Non-invasive brain stimulation techniques for the improvement of upper limb motor function and performance in activities of daily living after stroke: a systematic review and network meta-analysis.

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Highlights:

- Excitatory stimulation protocols (anodal tDCS and HF-rTMS) are most effective
- intervention in improving upper limb motor function and performance in ADLs after
- acute/sub-acute stroke and chronic stroke.
- Transcutanous Vagus nerve stimulation appeared to be a promising intervention in
- improving upper limb motor function and performance in ADLs after acute/sub-acute
- stroke and chronic stroke.
- More taVNS trials are needed to find optimal stimulation paradigm and relative
- superiority compared to other NIBS.

Non-invasive brain stimulation techniques for the improvement of upper limb motor function and performance in activities of daily living after stroke: a systematic review and network meta-analysis.

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Short Title: Non-invasive brain stimulation for stroke rehabilitation.

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Abstract

Objective: To compare the efficacy of non-invasive brain stimulation (NiBS) such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation

(rTMS), theta-burst stimulation (TBS), and transcutaneous vagus nerve stimulation (taVNS) in upper limb stroke rehabilitation.

Data sources: PubMed, Web of Science, and Cochrane databases were searched from January 2010 to June 2022.

Data Selection: Randomized controlled trials (RCT's) assessing the effects of "tDCS", "rTMS", "TBS", or "taVNS" on upper limb motor function and performance in activities of daily livings (ADLs) after stroke.

Data Extraction: Data were extracted by 2 independent reviewers. Risk of bias were was evaluated with the Cochrane Risk of Bias tool.

Data Synthesis: 87 RCTs with 3750 participants were included. Pairwise meta-analysis showed that all NiBS except continuous TBS (cTBS) and cathodal tDCS were significantly more efficacious than sham stimulation for motor function (Standard Meand Differerence (SMD) range 0.42 to 1.20) whereas taVNS, anodal tDCS, and both low and high frequency rTMS were significantly more efficacious than sham stimulation for ADLs (SMD range 0.54 to 0.99). NMA showed that taVNS was more effective than cTBS (SMD:1.00;95%CI(0.02 to 2.02), cathodal tDCS (SMD:1.07;95%CI(0.21 to 1.92) and Physical rehabilitation alone (SMD:1.46;95%CI(0.59 to 2.33)) for improving motor function. P-score found that taVNS is best ranked treatment in improving motor function (SMD: 1.20;95%CI(0.46 to 1.95) and ADLs (SMD:1.20;95%CI(0.45 to 1.94) after stroke. After taVNS, excitatory stimulation protocols (intermittent TBS, anodal tDCS and HF-rTMS) are most effective in improving motor function and ADLs after acute/sub-acute (SMD range 0.53 to 1.63) and chronic stroke (SMD range 0.39 to 1.16).

Conclusions: Evidence suggests that excitatory stimulation protocols are the most promising intervention in improving upper limb motor function and performance in ADLs. taVNS

appeared to be a promising intervention for stroke patients, but further large RCTs are required to confirm its relative superiority.

Keywords: Stroke, Upper Limb, brain stimulation, Motor recovery.

Prospero Registration number: CRD42022302542

Introduction

Upper limb motor impairment is one of the most common sequelae of stroke[1-3]. Approximately 80% of stroke survivors have upper limb motor impairment[4, 5] and only 20-30% of these survivors achieve functional recovery[6], while 50-60% still have persistent impaired upper limb function six months later [7]. Since the efficacy of standard physical rehabilitative approaches is limited[8], novel and possibly more effective alternative treatment methods to improve upper limb functionality after stroke, with positive impact on activities of daily living (ADLs), is a research priority for both stroke survivors and caregivers[7-9].

Currently available treatment methods to improve upper limb function after stroke include intensive, task-specific, repetitive rehabilitative interventions and non-invasive brain stimulation (NiBS) [7, 10-16]. In recent years, considerable evidence for NiBS strategies in stroke patients have emerged, particularly for transcranial direct current stimulation (tDCS) [17-20], repetitive transcranial magnetic stimulation (rTMS) [21-23], theta-burst stimulation (TBS)[24, 25] and transcutaneous vagus nerve stimulation (taVNS) [16, 26].The NiBS techniques potentialities for recovery rely on the principle of neuroplasticity, best defined as changes in neuronal function and structure to increase neural functioning through synaptogenesis, reorganization, and network strengthening and suppression[27, 28]. The tDCS, rTMS, and TBS stimulation paradigms may lead to motor recovery capitalizing from induced changes in synaptic function

