNS-related literature before 2000, only literature published after the 21st century was included in this study. This may

result in some errors and biases. Nevertheless, an analysis of global publications since the 21st century allows for the visualization of publishing trends and promising areas of research in the dynamic development of tVNS. This analysis informs the establishment of new research directions for tVNS.

Author contributions

SF: Writing – review & editing, Writing – original draft, Methodology, Data curation. LY: Writing – review & editing, Supervision. JZ: Writing – review & editing, Supervision, Investigation. YS: Writing – review & editing, Resources, Investigation. YQ: Writing – review & editing, Resources, Investigation, Conceptualization. MW: Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Data curation. TY: Writing – review & editing, Resources, Investigation, Funding acquisition, Data curation.

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Conflict of interest

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Publisher's note

Supplementary material

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References

Agarwal, V., Kaushik, A. S., Chaudhary, R., Rehman, M., Srivastava, S., and Mishra, V. (2024). Transcutaneous vagus nerve stimulation ameliorates cardiac abnormalities in chronically stressed rats. *Naunyn Schmiedeberg's Arch. Pharmacol.* 397, 281–303. doi: 10.1007/s00210-023-02611-5

Alam, M. J., and Chen, J. (2023). Non-invasive neuromodulation: an emerging intervention for visceral pain in gastrointestinal disorders. *Bioelectron Med* 9:27. doi: 10.1186/s42234-023-00130-5

Aranow, C., Atish-Fregoso, Y., Lesser, M., Mackay, M., Anderson, E., Chavan, S., et al. (2021). Transcutaneous auricular vagus nerve stimulation reduces pain and fatigue in patients with systemic lupus erythematosus: a randomised, double-blind, sham-controlled pilot trial. *Ann. Rheum. Dis.* 80, 203–208. doi: 10.1136/annrheumdis-2020-217872

Arsava, E. M., Topcuoglu, M. A., Ay, I., Ozdemir, A. O., Gungor, I. L., Togay, I. C., et al. (2022). Assessment of safety and feasibility of non-invasive vagus nerve stimulation for treatment of acute stroke. *Brain Stimul.* 15, 1467–1474. doi: 10.1016/j.brs.2022.10.012

Ay, I., Nasser, R., Simon, B., and Ay, H. (2016). Transcutaneous cervical vagus nerve stimulation ameliorates acute ischemic injury in rats. *Brain Stimul.* 9, 166–173. doi: 10.1016/j.brs.2015.11.008

Badran, B. W., Jenkins, D. D., Cook, D., Thompson, S., Dancy, M., DeVries, W. H., et al. (2020). Transcutaneous auricular vagus nerve stimulation-paired rehabilitation for oromotor feeding problems in newborns: an open-label pilot study. *Front. Hum. Neurosci.* 14:77. doi: 10.3389/fnhum.2020.00077

Badran, B. W., Yu, A. B., Adair, D., Mappin, G., DeVries, W. H., Jenkins, D. D., et al. (2019). Laboratory administration of transcutaneous auricular vagus nerve stimulation (tavns): technique, targeting, and considerations. *J. Vis. Exp.*:143. doi: 10.3791/58984

Baig, S. S., Kamarova, M., Ali, A., Su, L., Dawson, J., Redgrave, J. N., et al. (2022). Transcutaneous vagus nerve stimulation (tvns) in stroke: the evidence, challenges and future directions. *Auton. Neurosci.* 237:102909. doi: 10.1016/j.autneu.2021.102909

Baig, S. S., Kamarova, M., Bell, S. M., Ali, A. N., Su, L., Dimairo, M., et al. (2023). Tvns in stroke: a narrative review on the current state and the future. *Stroke* 54, 2676–2687. doi: 10.1161/STROKEAHA.123.043414

Bajbouj, M., Gallinat, J., Lang, U. E., Hellen, F., Vesper, J., Lisanby, S. H., et al. (2007). Motor cortex excitability after vagus nerve stimulation in major depression. *J. Clin. Psychopharmacol.* 27, 156–159. doi: 10.1097/JCP.0b013e31803308f3

Ben-Menachem, E., Revesz, D., Simon, B. J., and Silberstein, S. (2015). Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. *Eur. J. Neurol.* 22, 1260–1268. doi: 10.1111/ene.12629

Berthoud, H. R., and Neuhuber, W. L. (2000). Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.* 85, 1–17. doi: 10.1016/S1566-0702(00)00215-0

Bonaz, B. (2023). The gut-brain axis in parkinson's disease. *Rev. Neurol. (Paris)*. 99, 1877–2013. doi: 10.1152/physrev.00018.2018

Bonaz, B., Bazin, T., and Pellissier, S. (2018). The vagus nerve at the interface of the microbiota-gut-brain axis. *Front. Neurosci.* 12:49. doi: 10.3389/fnins.2018.00049

Bonaz, B., Sinniger, V., and Pellissier, S. (2016). Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J. Physiol.* 594, 5781–5790. doi: 10.1113/JP271539

Brambilla-Pisoni, C., Munoz-Moreno, E., Gallego-Amaro, I., Maldonado, R., Ivorra, A., Soria, G., et al. (2022). Auricular transcutaneous vagus nerve stimulation acutely modulates brain connectivity in mice. *Front. Cell. Neurosci.* 16:856855. doi: 10.3389/fncel.2022.856855

Brock, C., Brock, B., Aziz, Q., Møller, H. J., Pfeiffer, J. M., Drewes, A. M., et al. (2017). Transcutaneous cervical vagal nerve stimulation modulates cardiac vagal tone and tumor necrosis factor-alpha. *Neurogastroenterol. Motil.* 29:12999. doi: 10.1111/nmo.12999

Butt, M. F., Albusoda, A., Farmer, A. D., and Aziz, Q. (2020). The anatomical basis for transcutaneous auricular vagus nerve stimulation. *J. Anat.* 236, 588–611. doi: 10.1111/joa.13122

Chen, S. P., Ay, I., Lopes, D. M. A., Qin, T., Zheng, Y., Sadeghian, H., et al. (2016). Vagus nerve stimulation inhibits cortical spreading depression. *Pain* 157, 797–805. doi: 10.1097/j.pain.0000000000000437

Chen, X., Zhang, J., Shen, L. S., Chen, Y. P., Yang, J. Q., Tang, W. J., et al. (2024). Bibliometric analysis of myelin imaging studies of patients with multiple sclerosis (2000-2022). *Quant. Imaging Med. Surg.* 14, 837–851. doi: 10.21037/qims-23-1157

Chowdhury, T., Sandu, N., Sadr-Eshkevari, P., Meuwly, C., and Schaller, B. (2014). Trigeminocardiac reflex: current trends. *Expert. Rev. Cardiovasc. Ther.* 12, 9–11. doi: 10.1586/14779072.2014.862498

Chung, C. H., Bretherton, B., Zainalabidin, S., Deuchars, S. A., Deuchars, J., and Mahadi, M. K. (2020). Mediation of cardiac macrophage activity via auricular vagal nerve stimulation ameliorates cardiac ischemia/reperfusion injury. *Front. Neurosci.* 14:906. doi: 10.3389/fnins.2020.00906

Chunlei, G. (2023). Efficacy of transcutaneous auricular vagus nerve stimulation in the treatment of mild cognitive impairment and brain mechanism fmri study. *China Academy of Traditional Chinese Med.*

Clancy, J. A., Mary, D. A., Witte, K. K., Greenwood, J. P., Deuchars, S. A., and Deuchars, J. (2014). Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul.* 7, 871–877. doi: 10.1016/j.brs.2014.07.031

Colombo, M., Aggujaro, S., Lombardi, N., Pedrocchi, A., Molteni, F., and Guanziroli, E. (2023). Motor and cognitive modulation of a single session of transcutaneous auricular

vagus nerve stimulation in post stroke patients: a pilot study. *Ieee Open J Eng Med Biol* 4, 292–299. doi: 10.1109/OJEMB.2023.3268011

Colzato, L., and Beste, C. (2020). A literature review on the neurophysiological underpinnings and cognitive effects of transcutaneous vagus nerve stimulation: challenges and future directions. *J. Neurophysiol.* 123, 1739–1755. doi: 10.1152/jn.00057.2020

Colzato, L. S., Elmers, J., Beste, C., and Hommel, B. (2023). A prospect to ameliorate affective symptoms and to enhance cognition in long covid using auricular transcutaneous vagus nerve stimulation. *J. Clin. Med.* 12:1198. doi: 10.3390/jcm12031198

Cook, D. N., Thompson, S., Stomberg-Firestein, S., Bikson, M., George, M. S., Jenkins, D. D., et al. (2020). Design and validation of a closed-loop, motor-activated auricular vagus nerve stimulation (maavns) system for neurorehabilitation. *Brain Stimul.* 13, 800–803. doi: 10.1016/j.brs.2020.02.028

Cristancho, P., Cristancho, M. A., Baltuch, G. H., Thase, M. E., and O'Reardon, J. P. (2011). Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after fda approval: outcomes at 1 year. *J. Clin. Psychiatry* 72, 1376–1382. doi: 10.4088/JCP.09m05888blu

Dalgleish, A. S., Kania, A. M., Stauss, H. M., and Jelen, A. Z. (2021). Occipitoatlantal decompression and noninvasive vagus nerve stimulation slow conduction velocity through the atrioventricular node in healthy participants. *J Osteopath Med* 121, 349–359. doi: 10.1515/jom-2020-0213

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Meglio, M., et al. (2004). Effects of vagus nerve stimulation on cortical excitability in epileptic patients. *Neurology* 62, 2310–2312. doi: 10.1212/01.wnl.0000131743.45131.ae

Diener, H., Goadsby, P. J., Ashina, M., Al-Karagholi, M. A., Sinclair, A., Mitsikostas, D., et al. (2019). Non-invasive vagus nerve stimulation (nvns) for the preventive treatment of episodic migraine: the multicentre, double-blind, randomised, sham-controlled premium trial. *Cephalalgia* 39, 1475–1487. doi: 10.1177/0333102419876920

Doerr, J. M., Juenemann, M., Hakel, L., Schmidt, L., Menzler, K., Krause, K., et al. (2023). Effect of transcutaneous vagus nerve stimulation on stress-reactive neuroendocrine measures in a sample of persons with temporal lobe epilepsy. *Epilepsia Open* 8, 1013–1020. doi: 10.1002/epi4.12774

Drewes, A. M., Brock, C., Rasmussen, S. E., Moller, H. J., Brock, B., Deleuran, B. W., et al. (2021). Short-term transcutaneous non-invasive vagus nerve stimulation may reduce disease activity and pro-inflammatory cytokines in rheumatoid arthritis: results of a pilot study. *Scand. J. Rheumatol.* 50, 20–27. doi: 10.1080/03009742.2020.1764617

Duyu, D., and Wei, Z. (2019). Neuromodulation therapy for Alzheimer's disease. *Chin. Med. J.* 54, 474–477. doi: 10.3969/j.issn.1008-1070.2019.05.003

Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., et al. (2020). International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (version 2020). *Front. Hum. Neurosci.* 14:568051. doi: 10.3389/fnhum.2020.568051

Fischer, R., Ventura-Bort, C., Hamm, A., and Weymar, M. (2018). Transcutaneous vagus nerve stimulation (tvns) enhances conflict-triggered adjustment of cognitive control. *Cogn. Affect. Behav. Neurosci.* 18, 680–693. doi: 10.3758/s13415-018-0596-2

Frangos, E., Ellrich, J., and Komisaruk, B. R. (2015). Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fmri evidence in humans. *Brain Stimul.* 8, 624–636. doi: 10.1016/j.brs.2014.11.018

Garcia, R. G., Cohen, J. E., Stanford, A. D., Gabriel, A., Stowell, J., Aizley, H., et al. (2021). Respiratory-gated auricular vagal afferent nerve stimulation (ravans) modulates brain response to stress in major depression. *J. Psychiatr. Res.* 142, 188–197. doi: 10.1016/j.jpsychires.2021.07.048

Garcia, R. G., Lin, R. L., Lee, J., Kim, J., Barbieri, R., Sclocco, R., et al. (2017). Modulation of brainstem activity and connectivity by respiratory-gated auricular vagal afferent nerve stimulation in migraine patients. *Pain* 158, 1461–1472. doi: 10.1097/j.pain.0000000000000930

Gazi, A. H., Wittbrodt, M. T., Harrison, A. B., Sundararaj, S., Gurel, N. Z., Nye, J. A., et al. (2022). Robust estimation of respiratory variability uncovers correlates of limbic brain activity and transcutaneous cervical vagus nerve stimulation in the context of traumatic stress. *IEEE Trans. Biomed. Eng.* 69, 849–859. doi: 10.1109/TBME.2021.3108135

Geng, D., Yang, K., Fu, Z., Zhang, Y., Wang, C., and An, H. (2022). Circadian stage-dependent and stimulation duration effects of transcutaneous auricular vagus nerve stimulation on heart rate variability. *PLoS One* 17:e277090. doi: 10.1371/journal.pone.0277090

Goadsby, P. J., de Coo, I. F., Silver, N., Tyagi, A., Ahmed, F., Gaul, C., et al. (2018). Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled act2 study. *Cephalalgia* 38, 959–969. doi: 10.1177/0333102417744362

Grazzi, L., Egeo, G., Liebler, E., Padovan, A. M., and Barbanti, P. (2017). Non-invasive vagus nerve stimulation (nvns) as symptomatic treatment of migraine in young patients: a preliminary safety study. *Neurol. Sci.* 38, 197–199. doi: 10.1007/s10072-017-2942-5

Gu, N. N., and Li, C. H. (2020). Advances in percutaneous vagus nerve stimulation. *J. Shanghai Jiao Tong University (Medical Edition)* 40, 539–542. doi: 10.3969/j.issn.1674-8115.2020.04.021

Gurel, N. Z., Wittbrodt, M. T., Jung, H., Shandhi, M., Driggers, E. G., Ladd, S. L., et al. (2020). Transcutaneous cervical vagal nerve stimulation reduces sympathetic responses to stress in posttraumatic stress disorder: a double-blind, randomized, sham controlled trial. *Neurobiol Stress* 13:100264. doi: 10.1016/j.ynstr.2020.100264

Hansen, N. (2018). Memory reinforcement and attenuation by activating the human locus coeruleus via transcutaneous vagus nerve stimulation. *Front. Neurosci.* 12:955. doi: 10.3389/fnins.2018.00955

Hao Han, Z., Pei Jing, R., Yu, C., Xing Ke, S., and Jun Ying, W. (2023). Exploring the possible mechanism of auricular acupoints for migraine from the ear vagus nerve. *Acupuncture Res.*, 1–11. doi: 10.13702/j.1000-0607.20221262

He, H., Shen, W., Zheng, L., Guo, X., and Cline, H. T. (2018). Excitatory synaptic dysfunction cell-autonomously decreases inhibitory inputs and disrupts structural and functional plasticity. *Nat. Commun.* 9:2893. doi: 10.1038/s41467-018-05125-4

Hongxian, R., Ruirong, Z., and Xianze, M. (2023). Progress of anti-inflammatory effects of percutaneous ear vagus nerve stimulation. Joint. *Mil. Med.* 37, 632–636. doi: 10.13730/j.issn.2097-2148.2023.07.017

Hou, L. W., Fang, J. L., Zhang, J. L., Wang, L., Wu, D., Wang, J. Y., et al. (2022). Auricular vagus nerve stimulation ameliorates functional dyspepsia with depressive-like behavior and inhibits the hypothalamus-pituitary-adrenal axis in a rat model. *Dig. Dis. Sci.* 67, 4719–4731. doi: 10.1007/s10620-021-07332-4

Hou, L., Rong, P., Yang, Y., Fang, J., Wang, J., Wang, Y., et al. (2023). Auricular vagus nerve stimulation improves visceral hypersensitivity and gastric motility and depression-like behaviors via Vago-vagal pathway in a rat model of functional dyspepsia. *Brain Sci.* 13. doi: 10.3390/brainsci13020253

Huifeng, L. (2017). Research on methods and techniques of clustering analysis of big data in internet of things. China: North Polytechnic University.

Jiakai, H. E., Jinling, Z., Yu, W., Shaoyuan, L. I., Jiliang, F., Shuai, Z., et al. (2023). Transcutaneous auricular vagus nerve stimulation would be an alternative to implantable cervical vagus nerve stimulation in some situation. *J. Tradit. Chin. Med.* 43, 627–630. doi: 10.19852/j.cnki.jtcm.20230308.002

Jiang, S., Liu, Y., Zheng, H., Zhang, L., Zhao, H., Sang, X., et al. (2023). Evolutionary patterns and research frontiers in neoadjuvant immunotherapy: a bibliometric analysis. *Int. J. Surg.* 109, 2774–2783. doi: 10.1097/JS9.0000000000000492

Johnston, G. R., and Webster, N. R. (2009). Cytokines and the immunomodulatory function of the vagus nerve. *Br. J. Anaesth.* 102, 453–462. doi: 10.1093/bja/aep037

Kaczmarczyk, M., Antosik-Wójcińska, A., Dominiak, M., and Święcicki, Ł. (2021). Use of transcutaneous auricular vagus nerve stimulation (tavns) in the treatment of drug-resistant depression - a pilot study, presentation of five clinical cases. *Psychiatr. Pol.* 55, 555–564. doi: 10.12740/PP/OnlineFirst/115191

Kaczmarczyk, R., Tejera, D., Simon, B. J., and Heneka, M. T. (2017). Microglia modulation through external vagus nerve stimulation in a murine model of alzheimer's disease. *J. Neurochem.* doi: 10.1111/jnc.14284

Kaniusas, E., Kampusch, S., Tittgemeyer, M., Panetsos, F., Gines, R. F., Papa, M., et al. (2019). Current directions in the auricular vagus nerve stimulation i - a physiological perspective. *Front. Neurosci.* 13:854. doi: 10.3389/fnins.2019.00854

Kaniusas, E., Szeles, J. C., Kampusch, S., Alfageme-Lopez, N., Yucuma-Conde, D., Li, X., et al. (2020). Non-invasive auricular vagus nerve stimulation as a potential treatment for covid19-originated acute respiratory distress syndrome. *Front. Physiol.* 11:890. doi: 10.3389/fphys.2020.00890

Kaut, O., Janocha, L., Weismüller, T. J., and Wüllner, U. (2019). Transcutaneous vagal nerve stimulation improves gastroenteric complaints in parkinson's disease patients. *NeuroRehabilitation* 45, 449–451. doi: 10.3233/NRE-192909

Keute, M., Ruhnau, P., Heinze, H. J., and Zaehle, T. (2018). Behavioral and electrophysiological evidence for gabaergic modulation through transcutaneous vagus nerve stimulation. *Clin. Neurophysiol.* 129, 1789–1795. doi: 10.1016/j.clinph.2018.05.026

Kim, A. Y., Marduy, A., de Melo, P. S., Gianlorenco, A. C., Kim, C. K., Choi, H., et al. (2022). Safety of transcutaneous auricular vagus nerve stimulation (tavns): a systematic review and meta-analysis. *Sci. Rep.* 12:22055. doi: 10.1038/s41598-022-25864-1

Ko, D. (2021). Transcutaneous vagus nerve stimulation (tvns) as a potential therapeutic application for neurodegenerative disorders - a focus on dysautonomia in parkinson's disease. *Auton. Neurosci.* 235:102858. doi: 10.1016/j.autneu.2021.102858

Kornum, D. S., Bertoli, D., Kufaishi, H., Wegeberg, A., Okdahl, T., Mark, E. B., et al. (2024). Transcutaneous vagal nerve stimulation for treating gastrointestinal symptoms in individuals with diabetes: a randomised, double-blind, sham-controlled, multicentre trial. *Diabetologia* 67, 1122–1137. doi: 10.1007/s00125-024-06129-0

Kumaria, A., and Ashkan, K. (2023). Neuromodulation as an anticancer strategy. *Cancer Med.* 12, 20521–20522. doi: 10.1002/cam4.6624

Lanska, D. J. (2002). JL Corning and vagal nerve stimulation for seizures in the 1880s. *Neurology* 58, 452–459. doi: 10.1212/wnl.58.3.452

Lench, D. H., Turner, T. H., McLeod, C., Boger, H. A., Lovera, L., Heidelberg, L., et al. (2023). Multi-session transcutaneous auricular vagus nerve stimulation for parkinson's disease: evaluating feasibility, safety, and preliminary efficacy. *Front. Neurol.* 14:1210103. doi: 10.3389/fneur.2023.1210103

Li, J. (2020). Cholinergic anti-inflammatory pathway activity regulates axonal plasticity and neovascularization after cerebral ischemia/reperfusion injury and its mechanism [PhD]. China: Chongqing Medical University.

Li, S., Wang, Y., Gao, G., Guo, X., Zhang, Y., Zhang, Z., et al. (2020). Transcutaneous auricular vagus nerve stimulation at 20 hz improves depression-like behaviors and down-regulates the hyperactivity of hpa axis in chronic unpredictable mild stress model rats. *Front. Neurosci.* 14:680. doi: 10.3389/fnins.2020.00680

Li, J. N., Xie, C. C., Li, C. Q., Zhang, G. F., Tang, H., Jin, C. N., et al. (2022). Efficacy and safety of transcutaneous auricular vagus nerve stimulation combined with conventional rehabilitation training in acute stroke patients: a randomized controlled trial conducted for 1 year involving 60 patients. *Neural Regen. Res.* 17, 1809–1813. doi: 10.4103/1673-5374.332155

Li, S., Zhou, X., Yu, L., and Jiang, H. (2015). Low level non-invasive vagus nerve stimulation: a novel feasible therapeutic approach for atrial fibrillation. *Int. J. Cardiol.* 182, 189–190. doi: 10.1016/j.ijcard.2014.12.171

Lin, W. S., Chou, C. L., Chang, M. H., Chung, Y. M., Lin, F. G., and Tsai, P. Y. (2018). Vagus nerve magnetic modulation facilitates dysphagia recovery in patients with stroke involving the brainstem - a proof of concept study. *Brain Stimul.* 11, 264–270. doi: 10.1016/j.brs.2017.10.021

Liyanarachchi, K., Ross, R., and Debono, M. (2017). Human studies on hypothalamo-pituitary-adrenal (hpa) axis. *Best Pract. Res. Clin. Endocrinol. Metab.* 31, 459–473. doi: 10.1016/j.beem.2017.10.011

Luo, S. (1994). Introduction to Bibliometrics. Guangzhou: Sun Yat-sen University Press.

Ma, Y., He, J., Lu, X., Sun, J., Guo, C., Luo, Y., et al. (2023). Transcutaneous electrical cranial-auricular acupoint stimulation versus escitalopram for modulating the brain activity in mild to moderate major depressive disorder: an fmri study. *Neurosci. Lett.* 814:137414. doi: 10.1016/j.neulet.2023.137414

Marano, M., Anzini, G., Musumeci, G., Magliozzi, A., Pozzilli, V., Capone, F., et al. (2022). Transcutaneous auricular vagus stimulation improves gait and reaction time in parkinson's disease. *Mov. Disord.* 37, 2163–2164. doi: 10.1002/mds.29166

Martelli, D., Yao, S. T., McKinley, M. J., and McAllen, R. M. (2014). Reflex control of inflammation by sympathetic nerves, not the vagus. *J. Physiol.* 592, 1677–1686. doi: 10.1113/jphysiol.2013.268573

Meuwly, C., Chowdhury, T., Sandu, N., Golanov, E., Erne, P., Rosemann, T., et al. (2017). Definition and diagnosis of the trigeminocardiac reflex: a grounded theory approach for an update. *Front. Neurol.* 8:533. doi: 10.3389/fneur.2017.00533

Moazzami, K., Pearce, B. D., Gurel, N. Z., Wittbrodt, M. T., Levantsevych, O. M., Huang, M., et al. (2023). Transcutaneous vagal nerve stimulation modulates stress-induced plasma ghrelin levels: a double-blind, randomized, sham-controlled trial. *J. Affect. Disord.* 342, 85–90. doi: 10.1016/j.jad.2023.09.015

Müller, S. J., Teckentrup, V., Rebollo, I., Hallschmid, M., and Kroemer, N. B. (2022). Vagus nerve stimulation increases stomach-brain coupling via a vagal afferent pathway. *Brain Stimul.* 15, 1279–1289. doi: 10.1016/j.brs.2022.08.019

Nagai, M., Dote, K., Kato, M., Sasaki, S., Oda, N., and Förster, C. Y. (2023). Afterload reduction after non-invasive vagus nerve stimulation in acute heart failure. *Front. Hum. Neurosci.* 17:1149449. doi: 10.3389/fnhum.2023.1149449

Nesbitt, A. D., Marin, J. C., Tompkins, E., Ruttledge, M. H., and Goadsby, P. J. (2015). Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology* 84, 1249–1253. doi: 10.1212/WNL.0000000000001394

Ninkov, A., Frank, J. R., and Maggio, L. A. (2022). Bibliometrics: methods for studying academic publishing. *Perspect Med Educ* 11, 173–176. doi: 10.1007/s40037-021-00695-4

Nöthen, C., Sandu, N., Prabhakar, H., Filis, A., Arasho, B. D., Buchfelder, M., et al. (2010). Trigemino-cardiac reflex and antecedent transient ischemic attacks. *Expert. Rev. Cardiovasc. Ther.* 8, 509–512. doi: 10.1586/erc.10.19

Ooi, Q. Y., Qin, X., Yuan, Y., Zhang, X., Yao, Y., Hao, H., et al. (2023). Alteration of excitation/inhibition imbalance in the hippocampus and amygdala of drug-resistant epilepsy patients treated with acute vagus nerve stimulation. *Brain Sci.* 13:976. doi: 10.3390/brainsci13070976

Penry, J. K., and Dean, J. C. (1990). Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia* 31, S40–S43. doi: 10.1111/j.1528-1157.1990.tb05848.x

Rawat, J. K., Roy, S., Singh, M., Guatam, S., Yadav, R. K., Ansari, M. N., et al. (2019). Transcutaneous vagus nerve stimulation regulates the cholinergic anti-inflammatory pathway to counteract 1, 2-dimethylhydrazine induced colon carcinogenesis in albino wistar rats. *Front. Pharmacol.* 10:353. doi: 10.3389/fphar.2019.00353

Redgrave, J., Day, D., Leung, H., Laud, P. J., Ali, A., Lindert, R., et al. (2018). Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. *Brain Stimul.* 11, 1225–1238. doi: 10.1016/j.brs.2018.08.010

Rong, P., Liu, J., Wang, L., Liu, R., Fang, J., Zhao, J., et al. (2016). Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. *J. Affect. Disord.* 195, 172–179. doi: 10.1016/j.jad.2016.02.031

Rong, P., Liu, A., Zhang, J., Wang, Y., Yang, A., Li, L., et al. (2014). An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. *Chin. Med. J.* 127, 300–303. doi: 10.3760/cma.j.issn.0366-6999.20131511

Schaller, B. J., Sandu, N., Cornelius, J. F., Filis, A., and Perez-Pinzon, M. A. (2009). Oxygen-conserving implications of the trigemino-cardiac reflex in the brain: the molecular basis of neuroprotection? *Mol. Med.* 15, 125–126. doi: 10.2119/molmed.2009.00013

Schindler, E., and Burish, M. J. (2022). Recent advances in the diagnosis and management of cluster headache. *BMJ* 376:e59577. doi: 10.1136/bmj-2020-059577

Schiweck, C., Sausmekat, S., Zhao, T., Jacobsen, L., Reif, A., and Edwin, T. S. (2024). No consistent evidence for the anti-inflammatory effect of vagus nerve stimulation in humans: a systematic review and meta-analysis. *Brain Behav. Immun.* 116, 237–258. doi: 10.1016/j.bbi.2023.12.008

Shi, X., Hu, Y., Zhang, B., Li, W., Chen, J. D., and Liu, F. (2021). Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. *JCI Insight* 6:e150052. doi: 10.1172/jci.insight.150052

Simon, B., and Blake, J. (2017). Mechanism of action of non-invasive cervical vagus nerve stimulation for the treatment of primary headaches. *Am. J. Manag. Care* 23, S312–S316

Skandalakis, L. J., Donahue, P. E., and Skandalakis, J. E. (1993). The vagus nerve and its vagaries. *Surg. Clin. North Am.* 73, 769–784. doi: 10.1016/s0039-6109(16)46084-6

Song, D., Li, P., Wang, Y., and Cao, J. (2023). Noninvasive vagus nerve stimulation for migraine: a systematic review and meta-analysis of randomized controlled trials. *Front. Neurol.* 14:1190062. doi: 10.3389/fneur.2023.1190062

Stefan, H., Kreiselmeyer, G., Kerling, F., Kurzbuch, K., Rauch, C., Heers, M., et al. (2012). Transcutaneous vagus nerve stimulation (t-vns) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia* 53, e115–e118. doi: 10.1111/j.1528-1167.2012.03492.x

Steidel, K., Krause, K., Menzler, K., Strzelczyk, A., Immisch, I., Fuest, S., et al. (2021). Transcutaneous auricular vagus nerve stimulation influences gastric motility: a randomized, double-blind trial in healthy individuals. *Brain Stimul.* 14, 1126–1132. doi: 10.1016/j.brs.2021.06.006

Sternberg, Z., and Schaller, B. (2020). Central noradrenergic agonists in the treatment of ischemic stroke-an overview. *Transl. Stroke Res.* 11, 165–184. doi: 10.1007/s12975-019-00718-7

Stowell, J., Garcia, R. G., Staley, R., Sclocco, R., Fisher, H., Napadow, V., et al. (2019). Dose-optimization of respiratory-gated auricular vagal afferent nerve stimulation (ravans) for blood pressure modulation in hypertensive patients. *2019 Computing in Cardiology (CinC)* 2019, 8–11.