(long-term potentiation or depression) [29], whereas taVNS facilitate motor recovery by indirectly modulating the cortical re-organization of the motor cortex [15, 30]. Several randomized controlled trials (RCTs) have explored the effects of tDCS, rTMS, TBS, or taVNS combined with other therapies on upper limb motor function in the sub-acute[18, 22, 31, 32] and chronic stage of stroke [33-36]. Few studies demonstrated improvement in upper limb motor function [16, 18, 24-26, 37], but there is a mixed approach towards the output of NiBS combined with other therapies, and the effect on upper limb motor function is not well established yet [38].

Previous meta-analyses have determined the efficacy of NiBS techniques compared with sham stimulation[39-41] or within pairs of active stimulation[42]. Due to methodological limitations, those analyses were only able to draw a pairwise-comparison and were not able to provide an overall treatment hierarchy (network-evidence), because the estimated effects were calculated from the subset of relevant treatment comparison only. Secondly, to avoid multiple subgroup analyses, authors had to combine different types of brain stimulation into a single category, which results in masking possible differences in the treatment effect of various NiBS techniques[39]. Furthermore, the lack of clinical trials that compared different NIBS techniques, prevents clinicians to select the most effective intervention for the upper limb motor function recovery in stroke patients. A network meta-analysis (NMA) or multiple treatment comparison meta-analysis, the best level of evidence in treatment guidelines[43], allows the quantitative synthesis of network evidence by combining direct evidence from head-to-head comparisons of multiple interventions within RCTs and indirect evidence across RCTs on the basis of a common comparator [43, 44]. Previous NMAs of NiBS have provided the comprehensive synthesis of single brain stimulation protocols i.e tDCS but did not include rTMS, TBS or taVNS[45, 46]. Recently Ahmed et al. have compared the tDCS with VNS but did not include rTMS and TBS in their analysis[1]. Therefore, a comprehensive NMA comparing different types of NiBS (i.e., tDCS, rTMS, TBS, tRNS taVNS) is required to determine the

relative efficacy of NiBS in improving upper limb motor function and performance in ADLs after stroke.

Objective:

This is the first systematic review with NMA, which aimed to give an overview of the evidence network of RCTs of tDCS (cathodal, anodal, or dual), rTMS (low or high frequency rTMS), TBS (intermittent or continuous), and taVNS for improving upper limb motor function and performance in ADLs after stroke and to estimate and rank the relative effectiveness of the different NiBS techniques.

Material and Methods

2.1. Protocol and Registration

The study was conducted in accordance with guidelines based on evidence-based criteria in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for NMA[47]. The study protocol was designed a priori according to PRISMA extension statement for NMA guidelines and was registered in the PROSPERO database (Registration number: CRD42022302542).

2.2. Search strategy and study selection

Literature Search included the following electronic bibliographic databases: Medline (PubMed), Web of Science (WOS), and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL). Literature was searched for English articles (Spoken language of authors), which were published between January 1, 2010, and March 25, 2022, using specific keywords. The following keywords were employed: “Stroke”, “Cerebrovascular Accident”, “Transcranial Direct Current Stimulation”, “Transcranial Magnetic Stimulation”, “repetitive Transcranial Magnetic Stimulation”, “Theta Burst Stimulation”, “Transcranial Random Noise Stimulation”, “Transcranial Alternating Current Stimulation”, “Vagus Nerve Stimulation”,

"Transcutaneous Vagus Nerve Stimulation", "transcutaneous auricular Vagus Nerve Stimulation", "Non-invasive brain stimulation", and "Upper Extremity". The search strategy is given in Appendix 1. Initially, two pairs of the authors (I.A and R.M and S.M and F.A.Y) independently screened all titles, abstracts, and full texts for eligibility. Any discrepancies identified during the screening process were resolved through a consensus meeting (S.R, S.S, and M.P). Articles published as abstract, case reports, non-randomized controlled trials, reviews, and conference papers were excluded. In order to identify further articles, secondary searches were performed by manually screening of bibliographies of identified articles and tracking the citing articles to identify studies that were not identified by the database search, and an additional search was also made through Google Scholar.

2.3. Eligibility Criteria

We followed the Lefaucheur et al. evidence-based guidelines for clinical use of brain stimulation, which classified studies into four classes from I to IV according to decreasing level of evidence[48]. Class-I constitutes high-quality randomized, sham-controlled clinical trial with a representative sample i.e., 25 or more patients receiving active stimulation/treatment. Class-II constitutes good-quality randomized, sham-controlled clinical trial with a sample size ranges between 10 and 25 patients receiving active stimulation/treatment. Class-III constitutes controlled clinical trial with low methodological quality and sample size i.e., 9 patients or less receiving active stimulation/treatment. Class IV constitutes un-controlled studies, case report or case series. This classification was further used to determine the level of evidence from A to C (see Lefaucheur et al. [48]). Level A (requiring at least two studies from Class I or one study from Class I and at least two studies from Class II) evidence was constituted in the review to report the efficacy of NiBS i.e., ''definitely effective or ineffective".

2.3.1. Types of Studies

We included only Class I or Class II RCTs and cross over RCTs with a minimum sample size of 10 which determined the effect of “tDCS”, “rTMS”, “TBS”, “tRNS”, or “taVNS” with/without “upper limb physical rehabilitation approaches” on upper limb motor function and performance in ADLs after stroke. For cross-over design, only the first phase of intervention was analyzed and between-group difference was assumed to be identical to trials with parallel-group design.

2.3.2. Types of Participants

Only those studies were included that focused on adults (aged 18 years and over) with a confirmed diagnosis of acute/subacute (<6 months) or chronic (>6 months) ischemic and/or hemorrhagic stroke. The eligibility of the study was confirmed by reviewing the inclusion criteria of study.

2.3.3. Types of Interventions

Studies were included if they focused on interventions of “tDCS”, “rTMS”, “TBS”, “tRNS”, or “taVNS” combined with upper limb physical rehabilitation approaches. For tDCS, we grouped intervention according to treatment protocol and electrodes’ location: cathodal stimulation of non-lesioned hemisphere; anodal stimulation of lesioned hemisphere; dual tDCS-bilateral stimulation of both lesioned and non-lesioned hemispheres by anodal and cathodal stimulation, respectively. For rTMS, we grouped intervention according to stimulation frequency and coil location: low-frequency stimulation of non-lesioned hemisphere (LF-rTMS); and high-frequency stimulation of lesioned hemisphere (HF-rTMS). Similarly, we grouped TBS into intermittent Theta Burst Stimulation (iTBS) and continuous Theta Burst Stimulation (cTBS). Sham stimulations and active physical rehabilitation interventions were combined into their single group respectively for the main analysis. We combined different stimulation durations and different stimulation locations for the same NiBS type i.e., dual, anodal, or cathodal tDCS, LF-rTMS or HF- rTMS, and iTBS or cTBS.

2.3.4. Types of Comparators

We included those studies which have compared any type of "tDCS", "rTMS", "TBS", "tRNS", or "taVNS" for improving upper limb motor functions and performance in ADLs. In multi-arm study design, all comparators were included.

2.3.5. Types of Outcomes

Mean change from baseline to post intervention of outcomes related to upper limb motor function (such as Fugl Meyer Assessment scale-Upper extremity (FMA-UE), Wolf Motor Function Test (WMFT), Box and Block Test (BBT), Jebsen-Taylor Hand Function Test (JTHFT), Action Research Arm Test (ARAT) etc.) and performance in ADL (Barthel Index (BI), modified Barthel Index (mBI), modified Rankin Scale (mRS), Motor Activity Log -Quality of Movement (MAL-QoM), Nottingham Extended Activities of Daily Living Scale (NEADL), Functional Independence Measure (FIM), etc.) after stroke were included.

2.4. Data Extraction

Two independent authors (IA and RM) extracted the data from the selected studies. In case of any discrepancies identified during the screening process, a consensus was achieved through face-to-face discussion (RM, IA, and SR). The following information has been extracted from the selected articles: Publication year, Authors, Country, Stroke type, Number of Participants, Methodological design, Comparison groups, Intervention protocols, Outcome, and Summary of results.