Sun, L., Ma, S., Yu, Y., Li, X., Wei, Q., Min, L., et al. (2024). Transcutaneous auricular vagus nerve stimulation ameliorates adolescent depressive- and anxiety-like behaviors via hippocampus glycolysis and inflammation response. *CNS Neurosci. Ther.* 30:e14614. doi: 10.1111/cns.14614

Tornero, C., Pastor, E., Garzando, M., Orduña, J., Forner, M. J., Bocigas, I., et al. (2022). Non-invasive vagus nerve stimulation for covid-19: results from a randomized controlled trial (savior i). *Front. Neurol.* 13:820864. doi: 10.3389/fneur.2022.820864

Urbin, M. A., Lafe, C. W., Simpson, T. W., Wittenberg, G. F., Chandrasekaran, B., and Weber, D. J. (2021). Electrical stimulation of the external ear acutely activates noradrenergic mechanisms in humans. *Brain Stimul.* 14, 990–1001. doi: 10.1016/j.brs.2021.06.002

van Midden, V. M., Demšar, J., Pirtošek, Z., and Kojović, M. (2023). The effects of transcutaneous auricular vagal nerve stimulation on cortical gabaergic and cholinergic circuits: a transcranial magnetic stimulation study. *Eur. J. Neurosci.* 57, 2160–2173. doi: 10.1111/ejn.16004

Vargas-Caballero, M., Warming, H., Walker, R., Holmes, C., Cruickshank, G., and Patel, B. (2022). Vagus nerve stimulation as a potential therapy in early alzheimer's disease: a review. *Front. Hum. Neurosci.* 16:866434. doi: 10.3389/fnhum.2022.866434

Ventureyra, E. C. (2000). Transcutaneous vagus nerve stimulation for partial onset seizure therapy: A new concept. *Childs Nerv. Syst.* 16, 101–102. doi: 10.1007/s003810050021

von Wrede, R., Rings, T., Bröhl, T., Pukropski, J., Schach, S., Helmstaedter, C., et al. (2022). Transcutaneous auricular vagus nerve stimulation differently modifies functional brain networks of subjects with different epilepsy types. *Front. Hum. Neurosci.* 16:867563. doi: 10.3389/fnhum.2022.867563

Wang, L., Gao, F., Dai, Y., Wang, Z., Liang, F., Wu, J., et al. (2023). Transcutaneous auricular vagus nerve stimulation on upper limb motor function with stroke: a functional near-infrared spectroscopy pilot study. *Front. Neurosci.* 17:1297887. doi: 10.3389/fnins.2023.1297887

Wang, Y., Li, S. Y., Wang, D., Wu, M. Z., He, J. K., Zhang, J. L., et al. (2021). Transcutaneous auricular vagus nerve stimulation: from concept to application. *Neurosci. Bull.* 37, 853–862. doi: 10.1007/s12264-020-00619-y

Wang, L., Wu, Q., Yang, Z., Yang, Y., Luo, Y., Cao, Y., et al. (2022). Preliminary study of vagus nerve magnetic modulation in patients with prolonged disorders of consciousness. *Neuropsychiatr. Dis. Treat.* 18, 2171–2179. doi: 10.2147/NDT.S381681

Wang, H., Yu, M., Ochani, M., Amella, C. A., Tanovic, M., Susarla, S., et al. (2003). Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 421, 384–388. doi: 10.1038/nature01339

Wang, J. Y., Zhang, Y., Chen, Y., Wang, Y., Li, S. Y., Wang, Y. F., et al. (2021). Mechanisms underlying antidepressant effect of transcutaneous auricular vagus nerve stimulation on cums model rats based on hippocampal α7nachr/nf-κb signal pathway. *J. Neuroinflammation* 18:291. doi: 10.1186/s12974-021-02341-6

Wang, S., Zhang, L., Jin, Z., Wang, Y., Zhang, B., and Zhao, L. (2023). Visualizing temporal dynamics and research trends of macrophage-related diabetes studies between 2000 and 2022: a bibliometric analysis. *Front. Immunol.* 14:1194738. doi: 10.3389/fimmu.2023.1194738

Wei, N., Xu, Y., Li, Y., Shi, J., Zhang, X., You, Y., et al. (2022). A bibliometric analysis of t cell and atherosclerosis. *Front. Immunol.* 13:948314. doi: 10.3389/fimmu.2022.948314

Yan, L., Li, H., Qian, Y., Zhang, J., Cong, S., Zhang, X., et al. (2024). Transcutaneous vagus nerve stimulation: a new strategy for alzheimer's disease intervention through the brain-gut-microbiota axis? *Front. Aging Neurosci.* 16:1334887. doi: 10.3389/fnagi.2024.1334887

Yang, H., Shi, W., Fan, J., Wang, X., Song, Y., Lian, Y., et al. (2023). Transcutaneous auricular vagus nerve stimulation (ta-vns) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial. *Neurotherapeutics* 20, 870–880. doi: 10.1007/s13311-023-01353-9

Yap, J. Y. Y., Keatch, C., Lambert, E., Woods, W., Stoddart, P. R., and Kameneva, T. (2020). Critical review of transcutaneous vagus nerve stimulation: challenges for translation to clinical practice. *Front. Neurosci.* 14:284. doi: 10.3389/fnins.2020.00284

Yu, Y., Jiang, X., Fang, X., Wang, Y., Liu, P., Ling, J., et al. (2023). Transauricular vagal nerve stimulation at 40 hz inhibits hippocampal p2x7r/nlrp3/caspase-1 signaling and improves spatial learning and memory in 6-month-old app/ps1 mice. *Neuromodulation* 26, 589–600. doi: 10.1016/j.neurom.2022.03.011

Yu, C., Jun-Ying, W., Yue, Z., Zi-Xuan, Z., Yi-Fei, W., and Pei-Jing, R. (2023). Effects of transcutaneous auricular-vagus nerve stimulation on α7nachr/jak2/stat3 signaling pathway in the spleen of rats with lipopolysaccharide-induced depressive-like behavior. *Acupuncture Res.* 48, 933–938. doi: 10.13702/j.1000-0607.20220402

Yu, Y., Ling, J., Yu, L., Liu, P., and Jiang, M. (2021). Closed-loop transcutaneous auricular vagal nerve stimulation: current situation and future possibilities. *Front. Hum. Neurosci.* 15:785620. doi: 10.3389/fnhum.2021.785620

Yuan, Y., Wang, J., Wu, D., Zhang, D., and Song, W. (2019). Effect of transcutaneous vagus nerve stimulation in dysphagia after lateral medullary infarction: a case report. *Am. J. Speech Lang. Pathol.* 28, 1381–1387. doi: 10.1044/2019_AJSLP-18-0262

Yue, C., Chen, C., Liu, Z., Zhigang, H., and Wang, X. (2015). Methodological functions of Citespace knowledge graph. *Res. Sci.* 33, 242–253. doi: 10.16192/j.cnki.1003-2053.2015.02.009

Zeng, J., Chu, H., Lu, Y., Xiao, X., Lu, L., Li, J., et al. (2023). Research status and hotspots in the surgical treatment of tremor in parkinson's disease from 2002 to 2022: a bibliometric and visualization analysis. *Front. Aging Neurosci.* 15:1157443. doi: 10.3389/fnagi.2023.1157443

Zhang, H., Cao, X. Y., Wang, L. N., Tong, Q., Sun, H. M., Gan, C. T., et al. (2023). Transcutaneous auricular vagus nerve stimulation improves gait and cortical activity in parkinson's disease: a pilot randomized study. *CNS Neurosci. Ther.* 29, 3889–3900. doi: 10.1111/cns.14309

Zhang, S., He, J. K., Zhong, G. L., Wang, Y., Zhao, Y. N., Wang, L., et al. (2022). Prolonged longitudinal transcutaneous auricular vagus nerve stimulation effect on striatal functional connectivity in patients with major depressive disorder. *Brain Sci.* 12:1730. doi: 10.3390/brainsci12121730

Zhang, Y., Huang, Y., Li, H., Yan, Z., Zhang, Y., Liu, X., et al. (2021). Transcutaneous auricular vagus nerve stimulation (tavns) for migraine: an fmri study. *Reg. Anesth. Pain Med.* 46, 145–150. doi: 10.1136/rapm-2020-102088

Zhang, Y., Liu, J., Li, H., Yan, Z., Liu, X., Cao, J., et al. (2019). Transcutaneous auricular vagus nerve stimulation at 1 hz modulates locus coeruleus activity and resting state functional connectivity in patients with migraine: an fmri study. *Neuroimage Clin* 24:101971. doi: 10.1016/j.nicl.2019.101971

Zhang, H., Zhao, Y., Qu, Y., Du, J., and Peng, Y. (2023). Transcutaneous cervical vagus nerve magnetic stimulation in patients with traumatic brain injury: a feasibility study. *Neuromodulation* 27, 672–680. doi: 10.1016/j.neurom.2023.09.004

Zhilong, Z., Shengping, Y., Tianxin, C., and Yuqi, Z. (2023). Visualization and analysis of research hotspots and trends in the field of articular cartilage repair. *Chinese Tissue Eng.* 28, 4306–4311. doi: 10.12307/2024.547

Zhu, Y., Xu, F., Sun, C., Xu, W., Li, M., Gong, Y., et al. (2023). Noninvasive transcutaneous auricular vagal nerve stimulation improves gastric slow waves impaired by cold stress in healthy subjects. *Neuromodulation* 26, 1851–1857. doi: 10.1016/j.neurom.2022.03.010

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Transcutaneous electrical acupoint stimulation for upper limb motor recovery after stroke: a systematic review and meta-analysis

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Background: Transcutaneous electrical acupoint stimulation (TEAS) is an innovative, non-invasive therapy that stimulates the contraction of paralyzed muscles in the upper limbs, promoting functional recovery. Several studies have demonstrated the efficacy of TEAS in restoring upper limb function. This study aims to evaluate the impact of TEAS on upper limb motor recovery after stroke.

Objectives: This study aims to evaluate the influence of TEAS on upper limb motor recovery after stroke and improve the quality of life in such patients.

Methods: Eight databases were systematically searched from inception to 1st October 2024. Two independent reviewers conducted the screening and data extraction of the study. The primary outcome measure was the Fugl Meyer Assessment of the Upper Extremity (FMA-UE), which evaluates upper extremity motor function in stroke patients. Secondary outcomes included the Modified Ashworth Scale (MAS) for assessing spasticity and the Modified Barthel Index (MBI) to evaluate patients' abilities to perform activities of daily living. Data synthesis was conducted using RevMan 5.4 and Stata 14.0. The GRADE method was employed to assess the quality of evidence.

Results: A total of 16 trials involving 1,218 stroke patients were included in this meta-analysis. Meta-analysis showed that the TEAS significantly improved upper limb function (SMD = 1.70, 95CI% = 1.09 to 2.31, $p < 0.00001$, $I^2 = 93\%$; low certainty of evidence), reduced spasticity (SMD = −1.18, 95CI% = −1.79 to −0.58, $p < 0.00001$, $I^2 = 90\%$; very low certainty of evidence), and enhanced the ability to perform daily activities (SMD = 1.53, 95CI% = 0.85 to 2.20, $p < 0.00001$, $I^2 = 95\%$; low certainty of evidence).

Conclusion: Our results indicated that TEAS improved motor function and functional activities and reduced muscle tone in the upper limbs after stroke. However, these results should be interpreted with caution due to the limited strength of the evidence. High-quality, larger sample, multi-center studies are needed to validate these preliminary findings.

Systematic review registration: This study was registered on PROSPERO with registration number CRD42024592509. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024592509

KEYWORDS

transcutaneous electrical acupoint stimulation (TEAS), stroke, upper limb function, meta-analysis, systematic review

1 Introduction

Stroke is a condition characterized by damage to brain tissue caused by the rupture or obstruction of blood vessels within the brain (Sacco et al., 2013). According to the Global Burden of Disease Study (GBD), stroke ranks as the third leading cause of disability and mortality, accounting for 87.4 deaths (95% UI 79.5–94.4) per 100,000 population (GBD 2021 Causes of Death Collaborators, 2024). In China alone, more than 70 million individuals are affected by stroke, making it the leading cause of death in the country. Furthermore, as the population continues to age, the burden associated with stroke is expected to increase significantly (Tu and Wang, 2023; Wang et al., 2022).

After the onset of stroke, a variety of adverse manifestations can occur rapidly, most often accompanied by sensory and limb dysfunction, which severely impacts patients' daily lives (Dawson et al., 2021). Studies have shown that approximately 55–75% of patients experience varying degrees of upper limb motor dysfunction (Ma et al., 2021). Relevant studies have demonstrated a strong correlation between upper limb motor function and activities of daily living (ADL) in stroke patients, which places a significant burden on caregivers, families, and society (Meng et al., 2022).

Upper limb motor dysfunction resulting from damage to upper motor neurons is characterized by poor motor ability, spasticity and flexion of the fingers, and impaired fine motor control of the hand (Zhou et al., 2021). Compared to lower limb motor dysfunction after a stroke, upper limb motor dysfunction is more difficult to recover from, with a higher incidence and a longer recovery period (Julie et al., 2017). Because fine motor tasks, especially those involving the hand, require precision, regaining normal function is challenging, and relying solely on traditional rehabilitation training often yields unsatisfactory outcomes.

Neurorehabilitation for upper limb dysfunction has become a central focus of post-stroke recovery efforts (Huang et al., 2024; Tang et al., 2024). Based on insights into brain functional remodeling, brain functional connectivity, cortical reorganization, and neural plasticity, various rehabilitation methods have been developed (Muller et al., 2024). Some of these methods, such as robotic exoskeleton training and constraint-induced movement therapy, have shown significant effectiveness (Zhang et al., 2022; Thrane et al., 2015).

Constraint-induced movement therapy, in particular, has shown positive rehabilitation outcomes for patients with acute or subacute strokes (Liu et al., 2017). However, for stroke survivors with severe motor deficits, the treatment outcomes are often minimal, and recovery remains unpredictable (Coscia et al., 2019).

Robotic training may be a viable alternative for patients with severe upper limb injuries, though the high cost of robotic devices poses a challenge (Zhang et al., 2022). Other therapeutic techniques, such as mirror therapy (Nogueira et al., 2021) and neurodevelopmental treatment (Langhammer and Stanghelle, 2011), appear to lack strong evidence supporting their effectiveness in improving upper limb motor function after a stroke. Therefore, new rehabilitation methods should be developed to enhance upper limb motor function impairment following a stroke (Pollock et al., 2014).

Electrical stimulation therapy for post-stroke spasticity has become a major area of interest. The American Heart Association guidelines for adult stroke rehabilitation endorse neuromuscular electrical stimulation as an effective approach for the transient alleviation of spasticity (Winstein et al., 2013). Transcutaneous electrical acupoint stimulation (TEAS) is a non-invasive stimulation therapy that combines the advantages of Chinese acupuncture and transcutaneous electrical nerve stimulation (Pan et al., 2023). TEAS uses low-frequency pulsed direct current to electrically stimulate peripheral acupoints and surrounding tissues. This stimulation facilitates the transmission of information to the central nervous system, thereby enhancing local neuromuscular function (Szmit et al., 2023).

TEAS mimics the effects of acupuncture on specific acupoints, stimulating muscle cell activity and facilitating the restoration of upper limb function and active control capabilities as swiftly as possible. This approach effectively alleviates symptoms of spasticity (Yan and Hui-Chan, 2009). Moreover, it activates relevant regions of the cerebral cortex, eliciting responses from neurons associated with the upper limb. This process is beneficial for enhancing muscle strength and improving hand coordination (Alwhaibi et al., 2021). Compared to electroacupuncture and traditional acupuncture, TEAS can avoid discomforts such as pain and bleeding and has higher patient compliance (Chi et al., 2019). In addition, the input time and frequency of the pulse current can be set after setting the parameters, facilitating the quantification and standardization of acupuncture treatment (Xu et al., 2016).

Clinical practice has confirmed that combined rehabilitation training with TEAS can significantly enhance patients' muscle strength and improve hand function, grip strength, and manual dexterity. This approach facilitates the recovery of upper limb functionality while alleviating pain and addressing symptoms such as muscle spasms, ultimately enhancing the patient's quality of life (Wang, 2024). In addition, previous network meta-analysis showed that TEAS had the most significant effect on upper limb motor recovery in stroke (Tang et al., 2021). Factors such as the treatment regimen and TEAS parameters should be considered to accurately measure the effectiveness of TEAS. However, no comprehensive meta-analysis has included the above factors simultaneously to specifically analyze the effects of TEAS on upper limb motor recovery in stroke. In this systematic review, stratified analysis was conducted to summarize and analyze the scientific evidence of TEAS on upper limb motor recovery in stroke patients.

2 Methods

A systematic review and meta-analysis were conducted according to the reporting checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al., 2021). The study has been registered with Prospero (registration number

CRD42024592509). Ethics review board approval was not required for this study.

2.1 Search strategy

Two reviewers (LJY and XYW) independently searched databases to collect randomized controlled trials (RCTs) of TEAS on upper limb motor recovery in stroke patients, including eight databases: 4 English databases, Embase, Web of Science, PubMed, The Cochrane Library and 4 Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang database (WANFANG), VIP database (VIP) and Chinese Biomedical Literature Service system (CBM). The search period covered from the inception of each database to 1st October 2024, and references from the included literature were traced. The languages are Chinese and English. In addition, the key points used in this study include "transcutaneous electrical acupoint stimulation," "TEAS," "stroke," "cerebrovascular accident," "cerebrovascular disease," "upper limb motor," "upper limb," "randomized controlled trials," and "clinical trial." The specific search strategies are described in the Supplementary Appendix.

2.2 Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (1) Study designs: randomized controlled trials; (2) Participants: The selected stroke patients should meet the diagnostic criteria of stroke published in the literature or recognized at home and abroad and be further diagnosed by CT and MRI. The patient had stable vital signs, clear consciousness, and upper limb motor dysfunction. There were no restrictions based on gender, age, or race. (3) Intervention: TEAS stimulation (the acupoints, frequency, duration, and course of TEAS stimulation were not limited); (4) Comparison: sham TEAS treatment or conventional rehabilitation treatment; (5) Outcomes: the primary outcome measure was Fugl Meyer Assessment of the upper extremity (FMA-UE), and the secondary outcome measures were Modified Ashworth Scale (MAS) and Modified Barthel Index (MBI). The FMA-UE is the most commonly used instrument for assessing upper limb motor function in stroke patients and has demonstrated good reliability and validity. Spasticity was measured using the Modified Ashworth Scale (MAS), and the Modified Barthel Index (MBI) was used to evaluate the patient's ability to perform daily activities.

The exclusion criteria were as follows: (1) conferences and abstract papers; (2) unable to obtain the full text or extract relevant outcome indicators; (3) non-adult patients with stroke; (4) case reports, protocol studies, reviews, and meta-analysis; (5) duplicate published studies; (6) the number of study cases was less than 10; and (7) intervention measures, grouping methods and effect indicators were not consistent.

2.3 Study selection and data extraction

Two researchers (WXY and YLJ) independently audited the literature and extracted data. Endnote 20.1 software was used to eliminate duplicate records. Studies that did not meet the criteria were screened by reading titles and abstracts. Finally, the full text was read, the final literature was determined according to the inclusion and exclusion criteria, and the data were extracted. The extracted data were entered into RevMan 5.4 and double-checked for accuracy. If there was any disagreement, the third researcher (WYK) discussed and made a decision. The extracted contents mainly included the name of the first author, the year of publication, the characteristics of participants (age and sample size), the details of TEAS (acupoint selection, frequency, and intervention time), the control intervention, the content of quality assessment (randomized method, blind method, selection report, complete results, and so on), and the data of related outcome indicators.

2.4 Risk of bias assessment

Two reviewers (WXY and ZHN) independently used the Cochrane Collaboration tool to assess the risk of bias in the selected trials (Higgins et al., 2011). The evaluation included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The risk assessment results included high risk, low risk, and unclear. When there were differences in opinions between the two evaluators, they were discussed and resolved first. If the opinions differed, a third evaluator (ZSY) would re-evaluate the results to achieve consistency.

2.5 Data synthesis and statistical analysis

Statistical analysis was performed using Review Manager 5.4 and Stata 14.0 software. The outcome indicators involved in this study were all continuous variables. The effect value index was expressed as standard mean difference (SMD), and the 95% confidence interval of each effect value was calculated. If $p \geq 0.10$, $I^2 \leq 50\%$, there was no heterogeneity or small heterogeneity among the studies, so the fixed effect model was used. If $p < 0.1$, $I^2 > 50\%$, the heterogeneity among the studies was considered large, so the random effect model was used (Higgins and Thompson, 2002), and the source for heterogeneity was searched through sensitivity analysis and subgroup analysis. A p-value of <0.05 was considered statistically significant. According to the control methods (no TEAS and sham TEAS) and TEAS parameters (including frequency, treatment duration, and retention time) for subgroup analysis. If sufficient trials (≥10 trials) were included, publication bias was assessed using funnel plots and Egger's test (Egger et al., 1997).

2.6 Evidence quality evaluation

The quality of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) system. Based on factors such as methodological quality, consistency of results across studies, directness of evidence, precision of evidence, and possibility of publication bias, the evidence level of included RCTs was judged to be downgraded. The quality of evidence was categorized into high, medium, low, or very low (Guyatt et al., 2008). Two researchers conducted the assessments and

cross-checked the results. Any disagreement was resolved by consensus. Any disagreements were resolved through consensus, and if consensus could not be reached, a third researcher was consulted.

3 Results

3.1 Study selection

We conducted a thorough search of the aforementioned eight databases following our inclusion and exclusion criteria, initially identifying 1,030 articles. After removing duplicates, 332 articles remained in the database. By reviewing the titles and abstracts, we excluded those that did not meet our inclusion criteria, resulting in 41 articles remaining for further consideration. Upon examining the full texts of these articles, we excluded an additional 25 articles. Finally, 16 RCTs (Chao, 2016; Chen et al., 2015; Chen et al., 2019a; Chen et al., 2019b; Gu et al., 2019; Jia et al., 2018; Mao et al., 2017; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Xie et al., 2019; Yan et al., 2019; Yang, 2023; Yu et al., 2020; Zheng and Mao, 2020) were included. The flow chart and results of the literature screening are shown in Figure 1.

3.2 Study characteristics

The characteristics of the 16 trials included are summarized in Table 1.

A total of 16 trials involving 1,218 stroke patients (10 dropouts) were included in this meta-analysis, with 603 in the TEAS group and 605 in the control group. The trials were published between 2015 and 2023. Sample sizes ranged from 31 to 204. The sample included 431 women and 777 men. As described in the included trials, except for one trial (Yan et al., 2019), which did not report the type of stroke, the remaining trials included 377 patients with intra-cerebral hemorrhage and 712 patients with cerebral infarction. A total of 10 trials (Chen et al., 2015; Chen et al., 2019a; Chen et al., 2019b; Jia et al., 2018; Mao et al., 2017; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Zheng and Mao, 2020) specified Brunstrom stages. Moreover, three trials (Chen et al., 2015; Peng et al., 2015; Wang H. et al., 2023) used sham TEAS as the control group. The duration of treatment ranged from 21 to 120 days. The outcome measures included the FMA-UE, MAS, and MBI. A total of 13 trials (Chao, 2016; Chen et al., 2015; Chen et al., 2019b; Mao et al., 2017; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Yang, 2023; Zheng and Mao, 2020) used FMA-UE as an outcome measure, seven trials (Chen et al., 2015; Chen et al., 2019b; Gu et al., 2019; Mao et al., 2017; Wang H. et al., 2023; Yang, 2023; Zheng and Mao, 2020) used MAS, and 11 trials (Chen et al., 2015; Chen et al., 2019a; Chen et al., 2019b; Jia et al., 2018; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Xie et al., 2019; Yan et al., 2019; Yu et al., 2020) used MBI.

3.3 TEAS regimen

The details of TEAS for the included 16 trials are summarized in Table 2. For stimulation frequencies, 100 Hz and 2 Hz were popular across trials. The most commonly used acupoints were LI10 (Shousanli) and TE5 (Waiguan), used in 13 trials. The most commonly used treatment duration was 30 min (78.5%). The most commonly used frequency of treatment was 5 times per week (66.7%).

3.4 Risk of bias

A total of 14 (Chao, 2016; Chen et al., 2015; Chen et al., 2019a; Chen et al., 2019b; Gu et al., 2019; Jia et al., 2018; Mao et al., 2017; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Xie et al., 2019; Yang, 2023; Yu et al., 2020; Zheng and Mao, 2020) trials described detailed methods of randomization, except for two trials (Peng et al., 2015; Yan et al., 2019) in which the risks were not clear. Only two trials (Wang H. et al., 2023; Xie et al., 2019) emphasized allocation concealment. Two trials (Peng et al., 2015; Xie et al., 2019) performed a blinding method on subjects and operators as high-risk, and only two trials (Chen et al., 2019a; Chen et al., 2019b) performed blinding to outcome assessment. One trial (Yan et al., 2019) was conducted as an unclear risk due to incomplete outcome data. In addition, three trials (Gu et al., 2019; Jia et al., 2018; Yan et al., 2019) had unclear selective reporting bias, and four trials (Chao, 2016; Chen et al., 2019a; Mao et al., 2017; Yan et al., 2019) reported other biases. The risk of bias is summarized in Figure 2.

3.5 Meta-analysis

3.5.1 Fugl Meyer Assessment of the Upper Extremity (FMA-UE)

A total of 13 RCTs (Chao, 2016; Chen et al., 2015; Chen et al., 2019b; Mao et al., 2017; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Yang, 2023; Zheng and Mao, 2020) involving 865 patients reported FMA-UE. There was a significant difference in FMA-UE in the TEAS group (SMD = 1.70, 95CI% = 1.09 to 2.31, $p < 0.00001$, $I^2 = 93\%$; Figure 3), although the quality of evidence was low (Table 3). The results of subgroup analysis showed that TEAS had a statistically significant effect on improving FMA-UE compared with no TEAS (Figure 4) (SMD = 1.76, 95CI% = 1.22 to 2.30, $p < 0.00001$, $I^2 = 86\%$; Table 4), while there was no significant statistical difference compared with sham TEAS (SMD = 1.54, 95CI% = 0.00 to 3.09, $p = 0.05$, $I^2 = 96\%$; Table 4).

In addition, we also performed the subgroup analysis of the TEAS parameters (Figure 5). In the subgroup analysis of frequency of TEAS (Figure 5A), there was a statistically significant difference between the 5 times per week, and 6 times per week TEAS treatment (SMD = 1.57, 95CI% = 0.92 to 2.22, $p < 0.00001$, $I^2 = 92\%$; SMD = 2.43, 95CI% = 1.67 to 3.19, $p < 0.00001$; Table 4), while there was no significant difference between TEAS treatment once a day (SMD = 1.82, 95CI% = −0.13 to 3.77, $p = 0.07$, $I^2 = 97\%$; Table 4). Subgroup based on the treatment duration (Figure 5B): 0–4 weeks, 5–8 weeks, and more than 8 weeks, TEAS was superior to the control group in improving FMA-UE (SMD = 2.09, 95CI% = 1.33 to 2.86, $p < 0.00001$, $I^2 = 92\%$; SMD = 1.01, 95CI% = 0.60 to 1.42, $p < 0.00001$; SMD = 0.35, 95CI% = 0.06 to 0.63, $p = 0.02$; Table 4).

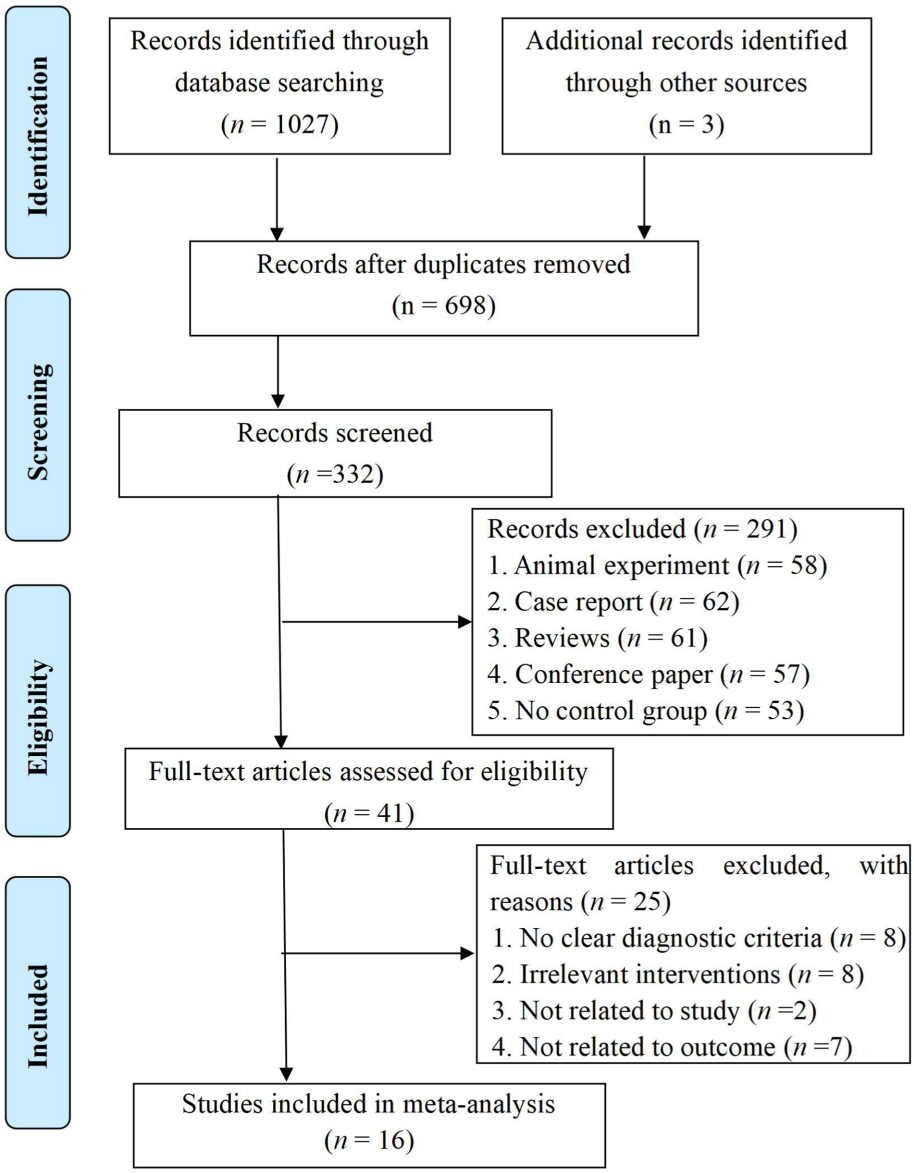

FIGURE 1
PRISMA flow chart.

Furthermore, in the subgroup analysis of retention time (Figure 5C), TEAS was superior to the control group in improving FMA-UE either less than 30 min or more than 30 min (SMD = 2.58, 95CI% = 1.68 to 3.49, $p < 0.00001$, $I^2 = 80\%$; SMD = 1.50, 95CI% = 0.83 to 2.16, $p < 0.0001$, $I^2 = 92\%$; Table 4).

3.5.2 Modified Ashworth Scale (MAS)

A total of 7 RCTs (Chen et al., 2015; Chen et al., 2019b; Gu et al., 2019; Mao et al., 2017; Wang H. et al., 2023; Yang, 2023; Zheng and Mao, 2020) reported MAS in a total of 552 patients. Meta-analysis results show that compared with the control group, the TEAS group had significant improvement in MAS (SMD = −1.18, 95CI% = −1.79 to −0.58, $p < 0.00001$, $I^2 = 90\%$; Figure 6), although the quality of evidence was very low (Table 3). The results of subgroup analysis showed that TEAS had significant advantages in improving MAS compared with no TEAS and sham TEAS (Figure 7) (SMD = −1.34, 95CI% = −2.03 to −0.65, $p = 0.0001$, $I^2 = 88\%$; SMD = −0.36, 95CI% = −0.65 to −0.08, $p = 0.01$; Table 4).

We performed the subgroup analysis of the TEAS parameters (Figure 8). In the subgroup analysis of the frequency of TEAS (Figure 8A), once a day and 5 times per week had statistical significance in the evaluation of MAS (SMD = −1.68, 95CI% = −3.23 to −0.13, $p = 0.03$, $I^2 = 91\%$; SMD = −1.01, 95CI% = −1.74 to −0.28, $p = 0.007$; Table 4). Subgroup analysis based on the treatment duration (Figure 8B): 0–4 weeks, 5–8 weeks, and more than 8 weeks, TEAS was superior to the control group in improving MAS (SMD = −1.51, 95CI% = −2.30 to −0.71, $p = 0.0002$, $I^2 = 89\%$; SMD = −0.56, 95CI% = −1.11 to −0.01, $p = 0.04$; SMD = −0.36, 95CI% = −0.65 to −0.08, $p = 0.01$; Table 4). Furthermore, in the subgroup analysis of retention time (Figure 8C), TEAS for less than 30 min or more than 30 min was superior to the control group in improving MAS

TABLE 1 Characteristics of the included studies.