2.5. Quality assessment

Cochrane Risk of Bias assessment tool (Review Manager version 5.4.1) was used to determine the risk of bias in randomized controlled trials [49]. The assessment tool includes 1-Random sequence generation, 2-Allocation concealment, 3-Blinding of participants and personnel, 4-Blinding of outcome assessors, 5-Intention-to-treat analysis, and 6-Description of exclusions and losses. Each domain was categorized as "Unclear", "Low" or "High" bias

risk. Studies were considered moderate to high quality if there was a low risk of bias in three or more than three domains [1, 39, 49-51]. Egger's regression asymmetry tests were used to assess publication bias [52].

2.6. Geometry of the network

The network geometry shows the interaction among articles included in NMA [53, 54] and characterizes the precision of possible direct comparisons. We analyzed the comparison of different types of NiBS techniques with sham-intervention. Network graphs were generated to assess the geometry of network [54, 55]. Each node in the network graph represents an intervention and lines between the nodes show the randomized comparison between interventions [53, 54].

2.7. Data synthesis and analyses

The results of the included studies were reported as median and interquartile range (IQR) or mean and standard deviation. When data were provided as median and range, we converted median and IQR to mean and standard deviation using appropriate statistical formulas[56, 57]. WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to extract numerical data from figures. If the data could not be retrieved from the selected publications, requests were made to corresponding Authors to provide the necessary data. We calculated the mean difference (MD) and their 95% confidence interval (CI) for studies that used the same outcome measure, whereas standard mean difference (SMD) and their 95% confidence interval (CI) were calculated for the studies that did not use the same outcome measure to evaluate the same construct. Contrast-based forest plots were generated for all the possible comparisons and all the competing interventions were ranked according to the P-score [1, 54, 58, 59]. P-score ranges from 0 to 1. The higher or closer to 1 the P-score, the higher the probability that the intervention is in the highest or top position [45, 46]. P-score describes the mean degree of certainty about a particular treatment is comparable to its surface under the cumulative

ranking curve (SUCRA) [45]. All the analysis was performed with package "netmeta" in statistical software R version 4.1.3.

2.8. Planned method of analysis

This NMA was conducted to analyze the indirect evidence based on multivariate regression with random effects by using the frequentist approach [60, 61]. The frequentist approach allows the incorporation of multi-arm trials and includes maximum-likelihood estimation [53, 61]. This NMA is based on two assumptions: (1) consistency of effects (transitivity) and (2) independence of trials [54, 62, 63]. We used random-effect-model to determine the summary estimate of the treatment effect.

2.9. Assessment of inconsistency

Cochran's Q chi-squared statistics for multivariate meta-analysis was used to determine the inconsistency and homogeneity assumption[63]. Both global (between design) and local (loop specific or within-design or between pairwise) inconsistency has been determined in this analysis. To determine the global inconsistency, the between-designs Cochran's Q score was calculated on the basis of a full design-by-treatment interaction by using the random effects model[64], defined with a generalized methods-of-moments (MoM) estimate of the between-studies variance (ie, τ^2)[64, 65]. To determine local inconsistency, net split method was used to split network estimates into the contribution of direct-and-indirect evidence. A direct and indirect comparison of treatment estimates can serve as check for consistency/coherence of NMA [64-66].

2.10. Sensitivity analyses

We conducted several sensitivity analyses to assess the robustness of our findings for motor function and performance in ADLs, by excluding stimulation protocol determining the effect of taVNS, iTBS, and cTBS in stroke. We also conducted the sub-group analysis according to stage of stroke i.e. acute/sub-acute and chronic stage of stroke.

3. Results

3.1. Study Selection

A total of 3382 potentially relevant articles were retrieved from the three considered electronic databases: PubMed (n=673), WOS (n=1156), and Cochrane (n=1553). In addition, 2 studies were identified by hand searching of bibliography of the included papers' reference lists from Google Scholar. Endnote duplicate citation checker found 863 duplicate studies which were also removed. After removing the duplicate, the remaining 2521 studies were screened based on title and abstract by two pairs of independent authors for eligibility, of which 2370 studies were excluded. Remaining 151 articles were screened for full text, of which 64 studies were removed because of the following reasons: a) full texts were not available (n=6); b) outcome measure not fitting our criteria (Kinematic measurements) (n=9); c) preliminary or intermediate result (n=5); d) ineligible article (n=11); e) non-English papers (n=4) and f) sample size less than 10 (n=29). Finally, 87 studies (42[18-20, 33-38, 67-99] performed with tDCS, three[16, 100, 101] with taVNS, 33[22, 23, 31, 102-131] with rTMS, and nine[24, 25, 132-138] with TBS) were included in the systematic review with network meta-analysis to determine the effect of NiBS on upper limb motor function and performance in ADLs as compared to sham stimulation. No studies were found investigating the effects of tRNS and tACS on upper limb motor function and performance in ADLs in stroke patients. The study selection and the search processes were performed in accordance with the PRISMA extension statement for NMA guidelines and is shown in Figure 1.

3.2.Study Characteristics

A comprehensive summary about the characteristics of studies examining NiBS for improving upper limb motor function and performance in ADLs is shown in Supplementary File, Table S1. Regarding the tDCS protocol, sample size ranged from 20[76] to 96[38], current intensity ranged between 0.7mA[91] to 2.2mA[84], number of sessions varied from 5[96] to 36[35]

and the time of stimulation ranged between 10[78] to 40[76] minutes. Considering rTMS protocol, sample size ranged from 20[105] to 199[31], stimulation frequency ranged between 1Hz[104] to 20 Hz[115], number of sessions varied from 5[116] to 40[129], and the time of stimulation ranged between 5[128] to 40[126] minutes. Regarding TBS protocol, sample size ranged from 23[133] to 71[135], stimulation intensity ranged between 60-80% of active and resting motor threshold potential, number of sessions varied from 9[137] to 40[25], and the number of pulses varied between 600[137] to 1200[133] per session. Considering taVNS protocols, sample size ranged from 21[16] to 60[100], stimulation frequency ranged between 20 Hz[16] to 30 Hz[101], number of sessions varied from 9[101] to 20[100], and duration of stimulation ranged 20[100] to 30[16] minutes.

3.3. Quality Assessment

Among the selected studies, 85% reported the random sequence generation, 77% reported allocation concealment, more than 80 % of studies have blinded the participants, personnel and assessor and have provided the information on losses and exclusion during the trial. However, only 65% of studies used intention-to-treat analysis to present the result. Majority of selected studies are of moderate to high quality (Supplementary File, Figure S1). Egger's regression analysis shows no evidence of publication bias for upper limb motor function ($p = 0.56$) and performance in ADLs ($p= 0.75$).

3.4. Network Map

Network graph comparing NiBS technique with sham stimulation for improving upper limb motor function is shown in Figure 2. The network graph comparing NiBS technique with sham stimulation for improving upper limb performance in ADLs is shown in Figure 3. The thickness of lines in the figures illustrates that more studies are in direct comparison in the loop

3.5. Exploration for inconsistency

The test for global inconsistency does not reveal any disagreement between the direct and indirect comparison (Q=10.65; df=20; p=0.95 for upper limb motor function and Q=8.20; df=11; p=0.69 for performance in ADLs). The p-value indicates that there was no significant inconsistency/ incoherence which supports the consistency test for every model, which is the null hypothesis, thus network model is acceptable. The net split test for loop-specific/local inconsistency showed that the p-value was statistically insignificant for all comparisons of treatments, which means there is no inconsistency between any of the loops (Supplementary File, Table S2-S3). Therefore, the consistency model is supported once again. As the inconsistency/ incoherence is absent at both local and global levels, the consistency/coherence assumption for NMA is accepted.

3.6. Synthesis of results

3.6.1. Summary of Network

A total of 1917 stroke patients received the real NiBS with the declared aim to improve upper limb motor function (number of studies: k = 79, number of arms = 103). The stimulation types studied were mostly LF-rTMS (26 study arm, 686 participants), anodal tDCS (24 study arm, 466 participants), HF-rTMS (11 study arm, 191 participants), dual tDCS (14 study arm, 190 participants), cathodal tDCS (8 study arm, 180 participants), iTBS (4 study arm, 90 participants), taVNS (3 study arm, 58 participants), and cTBS (3 study arm, 56 participants). A total of 1205 stroke patients received sham NiBS as a comparator intervention (67 studies) whereas 166 stroke patients received Physical rehabilitation as a comparator intervention.

A total of 1074 stroke patients received the real NiBS with the declared aim to improve Performance in ADL (number of studies: k = 46, number of arms = 58). The stimulation types studied were mostly LF-rTMS (15 study arm, 353 participants), anodal tDCS (11 study arm, 223 participants), HF-rTMS (8 study arm, 149 participants), dual tDCS (7 study arm, 118

participants), cathodal tDCS (6 study arm, 119 participants), iTBS (4 study arm, 58 participants), cTBS (2 study arm, 44 participants) and taVNS (1 study arm, 10 participants). A total of 728 stroke patients received sham NiBS as a comparator intervention (39 study arm) whereas 83 stroke patients received Physical rehabilitation as a comparator intervention.