Study	Type of stroke (ICH/CI)	Brunnstrom	Course of disease (days)	Sample size	Age (years)	Gender (M/F)	Intervention		Duration (days)	Outcome
							I	C		
Yang (2023)	I: (19/30) C: (17/32)	/	I: 161.4 ± 15.6 C: 162.6 ± 16.2	98	I: 68.49 ± 2.83 C: 68.51 ± 2.86	I: (25/24) C: (27/22)	TEAS + CR	CR	28	FMA-UE, MAS
Wang D. et al. (2023)	I: (34/68) C: (31/71)	I/V	/	204	I: 60.6 ± 12.5 C: 61.9 ± 10.5	I: (77/25) C: (72/30)	TEAS + CR	Sham TEAS + CR	72	FMA-UE, MBI, MAS
Xia et al. (2021)	I: (15/9) C: (12/12)	II/V	I: 35 ± 18.06 C: 36.4 ± 17.99	48	I: 56.2 ± 9.91 C: 56.5 ± 7.9	I: (17/7) C: (18/6)	TEAS + CR	CR	28	FMA-UE, MBI
Zheng and Mao (2020)	I: (15/19) C: (13/21)	I/V	I: 186 ± 54 C: 177 ± 21	68	I: 58.9 ± 1.3 C: 58.8 ± 1.1	I: (23/11) C: (22/12)	TEAS + CR	CR	28	FMA-UE, MAS
Yu et al. (2020)	I: (24/30) C: (22/32)	/	/	108	I: 62.5 ± 6.5 C: 61.8 ± 5.8	I: (30/24) C: (29/25)	TEAS + CR	CR	30	MBI
Chen et al. (2019a)	I: (5/23) C: (9/19)	< V	I: 152.39 ± 123.46 C: 156.36 ± 123.60	60 (Fall off 4 cases)	I: 64.50 ± 12.95 C: 64.57 ± 9.35	I: (22/6) C: (21/7)	TEAS + CR	CR	42	FMA-UE, MBI
Gu et al. (2019)	I: (6/15) C: (8/13)	/	/	42	I: 63.8 ± 7.1 C: 62.9 ± 8.3	I: (14/7) C: (12/9)	TEAS + CR	CR	28	FMA-UE, MAS
Xie et al. (2019)	I: (CI:42) C: (CI:40)	/	I: 40.28 ± 9.28 C: 41.95 ± 10.88	82	I: 50.38 ± 10.76 C: 49.68 ± 10.52	I: (23/19) C: (24/16)	TEAS + CR	CR	28	FMA-UE, MBI
Yan et al. (2019)	/	/	/	120	I: 62.40 C: 60.90	I: (33/27) C: (39/21)	TEAS + CR	CR	120	MBI
Chen et al. (2019b)	I: (8/18) C: (6/21)	III/V	I: 275.95 ± 59.11 C: 271.43 ± 74.01	53	I: 60.75 ± 16.62 C: 60.45 ± 11.25	I: (19/7) C: (20/7)	TEAS + CR	CR	42	FMA-UE, MBI, MAS
Jia et al. (2018)	I: (22/32) C: (20/34)	I/V	I: 144 ± 51 C: 150 ± 48	108	I: 64.7 ± 9.8 C: 64.2 ± 9.5	I: (29/25) C: (32/22)	TEAS + CR	CR	84	MBI
Mao et al. (2017)	I: (12/14) C: (11/15)	I/V	I: 177.60 ± 72.00 C: 186.90 ± 96.30	52	I: 59.52 ± 7.35 C: 58.92 ± 6.21	I: (14/12) C: (18/8)	TEAS + CR	CR	28	FMA-UE, MAS
Chao (2016)	I: (17/10) C: (12/16)	/	I: 161.4 ± 104.1 C: 169.2 ± 101.7	55	I: 52.26 ± 15.56 C: 49.54 ± 11.21	I: (22/5) C: (24/4)	TEAS + CR	Sham TEAS + CR	28	FMA-UE, MBI
Peng et al. (2015)	I: (7/14) C: (7/13)	< V	I: 67.5 ± 26.1 C: 60.6 ± 31.5	46 (Fall off 5 cases)	I: 66.4 ± 10.8 C: 65.5 ± 11.2	I: (9/12) C: (10/10)	TEAS + CR	Sham TEAS + CR	21	FMA-UE, MBI
Chen et al. (2015)	I: (7/13) C: (8/15)	I/V	I: 186.00 ± 85.50 C: 185.10 ± 92.40	43	I: 61.05 ± 9.24 C: 57.69 ± 8.79	I: (17/3) C: (19/4)	TEAS + CR	CR	28	FMA-UE, MBI, MAS
Tang et al. (2015)	I: (4/11) C: (6/10)	I/II	I: 40.23 ± 16.02 C: 37.64 ± 18.32	31	I: 54.69 ± 9.68 C: 57.93 ± 11.2	I: (12/3) C: (14/2)	TEAS + CR	CR	42	FMA-UE, MBI

I, Intervention group; C, Control group; ICH, Intra Cerebral Hemorrhage; CI, Cerebral Infarction; M, Male; F, Famale; /, not mention; CR, Conventional Rehabilitation; TEAS, Transcutaneous electrical acupoint stimulation; FMA-UE, Fugl-Meyer Assessment of the upper extremity; MAS, Modified Ashworth Scale; MBI, Modified Barthel Index.

TABLE 2 Details of transcutaneous electrical acupoint stimulation in included trials.

Study	Frequency (Hz)/ intensity (mA) of electrical stimulation	The site of electrical stimulation	Duration of treatments	Number of treatments	Frequency (weeks/days)
Yang (2023)	35 Hz/10/50 mA	LI10 (Shousanli), TE5 (Waiguan)	15 min	TEAS + CR: 28 CR: 28	Once a day
Wang D. et al. (2023)	2 Hz	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 30 Sham TEAS + CR: 30	5 times per week
Xia et al. (2021)	100 Hz/100 mA	LI15 (Jianyu), LI11 (Quchi), LI10 (Shousanli), TE5 (Waiguan)	20 min	TEAS + CR: 24 CR: 24	6 times per week
Zheng and Mao (2020)	/	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 34 CR: 34	5 times per week
Yu et al. (2020)	100 Hz/10/40 mA	Eight evil points	30 min	TEAS + CR: 54 CR: 54	Once a day
Chen et al. (2019a)	Brunnstrom I ~ II: 2 Hz, Brunnstrom III ~ IV: 4/15 Hz	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 28 CR: 28	5 times per week
Gu et al. (2019)	35 Hz/10/50 mA	LI10 (Shousanli), TE5 (Waiguan)	15 min	TEAS + CR: 21 CR: 21	Once a day
Xie et al. (2019)	2 Hz	TE5 (Waiguan), LI15 (Jianyu), LI11 (Quchi), LI10 (Shousanli)	30 min	TEAS + CR: 42 CR: 40	5 times per week
Yan et al. (2019)	General condition: 10 Hz, The disease is serious: 4 Hz	LI10 (Shousanli), TE5 (Waiguan)	30 min	CT + TEAS: 60 CT: 60	/
Chen et al. (2019b)	Brunnstrom III ~ IV: 10/15 Hz Brunnstrom V: 4 Hz	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 26 CR: 27	5 times per week
Jia et al. (2018)	Brunnstrom I/II: 2 Hz, Brunnstrom III/IV: 4/15 Hz, Brunnstrom V/VI: 4 Hz	LI10 (Shousanli), TE5 (Waiguan)	Brunnstrom I/II: 25/30 min, Brunnstrom III/IV: 20/30 min, Brunnstrom V/VI: 30 min	TEAS + CR: 54 CR: 54	5 times per week
Mao et al. (2017)	/	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 26 CR: 26	5 times per week
Chao (2016)	100 Hz/10/40 mA	Eight evil points	30 min	TEAS + CR: 28 Sham TEAS + CR: 28	Once a day
Peng et al. (2015)	100 Hz	TE5 (Waiguan), LI15 (Jianyu), LI11 (Quchi), LI14 (Hegu)	30 min	TEAS + CR: 21 Sham TEAS + CR: 20	5 times per week
Chen et al. (2015)	/	LI10 (Shousanli), TE5 (Waiguan)	/	TEAS + CR: 20 CR: 23	5 times per week
Tang et al. (2015)	/	LI10 (Shousanli), TE5 (Waiguan)	30 min	TEAS + CR: 30 CR: 30	5 times per week

CR, Conventional Rehabilitation; TEAS, Transcutaneous electrical acupoint stimulation; /, not mention.

(SMD = −1.68, 95CI% = −3.23 to −0.13, $p = 0.03$, $I^2 = 91\%$; SMD = 1.09, 95CI% = 2.00 to 0.17, $p = 0.02$, $I^2 = 93\%$; Table 4).

3.5.3 Modified Barthel Index (MBI)

A total of 11 RCTs (Chen et al., 2015; Chen et al., 2019a; Chen et al., 2019b; Jia et al., 2018; Peng et al., 2015; Tang et al., 2015; Wang H. et al., 2023; Xia et al., 2021; Xie et al., 2019; Yan et al., 2019; Yu et al., 2020) involving 886 patients reported MBI. Meta-analysis results showed that compared with the control group, the TEAS group had significant differences in MBI (SMD = 1.53, 95CI% = 0.85 to 2.20, $p < 0.00001$, $I^2 = 95\%$; Figure 9), although the quality of evidence was low (Table 3).

Subgroup analysis results show that, compared with no TEAS (Figure 10), TEAS was statistically different in improving the MBI. (SMD = 1.52, 95CI % = 0.84 to 2.21, $p < 0.0001$, $I^2 = 93\%$; Table 4), although there was no significant statistical difference compared with

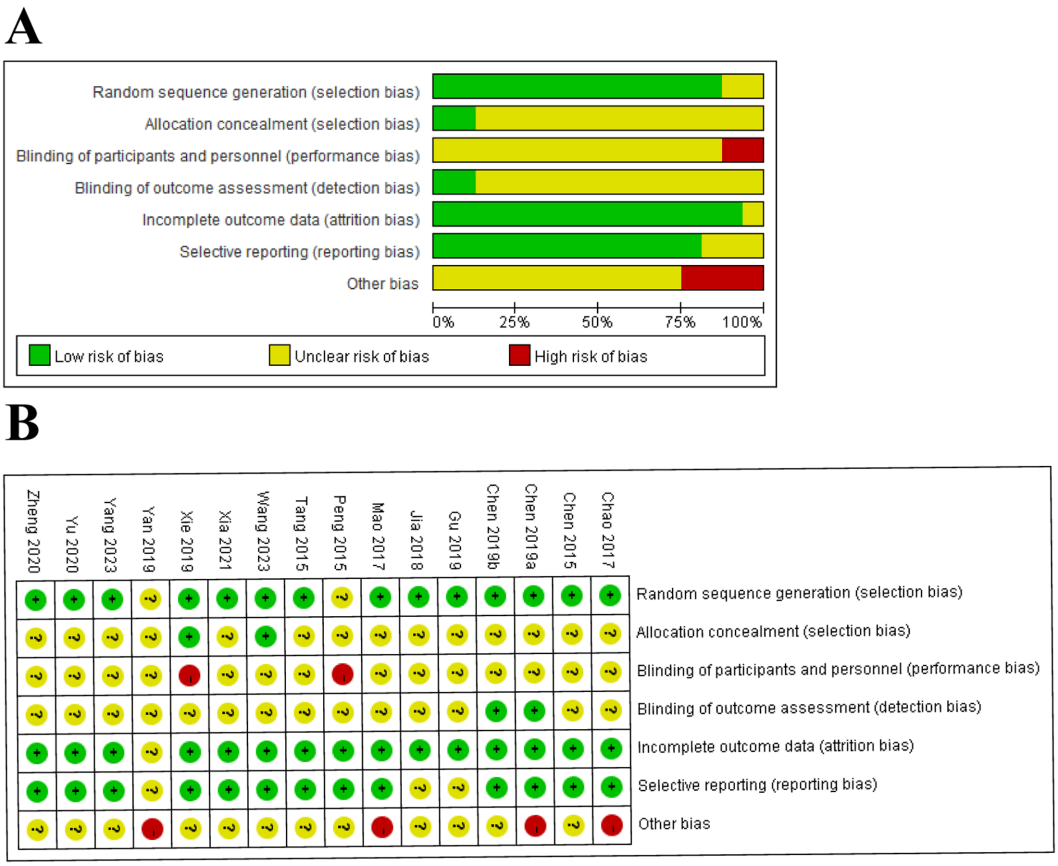

FIGURE 2
Risk of bias (ROB) assessments of included studies. **(A)** ROB graph. **(B)** ROB summary.

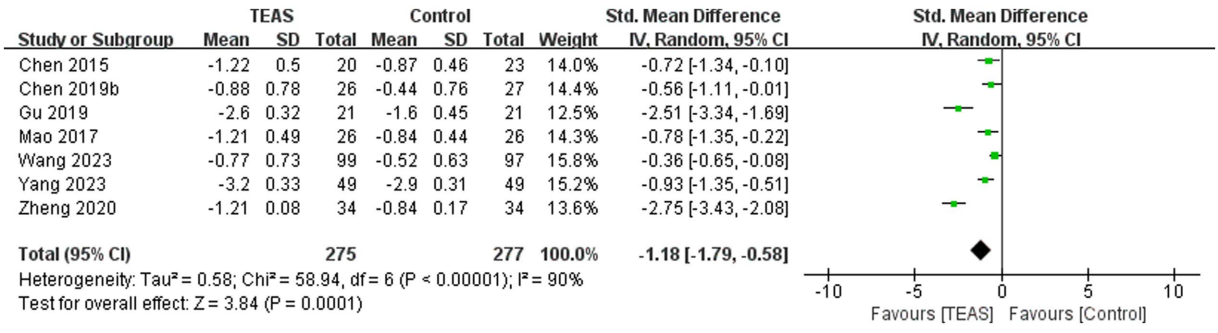

FIGURE 3
Forest plot and meta-analysis of FMA-UE.

sham TEAS (SMD = 1.61, 95CI% = −1.59 to 4.81, $p = 0.32$, $I^2 = 98\%$; Table 4).

In addition, we performed a subgroup analysis of the TEAS parameters (Figure 11). In the subgroup analysis of frequency of TEAS (Figure 11A), TEAS treatment administered once a day, 5 times per week, and 6 times per week showed statistical significance in the evaluation of MBI (SMD = 0.51, 95CI% = 0.13 to 0.90, $p = 0.009$; SMD = 1.48, 95CI% = 0.58 to 2.37, $p = 0.001$, $I^2 = 95\%$; SMD = 3.67, 95CI% = 2.72 to 4.62, $p < 0.00001$; Table 4). Subgroup based on the treatment duration (Figure 11B): 0–4 weeks, 5–8 weeks, and more than 8 weeks, TEAS was superior to the control group in improving MBI (SMD = 2.53, 95CI% = 0.54 to 4.52, $p = 0.01$, $I^2 = 95\%$; SMD = 1.17, 95CI% = 0.39 to 1.94, $p = 0.003$, $I^2 = 88\%$; SMD = 2.18, 95CI% = 1.03 to 3.32, $p = 0.0002$, $I^2 = 92\%$; Table 4). Furthermore, in the subgroup analysis of retention time (Figure 11C), TEAS was superior to the control group in improving MBI either less than 30 min or more than 30 min (SMD = 3.67, 95CI% = 2.72 to 4.62, $p < 0.00001$; SMD = 1.28, 95CI% = 0.57 to 2.00, $p = 0.0004$, $I^2 = 94\%$; Table 4).

TABLE 3 GRADE of evidence of outcomes of the included trials.

Outcomes	Certainty assessment						No. of patients	Effect sizes	Certainty
	No. of trials	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention/ Control	SMD (95% CI)	
FMA-UE	13	Serious	Serious	No serious	No serious	Undetected	432/433	SMD 1.70 (1.09,2.31)	⊕⊕⊖⊖ Low
MAS	7	Serious	Serious	No serious	No serious	Serious	275/277	SMD -1.18 (−1.79,-0.58)	⊕⊖⊖⊖ Very Low
MBI	11	Serious	Serious	No serious	No serious	Undetected	443/443	SMD 1.53 (0.85,2.20)	⊕⊕⊖⊖ Low

SMD, standard mean difference; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
Risk of bias: serious, study with unclear risk of bias; Inconsistency: Serious, $I^2 > 50\%$.
Indirectness: no indirectness of evidence was found in any study.
Imprecision (based on sample size): Serious, $n < 500$ participants.
Publication bias: Undetected due to the number of trials less than the recommended arbitrary minimum number of 10.

3.5.4 Safety of intervention

Only one trial (Wang H. et al., 2023) mentioned the safety of TEAS intervention, and no adverse reactions were reported. All the included trials reported that patients could tolerate TEAS intervention well without obvious adverse reactions. Therefore, larger-scale RCTs are needed to further confirm and report the safety of TEAS in the treatment of upper limb dysfunction after stroke.

3.5.5 Sensitivity analysis and publication bias

Sensitivity analysis was performed after sequentially excluding each study, and the recalculated summary results did not change significantly, indicating that no peripheral studies significantly affected the overall results (Figures 12A, 13A, 14A). Funnel plots and Egger's test were used to assess publication bias based on the FMA-UE, MSA, and MBI scales. The distribution of the funnel plot (Figures 12B, 14B) was asymmetrical. Egger's test showed FMA-UE ($p = 0.005$; Figure 12C), MSA ($p = 0.047$; Figure 13B), and MBI ($p = 0.008$; Figure 14C), suggesting that publication bias is difficult to rule out.

3.5.6 Quality of evidence

The GRADE approach was employed to assess the quality of evidence from 16 RCTs (Table 3). The analysis focused on three outcome measurements: FMA-UE improvement, MAS improvement, and MBI improvement. Overall, the quality of evidence was ranked from low to very low. The results indicated that none of the outcomes were supported by high-quality evidence; two out of three (2/3, 66.67%) outcomes had low-quality evidence, while one out of three outcomes (1/3, 33.33%) had very low-quality evidence. The main reasons for the low-quality ratings were risk of bias (ROB) and inconsistency.

4 Discussion

4.1 Summary of main findings

This meta-analysis included 16 RCTs involving 1,218 stroke patients and was conducted to investigate TEAS to the influence of the upper limb functional recovery after stroke. The findings from the meta-analysis indicate that TEAS can significantly improve upper limb motor function, spasticity, and functional independence in stroke patients compared with the control group. The results are consistent with previous research results (Tang et al., 2021). However, considering the literature, the overall quality is low, with issues such as lack of follow-up, absence of adverse reaction reports, and the case fatality rate affecting the credibility. According to the GRADE guidelines, the recommended level is "very low" to "low." This result is not very convincing, requiring a larger sample size and further evidence. In addition, the meta-analysis showed that the I^2 of FMA-UE, MAS, and MBI were all greater than 50%, indicating high heterogeneity among trials. To improve the reliability of the conclusions, subgroup analysis based on control interventions and TEAS parameters (including frequency, treatment duration, and retention time) was performed to find potential sources of heterogeneity.

The trials included in this meta-analysis had differences in the control group intervention, and the treatment measures of the control group included traditional rehabilitation therapies such as

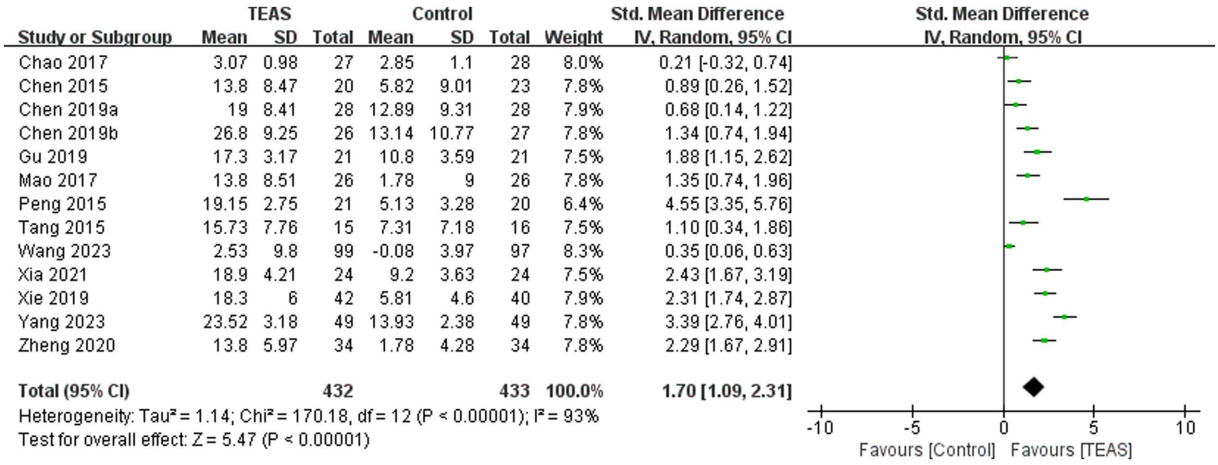

FIGURE 4
Subgroup analysis of FMA-UE is based on the types of control groups.

TABLE 4 The results of subgroup analyses.

			No. of studies	No. of patients	SMD (95% CI)	*p*	I^2	Effect model
FMA-UE	Types of control group	TEAS + CR vs. CR	10	573	1.76 (1.22, 2.30)	<0.00001	86%	Random
		TEAS + CR vs. Sham TEAS + CR	3	292	1.54 (0.00, 3.09)	0.05	96%	Random
	Frequency of TEAS	Once a day	3	195	1.82 (−0.13, 3.77)	0.07	97%	Random
		5 times per week	9	622	1.57 (0.92, 2.22)	<0.00001	92%	Random
		6 times per week	1	48	2.43 (1.67, 3.19)	<0.00001	/	/
	Treatment duration	0–4 weeks	9	529	2.09 (1.33, 2.86)	<0.00001	92%	Random
		5–8 weeks	3	140	1.01 (0.60, 1.42)	<0.00001	24%	Random
		>8 weeks	1	196	0.35 (0.06, 0.63)	0.02	/	/
	TEAS retention time	<30 min	3	188	2.58 (1.68, 3.49)	<0.00001	80%	Random
		≥30 min	9	600	1.50 (0.83, 2.16)	<0.0001	92%	Random
MAS	Types of control group	TEAS + CR vs. CR	6	356	−1.34 (−2.03, −0.65)	0.0001	88%	Random
		TEAS + CR vs. Sham TEAS + CR	1	196	−0.36 (−0.65, −0.08)	0.01	/	/
	Frequency of TEAS	Once a day	2	140	−1.68 (−3.23, −0.13)	0.03	91%	Random
		5 times per week	5	412	−1.01 (−1.74, −0.28)	0.007	90%	Random
	Treatment duration	0–4 weeks	5	303	−1.51 (−2.30, −0.71)	0.0002	89%	Random
		5–8 weeks	1	53	−0.56 (−1.11, −0.01)	0.04	/	/
		>8 weeks	1	196	−0.36 (−0.65, −0.08)	0.01	/	/
	TEAS retention time	<30 min	2	140	−1.68 (−3.23, −0.13)	0.03	91%	Random
		≥30 min	4	369	−1.09 (−2.00, 0.17)	0.02	93%	Random
MBI	Types of control group	TEAS + CR vs. CR	9	649	1.52 (0.84, 2.21)	<0.0001	93%	Random
		TEAS + CR vs. Sham TEAS + CR	2	237	1.61 (−1.59, 4.81)	0.32	98%	Random
	Frequency of TEAS	Once a day	1	108	0.51 (0.13, 0.90)	0.009	/	/
		5 times per week	8	610	1.48 (0.58, 2.37)	0.001	95%	Random
		6 times per week	1	48	3.67 (2.72, 4.62)	<0.00001	/	/
	Treatment duration	0–4 weeks	3	173	2.53 (0.54, 4.52)	0.01	95%	Random
		5–8 weeks	5	289	1.17 (0.39, 1.94)	0.003	88%	Random
		>8 weeks	3	299	2.18 (1.03, 3.32)	0.0002	92%	Random
	TEAS retention time	<30 min	1	48	3.67 (2.72, 4.62)	<0.00001	/	/
		≥30 min	8	687	1.28 (0.57, 2.00)	0.0004	94%	Random

CR, Conventional Rehabilitation; TEAS, Transcutaneous electrical acupoint stimulation; /, not mention; FMA-UE, Fugl-Meyer Assessment of the upper extremity; MAS, Modified Ashworth Scale; MBI, Modified Barthel Index.

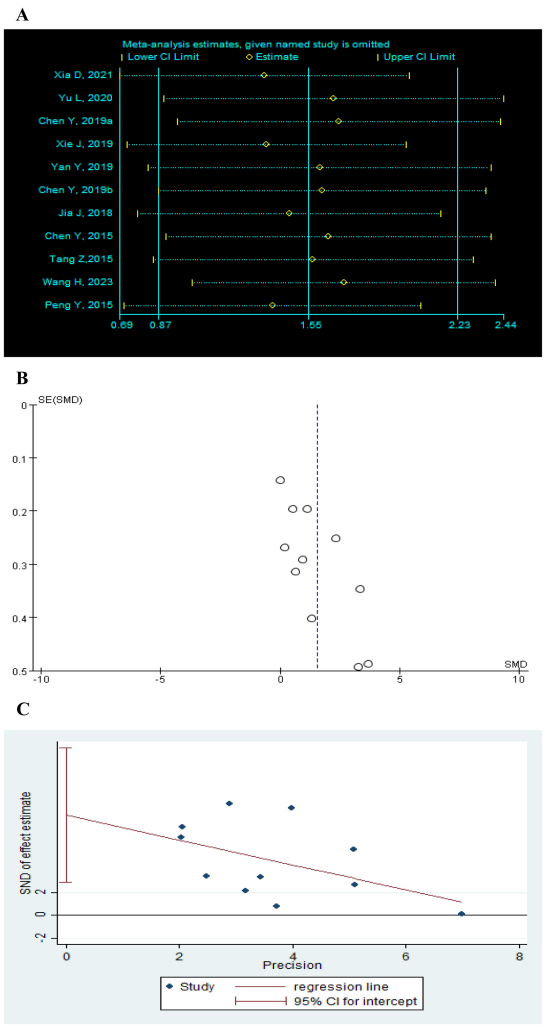

FIGURE 5
Subgroup analysis of FMA-UE based on TEAS parameters: **(A)** Frequency of TEAS. **(B)** Treatment duration. **(C)** TEAS retention time.

neurodevelopmental therapy, exercise therapy, and occupational therapy. Traditional rehabilitation therapy is based on the "motor relearning learning theory," which promotes the reconstruction of brain motor function through repeated purposeful exercise training (Dimyan and Cohen, 2011). Studies have confirmed that stroke patients often have multiple functional disorders, and task-oriented training and sensory stimulation of TEAS are complementary to each other, which can enhance the rehabilitation effect (Zhao et al., 2015). This is consistent with our results that treatment with the addition of TEAS significantly improved FMA-UE, MAS, and MBI scores compared with conventional rehabilitation alone. However, TEAS treatment did not significantly improve FMA and MBI compared with sham TEAS. This negative result is consistent with a previous TEAS study with a similar design (Alwhaibi et al., 2021). The prevalent methods for sham TEAS underwent identical settings and manipulations as those in the TEAS group, with the exception that the wire connecting the electrode pads to the TEAS stimulator was severed, thereby preventing any current from being delivered. Alwhaibi et al. (2021) compared the effects of task-specific training (TST) combined with TEAS (applied to LI4 and LI11) and sham TEAS combined with TST on upper limb movement in patients with chronic stroke. The results showed that patients in both groups improved significantly after treatment. However, when the two groups were compared, there was no significant improvement in the FMA-UE score after treatment. Even though sham TEAS is designed to have no therapeutic effect, it may still produce unintended consequences. Participants might perceive an improvement due to the placebo effect, which refers to the beneficial outcomes generated by an inactive or ineffective treatment. The experience of receiving stimulation, regardless of its sham nature, could lead to habituation or learning effects, potentially influencing participants' behavior and performance on the FMA-UE and BMI assessments. Furthermore, participants who believe they are undergoing treatment may become more attuned to their movement abilities, which could affect their performance.

TEAS stimulation parameters such as frequency, treatment duration, and retention time may significantly affect the

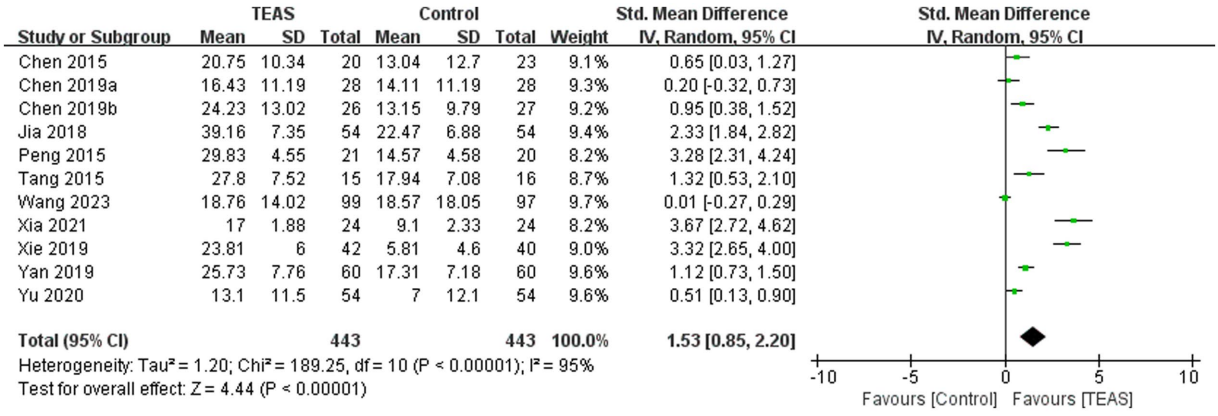

FIGURE 6
Forest plot and meta-analysis of MAS.

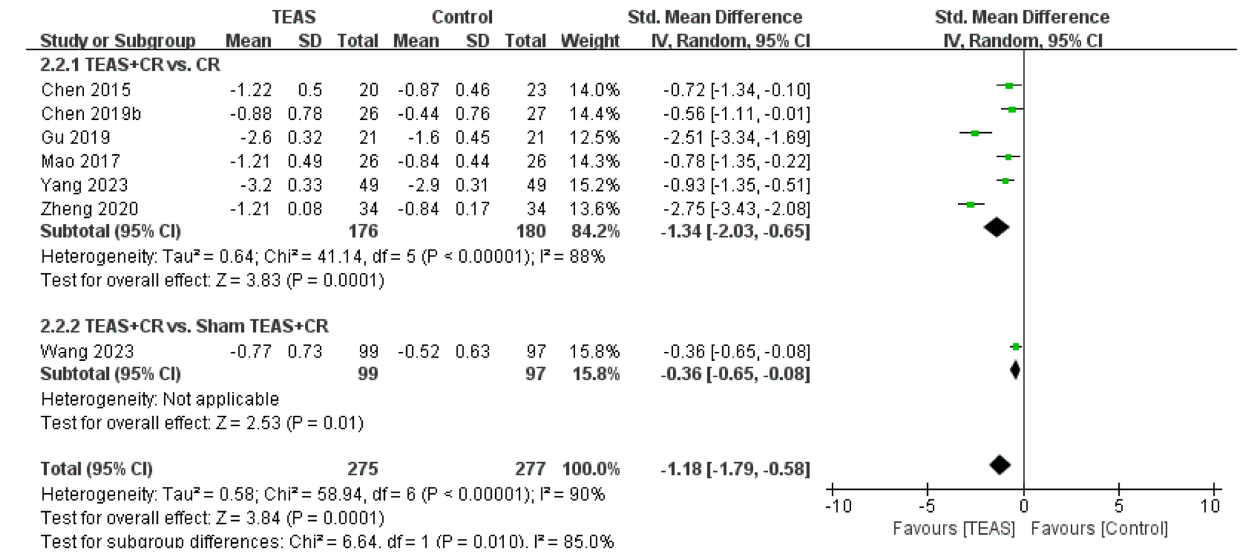

FIGURE 7
Subgroup analysis of MAS is based on the types of control groups.

intervention's efficacy. In terms of TEAS frequency, the 5/6 times per week treatment was superior to the control group in improving FMA-UE and MBI scores. In contrast, the once-a-day treatment was more effective in improving MAS. The possible explanation is that the effect of relieving spasticity is not sustainable due to the gradual weakening of the effector substance with the prolongation of the treatment interval (Yin et al., 2022). Regarding the duration of treatment, TEAS was superior to the control group in improving FMA-UE, MAS, and MBI scores in 0–4 weeks, 5–8 weeks, and more than 8 weeks. However, the improvement effect was most obvious during 0–4 weeks, which may be the most obvious response of the body at this effective stimulation amount. A previous study (Dimitrijević et al., 1972) suggested that regular and continuous electrical stimulation for a long time could lead to stimulation tolerance but could not cause stimulation of the motor area of the cerebral cortex (M1). For the retention time of TEAS, whether less than 30 min or more than 30 min, TEAS was superior to the control group in improving FMA-UE, MAS, and MBI scores. The study of Laddha (Laddha et al., 2015) showed that transcutaneous electrical stimulation for 30 min or 60 min for 3 weeks was effective on spasticity of lower limbs and walking ability, and there was no significant difference in efficacy. However, the lack of standardization of TEAS parameters is the limitation of its clinical treatment, and more RCTs with rigorous designs based on the differences in TEAS parameters are needed to explore the best TEAS regimen.