3.6.2. Pair-wise Meta-analysis

Supplementary File, Table S4 shows the result of pairwise meta-analysis. All NiBS protocols except cTBS and cathodal tDCS were significantly more efficacious than sham stimulation for upper limb motor function (SMD range 0.42 to 1.20). Among active stimulation, HF-rTMS was more effective than LF-rTMS (SMD: 0.01; 95%CI (-0.58 to 0.59); p=0.04, $\tau 2$ =0.23; I^2 =64%) in improving upper limb motor function.

Considering upper limb performance in ADLs, taVNS, anodal tDCS, LF-rTMS and HF-rTMS were significantly more efficacious than sham stimulation (SMD range 0.54 to 0.99) (Supplementary File, Table S4). Among active stimulation, LF-rTMS was more effective than HF-rTMS (SMD: 0.12; 95%CI (-0.63 to 0.87); p=0.04, $\tau 2$ =0.24; I^2 =61%).

3.6.3. Network meta-analysis

League-table providing effect estimate of NMA and pair-wise comparison of NiBS for improving upper limb motor function is available in Table 1. The result of NMA showed that taVNS was more efficacious than cTBS (SMD: 1.00 (0.02 to 2.02), cathodal tDCS (SMD: 1.07 (0.21 to 1.92)), sham stimulation (SMD: 1.20; 95%CI (0.46 to 1.95) and physical rehabilitation (SMD 1.46; 95%CI (0.59 to 2.33)) for upper limb motor function. No significant differences were found between the taVNS, iTBS, anodal or dual tDCS, and HF or LF rTMS (SMD range 0.04 to 0.78). Figure 4 shows the forest plot for NiBS for improving upper limb motor function in stroke. The highest effect for pairwise comparisons was for taVNS (SMD: 1.20; 95%CI (0.46 to 1.95) vs sham stimulation. P-score indicated that taVNS

is the best-ranked treatment for improving upper limb motor function in stroke followed by iTBS, HF-rTMS, and anodal tDCS, respectively (Figure 4).

League-table providing effect estimate of NMA and pair-wise comparison of NiBS for improving upper limb performance in ADLs is available in Table 2. The result of NMA showed that taVNS, anodal tDCS, HF-rTMS, and LF-rTMS were more efficacious than sham stimulation (SMD range 0.52 to 1.00) and physical rehabilitation (SMD range 0.74 to 1.21) for upper limb performance in ADLs. No significant differences were found between taVNS, iTBS or cTBS, anodal, cathodal or dual tDCS and HF-rTMS or LF-rTMS (SMD range 0.02 to 1.34). Figure 5 shows the forest plot for NiBS for improving upper limb performance in ADLs in stroke. The highest effect for pairwise comparisons was for taVNS (SMD: 1.20; 95%CI (0.45 to 1.94) vs sham stimulation. P-score indicated that taVNS is the best-ranked treatment for improving upper limb performance in ADLs in stroke followed by anodal tDCS, LF-rTMS and HF-rTMS, respectively (Figure 5).

3.7. Sensitivity analyses

3.7.1. Stimulation protocols

We conducted a sensitivity analysis by excluding the stimulation protocol determining the effect of taVNS on upper limb motor function and performance in ADLs after stroke. Excluding taVNS, the stimulation protocol did not change our results (motor function: Supplementary File, sensitivity analysis- Figure S2-S3; performance in ADLs: Supplementary File, sensitivity analysis-Figure S6-S7). The ranking and estimated effect size for other stimulation protocols remained the same (motor function: Supplementary File, sensitivity analysis-Table S5; performance in ADLs: Supplementary File, sensitivity analysis-Table S7). Further exclusion of TBS (iTBS, and cTBS) studies, due to the small number of trials, also did not change the ranking and estimated effect size for other stimulation protocols (motor function: Supplementary File, sensitivity analysis-Figure S4-S5 and Table S6; performance in

ADLs: Supplementary File, sensitivity analysis-Figure S8-S9 and Table S8). Unfortunately, after removing the studies with per protocol analysis, the transitivity and consistency assumption for NMA is not satisfied and so a sensitivity analysis using an NMA approach was not performed.