A total of six acupoints were included across 16 RCTs, with TE5 (Waiguan, used 14 times) and LI10 (Shousanli, used 13 times) being the most common. From the anatomical point of view, the main muscles under TE5 (Waiguan) are the extensor of the little finger, the extensor of the long thumb, and the extensor of the index finger. Stimulation is beneficial for improving the adverse movement of the wrist joint and promoting the extension of the thumb and index finger. The main muscles under the acupoint LI10 (Shousanli) are extensor carpi radialis longus, extensor carpi radialis brevis, and supinator. The forearm supination can be promoted by stimulating the acupoint, and the spasm can be relieved. TEAS can exert the effects of electrical stimulation and acupoints to promote the recovery of limb function after a stroke (Lim et al., 2023; Zhang et al., 2018).

4.2 Mechanisms of TEAS

A related study (Wang D. et al., 2023) has shown that the possible mechanism of limb spasticity and motor dysfunction is that the corresponding cortex of the brain is damaged after stroke, blocking its nerve conduction pathway, resulting in the reduction of local cerebral blood flow and the damage of neuromuscular innervation. TEAS can stimulate and contract the paralyzed muscles of limbs so that they can input information impulses to the nerve center, improve the excitability of relevant brain functional nerve areas, and promote the recovery of neuronal function (Li et al., 2022). Ischemia and hypoxia of brain tissue are the pathological basis of ischemic stroke. Studies have shown that TEAS, by adjusting the SIRT1/FOXO3a and SIRT1/BRCC3/NLRP3 signaling pathways following ischemic stroke, inhibits cell apoptosis, oxidative stress, and inflammation of the nerve to reduce brain damage (Tan et al., 2024) and accelerates the recovery of neurons and some functional metabolism (Nelles et al., 2001). In addition, TEAS can inhibit the TLR4/MyD88/NF-κB pathway, reduce ischemic brain damage after stroke, inhibit inflammation, cell death, and microglia activation (Wu et al., 2023), improve the motor neurons in spinal cord downlink control function, and reduce excessive muscle tone. Another study of TEAS in the treatment of upper limb spastic paralysis showed that TEAS had a significant effect on the excitability of motor-evoked potential in the affected cerebral hemisphere of stroke patients, which was speculated to be related to the enhancement of local cerebral cortical excitability through motor and sensory transduction pathways (Zhang et al., 2013).

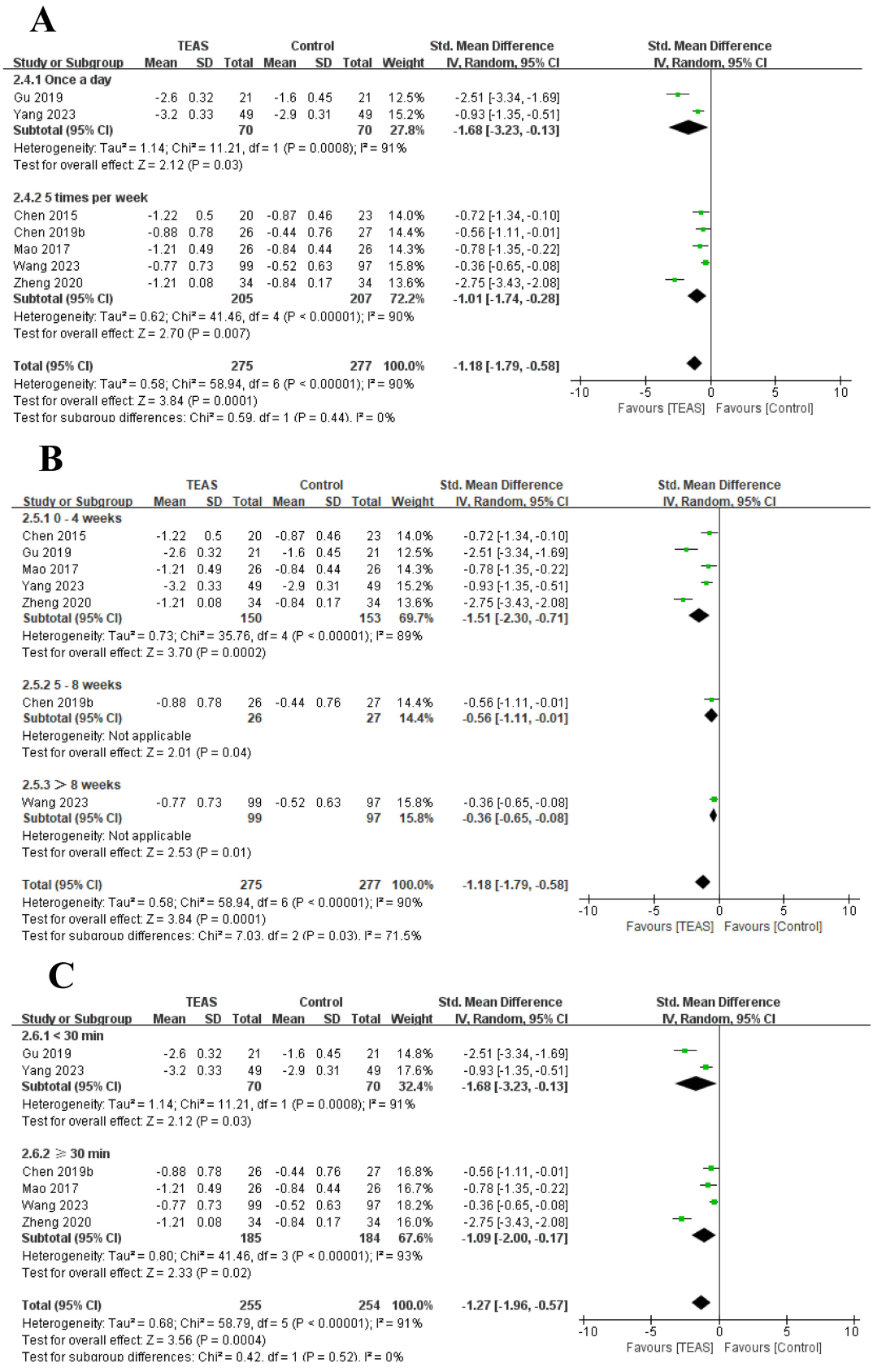

FIGURE 8
Subgroup analysis of MAS based on TEAS parameters: **(A)** Frequency of TEAS. **(B)** Treatment duration. **(C)** TEAS retention time.

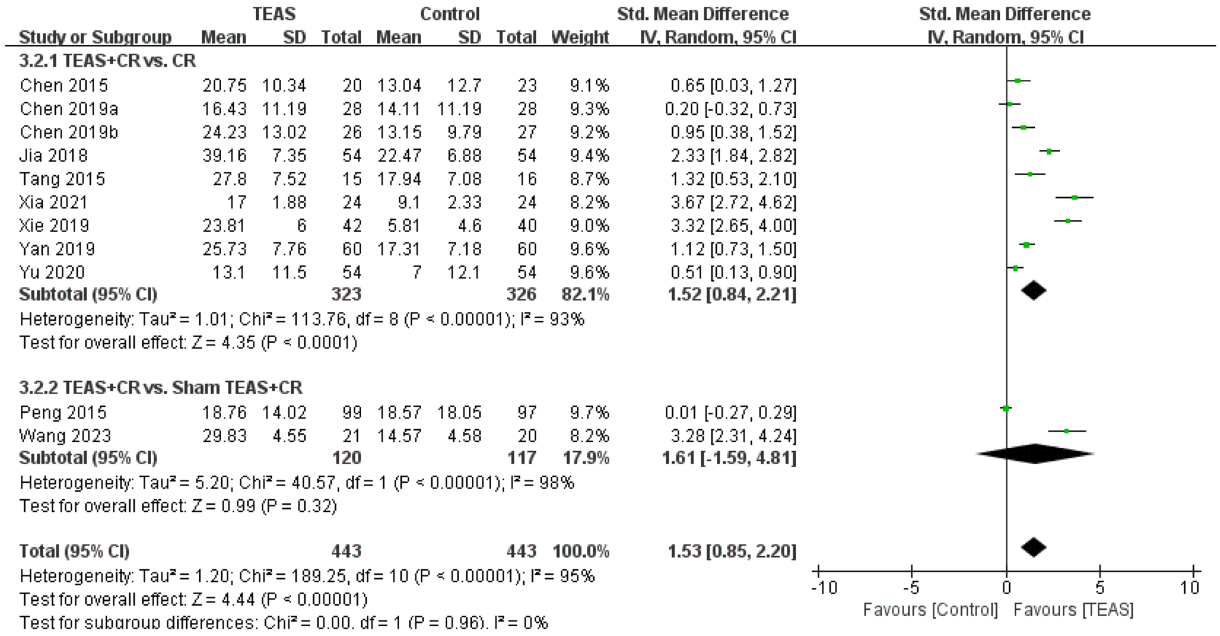

FIGURE 9
Forest plot and meta-analysis of MBI.

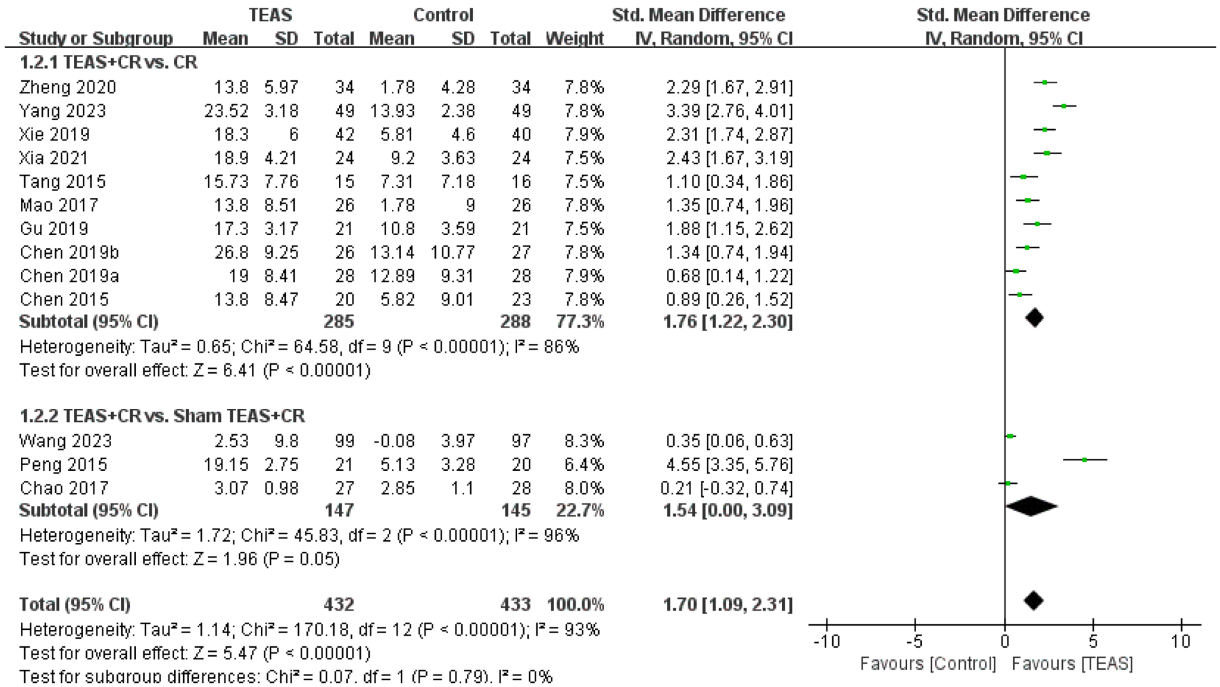

FIGURE 10
Subgroup analysis of MBI is based on the types of control groups.

4.3 Strengths and limitations

This review has some strengths. Our study includes the recent trial and comprehensive analysis of TEAS on upper limb function after stroke. We employed sensitivity analysis and subgroup analysis based on the different control groups and TEAS parameters (frequency, duration, and retention time) to investigate the sources of heterogeneity and assess the stability of our findings. In addition, funnel plots and Egger's test were employed to evaluate the potential for publication bias. However, this review has some limitations. First, the studies included in this analysis were not registered as clinical trials and did not provide details on sample size calculations. Second, the overall methodological quality

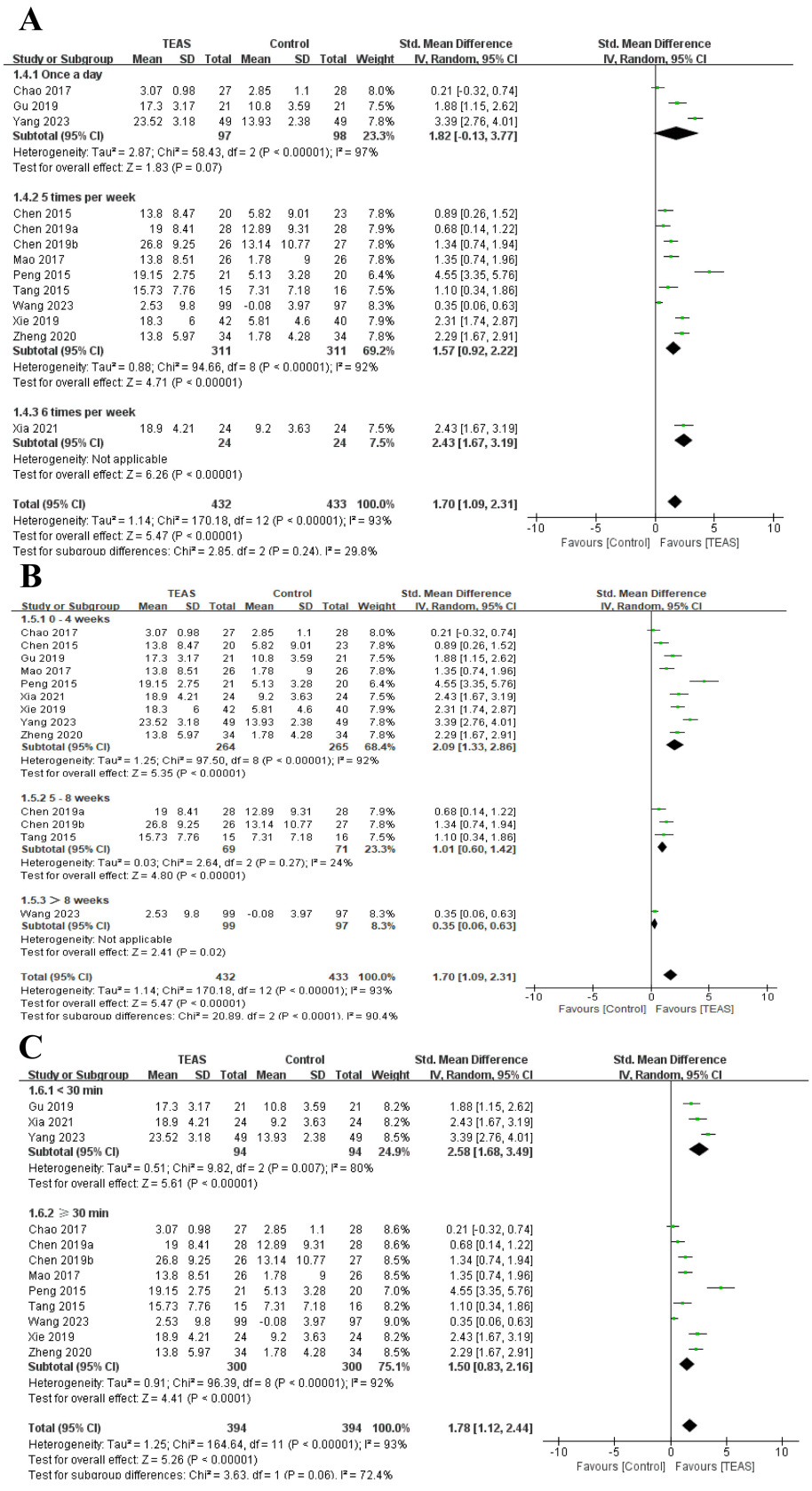

FIGURE 11
Subgroup analysis of MBI based on TEAS parameters: **(A)** Frequency of TEAS. **(B)** Treatment duration. **(C)** TEAS retention time.

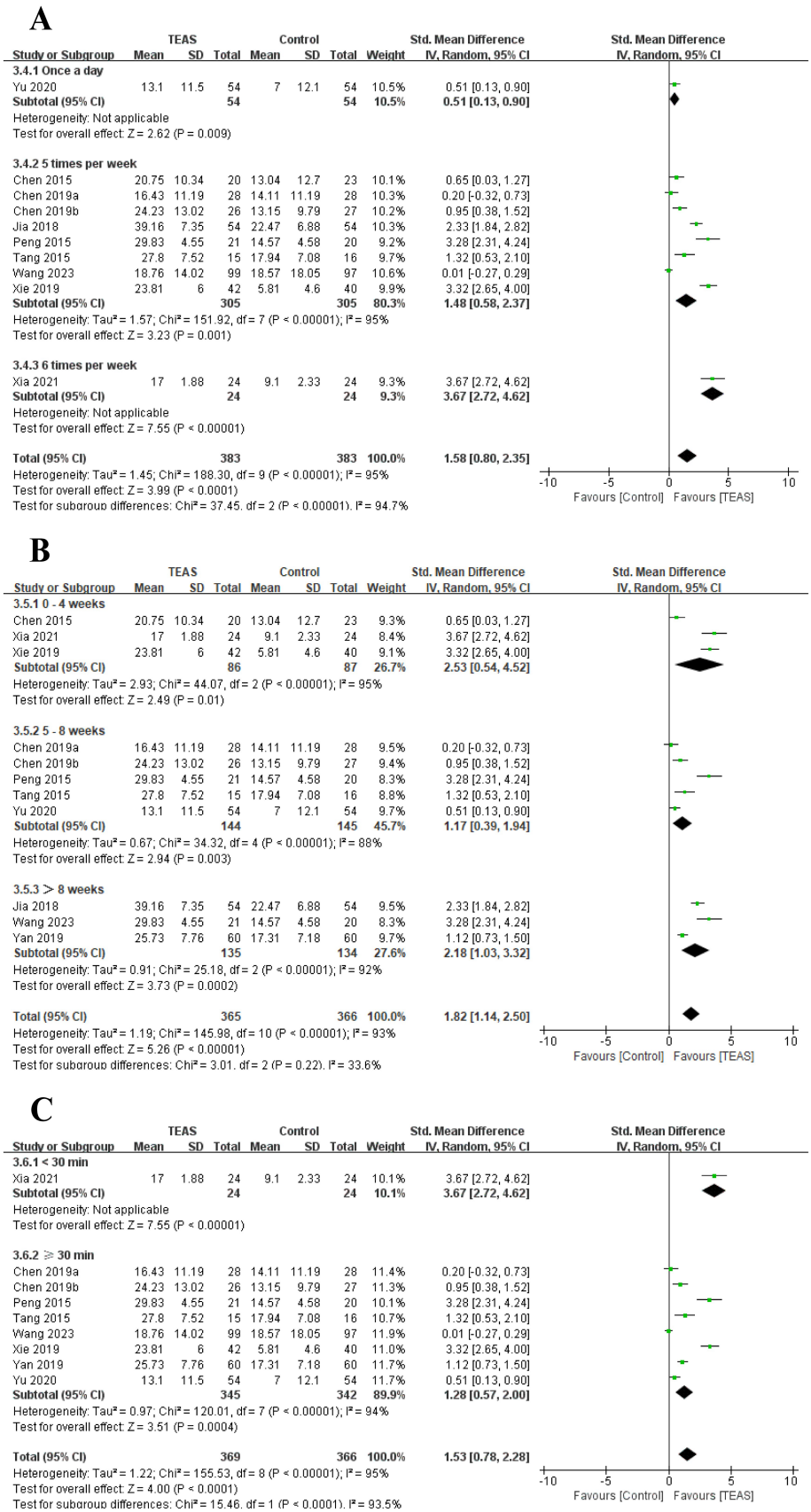

FIGURE 12
Effect of TEAS on FMA-UE. **(A)** Sensitivity analysis of FMA-UE. **(B)** A funnel plot analysis revealed potential publication bias. **(C)** Egger's test included studies on FMA-UE.

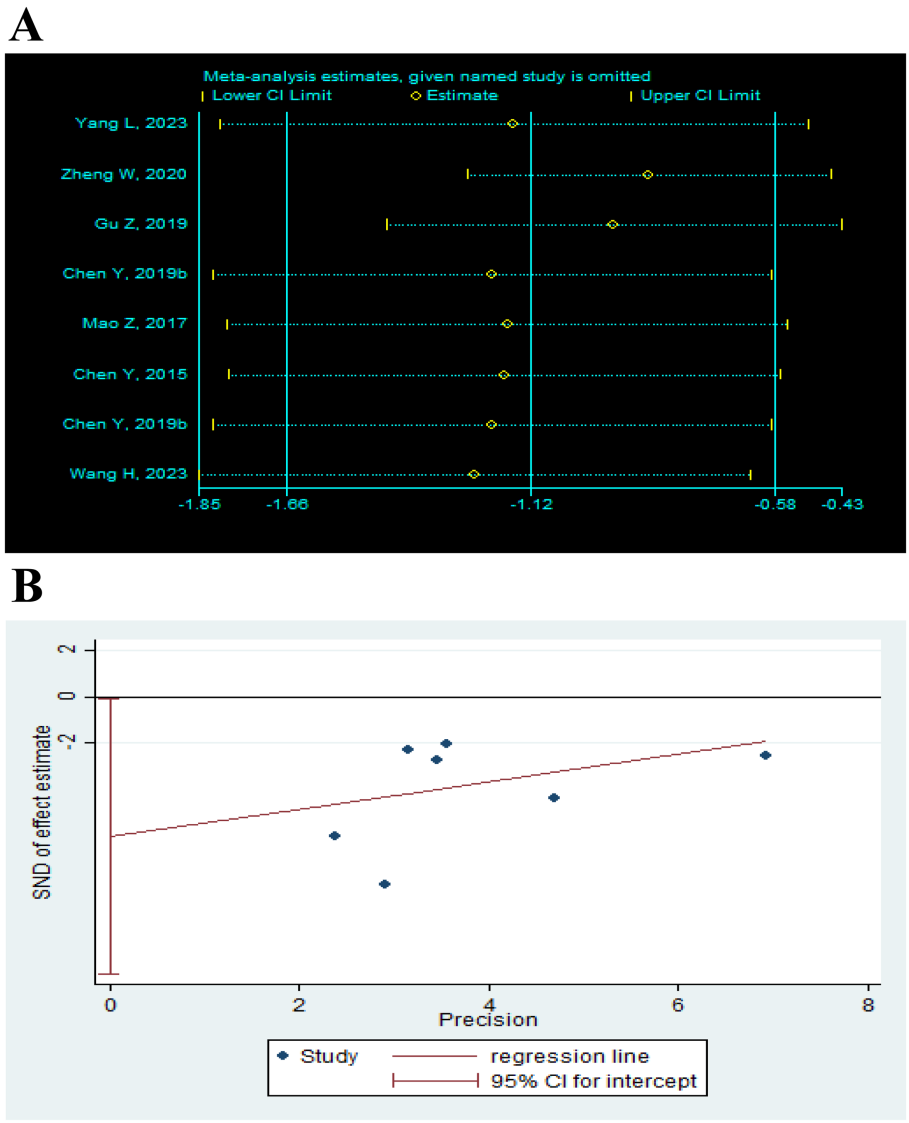

FIGURE 13
Effect of TEAS on MAS. **(A)** Sensitivity analysis of MAS. **(B)** Egger's test included studies on MAS.

of all the analyzed studies was low, and allocation concealment and blinding were not described in detail. Two studies had more than 5% missing outcome data, which may have been subject to implementation and measurement biases. Third, only studies published in Chinese and English were included, which may introduce publication bias. Finally, adverse events were rarely reported in the original study, and safety concerns cannot be assured. Therefore, we interpret the results cautiously.

5 Conclusion

Existing evidence suggests that TEAS can improve upper limb motor function and spasticity in stroke patients and improve daily life abilities. The improvement in upper limb motor function appears to have a dose-dependent relationship with the frequency, duration, and retention time of the TEAS intervention. However, these findings should be interpreted cautiously due to the restricted number and low methodological quality of the included trials. High-quality, large-sample, multi-center trials are needed to further confirm these preliminary findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LY: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Supervision, Validation. YW: Data curation, Investigation, Methodology, Supervision, Writing – review & editing. HZ: Data curation, Formal analysis, Investigation, Writing – review & editing,

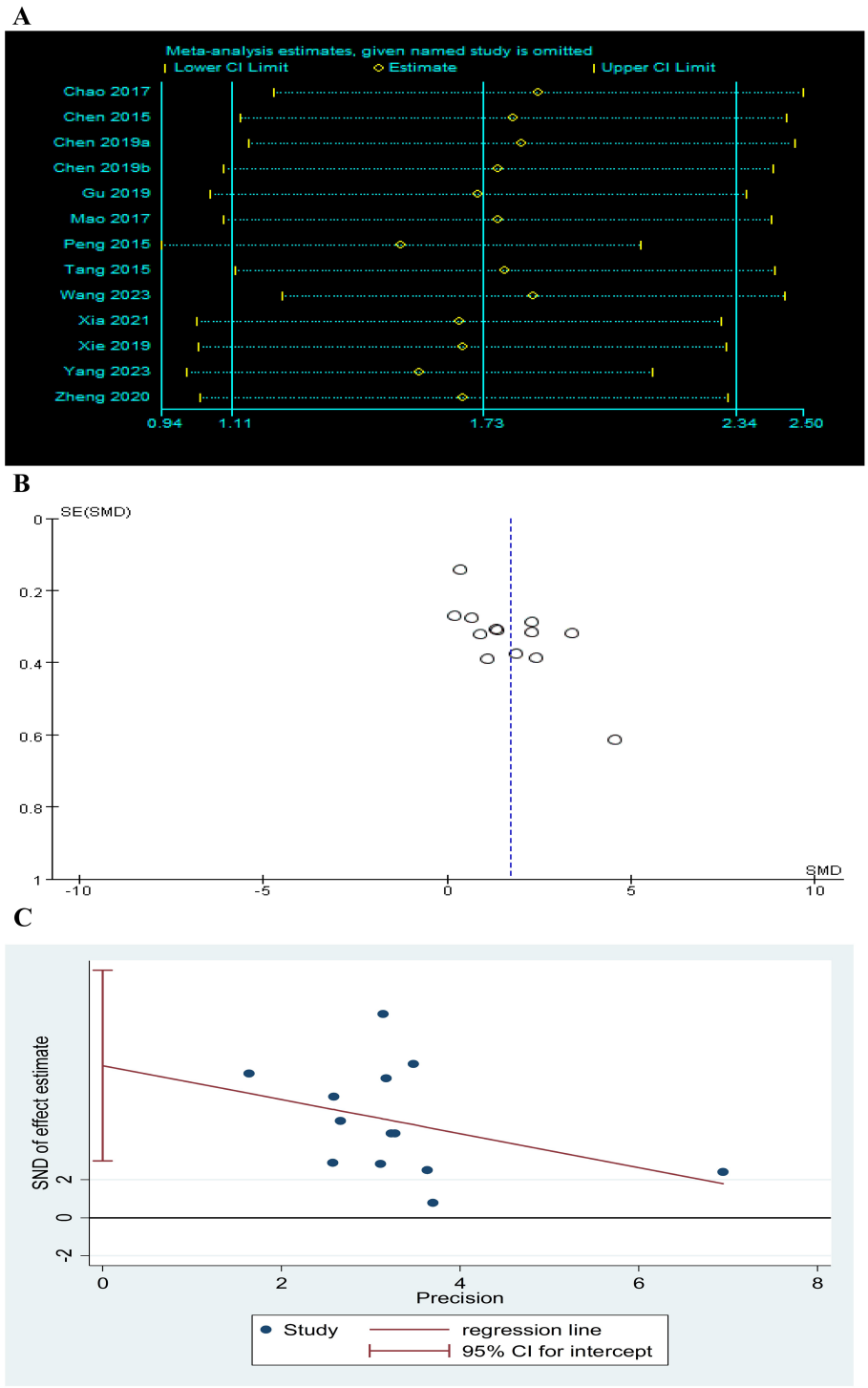

FIGURE 14
Effect of TEAS on MBI. **(A)** Sensitivity analysis of MBI. **(B)** A funnel plot analysis revealed potential publication bias. **(C)** Egger's test included studies on MBI.

Validation. SZ: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing, Validation. JWu: Data curation, Methodology, Writing – review & editing. SF: Investigation, Supervision, Validation, Writing – review & editing. ZL: Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Supervision. HL: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. JWa: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation,

Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1438994/full#supplementary-material

References

Alwhaibi, R. M., Mahmoud, N. F., Zakaria, H. M., Ragab, W. M., Awaji, N. N. A., Elzanaty, M. Y., et al. (2021). Therapeutic efficacy of transcutaneous electrical nerve stimulation Acupoints on motor and neural recovery of the affected upper extremity in chronic stroke: a sham-controlled randomized clinical trial. *Healthcare* 9:20. doi: 10.3390/healthcare9050614

Chao, M. (2016). Stndy on the effect of transcutaneous electrical acupoint stimulation Baxie point in teating hand dysfunction for stroke patients with spasticity (thesis). Nanjing, JS: Nanjing University of Traditional Chinese Medicine.

Chen, Y., Tian, J., Xie, B. J., Xu, Y. M., Tang, C. Z., Zhang, X. L., et al. (2015). Effects of transcutaneous electrical acupoint stimulation treatment in stroke survivors with upper dysfunction. *Chinese J. Rehabil. Med.* 30, 454–457. doi: 10.3969/j.issn.1001-1242.2015.05.009

Chen, Y., Wang, H. W., Xiang, Y. Z., Sun, X. Y., Dong, Q. L., Wang, Y. Y., et al. (2019a). Short-term effectiveness of community-based low frequency transcutaneous electric acupoint stimulation on upper limb and hand function rehabilitation in stroke patients. *Chinese J. Rehabil.* 34:4.

Chen, Y., Wang, H. W., Xiang, Y. Z., Wang, X. W., Zhao, K., Dou, X. Y., et al. (2019b). Effects of low frequency transcutaneous electric Acupoint stimulation on upper limbs and hands function for chronic stroke patients. *Chin. J. Rehabil. Theory Pract.* 24, 1371–1375. doi: 10.3969/j.issn.1006-9771.2018.12.002

Chi, Y. L., Zhang, W. L., Yang, F., Su, F., and Zhou, Y. K. (2019). Transcutaneous electrical Acupoint stimulation for improving postoperative recovery, reducing stress and inflammatory responses in elderly patient undergoing knee surgery. *Am. J. Chin. Med.* 47, 1445–1458. doi: 10.1142/S0192415X19500745

Coscia, M., Wessel, M. J., Chaudary, U., Millán, J. D. R., Micera, S., Guggisberg, A., et al. (2019). Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain* 142, 2182–2197. doi: 10.1093/brain/awz181

Dawson, J., Liu, C. Y., Francisco, G. E., Cramer, S. C., Wolf, S. L., Dixit, A., et al. (2021). Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet* 397, 1545–1553. doi: 10.1016/S0140-6736(21)00475-X

Dimitrijević, M. R., Faganel, J., Dimitrijević, M., Nathan, P. W., and Trontelj, J. K. (1972). Habituation: effects of regular and stochastic stimulation. *J. Neurol. Neurosurg. Psychiatry* 35, 234–242. doi: 10.1136/jnnp.35.2.234

Dimyan, M. A., and Cohen, L. G. (2011). Neuroplasticity in the context of motor rehabilitation after stroke. *Nat. Rev. Neurol.* 7, 76–85. doi: 10.1038/nrneurol.2010.200

Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634. doi: 10.1136/bmj.315.7109.629

GBD 2021 Causes of Death Collaborators (2024). Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet* 403, 2100–2132. doi: 10.1016/S0140-6736(24)00367-2

Gu, Z. W., Lei, B., Deng, W. Z., and Zhang, J. K. (2019). To observe the application effect of transcutaneous electrical acupoint stimulation in community patients with hand dysfunction after stroke. *Chin. J. Clin. Rational Drug Use* 12:2.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., et al. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336, 924–926. doi: 10.1136/bmj.39489.470347.AD

Higgins, J. P. T., Altman, D. G., Gtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928. doi: 10.1136/bmj.d5928

Higgins, J. P. T., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21, 1539–1558. doi: 10.1002/sim.1186

Huang, H. Y., Bach, J. R., Sharma, H. S., Chen, L., Wu, P., Sarnowska, A., et al. (2024). The 2023 yearbook of neurorestoratology. *J. Neuro Oncol.* 12:100136. doi: 10.1016/j.jnrt.2024.100136

Jia, J., Zhong, J. B., and Liu, J. (2018). Clinical study of TEAS coordinated with basic rehabilitation training on hand dysfunction after stroke. *J. Clin. Acupunct Moxibustion.* 34:4.

Julie, B., Erin, G., Liam, J., and Peter, L. (2017). Early rehabilitation after stroke. *Curr. Opin. Neurol.* 30, 48–54. doi: 10.1097/WCO.0000000000000404

Laddha, D., Ganesh, G. S., Pattnaik, M., Mohanty, P., and Mishra, C. (2015). Effect of transcutaneous electrical nerve stimulation on plantar flexor muscle spasticity and walking speed in stroke patients. *Physiother. Res. Int.* 21, 247–256. doi: 10.1002/pri.1638

Langhammer, B., and Stanghelle, J. K. (2011). Can physiotherapy after stroke based on the Bobath concept result in improved quality of movement compared to the motor relearning programme. *Physiother. Res. Int.* 16, 69–80. doi: 10.1002/pri.474

Li, J. L., Hao, M. D., Liu, M. N., Wang, J., Gao, D. Y., Han, S., et al. (2022). Transcutaneous electrical Acupoint stimulation pretreatment alleviates cerebral ischemia–reperfusion injury in rats by modulating microglia polarization and Neuroinflammation through Nrf2/HO-1 signaling pathway. *Neurochem. Res.* 48, 862–873. doi: 10.1007/s11064-022-03797-5

Lim, S. M., Go, E., Lee, J., Lee, G. E., Kim, E. J., and Son, C. (2023). Improving upper limb spasticity in patients with stroke by Electroacupuncture therapy: a pre-and post-treatment study. *J. Acupunct. Meridian Stud.* 16, 248–254. doi: 10.51507/j.jams.2023.16.6.248

Liu, X. H., Huai, J., Gao, J., Zhang, Y., and Yue, S. W. (2017). Constraint-induced movement therapy in treatment of acute and sub-acute stroke: a meta-analysis of 16 randomized controlled trials. *Neural Regen. Res.* 12, 1443–1450. doi: 10.4103/1673-5374.215255

Ma, Q. F., Li, R., Wang, L. J., Yin, P., and Yang, Y. (2021). Temporal trend and attributable risk factors of stroke burden in China, 1990–2019: an analysis for the global burden of disease study 2019. *Lancet Public Health* 6, e897–e906. doi: 10.1016/S2468-2667(21)00228-0

Mao, Z. F., Wang, X. L., Yang, R. C., Xu, L. X., Zhao, Y. R., and Yu, L. H. (2017). Effect of transcutaneous electrical acupoint stimulation in patients with hand dysfunction after stroke. *Mod. Pract. Med.* 29:2. doi: 10.3969/j.issn.1671-0800.2017.12.010

Meng, L., Jiang, X., Qin, H., Fan, J., Zeng, Z., Chen, C., et al. (2022). Automatic upper-limb Brunnstrom recovery stage evaluation via daily activity monitoring. *IEEE Trans. Neural Syst. Rehabil. Eng.* 30, 2589–2599. doi: 10.1109/TNSRE.2022.3204781

Muller, C. O., Faity, G., Muthalib, M., Perrey, S., Dray, G., Xu, B., et al. (2024). Brain-movement relationship during upper-limb functional movements in chronic post-stroke patients. *J. Neuroeng. Rehabil.* 21:188. doi: 10.1186/s12984-024-01461-3

Nelles, G., Jentzen, W., Jueptner, M., Müller, S., and Diener, H. C. (2001). Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *NeuroImage* 13, 1146–1154. doi: 10.1006/nimg.2001.0757

Nogueira, N., Parma, J. O., Leão, S., Sales, I. S., Macedo, L. C., Galvão, A., et al. (2021). Mirror therapy in upper limb motor recovery and activities of daily living, and its neural correlates in stroke individuals: a systematic review and meta-analysis. *Brain Res. Bull.* 177, 217–238. doi: 10.1016/j.brainresbull.2021.10.003

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., and Mckenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 372:n160. doi: 10.1136/bmj.n160

Pan, Y. Y., Shao, Y. F., Chi, Z. H., Jin, S. H., and Wang, J. L. (2023). Transcutaneous electrical Acupoint stimulation accelerates the recovery of patients undergoing laparoscopic myomectomy: a randomized controlled trial. *J. Pain Res.* 16, 809–819. doi: 10.2147/jpr.S399249

Peng, Y., Zhang, J., Su, C. C., Zhang, S. X., Wen, L. L., and Chen, Y. J. (2015). Effects of transcutaneous acupoint electrical stimulation on upper limb function and motor evoked potential in stroke patients. *Chinese J. Rehabil. Med.* 30:571.

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., et al. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database Syst. Rev.* 2014:Cd010820. doi: 10.1002/14651858.CD010820.pub2

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., Culebras, A., et al. (2013). An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 44, 2064–2089. doi: 10.1161/STR.0b013e318296aeca

Szmit, M., Krajewski, R., Rudnicki, J., and Agrawal, S. (2023). Application and efficacy of transcutaneous electrical acupoint stimulation (TEAS) in clinical practice: a systematic review. *Adv. Clin. Exp. Med.* 32, 1063–1074. doi: 10.17219/acem/159703

Tan, Z. X., Dong, F., Wu, L. Y., Xu, G. Y., and Zhang, F. (2024). Transcutaneous electrical acupoint stimulation attenuated neuroinflammation and oxidative stress by activating SIRT1-induced signaling pathway in MCAO/R rat models. *Exp. Neurol.* 373:114658. doi: 10.1016/j.expneurol.2023.114658

Tang, C. Z., Li, C. Y., Zhang, X. L., Wang, J. Y., Liu, Z. L., He, Z. J., et al. (2015). Effects of low frequency transcutaneous electric acupoint stimulation on hand and upper extremity dysfunction post stroke. *Chin. J. Rehabil. Theory Pract.* 21:4. doi: 10.3969/j.issn.1006-9771.2015.03.002

Tang, Y. Q., Wang, L. J., He, J. X., Xu, Y. P., Huang, S. J., and Fang, Y. (2021). Optimal method of electrical stimulation for the treatment of upper limb dysfunction after stroke: a systematic review and Bayesian network Meta-analysis of randomized controlled trials. *Neuropsychiatr. Dis. Treat.* 17, 2937–2954. doi: 10.2147/NDT.S332967

Tang, Q., Yang, X., Sun, M., He, M., Sa, R., Zhang, K., et al. (2024). Research trends and hotspots of post-stroke upper limb dysfunction: a bibliometric and visualization analysis. *Front. Neurol.* 15:1449729. doi: 10.3389/fneur.2024.1449729

Thrane, G., Askim, T., Stock, R., Indredavik, B., Gjone, R., Erichsen, A., et al. (2015). Efficacy of constraint-induced movement therapy in early stroke rehabilitation: a randomized controlled multisite trial. *Neurorehabil. Neural Repair* 29, 517–525. doi: 10.1177/1545968314558599

Tu, W. J., and Wang, L. D. (2023). China stroke surveillance report 2021. *Mil. Med. Res.* 10:33. doi: 10.1186/s40779-023-00463-x

Wang, C. L. (2024). Analysis of the effect of transcutaneous electrical stimulation of acupoints combined with rehabilitation training in the treatment of upper limb dysfunction after stroke. *J. Clin. Nurs. Res.* 8, 316–321. doi: 10.26689/jcnr.v8i6.7628

Wang, Y. J., Li, Z. X., Gu, H. Q., Zhai, Y., Zhou, Q., Jiang, Y., et al. (2022). China stroke statistics: an update on the 2019 report from the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for neurological diseases, the Chinese Stroke Association, National Center for chronic and non-communicable disease control and prevention, Chinese Center for Disease Control and Prevention and institute for global neuroscience and stroke collaborations. *Stroke Vasc. Neurol.* 7, 415–450. doi: 10.1136/svn-2021-001374

Wang, D., Wang, J., Zhao, H. B., Liang, Y. H., Zhang, W. Y., Li, M. X., et al. (2023). The relationship between the prefrontal cortex and limb motor function in stroke: a study based on resting-state functional near-infrared spectroscopy. *Brain Res.* 1805:148269. doi: 10.1016/j.brainres.2023.148269

Wang, H., Xiang, Y. Z., Wang, C. K., Wang, Y. Y., Chen, S. G., Ding, L., et al. (2023). Effects of transcutaneous electrical acupoint stimulation on upper-limb impairment after stroke: a randomized, controlled, single-blind trial. *Clin. Rehabil.* 37, 667–678. doi: 10.1177/02692155221138916

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., et al. (2013). Guidelines for adult stroke rehabilitation and recovery a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 47, e98–e169. doi: 10.1161/STR.0000000000000098

Wu, L. Y., Tan, Z. X., Su, L., Dong, F., Xu, G. Y., and Zhang, F. (2023). Transcutaneous electrical acupoint stimulation alleviates cerebral ischemic injury through the TLR4/MyD88/NF-κ B pathway. *Front. Cell. Neurosci.* 17:1343842. doi: 10.3389/fncel.2023.1343842

Xia, D. J., Xiong, X. S., Lv, Y. Q., Fan, R., and Peng, T. (2021). Effects of bilateral arm transcutaneous electrical acupoint stimulation on upper limb function for subacute stroke hemiplegic patients. *Chin. J. Rehabil. Theory Pract.* 27, 1318–1322. doi: 10.3969/j.issn.1006

Xie, J. J., Li, J. X., and Sun, Q. (2019). A randomized controlled trial of transcutaneous electrical acupoint stimulation for upper extremity dysfunction after stroke. *J. Basic Chinese Med.* 25:3.

Xu, J. M., Liu, L. Q., Li, Y. L., and Li, M. Y. (2016). Experiences of application of acupuncture in stroke rehabilitation with integrated traditional Chinese and Western medicine. *Chin. J. Rehabil. Theory Pract.* 22:4. doi: 10.3969/j.issn.1006-9771.2016.02.026

Yan, Y. L., Ding, X. M., and Lv, Y. J. (2019). Low frequency transcutaneous electrical acupoint stimulation for stroke sequelae stage hand and upper limb dysfunction. *Cardiovasc. Dis. J. Integrated Trad Chinese Western Med.* 7, 87–88. doi: 10.16282/j.cnki.cn11-9336/r.2019.12.060

Yan, T., and Hui-Chan, C. W. (2009). Transcutaneous electrical stimulation on acupuncture points improves muscle function in subjects after acute stroke: a randomized controlled trial. *J. Rehabil. Med.* 41, 312–316. doi: 10.2340/16501977-0325

Yang, L. L. (2023). Transcutaneous acupoint electrical stimulation combined rehabilitation training in the treatment of upper limb dysfunction after stroke clinical observation. *J. Prac. Tradit Chin. Med.* 39, 983–985.

Yin, C. S., Zhang, C., Meng, X. G., and Zhao, Q. (2022). Current research status on the dose-response and timeliness of acupuncture treatment for stroke. *Shanghai J. Acu Mox.* 41, 824–830. doi: 10.13460/j.issn.1005-0957.2022.08.0824

Yu, L. H., Jiang, M., and Mao, Z. F. (2020). Application of percutaneous acupoint electrical stimulation in the rehabilitation of hand dysfunction after stroke. *China Modern Doctor* 58:4.

Zhang, L., Jia, G., Ma, J., Wang, S., and Cheng, L. (2022). Short and long-term effects of robot-assisted therapy on upper limb motor function and activity of daily living in patients post-stroke: a meta-analysis of randomized controlled trials. *J. Neuroeng. Rehabil.* 19:76. doi: 10.1186/s12984-022-01058-8

Zhang, Y., Jiang, Y., Glielmi, C. B., Li, L. C., Hu, X. P., Wang, X. Y., et al. (2013). Long-duration transcutaneous electric acupoint stimulation alters small-world brain functional networks. *Magn. Reson. Imaging* 31, 1105–1111. doi: 10.1016/j.mri.2013.01.006

Zhang, B., Zhu, Y. L., Jiang, C. Y., Li, C., Li, Y. Y., Bai, Y. L., et al. (2018). Effects of transcutaneous electrical Acupoint stimulation on motor functions and self-care ability in children with cerebral palsy. *J. Altern. Complement. Med.* 24, 55–61. doi: 10.1089/acm.2016.0111

Zhao, W. L., Wang, C., Li, Z. Z., Chen, L., Li, J. B., Cui, W. D., et al. (2015). Efficacy and safety of transcutaneous electrical acupoint stimulation to treat muscle spasticity following brain injury: a double-blinded, multicenter, randomized controlled trial. *PLoS One* 10:e0116976. doi: 10.1371/journal.pone.0116976

Zheng, W. Y., and Mao, Z. F. (2020). Application of transcutaneous acupoint electrical stimulation in rehabilitation of elderly patients with post-stroke hand dysfunction. *China Modern Doctor.* 58:4.

Zhou, S., Guo, Z. Q., Wong, K. F., Zhu, H. L., Huang, Y. H., Hu, X. L., et al. (2021). Pathway-specific cortico-muscular coherence in proximal-to-distal compensation during fine motor control of finger extension after stroke. *J. Neural Eng.* 18:056034-. doi: 10.1088/1741-2552/ac20bc

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Eccentric strengthening vs. conventional therapy in sub-acute stroke survivors: a randomized controlled trial

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Spastic paresis, a frequent consequence of stroke, is characterized by both neurological and muscular alterations, leading to decreased muscle strength, increased passive muscle stiffness, and subsequently, diminished functional capacity. Although conventional rehabilitation programs are effective in enhancing muscle strength, they often fail to yield clinically significant improvements in functional capacities. Eccentric Training (ET) has shown promise in addressing the shortened muscle fascicle lengths and joint contractures commonly observed in stroke survivors. Despite the prevalence of contractures and rigidity in this population, the effects of ET on the structural and mechanical properties of muscles remain underexplored. This study aims to investigate the impact of ET on gait speed in sub-acute stroke patients compared to conventional therapy. Additionally, we aim to explore the effects of ET on the mechanical properties, structural characteristics, and neuromuscular parameters of the plantar flexors. A randomized controlled trial will be conducted, adhering to CONSORT guidelines, with participants assigned to either a Conventional Therapy Group or an Eccentric Training Group. Assessments will be conducted at baseline, and after ET intervention, encompassing clinical, biomechanical, and functional evaluations. This study seeks to provide empirical evidence on the efficacy of ET in improving motor outcomes in sub-acute stroke patients, thereby informing more effective rehabilitation strategies.

KEYWORDS

muscle strength, stiffness, ankle joint, eccentric training, stroke

1 Introduction

Stroke, as the leading cause of adult disability, presents a substantial challenge for affected individuals (1). Among the primary impairments following a stroke is the weakening of the lower limb muscles (2), impacting over 90% of stroke patients (3). While some recovery of lower limb function is observed, it often falls short of enabling independent and comfortable outdoor ambulation in daily life (4). Consequently, approximately half of stroke survivors are unable to resume their professional activities, and roughly two-thirds experience chronic disability (5).

One of the primary neuromotor consequences of a stroke is spastic paresis, known as the most common motor disorder following a cerebral injury (6). Generally, the spastic paresis syndrome is associated with both neurological and muscular disorders (7). Neurological issues manifest immediately after a stroke, leading to a quantitative reduction in the recruitment of motor units in agonist muscles (8). This has been explained by a failure of central voluntary control activation and changes in the structure and properties of spinal motoneurons (9).

These alterations lead to a decrease in muscle contraction efficiency, resulting in a diminished capacity to generate voluntary force (10). In addition to the previously mentioned neurological alterations, a stroke also triggers muscular changes (11). These alterations, referred to as spastic myopathy, result from a combination of two factors: the underuse of the paretic limb and immobilization in a shortened position (12). Spastic myopathy induces multiple adaptations in the mechanical and structural properties of the paretic muscle (2, 13). In this context, studies have demonstrated a loss of fascicular length and thickness of plantar flexors (PF) (14) and a decrease in pennation angle of the gastrocnemius medialis (GM) in stroke survivors (15). Regarding mechanical adaptation, stroke injury leads to muscle contracture, which is defined as an increased muscle stiffness during passive mobilization of the ankle joint (14, 16).

Several studies have investigated many rehabilitation programs for stroke survivors and found that a regular musculotendinous stretching is effective in short-term spasticity inhibition and in preventing long-term hypo-extensibility and muscle contracture; muscle strengthening is recommended as soon as voluntary motor control allows for it; relearning grasping (17), balance (18), and locomotion involves the repetition of motor tasks (19). Otherwise, many studies have concluded, with a high level of evidence, the effectiveness of botulinum toxin in reducing spasticity (20). However, motor improvement remains mild to moderate (21). These mixed results concerning motor function improvement are likely related to the evaluation methods of movement-limiting factors and muscle hyperactivity, which are lengthy, intrusive, and destructive (3, 13). They also do not focus on reducing the effects of spastic myopathy, which is still not well-understood in management (22, 23). Therefore, it is both justified and necessary to question the post-stroke rehabilitation and readaptation methodologies.

Recently, an increasing amount of recent research is focusing on muscle strengthening, particularly eccentric training (ET) (24). ET, a traditional method used to boost muscle strength in athletes, involves muscle contraction during the lengthening of the musculotendinous complex (25). Compared to other training modalities at the same force exertion level, eccentric exercise requires less muscle activity (26). Therefore, this approach could be particularly effective for addressing muscle fascicle shortening and stiffness observed in stroke survivors, due to the increased mechanical load involved during active lengthening (14). This increased load is hypothesized to lead to more significant gains in muscle strength and volume and may also reduce hyperactivity in affected muscles (24). In this context, ET has been demonstrated to enhance muscle strength, reduce spasticity, and improve functional performance and quality of life in chronic stroke survivors following 4 to 6 weeks of intervention (27, 28). As a result, ET offers a myriad of benefits that may be relevant for individuals with neurological conditions (27). However, to our knowledge, no study has investigated the effects of ET on the structural and mechanical properties of the PF, nor on their implications for improving functional capacities. This is particularly relevant given the high prevalence of stiffness in post-stroke patients, which is associated with alterations in the structural and mechanical properties of the muscle-tendon complex, consequently limiting functional capacities (29). These issues are challenging to address in neurorehabilitation, where conventional therapy often fail to produce clinically significant results (30, 31). In fact, conventional therapy, which generally involves stretching exercises, concentric training, and repetitive movements to relearn skills such as balance and locomotion, does not appear to significantly improve the patient's functional walking abilities beyond 0.04 m/s (32).

The objectives of this study are: (i) investigating the effects of eccentric training on the structural and mechanical properties of PF in stroke survivors compared to conventional therapy, and (ii) analyzing the relationships between changes in structural and mechanical parameters of PF and improvements in walking speed and maximal range of motion.

2 Materials and methods

2.1 Ethical approval and trial registration

The study protocol, patient information letter, and informed consent form received Institutional Ethics Committee approval (CPP 2022–038 = 000117). The study is registered in the ClinicalTrials.gov database (ID = NCT06140381). The procedures will be conducted according to the principles expressed in the Declaration of Helsinki. Written consent to participate in the protocol will be signed directly by the patient.

2.2 Study design

This study will be conducted in strict adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines, and will employ a single-blinded, controlled, randomized design, wherein participants will be randomly assigned to one of two groups: the conventional therapy group (CTG) or the Eccentric training group (ETG). Both groups will undergo a series of assessments at: Ji (initial assessment) and Jf (final assessment) as illustrated in Figure 1. The study will begin with a recruitment phase, followed by a screening phase. Subsequently, there will be a 4-week period allocated for experimental testing before the intervention, and an additional 4 weeks for experimental testing after the intervention. The experimental testing will include clinical health assessments, biomechanical assessments, neuromuscular evaluations, and functional assessments.

2.3 Randomization

The random assignment of participants to their respective groups will take place on the day they will be included in the study and will be supervised by the investigator. The randomization list will be created by an independent statistician from the clinical research unit. For the randomization process, a computer-generated list will be generated using the Clinical Trial Randomization Tool. This list will then be uploaded into an online case report form. Each study participant will be assigned a unique allocation study number in a sequential format (TMP00X). The rigorous blinding will be maintained until the database will

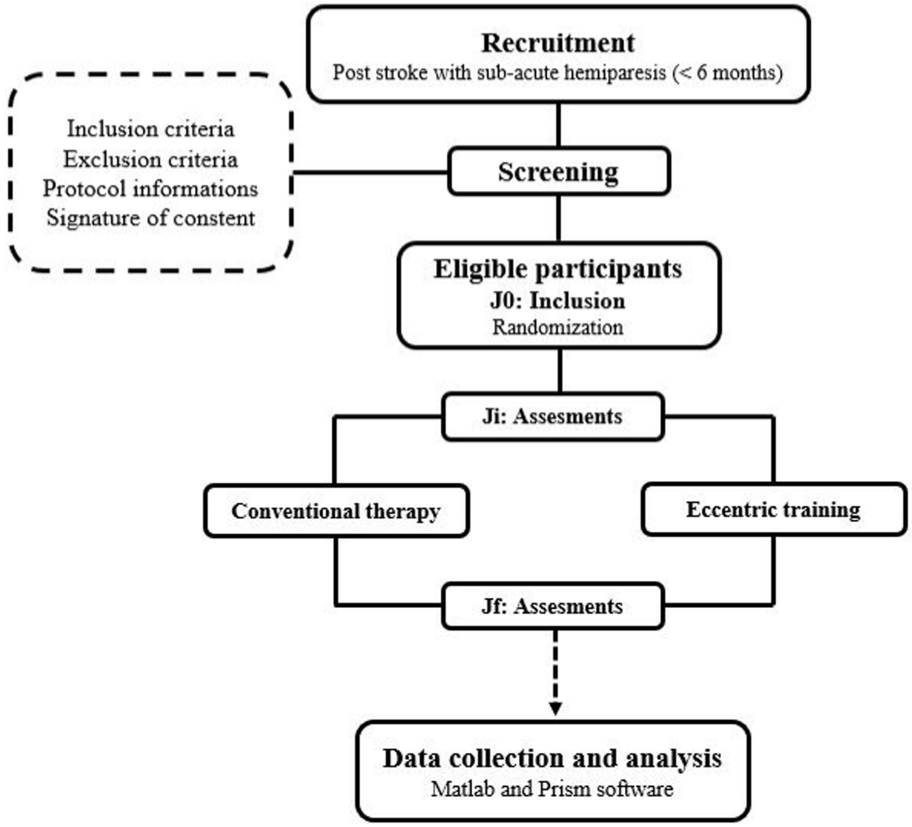

FIGURE 1
Study design.

be finalized. A blinded assessor will conduct three visits: one before, one in the middle, and one after the interventions, while unblinded kinesiologists, who provide treatment and exercise sessions, will not be involved in the assessment sessions. All required information stipulated by the study protocol will be entered diligently into the Electronic Data Capture system in real-time as it will be acquired.

2.4 Recruitment

Participants will be recruited from the clinic of Parc de Belleville in Paris between the 1st of January 2024 to 31st May 2024. Recruitment will be accomplished by disseminating study participation offers in clinical centers, and subsequently, the medical staff will compile a list of volunteers to the experimenter. To participate in this study, subjects will be invited for an admission consultation (Pre-inclusion) (J0) with the principal investigator. Before this consultation, the investigator will need to ensure that the patient meets the study's inclusion and exclusion criteria.

2.4.1 Inclusion criteria

- Adult aged 20 to 75 years.
- Subacute hemiparesis (< 6 months).
- BMI between 18.5 and 25.
- Written consent to participate in the study.

2.4.2 Exclusion criteria

- Ankle impairment
- Botulinum toxin injections in PF within the last 4 months before study inclusion to ensure that the muscle properties were not influenced by the toxin's effects.
- Medical contraindication for maximal effort.
- Neurodegenerative disorders.
- Cardiovascular disorders.
- History of epilepsy.

The investigator will explain the purpose of the study, and the experimental protocol. The patient will then be given time for consideration. If they will agree, on the day of admission, they will sign an informed written consent to participate in the study, and then they will undergo their initial evaluation (Ji).

2.5 Intervention

2.5.1 Conventional therapy

The conventional therapy program will extend over a period of 12 weeks, consisting of a total of 36 sessions with three sessions per week conducted by physiotherapists. The program will include both isometric and concentric strengthening exercises specifically targeting the plantar flexors. The load and intensity of these

exercises will be individualized according to each participant's capabilities. The conventional therapy will consist of:

- Isometric Exercises: Participants will perform isometric contractions at 70% of their MVC for 10 s, followed by a 20 s rest interval. This cycle will be repeated in sets of 10.
- Concentric Exercises: These exercises will involve the use of weights or resistance bands. The intensity of these exercises will progressively increase from 50 to 80% of the MVC over the course of the program. The number of repetitions per set will also gradually increase from 8 to 12, with each exercise being performed in three sets.
- Stretching Sessions: The program will incorporate stretching exercises for the plantar flexors, performed both passively and actively. Each stretch will be held for 30 s and repeated three times for each target muscle.

2.5.2 Eccentric training protocol

In the absence of a standardized eccentric isokinetic training protocol established for hemiparetic subjects on the plantar flexor muscles, the protocol designed for this study drew inspiration from the one established by Clark and Patten (28) and by Harris-Love et al. (33). This protocol will allow the introduction of eccentric stimulus to individuals who are new to this type of training. It will progressively advance their program to include workload levels that are sufficient to stimulate muscular plasticity optimally, thereby inducing skeletal muscle adaptations. The ET protocol will adhere to guidelines provided by the TiDieR, which encompass the following 12 items:

1. *Name:* The ET protocol.
2. *Why:* The ET protocol will aim to enhance walking capacity and reduce spasticity.
3. *What (Materials):* The eccentric exercise program will be carried out using the BIODEX isokinetic device (Biodex 4 Medical Systems, Inc., Shirley, NY, USA).
4. *What (Procedures):* The eccentric program will last for 12 weeks, with a frequency of 3 sessions per week, totaling 36 sessions. At least 1 day of rest will be required between two training sessions. The participants will be placed in the similar position of the neuromuscular assessments (reference position). The Biodex System 4 dynamometer settings for the exercise sessions will be conducted under settings like those used for the assessments. The training program will be divided into two phases: a familiarization phase and a progression phase. Training will be progressing according to the schedule presented in the Figure 2. The familiarization phase, involving the manipulation of three key variables, will aim to reduce risks and enhance the advantages of eccentric strength training. This phase will unfold in two stages (33). The first stage will consist of two sessions designed to familiarize participants with the muscle recruitment patterns associated with isokinetic eccentric exercises. The second stage will span a one-week preparation period, intended to elicit a protective muscular response, and progressively condition the muscles for higher eccentric intensities (33). For the progression phase, a triangular pyramid training paradigm will be employed (28). The rationale will be to, first, train to increase the speed at which force can be produced and second increase the load produced during dynamic contractions. Custom-designed attachments will be used to enable optimal biomechanical alignment for proper performance of the ankle joint movement (28). Participants will be instructed to "resist and try to stop the dynamometer." Verbal encouragement will continue to be provided throughout the training sessions to motivate maximal effort. This form of training will conceptually remain like power training, which involves rapid muscle contractions. Power training will continue to be considered a safe but intense form of training that is more effective than traditional resistance training using slower contractions.
5. *Who:* By a kinesiologists specialized in adapted physical activity.
6. *How:* Face to face sessions.
7. *Where:* Rehabilitation department.
8. *When and how much:* the ET protocol begins the 1st of January 2024 and concludes on the 31$^{st\ of}$ May 2024. Each week will include three sessions, making a cumulative total of 36 sessions. Each session lasts 45 min, with a 15-min warm-up and 30 min of actual exercise.
9. *Tailoring:* The determination of the number of sets will be tailored to the patient's abilities.
10. *Modifications:* Modifications will be implemented to the protocol in each session, involving adjustments such as an increase in the number of sets or repetitions.
11. *How well (planned):* The training program will be divided into two phases: a familiarization phase and a progression phase. Training will be progressing according to the schedule presented in the Figure 2. The program's progression will be determined by two factors: a quantitative element linked to the training load (volume/intensity) and a qualitative aspect associated with the nature of the exercises (eccentric exercise).
12. *How well (actual):* Not started yet.

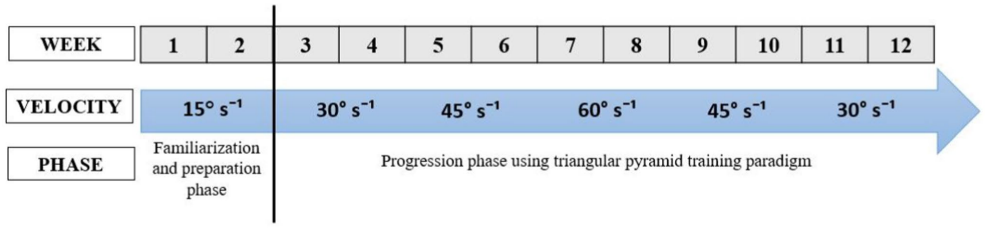

FIGURE 2
The progression of eccentric training protocol.

2.6 Outcome measures

2.6.1 Functional parameters

First, gait speed (m/s) will be measured through the 10-meter walking test. Secondly, the maximal range of motion (ROM), defined as the extent of stretch that the participant can comfortably endure during the stretching maneuver, will be measured using the BIODEX isokinetic device (Biodex 4 Medical Systems, Inc., Shirley, NY, United States). Participants will be positioned prone on the isokinetic machine and instructed to achieve complete relaxation. To minimize the involvement of unrecorded muscles, the ankle will be securely fixed in a relaxed position on the isokinetic dynamometer. Starting from the neutral position (0°), the ankle joint will be passively mobilized from plantar to dorsiflexion at a slow angular velocity (2°/s). Participants will be encouraged to maintain a state of relaxation and halt ankle rotation when they will perceive a tolerable maximum stretch. Then, the ROM (°) will be recorded for each participant.

2.6.2 Biomechanical proprieties of plantar flexors

Muscle stiffness, as expressed by the shear modulus (μ, in Kpa), will be assessed during passive ankle joint mobilization and during MVC of PF (34). An Aixplorer® ultrasound scanner (Supersonic Imagine, version 6.1, Aix-en-Provence, France) will be used in Shear Wave Elastography (SWE) mode (musculoskeletal preset, penetration mode, scale: 600 kPa) to quantify muscle stiffness in PF (GM, GL, and SOL). During the evaluations, two ultrasound probes will be used: probe 1 (4–15 MHz, SL15-4; SuperSonic Imagine, Aix-en-Provence, France) for the GM and GL, and probe 2 (2–10 MHz, SL10-2; SuperSonic Imagine, Aix-en-Provence, France) for the SOL. Acoustic gel will be used as an interface between the skin and the probe. For passive muscle stiffness evaluation, three positions will be identified: P0 = 0° (Neutral position), P1 = 10° and P2 = 20° (from neutral position to dorsiflexion). For each position, the SWE measurement will be conducted twice in predetermined regions, with the order randomized and a 1-min rest period between measurements. Regarding the active stiffness evaluation, the reference position will require the hips to be flexed at 45°, the knee on the paretic side to be fully extended, and the ankle on the paretic side to be positioned at 90°. The ankle joint's axis will align with the dynamometer's axis of rotation, and the foot will be securely fastened to the dynamometer platform. To ensure stability, additional attachments will be employed to secure the thigh and trunk to the isokinetic ergometer seat. Then, participants will receive instructions to perform two maximal isometric contractions (MVC) of PF. For submaximal contractions (30, 50, 70% of MVC), participants will receive immediate visual feedback on their %MVC torque to achieve the experimenter's target %MVC torque. Once the desired torque level will be reached, an ultrasound image will be taken. For each MVC torque level, the SWE measurement will be performed twice in each muscle in a randomized order. Each trial will have a maximum duration of 5 s, and subjects will be allowed rest periods between trials. SWE measurement during passive and active conditions will be used for further analysis.

2.6.3 Structural parameters

Fascicle length, thickness and pennation angle will be assessed using the ultrasound scanner (Supersonic Imagine, version 6.1, Aix-en-Provence, France) in B-mode (echography mode). Muscle thickness will be determined as the distance between the superficial and deep aponeuroses of the GM muscle (35). Fascicle length will be calculated by extrapolating the intersection with both aponeuroses and measuring the distance between their respective intersection points (35). Pennation angle will be defined as the angle between the fascicle and the deep aponeurosis (35). Fascicle length and pennation angle will be measured for three fibers, and the average will be used for analysis. For each parameter, the average of three measurements will be used for further analysis.

2.6.4 Neuromuscular parameters

Peak force and rate of force development (RFD) will be evaluated using the BIODEX isokinetic device (Biodex 4 Medical Systems, Inc., Shirley, NY, United States) during MVC of PF. The peak force value from the two trials of MVC will be recorded (aPeak, N). The relative peak force (rPeak, N/kg) will be calculated by normalizing the peak force to the participant's body mass (aPeak/BM, N/kg). The dynamometer signals will be stored offline for subsequent analysis. Early RFD will also be obtained from each MVC contraction onset to 50 ms (RFD50-100). Late RFD will be acquired from 100 to 200 ms (RFD100-200). All RFD will be calculated from the linear slop of the force – time curve (Δ force/Δ time). Finally, maximal activation will be evaluated using the Trigno Wireless Electromyography (EMG) system (Delsys, Inc., Boston, United States) during the MVC of PF. Four EMG sensors will be placed on the GM, GL, SOL, and tibialis anterior (TA) muscles. Before attaching the electrodes, the skin will be carefully prepared by shaving and cleaning it with an abrasive cleaner and alcohol swab to minimize impedance. EMG sensors will be positioned on each muscle's belly, aligned parallel to the muscle fibers as recommended by SENIAM guidelines (36). The placement of EMG electrodes will be meticulously verified using ultrasound to ensure longitudinal alignment with the muscle fascicles and proper positioning away from neighboring muscles (37). EMG signal will also be recorded during passive evaluation.

2.7 Data analysis

Data will be processed using MATLAB software (MATLAB R2024a, MathWorks, Natick, USA). Ultrasound images will be exported from Aixplorer's software. Shear displacements will be calculated using a speckle-tracking algorithm. Tissue displacement maps will be used to calculate shear-wave velocity (SWV, m/s) in each pixel of the map. Then, the shear modulus (μ) will be calculated as follows:

$$\mu = \rho.SWV^2, where\ \rho\ is\ the\ muscle\ mass\ density\left(1{,}000\ kg/m^3\right).$$

Image processing will be converted each pixel of the color map into a shear modulus based on the recorded color scale. Mean shear modulus values will be calculated in a 15 × 15 mm^2 region of interest in different regions of each muscle fascicular area (38).

The raw EMG signals will be band-pass filtered at 15–500 Hz through a second-order Butterworth digital filter to remove noise or movement interference (39). The data from the different assessments will be collected, rectified, and smoothed using root mean square analysis (RMS) with a 20–ms window (40) calculated using the following equation (36):

$$\sqrt{\frac{1}{T}\int_{T0-T/2}^{t0+T/2}(EMG)^2\,dt, where\ T\ is\ the\ Time\ of\ integration}$$

For the MVC assessments, a moving window with a width of 20 ms will be used to find the maximum RMS EMG activity resulting from the three efforts of MVC for each kind of contraction. Then, all RMS EMG data from the different tests will be normalized using the following equation for each muscle:

$$\text{EMG RMS\%} = \left[\left(\text{RMS EMG assessment} / \text{RMS EMG MVC}\right) \text{x } 100\%\right].$$

2.8 Statistical methods

Statistical analysis will be conducted using Prism 7.0 software (GraphPad Software, Inc., San Diego, United States). The normality of data distribution will be assessed using Kolmogorov–Smirnov tests. If the data follows a normal distribution, the paired t-test (for comparing the same group before and after intervention) and independent t-test (for comparing the control and experimental groups) will be employed. If the data does not follow a normal distribution, the Wilcoxon signed-rank test (paired samples) and the Mann–Whitney U test (independent samples) will be applied. Relationships between different parameters and their variations will be evaluated using Pearson's correlation analysis. Data will be presented by their means and standard deviations. The chosen significance threshold will be set at $p < 0.05$ for all results.

3 Discussion

To the best of our knowledge, this study protocol will be the first to investigate the effects of eccentric training on the structural and mechanical properties of PF in stroke survivors compared to conventional therapy. We hypothesize that a notable distinction will emerge between the two interventions, with the protocol incorporating eccentric strengthening demonstrating favorable outcomes. Moreover, the enhancement in gait speed and ROM will be associated with an improvement in passive and active PF stiffness.

The conceptualized program for this study aims to provide high-intensity training for individuals in sub-acute phase to effectively stimulate various forms of plasticity. The speed, load, and number of repetitions are the factors that form the basis of the eccentric work and upon which its relevance depends. Therefore, these parameters will be considered to achieve the targeted objective. In this context, a recent study conducted by Le Sant et al. (24) has presented compelling evidence that ET significantly enhances motor performance, particularly in terms of maximal strength and power, among individuals within neurological populations. This finding aligns with the observations of Clark and Patten (28) suggesting that the remarkable strength improvements attributed to eccentric training post-stroke may be linked to heightened quadriceps stretch reflex activity. This increased reflex activity supplements the voluntary neural drive during eccentric knee flexion contractions. Conversely, when considering the structural properties of the paretic muscle, (41) calculated the minimum detectable change for the thickness parameter, estimating it to be at 3 mm. Remarkably, these authors observed a noteworthy increase of 3 mm in the thickness of the SOL muscle following a 23-session eccentric training program focused on the PF, but this research was conducted with healthy individuals.

The conceptualized program for this study aims to provide high-intensity training for individuals in the sub-acute phase to effectively stimulate various forms of plasticity. The key factors—speed, load, and number of repetitions—form the basis of eccentric work and are critical to its efficacy. Therefore, these factors will be meticulously considered to achieve the targeted objectives. In this context, a recent systematic review by Le Sant et al. (24) presents compelling evidence that ET could significantly enhance motor performance, particularly in terms of maximal strength and power, among individuals with neurological diseases. The remarkable strength improvements attributed to ET post-stroke may be linked to heightened stretch reflex activity (28). Increased reflex activity may supplement the voluntary neural drive during eccentric contractions. Furthermore, regarding the structural properties of the paretic muscle, Geremia et al. (41) observed noteworthy increases of fascicle lengths (GM: 13.2%; GL: 8.8%; SOL: 21%) and muscle thickness (GM: 14.9%; GL: 15.3%; SOL: 19.1%) following 12 weeks ET focused on the PF in healthy individuals. We hypothesize that similar structural enhancements could be observed in post-stroke individuals after ET.

In our recent study, we demonstrated that the paretic muscles exhibited greater stiffness in comparison to the healthy muscles and the highest stiffness was predominantly observed in the GM, especially in the distal region at 20° (42). These observations prompt considerations regarding the potential relevance of eccentric exercise in the context of paretic muscle. In fact, eccentric exercise involves active stretching of the muscle, thereby engaging both the contractile and elastic components of the skeletal muscle. Notably, studies involving ultrasound imaging in healthy individuals have shown that this type of training can induce a reduction in passive muscle stiffness (43, 44), an increase in fascicle length, and muscle thickness (45, 46). These adaptations are likely the result of an increase in the number of sarcomeres in series and in parallel (47). Such muscle adaptations contribute to enhanced muscular strength, particularly at greater muscle lengths (48), by improving the tension-length relationship of the muscle (48, 49). Moreover, ET, which involves lengthening the muscle while producing force, is particularly effective in the context of stroke rehabilitation. It can increase force production, reduce muscle stiffness, and consequently improve the overall function of the muscle-tendon complex and functional capacity (45, 50, 51). However, to the best of our knowledge, no studies have thoroughly examined the potential modifications or improvements in the biomechanical properties of the paretic muscle following eccentric exercise. This gap in research limits our ability to draw conclusive insights into the potential enhancements or lack thereof in addressing the inherent issues associated with spastic paresis.

Walking performance is influenced by lower-extremity muscle strength (28). Particularly, the PF are pivotal in the walking process, serving as agonists and contributing to concentric activity that significantly impacts the quality of propulsion during walking (52). However, the effect of ET interventions on walking function in individuals with spastic paresis has produced mixed results in prior studies. While some investigations have reported significant improvements in walking speed and function (53, 54), others have not

observed significant enhancements (55). This variability in outcomes may be attributed to the timing of intervention, as some studies were conducted during the chronic phase, typically after six months post-injury, when spasticity may have become fully established. This study seeks to address this potential limitation by implementing the intervention during the sub-acute phase. Furthermore, other factors such as the intensity of eccentric exercise, its duration, and the overall methodology of intervention may also play a role in these divergent findings, warranting further investigation.

4 Limitations

One notable limitation of this study is the heterogeneity within the stroke patient population. Even though participants are in the sub-acute phase, the variability in individual recovery trajectories, severity of stroke, and pre-existing health conditions could lead to significant differences in response to the interventions. This heterogeneity may influence the outcomes and interpretations, making it challenging to draw definitive conclusions that are broadly applicable to all sub-acute stroke patients. We aim to increase the sample size to minimize the effects of data heterogeneity and interpretation bias. Furthermore, this study will focus on penniform muscles. It has been suggested that SWV measurements with small deviations from the fiber direction, as determined by the probe-fascicle angle, may be potentially inaccurate (56). However, previous study on the GM have shown relatively reproducible stiffness measurements (57).

5 Conclusion

This study protocol proposes an innovative comparison between ET and conventional therapy for improving outcomes in post-stroke survivors during the sub-acute phase. Preliminary evidence supports ET's potential to enhance structural, neuromuscular, biomechanical, and functional parameters, with notable improvements expected in muscle strength, stiffness, and walking performance. However, existing research has yet to fully elucidate the specific biomechanical adaptations in paretic muscles following ET, highlighting a significant gap in our understanding. This study aims to address this gap, offering new insights into stroke rehabilitation practices. The outcomes of this research could inform future clinical approaches, emphasizing the critical need for high-quality, targeted interventions in the early stages of stroke recovery.

Ethics statement

The studies involving humans were approved by Personal Protection Committee of Sud-Est I in France (CPP2022-038 = 000117). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

KB: Conceptualization, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. MZ: Project administration, Supervision, Writing – review & editing, Validation. LV: Conceptualization, Methodology, Writing – review & editing, Validation. J-MF: Formal analysis, Methodology, Resources, Visualization, Writing – review & editing. RB-S: Writing – review & editing, Methodology, Project administration, Resources. WM: Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing, Visualization, Project administration.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Pradines M, Baude M, Marciniak C, Francisco G, Gracies JM, Hutin E, et al. Effect on passive range of motion and functional correlates after a long-term lower limb self-stretch program in patients with chronic spastic paresis. *PM R.* (2018) 10:1020–31. doi: 10.1016/j.pmrj.2018.02.013

3. Smith MC, Byblow WD, Barber PA, Stinear CM. Proportional recovery from lower limb motor impairment after stroke. *Stroke*. (2017) 48:1400–3. doi: 10.1161/STROKEAHA.116.016478

4. Schinwelski MJ, Sitek EJ, Wąż P, Sławek JW. Prevalence and predictors of post-stroke spasticity and its impact on daily living and quality of life. *Neurol Neurochir Pol*. (2019) 53:449–57. doi: 10.5603/PJNNS.a2019.0067

5. Rutkowski NA, Sabri E, Yang C. Post-stroke fatigue: a factor associated with inability to return to work in patients <60 years—a 1-year follow-up. *PLoS One*. (2021) 16:e0255538. doi: 10.1371/journal.pone.0255538

6. Azzollini V, Dalise S, Chisari C. How does stroke affect skeletal muscle? State of the art and rehabilitation perspective. *Front Neurol*. (2021) 12:797559. doi: 10.3389/fneur.2021.797559

7. Jalal N, Gracies JM, Zidi M. Mechanical and microstructural changes of skeletal muscle following immobilization and/or stroke. *Biomech Model Mechanobiol*. (2020) 19:61–80. doi: 10.1007/s10237-019-01196-4

8. Tan AM, Chakrabarty S, Kimura H, Martin JH. Selective corticospinal tract injury in the rat induces primary afferent fiber sprouting in the spinal cord and hyperreflexia. *J Neurosci*. (2012) 32:12896–908. doi: 10.1523/JNEUROSCI.6451-11.2012

9. Gracies JM, Bayle N, Vinti M, Alkandari S, Vu P, Loche CM, et al. Five-step clinical assessment in spastic paresis. *Eur J Phys Rehabil Med*. (2010) 46:411–21.

10. English C, McLennan H, Thoirs K, Coates A, Bernhardt J. Loss of skeletal muscle mass after stroke: a systematic review. *Int J Stroke*. (2010) 5:395–402. doi: 10.1111/j.1747-4949.2010.00467.x

11. Beckwée D, Lefeber N, Bautmans I, Cuypers L, De Keersmaecker E, De Raedt S, et al. Muscle changes after stroke and their impact on recovery: time for a paradigm shift? *Rev Comment Top Stroke Rehabil*. (2021) 28:104–11. doi: 10.1080/10749357.2020.1783916

12. Davis JF, Khir AW, Barber L, Reeves ND, Khan T, DeLuca M, et al. The mechanisms of adaptation for muscle fascicle length changes with exercise: implications for spastic muscle. *Med Hypotheses*. (2020) 144:110189. doi: 10.1016/j.mehy.2020.110189

13. Meimoun M, Bayle N, Baude M, Gracies JM. Intensity in the neurorehabilitation of spastic paresis. *Rev Neurol (Paris)*. (2015) 171:130–40. doi: 10.1016/j.neurol.2014.09.011

14. Kwah LK, Herbert RD, Harvey LA, Diong J, Clarke JL, Martin JH, et al. Passive mechanical properties of gastrocnemius muscles of people with ankle contracture after stroke. *Arch Phys Med Rehabil*. (2012) 93:1185–90. doi: 10.1016/j.apmr.2012.02.009

15. Ramsay JW, Buchanan TS, Higginson JS. Differences in plantar flexor fascicle length and pennation angle between healthy and poststroke individuals and implications for poststroke plantar flexor force contributions. *Stroke Res Treat*. (2014) 2014:1–11. doi: 10.1155/2014/720652

16. Gray V, Rice CL, Garland SJ. Factors that influence muscle weakness following stroke and their clinical implications: a critical review. *Physiother Can*. (2012) 64:415–26. doi: 10.3138/ptc.2011-03

17. Kapadia N, Moineau B, Popovic MR. Functional electrical stimulation therapy for retraining reaching and grasping after spinal cord injury and stroke. *Front Neurosci*. (2020) 14:718. doi: 10.3389/fnins.2020.00718

18. Arienti C, Lazzarini SG, Pollock A, Negrini S. Rehabilitation interventions for improving balance following stroke: an overview of systematic reviews. *PLoS One*. (2019) 14:e0219781. doi: 10.1371/journal.pone.0219781

19. Roussel M, Godefroy O, de Boissezon X. Troubles neurocognitifs vasculaires et post-AVC: De l'évaluation à la prise en charge [Vascular and post-stroke neurocognitive disorders: From evaluation to management]. Brussels: De Boeck Supérieur. (2017) 303–310.

20. Teasell R, Foley N, Pereira S, Sequeira K, Miller T. Evidence to practice: botulinum toxin in the treatment of spasticity post-stroke. *Top Stroke Rehabil*. (2012) 19:115–21. doi: 10.1310/tsr1902-115

21. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of botulinum toxin treatment for upper limb spasticity post-stroke over different ICF domains: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. (2019) 100:1703–25. doi: 10.1016/j.apmr.2019.01.016

22. Beyaert C, Vasa R, Frykberg GE. Gait post-stroke: pathophysiology and rehabilitation strategies. *Neurophysiol Clin*. (2015) 45:335–55. doi: 10.1016/j.neucli.2015.09.005

23. Hong YNG, Ballekere AN, Fregly BJ, Roh J. Are muscle synergies useful for stroke rehabilitation? *Curr Opin Biomed Eng*. (2021) 19:100315. doi: 10.1016/j.cobme.2021.100315

24. Le Sant G, Lecharte T, Goreau V, Nordez A, Gross R, Cattagni T. Motor performance, motor impairments, and quality of life after eccentric resistance training in neurological populations: a systematic review and meta-analyses. *Neuro Rehabil*. (2023) 53:33–50. doi: 10.3233/NRE-230035

25. Isner-Horobeti ME, Dufour SP, Vautravers P, Geny B, Coudeyre E, Richard R. Eccentric exercise training: modalities, applications and perspectives. *Sports Med*. (2013) 43:483–512. doi: 10.1007/s40279-013-0052-y

26. Douglas J, Pearson S, Ross A, McGuigan M. Eccentric exercise: physiological characteristics and acute responses. *Sports Med*. (2017) 47:663–75. doi: 10.1007/s40279-016-0624-8

27. Lee SB, Kang KY. The effects of isokinetic eccentric resistance exercise for the hip joint on functional gait of stroke patients. *J Phys Ther Sci*. (2013) 25:1177–9. doi: 10.1589/jpts.25.1177

28. Clark DJ, Patten C. Eccentric versus concentric resistance training to enhance neuromuscular activation and walking speed following stroke. *Neurorehabil Neural Repair*. (2013) 27:335–44. doi: 10.1177/1545968312469833

29. Lieber RL, Fridén J. Muscle contracture and passive mechanics in cerebral palsy. *J Appl Physiol*. (2019) 126:1492–501. doi: 10.1152/japplphysiol.00278.2018

30. Lecharte T, Gross R, Nordez A, Le Sant G. Effect of chronic stretching interventions on the mechanical properties of muscles in patients with stroke: a systematic review. *Ann Phys Rehabil Med*. (2020) 63:222–9. doi: 10.1016/j.rehab.2019.12.003

31. Harvey LA, Katalinic OM, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contractures. *Cochrane Database Syst Rev*. (2017) 2017:CD007455. doi: 10.1002/14651858.CD007455.pub3

32. Green J, Young J, Forster A, Collen F, Wade D. Combined analysis of two randomized trials of community physiotherapy for patients more than one year post-stroke. *Clin Rehabil*. (2004) 18:249–52. doi: 10.1191/0269215504cr747oa

33. Harris-Love MO, Seamon BA, Gonzales TI, Hernandez HJ, Pennington D, Hoover BM. Eccentric exercise program design: a periodization model for rehabilitation applications. *Front Physiol*. (2017) 8:112. doi: 10.3389/fphys.2017.00112

34. Belghith K, Zidi M, Fedele JM, Bou-Serhal R, Maktouf W. Quantifying plantar flexor muscles stiffness during passive and active force generation using shear wave elastography in individuals with chronic stroke. *Ultrasound Med Biol*. (2024) 50:735–42. doi: 10.1016/j.ultrasmedbio.2024.01.072

35. Gao F, Grant TH, Roth EJ, Zhang LQ. Changes in passive mechanical properties of the gastrocnemius muscle at the muscle fascicle and joint levels in stroke survivors. *Arch Phys Med Rehabil*. (2009) 90:819–26. doi: 10.1016/j.apmr.2008.11.004

36. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. *J Electromyogr Kinesiol*. (2000) 10:361–74. doi: 10.1016/S1050-6411(00)00027-4

37. Le Sant G, Gross R, Hug F, Nordez A. Influence of low muscle activation levels on the ankle torque and muscle shear modulus during plantar flexor stretching. *J Biomech*. (2019) 93:111–7. doi: 10.1016/j.jbiomech.2019.06.018

38. Belghith K, Zidi M, Fedele JM, Bou Serhal R, Maktouf W. Dataset of inter and intramuscular variability of stiffness in paretic individuals during prone and standing positions. *Data Brief*. (2024) 53:110190. doi: 10.1016/j.dib.2024.110190

39. De Luca CJ, Gilmore LD, Kuznetsov M, Roy SH. Filtering the surface EMG signal: movement artifact and baseline noise contamination. *J Biomech*. (2010) 43:1573–9. doi: 10.1016/j.jbiomech.2010.01.027

40. Maktouf W, Boyas S, Beaune B, Durand S. Differences in lower extremity muscular coactivation during postural control between healthy and obese adults. *Gait Posture*. (2020) 81:197–204. doi: 10.1016/j.gaitpost.2020.07.068

41. Geremia JM, Baroni BM, Bini RR, Lanferdini FJ, de Lima AR, Herzog W, et al. Triceps surae muscle architecture adaptations to eccentric training. *Front Physiol*. (2019) 10:1456. doi: 10.3389/fphys.2019.01456

42. Belghith K, Zidi M, Fedele JM, Bou Serhal R, Maktouf W. Spatial distribution of stiffness between and within muscles in paretic and healthy individuals during prone and standing positions. *J Biomech*. (2023) 161:111838. doi: 10.1016/j.jbiomech.2023.111838

43. Fouré A, Nordez A, Cornu C. Effects of eccentric training on mechanical properties of the plantar flexor muscle-tendon complex. *J Appl Physiol*. (2013) 114:523–37. doi: 10.1152/japplphysiol.01313.2011

44. Franchi MV, Atherton PJ, Reeves ND, Flück M, Williams J, Mitchell WK, et al. Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle. *Acta Physiol*. (2014) 210:642–54. doi: 10.1111/apha.12225

45. Alonso-Fernandez D, Docampo-Blanco P, Martinez-Fernandez J. Changes in muscle architecture of biceps femoris induced by eccentric strength training with nordic hamstring exercise. *Scand J Med Sci Sports*. (2018) 28:88–94. doi: 10.1111/sms.12877

46. Kay AD, Blazevich AJ, Fraser M, Ashmore L, Hill MW. Isokinetic eccentric exercise substantially improves mobility, muscle strength and size, but not postural sway metrics in older adults, with limited regression observed following a detraining period. *Eur J Appl Physiol*. (2020) 120:2383–95. doi: 10.1007/s00421-020-04466-7

47. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res*. (2010) 24:2857–72. doi: 10.1519/JSC.0b013e3181e840f3

48. Geremia JM, Baroni BM, Lanferdini FJ, Bini RR, Sonda FC, Vaz MA. Time course of neuromechanical and morphological adaptations to triceps surae isokinetic eccentric training. *Phys Ther Sport*. (2018) 34:84–91. doi: 10.1016/j.ptsp.2018.09.003

49. Brughelli M, Cronin J. Altering the length-tension relationship with eccentric exercise: implications for performance and injury. *Sports Med*. (2007) 37:807–26. doi: 10.2165/00007256-200737090-00004

50. Fernandez-Gonzalo R, Fernandez-Gonzalo S, Turon M, Prieto C, Tesch PA, García-Carreira MDC. Muscle, functional and cognitive adaptations after flywheel resistance training in stroke patients: a pilot randomized controlled trial. *J Neuroeng Rehabil*. (2016) 13:77. doi: 10.1186/s12984-016-0188-7

51. Abdelnour Lattouf N, Tomb R, Assi A, Maynard L, Mesure S. Eccentric training effects for patients with post-stroke hemiparesis on strength and speed gait: a randomized controlled trial. *Neuro Rehabilitation*. (2021) 49:349–62. doi: 10.3233/NRE-210099

52. Zelik KE, Adamczyk PG. A unified perspective on ankle push-off in human walking. *J Exp Biol*. (2016) 219:3676–83. doi: 10.1242/jeb.140376

53. Andersen LL, Zeeman P, Jørgensen JR, Bech-Pedersen DT, Sørensen J, Kjær M, et al. Effects of intensive physical rehabilitation on neuromuscular adaptations in adults with poststroke hemiparesis. *J Strength Cond Res*. (2011) 25:2808–17. doi: 10.1519/JSC.0b013e31822a62ef

54. Flansbjer UB, Miller M, Downham D, Lexell J. Progressive resistance training after stroke: effects on muscle strength, muscle tone, gait performance and perceived participation. *J Rehabil Med*. (2008) 40:42–8. doi: 10.2340/16501977-0129

55. Sullivan KJ, Brown DA, Klassen T, Mulroy S, Ge T, Azen SP, et al. Effects of task-specific locomotor and strength training in adults who were ambulatory after stroke: results of the STEPS randomized clinical trial. *Phys Ther*. (2007) 87:1580–602. doi: 10.2522/ptj.20060310

56. Miyamoto N, Hirata K, Kanehisa H, Yoshitake Y. Validity of measurement of shear modulus by ultrasound shear wave elastography in human pennate muscle. *PLoS One*. (2015) 10:e0124311. doi: 10.1371/journal.pone.0124311

57. Romano A, Staber D, Grimm A, Kronlage C, Marquetand J. Limitations of muscle ultrasound shear wave elastography for clinical routine—positioning and muscle selection. *Sensors*. (2021) 21:8234. doi: 10.3390/s21248234

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Exploring cerebellar transcranial magnetic stimulation in post-stroke limb dysfunction rehabilitation: a narrative review

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This review delves into the emerging field of cerebellar Transcranial Magnetic Stimulation (TMS) in the rehabilitation of limb dysfunction following a stroke. It synthesizes findings from randomized controlled trials and case studies, examining the efficacy, safety, and underlying mechanisms of cerebellar TMS. The review outlines advancements in TMS technologies, such as low-frequency repetitive TMS, intermittent Theta Burst Stimulation, and Cerebello-Motor Paired Associative Stimulation, and their integration with physiotherapy. The role of the cerebellum in motor control, the theoretical underpinnings of cerebellar stimulation on motor cortex excitability, and the indirect effects on cognition and motor learning are explored. Additionally, the review discusses current challenges, including coil types, safety, and optimal timing and modes of stimulation, and suggests future research directions. This comprehensive analysis highlights cerebellar TMS as a promising, though complex, approach in stroke rehabilitation, offering insights for its clinical optimization.

KEYWORDS

cerebellar transcranial magnetic stimulation, stroke rehabilitation, limb dysfunction, neuroplasticity, motor recovery

1 Introduction

Stroke remains a preeminent cause of chronic disability on a global scale, severely affecting countless individuals annually (Dhuri et al., 2021). It is primarily characterized by an abrupt interruption of blood flow to a specific brain region, resulting in neuronal damage (Premilovac et al., 2020). Such cerebral ischemic events frequently lead to extensive physical disabilities, with limb dysfunction being notably incapacitating (McHutchison et al., 2019). This diminution in limb capability not only markedly deteriorates a patient's life quality but also imposes substantial dependence on caregivers and a consequent societal burden.

Traditional Transcranial Magnetic Stimulation (TMS), focusing primarily on the primary motor cortex (M1) for upper limb rehabilitation, has demonstrated potential in stroke recovery. However, its effectiveness in ameliorating lower limb dysfunction and balance issues is somewhat constrained. This limitation largely stems from the inadequate penetration depth of the standard figure-8 coil, which often fails to sufficiently stimulate lower limb regions of the M1 (Zhao et al., 2019). Moreover, patient-specific response variability and the extent of neural damage further limit the efficacy of conventional TMS (Pasley et al., 2009). As a result, recent researches have

begun exploring stimulation of non-motor cortical areas, such as the prefrontal cortex, and non-cortical areas like the cerebellum, in search of more effective rehabilitation strategies. A distinctive feature of cerebellar TMS is its capacity to activate motor-related cortical and subcortical regions, including the thalamus, M1, posterior parietal cortex (PPC), and premotor cortices (PMC) (Casula et al., 2016). Such unique activation leverages the cerebellum's intrinsic capability for motor adaptation and integration, thus offering an innovative approach in addressing post-stroke limb dysfunction. Additionally, cerebellar TMS has been linked to changes in resting-state functional connectivity of brain networks, showing promise in rehabilitation and motor learning processes (Dum and Strick, 2003; Spampinato D. A. et al., 2020; Xia et al., 2022). Emerging research on cerebellar TMS distinguishes it as a forward-looking and promising therapeutic avenue, potentially exceeding traditional methods in targeting deeper motor areas and efficaciously managing lower limb and balance dysfunctions.

The purpose of this review is to meticulously explore and synthesize the current research on cerebellar TMS as it pertains to limb dysfunction post-stroke. By examining a spectrum of studies, ranging from randomized clinical trials to case reports, this review aims to present a comprehensive overview of the efficacy, safety and mechanisms of action of cerebellar TMS. Furthermore, it seeks to highlight the challenges and limitations encountered in the current research landscape, while also identifying future directions that could contribute to the optimization of this therapeutic intervention in clinical practice.

2 Background

2.1 The evolution and theoretical foundations of TMS in stroke rehabilitation

TMS, a non-invasive cerebral stimulation modality, has undergone significant advancements since its inception in 1985 (Barker et al., 1985). TMS employs magnetic fields to generate electric currents within specific cerebral regions by positioning a magnetic coil close to the scalp (Gilbert et al., 2019). Activation of this coil induces a magnetic pulse that penetrates the skull, subsequently eliciting a minor electric current in the brain tissue beneath (Schluter et al., 2019). The impact of this current on neuronal functioning varies according to the frequency of stimulation: high-frequency TMS (exceeding 5 Hz) tends to augment cortical excitability, whereas low-frequency TMS (1 Hz or below) is associated with reduced excitability (Zhang et al., 2022).

A critical development in TMS technology is Theta Burst Stimulation (TBS), an time-effective stimulation mode that can accomplish in mere minutes what conventional repetitive TMS (rTMS) achieves in 20–30 min (Corp et al., 2020). TBS is categorized into two forms: continuous TBS (cTBS), which yields prolonged inhibitory effects on the cerebral cortex, and intermittent TBS (iTBS), known for inducing long-term potentiation (LTP) like effects when applied to the cerebral and cerebellar cortex. This form of stimulation bolsters neuroplasticity in the cerebral cortex and has demonstrated efficacy in enhancing motor function recovery in stroke survivors, with benefits persisting for at least 30 min post-stimulation (Pauly et al., 2021).

The integration of TMS into stroke rehabilitation has progressively evolved, initially focusing on the M1 for motor restoration. Subsequent investigations expanded its application to encompass modulation of other cerebral regions, notably the cerebellum. The advent of diverse TMS protocols, including rTMS and iTBS, has refined clinical applications, facilitating more targeted interventions for an array of stroke-related impairments.

The advancement of TMS in stroke rehabilitation is anchored in three principal theoretical frameworks concerning limb recovery. The compensation model posits that recovery involves engaging alternative neural pathways to offset those impaired by stroke (Jaillard et al., 2005). The interhemispheric competition model hypothesizes a post-stroke imbalance in excitatory and inhibitory interactions between the brain's hemispheres affecting motor functions, which TMS can modulate (Grefkes and Fink, 2014). Finally, the "biphasic balance" recovery model posits a two-phase recovery process, commencing with interhemispheric inhibition and evolving into a balanced bilateral activation (Di Pino et al., 2014). These theoretical frameworks offer valuable insight for the application of TMS in neural rehabilitation, guiding the refinement and optimization of TMS protocols for enhancing functional outcomes post-stroke.

Paired Associative Stimulation (PAS) is a specialized variant of paired-pulse transcranial magnetic stimulation (ppTMS). Unlike traditional TMS, which typically involves direct stimulation of the motor cortex or other brain regions (Derosiere et al., 2022), PAS combines a TMS pulse directed at a cortical area with peripheral nerve electrical stimulation. This approach leverages the temporal relationship between sensory input and cortical excitability (Stampanoni Bassi et al., 2020). This method is grounded in the Hebbian plasticity model (Shikauchi et al., 2023), where the sequence and timing of stimuli can induce LTP or long-term depression (LTD) of synaptic connections. Specifically, when the peripheral stimulus precedes cortical stimulation, LTP is induced, promoting synaptic strengthening, whereas the reverse sequence leads to LTD, which weakens synaptic connections (Chindemi et al., 2022). This dynamic interaction facilitates cortical plasticity, which is essential for motor recovery following neurological injuries. Furthermore, PAS can also involve cortical–cortical stimulation using a double-coil setup to target different brain regions, thereby enhancing the precision and efficacy of neuromodulation. Clinically, PAS has demonstrated promise in treating conditions such as stroke, Parkinson's disease, and chronic pain, with evidence indicating improvements in motor performance and neuroplasticity (Shikauchi et al., 2023). In the context of stroke rehabilitation, PAS is emerging as a key mechanism for enhancing motor recovery, with the potential to synergize with other neuromodulatory interventions, such as cerebellar TMS, to further promote cortical reorganization and functional recovery.

2.2 Role of the cerebellum in motor control

Traditionally, the cerebellum has been acknowledged for its critical role in refining motor actions and maintaining balance and coordination (Mirdamadi and Block, 2021). This perception, while

Abbreviations: TMS, Transcranial magnetic stimulation; M1, Primary motor cortex; PPC, Posterior parietal cortex; PMC, Premotor cortices; TBS, Theta burst stimulation; rTMS, repetitive TMS; cTBS, Continuous TBS; iTBS, Intermittent TBS; PAS, Paired associative stimulation; fMRI, Functional magnetic resonance imaging; EEG, Electroencephalogram; SICI, Short-interval cortical inhibition; LICI, Long-interval cortical inhibition; CBI, Cerebellar-brain inhibition; ICF, Intracortical facilitation.

accurate, only partially represents the cerebellum's complex involvement in motor control. Contemporary neuroscience has substantially expanded our understanding, revealing the cerebellum's integral role in a myriad of motor and cognitive functions (De Doncker et al., 2021).

Recent advancements in research have elucidated the cerebellum's expansive role in motor control, highlighting a complex network of connections extending well beyond mere coordination. Cerebro-cerebellar loops, for instance, establish links between the cerebellum and the cerebral cortex (Caligiore et al., 2017; Spampinato D. et al., 2020; Carey, 2024). These connections facilitate intercommunication between the cerebellum and brain regions involved in motor planning, such as the prefrontal cortex, execution (like the M1), and sensory processing (Zhang et al., 2019; Carey, 2024). The cerebellar-thalamic-cortical pathway, pivotal in modulating motor commands, is instrumental for motor learning (Mawase et al., 2017). It enables the cerebellum to fine-tune and adapt motor actions (Hirjak et al., 2020), a capability critical for acquiring new motor skills or reacquiring skills after a stroke. Furthermore, the cerebellum's integration with the vestibular system through vestibulo-cerebellar connections is essential for balance and spatial orientation (Pushchina et al., 2022). Recent studies (Blatt et al., 2013; Ferrari et al., 2022) also suggest the presence of limbic-cerebellar connections, indicating the cerebellum's involvement in the emotional dimensions of movement. Additionally, spino-cerebellar tracts relay essential sensory feedback from the spinal cord regarding the state of muscles and joints (Baek et al., 2019), further enhancing the cerebellum's ability for precise motor control. Collectively, these pathways highlight the cerebellum's comprehensive role in the adaptive control of movement, a factor of considerable relevance in formulating targeted strategies for stroke rehabilitation.

In the context of stroke recovery, the cerebellum's role in adaptive motor control assumes significant importance. Moreover, contemporary research is delving into the cerebellum's involvement in the higher-order processing of motor tasks, suggesting its participation in the cognitive aspects of motor planning and decision-making. This evolving perspective accentuates the cerebellum's potential as a therapeutic target in stroke rehabilitation, extending beyond the traditional focus on the M1.

2.3 Molecular pathways activated by cerebellar TMS in synaptic plasticity

Cerebellar TMS is a powerful neuromodulatory tool that induces plasticity within the cerebellum, a brain region crucial for motor control, cognitive processing, and emotional regulation. Key molecular mechanisms involved in cerebellar plasticity during TMS include glutamatergic signaling, calcium signaling, gamma-aminobutyric acid (GABA) pathways, Brain-Derived Neurotrophic Factor (BDNF) upregulation, and cAMP/PKA pathways.

Purkinje cells in the cerebellum play a crucial role in inhibiting cerebellar neuronal activity through the neurotransmitter GABA. Cerebellar TMS of the cerebellum can modulate the activity of these Purkinje cells, thus influencing cortical cerebellar inhibition (CBI) (Spampinato et al., 2021). Notably, GABA-B receptors, which are the most widely distributed inhibitory receptors in the cerebellum, are involved in mediating both immediate and long-term functional and structural changes induced by magnetic stimulation (Rowan et al., 2018). Through cerebellar TMS, GABA-B receptor activation can induce alterations in the synthesis of GABA, the presynaptic GABA transporter, and cortical inhibitory interneurons, ultimately modulating the balance between excitation and inhibition within cerebellar circuits (Harrington and Hammond-Tooke, 2015). In this way, cerebellar TMS can facilitate neural plasticity and motor recovery, especially after stroke, where cerebellar inhibition is often impaired.

One of the key molecular pathways activated by cerebellar TMS is the BDNF pathway. BDNF regulates presynaptic GABA release (Song et al., 2022), which plays a pivotal role in synaptic plasticity, neuronal survival, and neurogenesis (Negrete-Hurtado et al., 2020). Cerebellar TMS has been shown to increase BDNF expression in the cerebellum and associated brain regions, thereby promoting the formation of new synapses, strengthening existing synapses, and supporting neuronal survival.

The receptor for BDNF, Tropomyosin Receptor Kinase B (TrkB), is activated during cerebellar TMS. The binding of BDNF to TrkB initiates a cascade of downstream signaling pathways that promote cellular survival, synaptic remodeling, and neuroplasticity. Furthermore, BDNF activation enhances synaptic efficiency and induces long-term alterations in neuronal connectivity, both of which are essential for motor learning and rehabilitation. Research by Mancic et al. (2016) has demonstrated that TMS interventions on the rat cerebellum can significantly affect the metabolic pathways of neuronal cells. In particular, TMS influences the expression of key metabolic enzymes and transporters, including glucose-6-phosphate dehydrogenase, vesicular glutamate transporter 1, plasma glutamate transporter 1, and glial fibrillary acidic protein. These metabolic alterations may support the energetic demands of neurons during the plasticity processes induced by TMS, further promoting functional recovery and synaptic plasticity.

3 Application of cerebellar TMS in stroke rehabilitation

A comprehensive literature search was conducted across several databases, including Web of Science, PubMed, Cochrane Library, and EMBASE, to identify relevant studies on cerebellar TMS. The search was executed by three reviewers (ZW, LikW, and FG) using the following terms: (cerebellum) AND (transcranial magnetic stimulation) AND (stroke) AND (movement). We also examined the references cited in the retrieved literature and the articles that cited these sources. The following criteria were used for cerebellar TMS studies: (1) clinical studies on stroke patients with impaired motor function, such as randomized controlled trials (RCTs) or case reports, etc.; (2) treatment groups received TMS; (3) published on peer-reviewed articles The exclusion criteria were as follows: (1) Duplicate reports; (2) Research protocols, conference abstracts, or incomplete studies; (3) Non-human research; and (4) Missing outcome information. This literature search was completed prior to March 1, 2024.

In our comprehensive review of current literature, we have identified 11 clinical trials and one case report predominantly focusing on the impact of cerebellar TMS on lower limb motor function and balance impairments post-stroke. Additionally, two singular study emphasized upper limb motor function (as detailed in Table 1). The majority of these studies encompass patients with subacute and

TABLE 1 Characteristics of the relevant studies.

Author/ year	*N*	Experiment design	Movement disorder(s)	Target	Coil type (diameter/ figure)	Coil placement/ orientation	Intervention	Control	Behavioral training	Side effects	Main findings
Kim et al. (2014)	rTMS: sham (22: 10)	Pilot study	PCS with ataxia	Cerebellar hemisphere ipsilateral to the ataxic side (2 cm below and lateral to the middle line)	75 mm/8 coil by MagPro® (Medtronic, Minneapolis, MN, United States)	Manually placed/with the handle pointing superiorly	100% RMT 1 Hz rTMS (900 pulses per session, 5 sessions per day, 5 days)	Same parameters (coil perpendicular to the scalp)	None	None	1 Hz cerebellum rTMS, feasible and may have a beneficial effect in ataxic patients with posterior circulation stroke
Bonnì et al. (2014)	iTBS (6), no sham	Prospective pilot trial	Chronic stroke with PCS	The damaged lateral cerebellum	Monophasic Magstim 200 stimulator (Magstim Co., Whitland, Dyfeld, UK); 70 mm/8 coil	Neuronavigation system (Softaxic, E.M.S., Bologna, Italy)/ The handle of the coil pointed backward and was perpendicular to the presumed direction of the central sulcus	80% AMT iTBS (600 pulses; 10 sessions, 2 weeks)	None	PT	None	Cerebellar iTBS could be a promising tool to promote recovery of cerebellar stroke patients
Koch et al. (2019)	iTBS: sham (18: 18)	RCT	Stroke with gait and balance impairment	Contralateral cerebellum to the affected cerebral hemisphere	70 mm/8 coil (Magstim Company)	Neuronavigation system (SofTaxic; EMS) coupled with a Polaris Vicra infrared camera/ the handle pointing superiorly	80% AMT iTBS (1,200 pulses per session, 3 weeks)	Sham iTBS (coil perpendicular to the cerebellum)	PT	None	Cerebellar intermittent θ-burst stimulation promotes gait and balance recovery in patients with stroke by acting on cerebello-cortical plasticity
Xie et al. (2021)	iTBS: sham (17: 17)	Parallel group trial	Stroke with walking dysfunction	Contralateral cerebellum (1 cm inferior to and 3 cm lateral to the inion)	70 mm/8 coil (YIRUIDE medical, Wuhan, China)	Manually placed/the handle directed backward and laterally and at an angle of approximately 45° to the mid-sagittal line of the head	80% AMT iTBS (600 pulses per session, 10 sessions, 2 weeks)	Same parameters (coil pedicular to the scalp)	PT	None	iTBS over the contralesional cerebellum paired with physical therapy could improve walking performance in patients after stroke

(Continued)

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TABLE 1 (Continued)

Author/ year	*N*	Experiment design	Movement disorder(s)	Target	Coil type (diameter/ figure)	Coil placement/ orientation	Intervention	Control	Behavioral training	Side effects	Main findings
Liao et al. (2021)	iTBS: sham (15: 15)	RCT	Stroke with balance and motor dysfunction	The cerebellar hemisphere contralateral to the affected cerebral hemisphere (3 cm lateral to the midline and 1 cm below the inion)	70 mm/8 coil (YIRUIDE medical, Wuhan, China)	manually placed/with the handle pointing superiorly	80% AMT iTBS (600 pulses per session, 10 sessions, 2 weeks)	Sham iTBS (coil angled at 90° to the scalp)	PT	Mild headache ($n = 1$) in the treatment group	Cerebellar iTBS associated with PT improves BBS score; no significant difference in FMA-LE scores; no difference in the BI scores
Li et al. (2021)	rTMS + cTBS: rTMS: cTBS (30: 30: 30)	RCT	Stroke with spasticity and limb dyskinesia	M1 on the unaffected side of the brain; right cerebellar hemisphere (3 cm lateral to the midline and 1 cm below the inion)	Circular coil	Manually placed/none	80% AMT cTBS (1,200 pulses); 80% RMT 1 Hz rTMS (1,000 pulses); 1 session per day, 6 sessions per week, 4 weeks	Only cTBS; only LF-rTMS	PT + acupuncture therapy	Not to mention	The MAS score was markedly decreased; FMA and MBI scores were markedly increased in the three groups; LF-rTMS + cTBS group showed lower MAS score, higher FMA, and MBI scores
Chen et al. (2021)	iTBS: sham (16: 16)	RCT	Stroke with upper limb spasticity	Ipsilesional lateral cerebellum (1 cm inferior and 3 cm lateral to the inion)	70 mm/8 coil (YIRUIDE medical, Wuhan, China)	Manually placed/with the handle pointing superiorly	80% AMT iTBS (600 pulses per sessions, 10 sessions, 2 weeks)	Same parameters (coil was rotated 90°)	PT	None	Both groups showed significant improvements in the MAS, MTS, SWV, and BI. Compared with the sham stimulation group, MAS, MTS, SWV, and MEP amplitude are improved more in the cerebellar iTBS group

(Continued)

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TABLE 1 (Continued)

Author/ year	*N*	Experiment design	Movement disorder(s)	Target	Coil type (diameter/ figure)	Coil placement/ orientation	Intervention	Control	Behavioral training	Side effects	Main findings
Rosso et al. (2022)	CER_M1 PAS: sham (14: 14)	RCT	Stroke with upper limb dysfunction	The coil was moved right- or left- wards off the midpoint by 3 cm along a line between the inion and the mastoid process	110 mm/double-cone coil; 70 mm/8 coil	By the anatomical 3D reconstruction of each participant's brain (Brainsight2, Rogue Research, Inc., Montreal, Canada)/ none	PAS (120 pairs of stimuli at 0.2 Hz) (Magstim, Dyfed, UK); conditioning stimulus: 90% RMT; test stimulus:140% RMT; 5 sessions, 1 week	same place (sham coil produces a sound mimicking)	PT	transient cephalalgia ($n = 1$) in each group; reflex syncope right ($n = 1$) in the sham group	Cerebello-motor PAS was effective compared to sham in improving hand dexterity but not grip strength
Im et al. (2022)	rTMS:control (16:16)	Placebo-controlled study	Cerebral infarction with balance impairment	2 cm below and 2 cm lateral to the inion by targeting the cerebellar hemisphere contralateral to the site of cerebral infarction	8 coil Magpro R30 (Magventure, Farum, Denmark)	Manually placed/none	90% RMT 1 Hz (900 pulses)	Sham coil (the sound and scalp sensation were similar)	PT	vertigo ($n = 1$) in the treatment group	Low-frequency cerebellar rTMS is helpful for improving balance in patient with cerebral infarction, and maybe a beneficial treatment for these patients
Xia et al. (2022)	CB-single iTBS: CB-M1 iTBS:CB-SMA iTBS (9:10:11)	Pilot study	Stroke with motor and balance defects	M1: motor hot spot; SMA: 3 cm in front of Cz and 0.5 cm close to the hemisphere; cerebellum stimulation point: 1 cm below and 3 cm lateral to the inion	90 mm/8 coil (YIRUIDE medical, Wuhan, China)	Manually placed/none	3 pulses at 50 Hz repeated at 5 Hz (600 pulses in 192 s)	None	None	None	The CB-SMA group exhibited a significant inhibitory pattern in the resting-state functional connectivity, which was not observed in the other two groups. In conclusion, we believe that paired targeting of the CB-SMA can reshape the brain network and improve the balance function of patients with stroke

(Continued)

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TABLE 1 (Continued)

Author/ year	*N*	Experiment design	Movement disorder(s)	Target	Coil type (diameter/ figure)	Coil placement/ orientation	Intervention	Control	Behavioral training	Side effects	Main findings
Einstein et al. (2023)	None	Case report	Hemorrhagic stroke with chronic nonlateralized ataxia	Left: 2 cm laterally from the midline and approximately 1 cm below the inion. Right: 2 cm laterally from the midline and 2 cm below the inion	B-70 coil (Magventure, Denmark)	Using a Brainsight system (Rogue Research, Montreal, Canada) that was then used to guide stimulation/none	100%MT 1 Hz rTMS (900 pulses, 5 sessions per day, 2 days)	None	None	None	The case of a patient with chronic cerebellar ataxia following a hemorrhagic stroke who underwent inhibitory rTMS to bilateral cerebellar targets with demonstrated improvement in symptoms
Liao et al. (2024)	M1 iTBS: cerebellum iTBS: sham (12: 12: 12)	RCT	Stroke with motor and balance defects	Contralateral cerebellar hemisphere (3 cm lateral to the midline and 1 cm below the inion of the occipital bone); ipsilesional M1	70 mm/8 coil (YIRUIDE medical, Wuhan, China)	Manually placed/with the handle pointing superiorly	80% RMT 50 Hz iTBS, (1,200 pulses per session, 15 sessions, 3 weeks)	Sham stimulation (coil was rotated 90°)	PT	None	Stimulation of the cerebellum and M1 both improves BBS score and change FAC scores. Cerebellar stimulation may be better than stimulation of the M1 since the changes in the BBS scores in the cerebellar-iTBS group seemed to be larger than M1-iTBS group although there was no statistical significance

RCT, randomized controlled trial; PAS, paired associative stimulation; PCS, posterior circulation stroke; CB-single, unilateral cerebellar; CB-M1, cerebellar–primary motor cortex; CB-SMA, cerebellar–supplementary motor area; AMT, the active motor threshold; MT, motor threshold; RMT, resting motor threshold; PT, physical therapy; FMA, FMA-LE scores; MAS, the modified Ashworth scale; MBI, modified Barthel index; MTS, the modified Tardieu scale; SWV, the shear wave velocity; MEP, motor-evoked potential; BBS, Berg balance scale; BI, the Barthel index.

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chronic stroke, with the exception of three trials report that involved patients with acute stroke.

The array of methodologies in cerebellar TMS, ranging from low-frequency rTMS to iTBS and cTBS, supplemented by advanced techniques such as Cerebello-Motor Paired Associative Stimulation (PAS), presents a diverse and adaptable toolkit for stroke rehabilitation.

3.1 Low-frequency rTMS

Low-frequency rTMS is characterized by its inhibitory effects on cerebellar activity and has demonstrated efficacy in alleviating ataxia and balance disorders symptoms. For instance, Kim et al. (2014) applied this technique in patients with posterior circulation stroke and observed significant improvements in gait dynamics and balance. The enhancements noted in the 10-Meter Walk Test (10MWT) and Berg Balance Scale (BBS) scores translated into substantial gains in daily activities and mobility.

The application of low-frequency rTMS to the cerebellum primarily works by modulating cerebellar-brain inhibition (CBI), a process that regulates how the cerebellum communicates with the M1 (Im et al., 2022; Einstein et al., 2023). By inhibiting excessive cerebellar excitability, low-frequency rTMS helps recalibrate overactive cerebellar output, commonly seen in conditions like ataxia. This modulation likely reduces the disruptive effects of impaired cerebellar signals on motor coordination, allowing for more controlled movement patterns (Lien et al., 2022). Additionally, rTMS may promote plastic changes in cerebello-cortical pathways, enhancing the reorganization of motor networks that are crucial for motor recovery post-stroke.

3.2 Intermittent TBS

The utilization of iTBS targeting the cerebellum is predominantly applied in addressing limb dysfunction following a stroke. Xia's review (Xia et al., 2023) posits that the effectiveness of cerebellar stimulation is not attributable to a single session, but rather to the cumulative impact of TMS. This was later substantiated by further research conducted by Xia et al. (2022). In the study conducted by Bonnì et al. (2014), iTBS was directed toward the impaired lateral cerebellum in patients with chronic stroke, resulting in heightened excitability of the cerebellar cortex. This approach led to notable enhancements in both the subacute and chronic stages of stroke rehabilitation.

Building on this, Koch et al. (2019) provided evidence for the efficacy of iTBS in improving balance and gait functions. This was demonstrated through significant improvements in various assessments including the BBS, Scale Trunk Impairment Scale, Fugl-Meyer Assessment-Lower Extremity, and the Melbourne Assessment of Unilateral Upper Limb Function. These improvements collectively indicate advancements in balance, trunk control, lower limb motor functionality, and ataxia. Moreover, Xie et al. (2021) observed that integrating iTBS with physical therapy notably enhanced walking performance in stroke patients.

The primary mechanism through which iTBS enhances motor recovery lies in its ability to induce LTP-like effects in the cerebellar cortex. By increasing the excitability of cerebellar networks, iTBS promotes synaptic plasticity, facilitating the reorganization of damaged motor circuits and enhancing communication between the cerebellum and M1 (Chen et al., 2019; Hensel et al., 2019). This improved connectivity strengthens motor coordination and learning, which is especially critical in post-stroke recovery.

3.3 Continuous TBS

CTBS, akin to low-frequency rTMS, has shown particular efficacy in combined therapy approaches. Li et al. (2021) demonstrated that when combined with low frequency rTMS (LF-rTMS), cTBS contributed to significant reductions in muscle spasticity and improvements in limb dyskinesia, offering a synergistic benefit surpassing individual treatments.

The effectiveness of cTBS lies in its ability to induce LTD-like effects (Romero et al., 2022) in the cerebellum, which inhibits excessive neural excitability. This downregulation of overactive motor circuits contributes to the reduction of spasticity and dyskinesia by restoring a more balanced and controlled output from the motor cortex. When combined with LF-rTMS, which exerts an inhibitory effect on hyperexcitable neural circuits in the motor cortex, this dual therapy effectively targets both cortical and cerebellar pathways. This approach enhances the neuroplastic changes essential for improving motor control, particularly in conditions characterized by increased muscle tone and involuntary movements.

3.4 Cerebello-motor paired associative stimulation

By combining TMS with peripheral nerve stimulation, PAS facilitates spike-timing-dependent plasticity, targeting either cortical–cortical (C/C PAS), cortical-peripheral (C/P PAS), or even cerebellar-motor (Cerebello-M1 PAS) connections to strengthen neural pathways involved in motor control. Stimulating both the M1 and the cerebellum simultaneously can further enhance the reorganization of motor networks, offering an additional pathway to improve motor outcomes.

The targeting of paired sites within the cerebellum and cerebral cortex may yield more advantageous outcomes compared to stimulating individual sites. Xia's investigation (Xia et al., 2022) into the effects of a single TMS session on balance, with eyes open and closed, in stroke patients utilized three distinct stimulation targets: unilateral cerebellum, cerebellar-M1, and cerebellar-SMA. The findings indicated that combined targeting of the cerebellum and SMA facilitated the restructuring of brain networks, leading to improved balance functions in these patients. Rosso et al. (2022) investigated the efficacy of Cerebello-Motor PAS, revealing its effectiveness in improving hand dexterity compared to sham interventions. This technique, which synergizes cerebellar and cortical stimulation, employs associative plasticity principles with the objective of bolstering functional connectivity between the cerebellum and motor cortex, potentially facilitating cortical reorganization conducive to motor recovery.

3.5 Integration with physiotherapy

The integration of cerebellar TMS techniques with traditional physiotherapy has proven more effective than isolated interventions.

Liao et al. (2021) combined iTBS with physical therapy, leading to improvements in BBS scores, indicative of enhanced balance and motor recovery. Similarly, Chen et al. (2021) found that iTBS could augment the effects of physical therapy in addressing upper limb spasticity post-stroke. This collaborative approach, melding neural modulation with physical therapy, hints at a more holistic model of rehabilitation. This model is further supported by Liao's comparative study (Liao et al., 2024), which suggested that cerebellar stimulation might surpass M1 iTBS in facilitating balance and motor recovery.

The neuroplasticity mechanisms underlying this combined application of cerebellar TMS and physical therapy are rooted in both specific and generalized processes. A key specific mechanism is spike-timing-dependent plasticity (STDP) (Bi and Poo, 2001; Dan and Poo, 2006), which occurs when the timing of TMS pulses is aligned with motor or sensory input from physical therapy, leading to the targeted strengthening or weakening of synaptic connections (Rosenkranz et al., 2014). This precise timing enhances corticomotor excitability and strengthens neural circuits critical for motor learning and recovery.

4 Predictors of response to cerebellar TMS in stroke rehabilitation

However, not all patients respond equally to cerebellar TMS, and identifying predictors of response is essential for optimizing treatment outcomes. These predictors can help guide clinicians in tailoring cerebellar TMS protocols, such as stimulation intensity, frequency, and target sites, according to individual patient characteristics.

Predictors of response to cerebellar TMS encompass a range of biological, neurophysiological, neuroimaging, genetic, and clinical markers that can influence how effectively cerebellar stimulation facilitates motor and cognitive recovery. Unlike TMS targeting the M1, cerebellar TMS engages distinct neural circuits and mechanisms, such as CBI and cerebello-cortical connectivity, which may necessitate unique predictors to accurately forecast treatment success. For instance, neurophysiological markers like cerebellar-specific MEPs and neuroimaging indicators of cerebello-cortical connectivity provide insights into the integrity and plasticity of cerebellar pathways, directly influencing the responsiveness to cerebellar TMS (Koch et al., 2019; Tan et al., 2021).

4.1 Motor evoked potentials in cerebellar stimulation

The cerebellum's influence on motor cortex excitability has garnered significant interest in neurophysiology and rehabilitation, particularly in understanding how cerebellar stimulation can enhance Motor Evoked Potentials (MEPs), which are critical indicators of corticospinal tract functionality and neuroplasticity. Studies utilizing cerebellar TBS have revealed its significant effects on M1 excitability and intracortical dynamics, which can serve as potential predictors of motor recovery.

Koch et al. (2008) demonstrated that cTBS applied to the lateral cerebellum leads to a decrease in short-interval cortical inhibition (SICI) and an increase in long-interval cortical inhibition (LICI), while iTBS demonstrates the opposite effect, increasing M1 excitability. These changes in MEPs indicate how different patterns of cerebellar stimulation can modulate motor cortex activity, offering insights into which stimulation protocols may yield better recovery outcomes for specific patients. Spampinato D. et al. (2020) further investigated how cerebellar-M1 networks are activated by different TMS pulse orientations, suggesting that distinct neural networks are engaged based on stimulation parameters, contributing uniquely to motor recovery.

Additionally, Pauly et al. (2021) examined the effects of rTMS and PAS on cerebellar plasticity in healthy individuals, showing that rTMS at 1 Hz facilitates cerebellar-M1 interactions, as evidenced by increased MEP amplitudes and higher motor thresholds. Conversely, PAS produced inhibitory effects, characterized by decreased MEP amplitudes, suggesting that the type of stimulation directly impacts how motor circuits are modulated. Bonnì et al. (2014) observed that iTBS applied to the cerebellum induced changes in CBI and intracortical facilitation (ICF), which were paralleled by clinical improvements in motor function.

These findings collectively highlight the dynamic role of cerebellar stimulation in modulating MEPs and their potential as predictors of response to TMS in stroke rehabilitation. By monitoring changes in MEPs following cerebellar TMS, clinicians can better assess the likelihood of motor recovery and adjust treatment protocols accordingly.

4.2 Neuroimaging predictors: brain activity and connectivity in cerebellar TMS response

In stroke rehabilitation, the activity of specific brain regions and the connectivity between them have emerged as promising predictors of response to cerebellar TMS. Neuroimaging tools such as Functional Magnetic Resonance Imaging (fMRI) and Functional Near-Infrared Spectroscopy (fNIRS) are critical in assessing these neural patterns, helping to identify patients who are more likely to benefit from cerebellar stimulation.

The activation of motor-related brain regions, particularly the M1, can serve as a key indicator of how well a patient may respond to cerebellar TMS. Studies using fMRI have shown that increased activity in the ipsilesional M1 following cerebellar stimulation correlates with improved motor function. For example, Rosso et al. (2022) demonstrated that patients with greater post-stimulation activation in M1 exhibited better hand dexterity recovery. This suggests that the level of motor cortex activation could act as a biomarker for predicting motor improvements in response to cerebellar TMS.

Additionally, changes in activity within other motor-related areas, such as the premotor cortex and supplementary motor area (SMA), could also provide predictive value. These regions are involved in motor planning and coordination, and their engagement during rehabilitation may indicate how well a patient can adapt to and benefit from stimulation therapies.

Beyond the activity of individual brain regions, the functional connectivity between brain regions can also serve as a powerful predictor of TMS response. fMRI and fNIRS can measure the strength of connections between the cerebellum and cortical motor areas, such as M1 and the SMA, providing insights into the brain's network-level adaptations. For instance, Xia et al. (2022) used fNIRS to explore how

different iTBS protocols affected connectivity between the cerebellum and motor networks. They found that specific protocols, such as cerebellum-SMA stimulation, produced significant connectivity changes that correlated with improvements in balance and motor control. This suggests that enhanced connectivity between motor regions may serve as a predictor of positive outcomes in response to cerebellar TMS.

By using the activity of specific brain regions and the connectivity between them as predictors, clinicians can tailor cerebellar TMS protocols to target the most responsive areas of the brain. This approach can help optimize rehabilitation strategies for stroke patients by focusing on regions and networks that are most likely to contribute to motor and balance recovery. Neuroimaging techniques such as fMRI and fNIRS offer valuable tools for monitoring these neural markers, enabling personalized and effective treatment plans.

4.3 Cognitive predictors in cerebellar TMS response

When investigating the effects of cerebellar TMS in noninvasive studies, it is essential to consider potential cognitive confounders, as cognitive processes are intricately linked with motor learning and recovery (Hardwick et al., 2021). While much of the existing research on cerebellar TMS and cognition has been conducted in healthy individuals, we believe that these findings can still be relevant to stroke rehabilitation. Cognitive processes, such as working memory, attention, and error monitoring, are critical to motor learning and the reacquisition of motor skills post-stroke (Liu et al., 2022). These cognitive functions, although less frequently studied in stroke patients, may serve as important predictors of a patient's response to cerebellar TMS.

The cerebellum's role extends beyond motor coordination; specific regions, such as Crus I and II, are implicated in cognitive functions like the perception of emotional states and interaction with prefrontal cognitive areas (Ramnani, 2006; Strick et al., 2009). Neuroimaging studies have revealed that cerebellar activation patterns correlate with enhanced cognitive processing and improved motor learning outcomes (Riedel et al., 2015). Casula et al. (2016) demonstrated that cerebellar TMS can modulate neural activity in motor-cognitive networks, with cTBS reducing alpha activity and intermittent iTBS enhancing beta activity in the M1. This bidirectional modulation highlights the potential for cerebellar TMS to influence cognitive processes. Although these studies have largely focused on healthy populations, the cognitive-motor interactions identified may also apply to stroke recovery, where cognitive impairments can impact the success of motor rehabilitation.

Cognitive functions, closely intertwined with motor abilities, may serve as predictors of response to cerebellar TMS. Evidence from healthy individuals suggests that enhancing cognitive processes through cerebellar TMS can improve task performance and decrease error rates in motor learning tasks (Matsugi et al., 2022). Although data specific to stroke patients are limited, it is plausible that those with stronger baseline cognitive function may respond better to cerebellar TMS interventions aimed at improving motor skills. Moreover, cerebellar TMS has been shown to expedite learning in tasks such as force field and locomotor adaptation (Celnik, 2015). These enhancements are likely mediated by cognitive processes essential to motor adaptation, further underscoring the role of cognition in rehabilitation. Given the cerebellum's involvement in both motor and cognitive networks, it is feasible to speculate that cognitive abilities may predict how well a patient responds to TMS in stroke rehabilitation.

Future studies should investigate the role of cognition in cerebellar TMS response more directly in stroke patients, given the potential for cognitive functions to serve as predictors of motor rehabilitation outcomes.

5 Challenges and future directions

Despite the potential of cerebellar TMS in stroke rehabilitation, its application is met with several challenges and limitations, which necessitate future exploration and refinement.

5.1 TMS coil type

Whether differences in the type of TMS coil used significantly affects treatment outcomes is uncertain. Most cerebellar TMS studies (Bonnì et al., 2014; Kim et al., 2014; Koch et al., 2019; Chen et al., 2021; Li et al., 2021; Liao et al., 2021; Xie et al., 2021; Im et al., 2022; Einstein et al., 2023; Liao et al., 2024) have utilized flatter coils, such as figure-eight or circular coils, offering a spatial resolution of about 1 cm and a penetration depth of approximately 2 cm (Li et al., 2019). While the figure-eight coil provides more focused stimulation than the circular coil, its depth and intensity are inferior to that of angled coils (Deng et al., 2013; Drakaki et al., 2022). The cerebellum, situated in the posterior cranial fossa and covered by the tentorium cerebelli, is deeper from the skull, necessitating coils that can accommodate this depth. Previous research has indicated that while flat coils improve stimulation tolerance, they are limited in depth range, and smaller coils are less effective for cerebellar stimulation (Spampinato D. et al., 2020). Therefore, angled coils with superior depth properties are essential for reliable CBI excitation (Fernandez et al., 2018). Innovations in coil design, such as the use of a biconical coil, have shown promise. Rosso et al. (2022) demonstrated significant improvements in hand dexterity in stroke patients using cerebellar motor paired associative stimulation with a 110 mm biconical coil combined with physical therapy. This coil type can stimulate a depth of 3–4 cm, activating specific GABA-dependent interneurons in the cerebellum and enhancing LTP effects (Lu and Ueno, 2017). Currently, the MEP amplitude produced by biconical coils is believed to be higher than that of figure-eight coils under the same stimulation intensity, making it more effective for cerebellar stimulation at tolerable intensities (Liao et al., 2021; Xue et al., 2021). However, there is a risk of stimulating non-target functional areas, which may reduce patient tolerance (Fernandez et al., 2018; Xie et al., 2021).

In summary, the challenges in cerebellar TMS primarily revolve around the optimization of coil types and stimulation parameters. Future research should focus on developing and testing coils that offer the right balance between depth of penetration, focus of stimulation, patient tolerance, and therapeutic efficacy. Such advancements could significantly enhance the effectiveness of cerebellar TMS in stroke rehabilitation and potentially in other neurological disorders.

5.2 Safety and tolerability

The 2020 TMS Use Guidelines emphasize seizures as the primary risk in TMS across different stimulation methods. Regarding cerebellar TMS specifically, side effects have been infrequently reported in the literature (Table 1). In 11 studies using flat coils, one noted a mild headache in the treatment group and reflex syncope in an individual in the sham group (Liao et al., 2021), while another recorded a case of vertigo in the treatment group (Im et al., 2022). A singular study employing a conical coil reported transient cephalalgia in one participant each in the intervention and non-intervention groups (Rosso et al., 2022). Notably, five patients in the active group and two in the sham group reported discomfort post-intervention. In a recent study by Dai et al. (2023), a biconical coil was used to assess the efficacy of 10-Hz cerebellar rTMS in patients with poststroke dysphagia who had suffered infratentorial strokes. The study demonstrated that all 42 participants successfully tolerated the treatment. However, this transient twitching was reported by patients undergoing both bilateral (14 patients) and unilateral (8 patients) cerebellar rTMS, as well as one patient receiving sham rTMS, which resolved quickly after each session. Notably, one individual noted a gradual increase in the intensity of the twitching sensation over the course of the treatment. Additionally, a thorough meta-analysis on the safety of cTBS included 45 studies (Hurtado-Puerto et al., 2020), none of which reported severe adverse events. The withdrawal rate due to adverse events was only 0.72%. However, the maximum safe dosage for cerebellar TMS remains undefined. Consequently, more research to determine the maximum safe dose of cerebellar TMS is crucial for safeguarding patient well-being and enhancing therapeutic effectiveness.

5.3 Optimal timing for stimulation

To date, research has yet to establish the ideal time frame for commencing treatment of cerebellar TMS following a stroke. Eline's meta-analysis (van Lieshout et al., 2019) suggests that rTMS may offer greater benefits when initiated within the first month after a stroke. Although many clinical practice guidelines recommend the early start of rehabilitation post-stroke, these studies focus on patients in the subacute and chronic phases of stroke recovery (Bonnì et al., 2014; Koch et al., 2019; Chen et al., 2021; Li et al., 2021; Liao et al., 2021; Rosso et al., 2022; Xia et al., 2022). However, there are exceptions, as three RCTs (Kim et al., 2014; Xie et al., 2021; Liao et al., 2024) have reported on patients in the acute stage of stroke, indicating the potential applicability of cerebellar TMS across various stages post-stroke.

5.4 Stimulation modes and targets

In the field of cerebellar research, the majority of cerebellar TMS parameters are adapted from those used for cerebral cortex stimulation. Presently, there is an absence of standardized protocols specifically tailored for effective cerebellar stimulation. Common targets for cerebellar stimulation for patients, a typical approach involves positioning the stimulation site 3 cm lateral to the occipital tuberosity and then moving it 1 cm downward. This is particularly challenging given the higher complexity and deeper distribution of the cerebellar cortex compared to other brain regions (Hardwick et al., 2014). Because it is difficult to stimulate motor regions of the cerebellum without also stimulating the cognitive cerebellum. These anatomical variances among individuals can significantly influence the response to cerebellar stimulation, potentially leading to less effective outcomes compared to stimulation of cerebral targets (Chung et al., 2016). Excessively low stimulation intensities may be less efficacious, while overly high intensities could diminish patient compliance and elevate the risk of adverse effects (Fernandez et al., 2018). Moreover, the individual preservation of neural network structure and the integrity of efferent pathways are crucial factors in customizing stimulation patterns (Hardwick et al., 2021). This highlights the ongoing need to explore and identify more appropriate cerebellar stimulation sites for future research.

The mechanisms through which cerebellar TMS enhances function in stroke patients vary according to the injury's location. Nevertheless, the existing literature on this topic remains limited, highlighting the need for a more detailed examination of the specific disease locations (Dai et al., 2023). In supratentorial strokes, cerebellar TMS primarily enhances motor recovery by leveraging the cerebellum's role in modulating cortical activity. The cerebellum communicates with both the motor and premotor areas of the cortex (Wessel and Hummel, 2018), and TMS applied to the cerebellum can increase the excitability of motor pathways, improving motor control and coordination. This can help in restoring motor function by compensating for cortical damage. In contrast, for cerebellar or brainstem injuries, TMS likely works by promoting neuroplasticity within the cerebellum and its connections to the rest of the brain. The cerebellum's extensive connections with the brainstem, spinal cord, and thalamus can facilitate compensatory reorganization in these areas (Li et al., 2018; Tan et al., 2021). There are numerous methods to stimulate the cerebellum; however, accurately locating it and understanding the heterogeneity caused by the disease's location still require further investigation.

6 Limitations of this review

Reviews based on high-quality RCTs are essential for clinical decision-making in evidence-based medicine. However, the limited number of included studies and considerable clinical heterogeneity—such as varying TMS treatment regimens and combination approaches—pose challenges for this review. The study primarily employed qualitative analysis through narrative reviews instead of quantitative methods like meta-analysis. Additionally, it is important to acknowledge that quality assessment remains a subjective process. The article underwent review by three independent reviewers, who may have made differing judgments on each factor, potentially leading to variations in the results. Lastly, due to resource constraints, only studies published in English were included, which may introduce a language bias and exclude relevant literature published in other languages.

7 Conclusion

In conclusion, cerebellar TMS emerges as a promising therapeutic modality in the rehabilitation of post-stroke limb

dysfunction. The research reviewed underscores its potential to target deeper motor areas, manage lower limb and balance dysfunctions, and improve motor and cognitive aspects of stroke recovery. While challenges related to coil design, safety, and stimulation parameters remain, ongoing research and technological advancements hold promise for more refined, effective treatments. The future of cerebellar TMS in stroke rehabilitation is poised for significant growth, particularly as our understanding of cerebellar functions in motor control and learning deepens. To fully harness the potential of cerebellar TMS, further research should focus on optimizing stimulation protocols, understanding individual variability in responses, and integrating TMS with other rehabilitation strategies. This holistic approach could revolutionize stroke rehabilitation, enhancing the quality of life for countless individuals affected by this debilitating condition.

Author contributions

ZW: Conceptualization, Methodology, Project administration, Writing – review & editing. LikW: Conceptualization, Methodology, Formal Analysis, Writing – review & editing. FG: Conceptualization, Methodology, Formal Analysis, Writing – review & editing. YD: Conceptualization, Methodology, Writing – original draft. CL: Conceptualization, Methodology, Writing – original draft. JW: Conceptualization, Methodology, Writing – original draft. MW: Conceptualization, Methodology, Writing – original draft. QY: Writing – review & editing. YC: Writing – review & editing. CW: Writing – review & editing. LitW: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Baek, M., Menon, V., Jessell, T. M., Hantman, A. W., and Dasen, J. S. (2019). Molecular logic of spinocerebellar tract neuron diversity and connectivity. *Cell Rep.* 27, 2620–2635.e4. doi: 10.1016/j.celrep.2019.04.113

Barker, A. T., Jalinous, R., and Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1, 1106–1107. doi: 10.1016/s0140-6736(85)92413-4

Bi, G., and Poo, M. (2001). Synaptic modification by correlated activity: Hebb's postulate revisited. *Annu. Rev. Neurosci.* 24, 139–166. doi: 10.1146/annurev.neuro.24.1.139

Blatt, G. J., Oblak, A. L., and Schmahmann, J. D. (2013). "Cerebellar connections with limbic circuits: anatomy and functional implications" in Handbook of the cerebellum and cerebellar disorders. eds. M. Manto, J. D. Schmahmann, F. Rossi, D. L. Gruol and N. Koibuchi (Dordrecht: Springer Netherlands), 479–496.

Bonnì, S., Ponzo, V., Caltagirone, C., and Koch, G. (2014). Cerebellar theta burst stimulation in stroke patients with ataxia. *Funct. Neurol.* 29, 41–45. doi: 10.11138/FNeur/2014.29.1.041

Caligiore, D., Pezzulo, G., Baldassarre, G., Bostan, A. C., Strick, P. L., Doya, K., et al. (2017). Consensus paper: towards a systems-level view of cerebellar function: the interplay between cerebellum, basal ganglia, and cortex. *Cerebellum* 16, 203–229. doi: 10.1007/s12311-016-0763-3

Carey, M. R. (2024). The cerebellum. *Curr. Biol.* 34, R7–r11. doi: 10.1016/j.cub.2023.11.048

Casula, E. P., Pellicciari, M. C., Ponzo, V., Stampanoni Bassi, M., Veniero, D., Caltagirone, C., et al. (2016). Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. *Sci. Rep.* 6:36191. doi: 10.1038/srep36191

Celnik, P. (2015). Understanding and modulating motor learning with cerebellar stimulation. *Cerebellum* 14, 171–174. doi: 10.1007/s12311-014-0607-y

Chen, Y. J., Huang, Y. Z., Chen, C. Y., Chen, C. L., Chen, H. C., Wu, C. Y., et al. (2019). Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol.* 19:69. doi: 10.1186/s12883-019-1302-x

Chen, Y., Wei, Q.-C., Zhang, M.-Z., Xie, Y.-J., Liao, L.-Y., Tan, H.-X., et al. (2021). Cerebellar intermittent Theta-burst stimulation reduces upper limb spasticity after subacute stroke: a randomized controlled trial. *Front. Neural Circuits* 15:655502. doi: 10.3389/fncir.2021.655502

Chindemi, G., Abdellah, M., Amsalem, O., Benavides-Piccione, R., Delattre, V., Doron, M., et al. (2022). A calcium-based plasticity model for predicting long-term potentiation and depression in the neocortex. *Nat. Commun.* 13:3038. doi: 10.1038/s41467-022-30214-w

Chung, S. W., Hill, A. T., Rogasch, N. C., Hoy, K. E., and Fitzgerald, P. B. (2016). Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 63, 43–64. doi: 10.1016/j.neubiorev.2016.01.008

Corp, D. T., Bereznicki, H. G. K., Clark, G. M., Youssef, G. J., Fried, P. J., Jannati, A., et al. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: results from the 'Big TMS data Collaboration'. *Brain Stimul.* 13, 1476–1488. doi: 10.1016/j.brs.2020.07.018

Dai, M., Qiao, J., Shi, Z., Wei, X., Chen, H., Shen, L., et al. (2023). Effect of cerebellar transcranial magnetic stimulation with double-cone coil on dysphagia after subacute infratentorial stroke: a randomized, single-blinded, controlled trial. *Brain Stimul.* 16, 1012–1020. doi: 10.1016/j.brs.2023.05.023

Dan, Y., and Poo, M. M. (2006). Spike timing-dependent plasticity: from synapse to perception. *Physiol. Rev.* 86, 1033–1048. doi: 10.1152/physrev.00030.2005

De Doncker, W., Ondobaka, S., and Kuppuswamy, A. (2021). Effect of transcranial direct current stimulation on post-stroke fatigue. *J. Neurol.* 268, 2831–2842. doi: 10.1007/s00415-021-10442-8

Deng, Z. D., Lisanby, S. H., and Peterchev, A. V. (2013). Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. *Brain Stimul.* 6, 1–13. doi: 10.1016/j.brs.2012.02.005

Derosiere, G., Thura, D., Cisek, P., and Duque, J. (2022). Hasty sensorimotor decisions rely on an overlap of broad and selective changes in motor activity. *PLoS Biol.* 20:e3001598. doi: 10.1371/journal.pbio.3001598

Dhuri, K., Vyas, R. N., Blumenfeld, L., Verma, R., and Bahal, R. (2021). Nanoparticle delivered anti-miR-141-3p for stroke therapy. *Cells* 10:1011. doi: 10.3390/cells10051011

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., et al. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat. Rev. Neurol.* 10, 597–608. doi: 10.1038/nrneurol.2014.162

Drakaki, M., Mathiesen, C., Siebner, H. R., Madsen, K., and Thielscher, A. (2022). Database of 25 validated coil models for electric field simulations for TMS. *Brain Stimul.* 15, 697–706. doi: 10.1016/j.brs.2022.04.017

Dum, R. P., and Strick, P. L. (2003). An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J. Neurophysiol.* 89, 634–639. doi: 10.1152/jn.00626.2002

Einstein, E. H., Corlier, J., Matthews, C., Ngo, D., Leuchter, M. K., Citrenbaum, C., et al. (2023). Bilateral cerebellar repetitive transcranial magnetic stimulation for chronic Ataxia after hemorrhagic stroke: a case report. *Cerebellum* 23, 1254–1256. doi: 10.1007/s12311-023-01618-1

Fernandez, L., Major, B. P., Teo, W.-P., Byrne, L. K., and Enticott, P. G. (2018). The impact of stimulation intensity and coil type on reliability and tolerability of cerebellar brain inhibition (CBI) via dual-coil TMS. *Cerebellum* 17, 540–549. doi: 10.1007/s12311-018-0942-5

Ferrari, C., Ciricugno, A., Urgesi, C., and Cattaneo, Z. (2022). Cerebellar contribution to emotional body language perception: a TMS study. *Soc. Cogn. Affect. Neurosci.* 17, 81–90. doi: 10.1093/scan/nsz074

Gilbert, D. L., Huddleston, D. A., Wu, S. W., Pedapati, E. V., Horn, P. S., Hirabayashi, K., et al. (2019). Motor cortex inhibition and modulation in children with ADHD. *Neurology* 93, e599–e610. doi: 10.1212/wnl.0000000000007899

Grefkes, C., and Fink, G. R. (2014). Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol.* 13, 206–216. doi: 10.1016/S1474-4422(13)70264-3

Hardwick, R. M., Lesage, E., and Miall, R. C. (2014). Cerebellar transcranial magnetic stimulation: the role of coil geometry and tissue depth. *Brain Stimul.* 7, 643–649. doi: 10.1016/j.brs.2014.04.009

Hardwick, R. M., Therrien, A. S., and Lesage, E. (2021). Non-invasive stimulation of the motor cerebellum has potential cognitive confounds. *Brain Stimul.* 14, 922–923. doi: 10.1016/j.brs.2021.05.011

Harrington, A., and Hammond-Tooke, G. D. (2015). Theta burst stimulation of the cerebellum modifies the TMS-evoked N100 potential, a marker of GABA inhibition. *PLoS One* 10:e0141284. doi: 10.1371/journal.pone.0141284

Hensel, L., Grefkes, C., Tscherpel, C., Ringmaier, C., Kraus, D., Hamacher, S., et al. (2019). Intermittent theta burst stimulation applied during early rehabilitation after stroke: study protocol for a randomised controlled trial. *BMJ Open* 9:e034088. doi: 10.1136/bmjopen-2019-034088

Hirjak, D., Rashidi, M., Kubera, K. M., Northoff, G., Fritze, S., Schmitgen, M. M., et al. (2020). Multimodal magnetic resonance imaging data fusion reveals distinct patterns of abnormal brain structure and function in catatonia. *Schizophr. Bull.* 46, 202–210. doi: 10.1093/schbul/sbz042

Hurtado-Puerto, A. M., Nestor, K., Eldaief, M., and Camprodon, J. A. (2020). Safety considerations for cerebellar Theta burst stimulation. *Clin. Ther.* 42, 1169–1190.e1. doi: 10.1016/j.clinthera.2020.06.001

Im, N. G., Oh, K. R., Kim, M. G., Lee, Y., Lim, N. N., Cho, T. H., et al. (2022). Effect of low frequency cerebellar repetitive transcranial magnetic stimulation on balance impairment in patients with cerebral infarction. *Ann. Rehabil. Med.* 46, 275–283. doi: 10.5535/arm.22058

Jaillard, A., Martin, C. D., Garambois, K., Lebas, J. F., and Hommel, M. (2005). Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. *Brain* 128, 1122–1138. doi: 10.1093/brain/awh456

Kim, W. S., Jung, S. H., Oh, M. K., Min, Y. S., Lim, J. Y., and Paik, N. J. (2014). Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: a pilot study. *J. Rehabil. Med.* 46, 418–423. doi: 10.2340/16501977-1802

Koch, G., Bonnì, S., Casula, E. P., Iosa, M., Paolucci, S., Pellicciari, M. C., et al. (2019). Effect of cerebellar stimulation on gait and balance recovery in patients with Hemiparetic stroke: a randomized clinical trial. *JAMA Neurol.* 76, 170–178. doi: 10.1001/jamaneurol.2018.3639

Koch, G., Mori, F., Marconi, B., Codecà, C., Pecchioli, C., Salerno, S., et al. (2008). Changes in intracortical circuits of the human motor cortex following theta burst stimulation of the lateral cerebellum. *Clin. Neurophysiol.* 119, 2559–2569. doi: 10.1016/j.clinph.2008.08.008

Li, D., Cheng, A., Zhang, Z., Sun, Y., and Liu, Y. (2021). Effects of low-frequency repetitive transcranial magnetic stimulation combined with cerebellar continuous theta burst stimulation on spasticity and limb dyskinesia in patients with stroke. *BMC Neurol.* 21:369. doi: 10.1186/s12883-021-02406-2

Li, S., Wang, Y., Li, S., Lv, Y., Zhang, L., Zou, J., et al. (2019). Research on assisting clinicians to operate rTMS precisely based on the coil magnetic field spatial distribution with magnetic resonance imaging navigation. *Front. Neurosci.* 13:858. doi: 10.3389/fnins.2019.00858

Li, J., Zuo, Z., Zhang, X., Shao, X., Lu, J., Xue, R., et al. (2018). Excitatory repetitive transcranial magnetic stimulation induces Contralesional Cortico-cerebellar pathways after acute ischemic stroke: a preliminary DTI study. *Front. Behav. Neurosci.* 12:160. doi: 10.3389/fnbeh.2018.00160

Liao, L. Y., Xie, Y. J., Chen, Y., and Gao, Q. (2021). Cerebellar Theta-burst stimulation combined with physiotherapy in subacute and chronic stroke patients: a pilot randomized controlled trial. *Neurorehabil. Neural Repair* 35, 23–32. doi: 10.1177/1545968320971735

Liao, L. Y., Zhu, Y., Peng, Q. Y., Gao, Q., Liu, L., Wang, Q. H., et al. (2024). Intermittent Theta-burst stimulation for stroke: primary motor cortex versus cerebellar stimulation: a randomized sham-controlled trial. *Stroke* 55, 156–165. doi: 10.1161/STROKEAHA.123.044892

Lien, Y. R., Lin, Y. C., Lin, S. N., Lin, C. P., and Chang, L. H. (2022). Frequency-dependent effects of cerebellar repetitive transcranial magnetic stimulation on Visuomotor accuracy. *Front. Neurosci.* 16:804027. doi: 10.3389/fnins.2022.804027

Liu, W. C., Landstrom, M., Cealie, M., and MacKillop, I. (2022). A juvenile locomotor program promotes vocal learning in zebra finches. *Commun. Biol.* 5:573. doi: 10.1038/s42003-022-03533-3

Lu, M., and Ueno, S. (2017). Comparison of the induced fields using different coil configurations during deep transcranial magnetic stimulation. *PLoS One* 12:e0178422. doi: 10.1371/journal.pone.0178422

Mancic, B., Stevanovic, I., Ilic, T. V., Djuric, A., Stojanovic, I., Milanovic, S., et al. (2016). Transcranial theta-burst stimulation alters GLT-1 and vGluT1 expression in rat cerebellar cortex. *Neurochem. Int.* 100, 120–127. doi: 10.1016/j.neuint.2016.09.009

Matsugi, A., Mori, N., Hosomi, K., and Saitoh, Y. (2022). Cerebellar repetitive transcranial magnetic stimulation modulates the motor learning of visually guided voluntary postural control task. *Neurosci. Lett.* 788:136859. doi: 10.1016/j.neulet.2022.136859

Mawase, F., Bar-Haim, S., and Shmuelof, L. (2017). Formation of long-term locomotor memories is associated with functional connectivity changes in the cerebellar-thalamic-cortical network. *J. Neurosci.* 37, 349–361. doi: 10.1523/jneurosci.2733-16.2016

McHutchison, C. A., Cvoro, V., Makin, S., Chappell, F. M., Shuler, K., and Wardlaw, J. M. (2019). Functional, cognitive and physical outcomes 3 years after minor lacunar or cortical ischaemic stroke. *J. Neurol. Neurosurg. Psychiatry* 90, 436–443. doi: 10.1136/jnnp-2018-319134

Mirdamadi, J. L., and Block, H. J. (2021). Somatosensory versus cerebellar contributions to proprioceptive changes associated with motor skill learning: a theta burst stimulation study. *Cortex* 140, 98–109. doi: 10.1016/j.cortex.2021.03.019

Negrete-Hurtado, A., Overhoff, M., Bera, S., de, E., Schätzmüller, K., Kye, M. J., et al. (2020). Autophagy lipidation machinery regulates axonal microtubule dynamics but is dispensable for survival of mammalian neurons. *Nat. Commun.* 11:1535. doi: 10.1038/s41467-020-15287-9

Pasley, B. N., Allen, E. A., and Freeman, R. D. (2009). State-dependent variability of neuronal responses to transcranial magnetic stimulation of the visual cortex. *Neuron* 62, 291–303. doi: 10.1016/j.neuron.2009.03.012

Pauly, M. G., Steinmeier, A., Bolte, C., Hamami, F., Tzvi, E., Münchau, A., et al. (2021). Cerebellar rTMS and PAS effectively induce cerebellar plasticity. *Sci. Rep.* 11:3070. doi: 10.1038/s41598-021-82496-7

Premilovac, D., Blackwood, S. J., Ramsay, C. J., Keske, M. A., Howells, D. W., and Sutherland, B. A. (2020). Transcranial contrast-enhanced ultrasound in the rat brain reveals substantial hyperperfusion acutely post-stroke. *J. Cereb. Blood Flow Metab.* 40, 939–953. doi: 10.1177/0271678x20905493

Pushchina, E. V., Bykova, M. E., Shamshurina, E. V., and Varaksin, A. A. (2022). Transduction of brain neurons in juvenile chum Salmon (*Oncorhynchus keta*) with recombinant adeno-associated hippocampal virus injected into the cerebellum during long-term monitoring. *Int. J. Mol. Sci.* 23:4947. doi: 10.3390/ijms23094947

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. *Nat. Rev. Neurosci.* 7, 511–522. doi: 10.1038/nrn1953

Riedel, M. C., Ray, K. L., Dick, A. S., Sutherland, M. T., Hernandez, Z., Fox, P. M., et al. (2015). Meta-analytic connectivity and behavioral parcellation of the human cerebellum. *NeuroImage* 117, 327–342. doi: 10.1016/j.neuroimage.2015.05.008

Romero, M. C., Merken, L., Janssen, P., and Davare, M. (2022). Neural effects of continuous theta-burst stimulation in macaque parietal neurons. *eLife* 11:e65536. doi: 10.7554/eLife.65536

Rosenkranz, K., Seibel, J., Kacar, A., and Rothwell, J. (2014). Sensorimotor deprivation induces interdependent changes in excitability and plasticity of the human hand motor cortex. *J. Neurosci.* 34, 7375–7382. doi: 10.1523/jneurosci.5139-13.2014

Rosso, C., Moulton, E. J., Kemlin, C., Leder, S., Corvol, J. C., Mehdi, S., et al. (2022). Cerebello-motor paired associative stimulation and motor recovery in stroke: a randomized, sham-controlled, double-blind pilot trial. *Neurotherapeutics* 19, 491–500. doi: 10.1007/s13311-022-01205-y

Rowan, M. J. M., Bonnan, A., Zhang, K., Amat, S. B., Kikuchi, C., Taniguchi, H., et al. (2018). Graded control of climbing-Fiber-mediated plasticity and learning by inhibition in the cerebellum. *Neuron* 99, 999–1015.e6. doi: 10.1016/j.neuron.2018.07.024

Schluter, R. S., van Holst, R. J., and Goudriaan, A. E. (2019). Effects of ten sessions of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) add-on treatment on impulsivity in alcohol use disorder. *Front. Neurosci.* 13:1257. doi: 10.3389/fnins.2019.01257

Shikauchi, Y., Uehara, K., Okazaki, Y. O., and Kitajo, K. (2023). A PAS-EEG concurrent recording dataset: electroencephalographic responses before, during,

and after upper limb paired associative stimulation. *Brain Stimul.* 16:306. doi: 10.1016/j.brs.2023.01.555

Song, C., Duan, F., Ju, T., Qin, Y., Zeng, D., Shan, S., et al. (2022). Eleutheroside E supplementation prevents radiation-induced cognitive impairment and activates PKA signaling via gut microbiota. *Commun. Biol.* 5:680. doi: 10.1038/s42003-022-03602-7

Spampinato, D., Avci, E., Rothwell, J., and Rocchi, L. (2021). Frequency-dependent modulation of cerebellar excitability during the application of non-invasive alternating current stimulation. *Brain Stimul.* 14, 277–283. doi: 10.1016/j.brs.2021.01.007

Spampinato, D. A., Celnik, P. A., and Rothwell, J. C. (2020). Cerebellar-motor cortex connectivity: one or two different networks? *J. Neurosci.* 40, 4230–4239. doi: 10.1523/jneurosci.2397-19.2020

Spampinato, D., Ibanez, J., Spanoudakis, M., Hammond, P., and Rothwell, J. C. (2020). Cerebellar transcranial magnetic stimulation: the role of coil type from distinct manufacturers. *Brain Stimul.* 13, 153–156. doi: 10.1016/j.brs.2019.09.005

Stampanoni Bassi, M., Buttari, F., Nicoletti, C. G., Mori, F., Gilio, L., Simonelli, I., et al. (2020). Interleukin-1β alters Hebbian synaptic plasticity in multiple sclerosis. *Int. J. Mol. Sci.* 21:6982. doi: 10.3390/ijms21196982

Strick, P. L., Dum, R. P., and Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 413–434. doi: 10.1146/annurev.neuro.31.060407.125606

Tan, H.-X., Wei, Q.-C., Chen, Y., Xie, Y.-J., Guo, Q.-F., He, L., et al. (2021). The immediate effects of intermittent Theta burst stimulation of the cerebellar vermis on cerebral cortical excitability during a balance task in healthy individuals: a pilot study. *Front. Hum. Neurosci.* 15:748241. doi: 10.3389/fnhum.2021.748241

van Lieshout, E. C. C., van der Worp, H. B., Visser-Meily, J. M. A., and Dijkhuizen, R. M. (2019). Timing of repetitive transcranial magnetic stimulation onset for upper limb function after stroke: a systematic review and Meta-analysis. *Front. Neurol.* 10:1269. doi: 10.3389/fneur.2019.01269

Wessel, M. J., and Hummel, F. C. (2018). Non-invasive cerebellar stimulation: a promising approach for stroke recovery? *Cerebellum* 17, 359–371. doi: 10.1007/s12311-017-0906-1

Xia, Y., Tang, X., Hu, R., Liu, J., Zhang, Q., Tian, S., et al. (2022). Cerebellum-cerebrum paired target magnetic stimulation on balance function and brain network of patients with stroke: a functional near-infrared spectroscopy pilot study. *Front. Neurol.* 13:1071328. doi: 10.3389/fneur.2022.1071328

Xia, Y., Wang, M., and Zhu, Y. (2023). The effect of cerebellar rTMS on modulating motor dysfunction in neurological disorders: a systematic review. *Cerebellum* 22, 954–972. doi: 10.1007/s12311-022-01465-6

Xie, Y. J., Wei, Q. C., Chen, Y., Liao, L. Y., Li, B. J., Tan, H. X., et al. (2021). Cerebellar Theta burst stimulation on walking function in stroke patients: a randomized clinical trial. *Front. Neurosci.* 15:688569. doi: 10.3389/fnins.2021.688569

Xue, A., Kong, R., Yang, Q., Eldaief, M. C., Angeli, P. A., DiNicola, L. M., et al. (2021). The detailed organization of the human cerebellum estimated by intrinsic functional connectivity within the individual. *J. Neurophysiol.* 125, 358–384. doi: 10.1152/jn.00561.2020

Zhang, W., Deng, B., Xie, F., Zhou, H., Guo, J. F., Jiang, H., et al. (2022). Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: a systematic review and meta-analysis of randomised controlled trials. *EClinicalMedicine* 52:101589. doi: 10.1016/j.eclinm.2022.101589

Zhang, Q., Wu, J. F., Shi, Q. L., Li, M. Y., Wang, C. J., Wang, X., et al. (2019). The neuronal activation of deep cerebellar nuclei is essential for environmental enrichment-induced post-stroke motor recovery. *Aging Dis.* 10, 530–543. doi: 10.14336/ad.2018.1220

Zhao, C. G., Qin, J., Sun, W., Ju, F., Zhao, Y. L., Wang, R., et al. (2019). rTMS regulates the balance between proliferation and apoptosis of spinal cord derived neural stem/progenitor cells. *Front. Cell. Neurosci.* 13:584. doi: 10.3389/fncel.2019.00584

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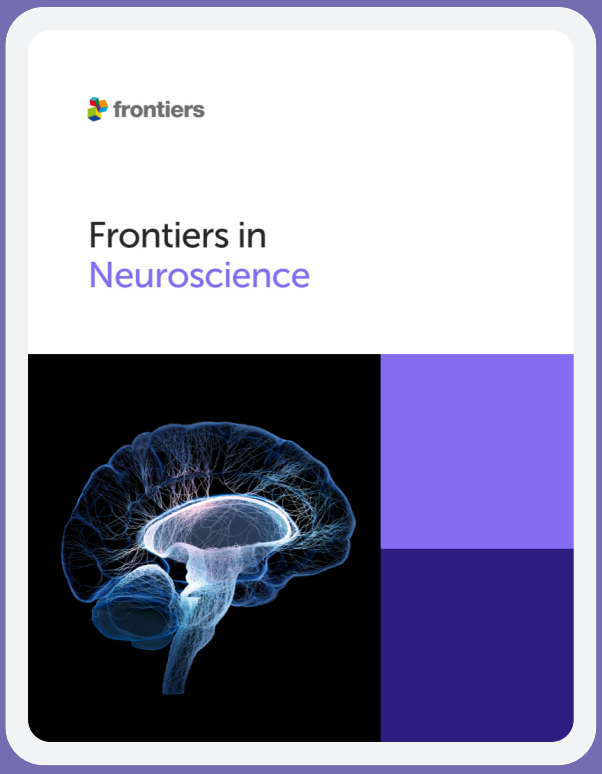

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