3.7.2. Acute/sub-acute and chronic stroke

Sub-group analysis according to the stage of stroke showed that taVNS, anodal tDCS, HF-rTMS, and LF-rTMS were more efficacious than sham stimulation for improving upper limb motor function (SMD range 0.53 to 1.63), and performance in ADLs (SMD range 0.56 to 0.95) in acute/sub-acute stroke whereas iTBS, anodal and dual tDCS were more efficacious than sham stimulation for improving upper limb motor function in chronic stroke (SMD range 0.39 to 1.16) (Supplementary File, sensitivity analysis-Table S9-Table S11). P-score indicated that taVNS is the best-ranked treatment for improving upper limb motor function in acute/sub-acute stroke followed by anodal tDCS, HF-rTMS and LF-rTMS, respectively, whereas iTBS is the best ranked treatment for improving upper limb motor function in chronic stroke followed by, HF-rTMS, dual and anodal tDCS, respectively (Supplementary File, sensitivity analysis-Figure S10 and Figure S11). Considering upper limb performance in ADLs, P-score indicated that anodal tDCS is the best ranked treatment for improving upper limb performance in ADLs in acute/sub-acute stroke followed by taVNS, LF-rTMS and HF-rTMS, respectively (Supplementary File, sensitivity analysis-Figure S12).

Discussion

This systematic review and NMA compares all available NiBS protocols for the improvement of upper limb motor function and performance in ADLs and has included 87 RCTs with 3750 (1697 tDCS, 1537 rTMS, 399 TBS, and 117 taVNS) patients with acute/subacute (<6 months) or chronic (>6 months) ischemic and/or hemorrhagic stroke who were randomized to 8 distinct stimulation protocols or sham stimulation. Current evidence

revealed that taVNS and excitatory stimulation protocol (that is, iTBS, anodal tDCS, and HF-rTMS) were found to be more effective than sham stimulation in improving upper limb motor functions and performance in ADLs in acute/subacute and chronic stroke. The taVNS is best-ranked treatment in improving upper limb motor functions and performance in ADLs after stroke.

The result from NMA provides further clarification about the comparative efficacy of different NiBS protocols. taVNS was found to be significantly more effective than cathodal tDCS, cTBS, sham stimulation, and physical rehabilitation for improving upper limb motor function after stroke. The reason for this might be that stimulation of vagus nerve increases the level of brain-derived neurotrophic factors (BDNF) and neurotransmitters, such as noradrenaline, which are linked to neuroplasticity and recovery after brain lesion [139]. The results of our NMA are in line with the previous reviews accessing the effect of VNS in improving upper limb motor function [15, 140]. The analysis reported that VNS is effective in improving upper limb motor function after stroke (Jiang et al., (2020); SMD 3.86; 95%CI (1.19-6.52, 3 studies, 49 participants); Liu et al., (2017); MD 3.31; 95%CI (2.33-4.29, 5 studies, 168 participants)), which is in accordance with our findings. Recent NMA compared the effect of taVNS with tDCS and reported that taVNS is more effective in improving upper limb motor function after stroke (MD:5.50; 95%CI (0.67, 11.67), which is in accordance with our NMA findings [1].

The taVNS is comparatively new investigational treatment and early-phase positive findings of studies may likely to be biased in favor of pilot interventions. The sensitivity analysis after removing taVNS revealed that iTBS is the best ranked treatment in improving upper limb motor function after stroke. The reason for this might be that iTBS increase the excitability of lesioned hemisphere which may enhance motor function[141]. Ackerley et al., also reported that iTBS increases cortical excitability whereas cTBS decreases cortical

excitability and motor function deteriorated after cTBS[142]. The result was supported by previous meta-analysis which revealed that iTBS may be more helpful for motor function than cTBS (0.60 vs 0.35, respectively)[21, 143]. Although our analysis revealed that iTBS is effective in improving upper limb motor function after stroke, the result should be interpreted with great caution because recent studies indicate that TBS effects on cortical excitability may not be reliable[144, 145]. The reason for this might be that the TBS is generally performed at an intensity (80-90% of the threshold) which, by definition, is unlikely to excite cortical neurons (i.e., it is sub-threshold). Because of these reasons we performed the sensitivity analysis by removing TBS and found that excitatory stimulation protocols (HF-rTMS and anodal tDCS) are the best-ranked treatment for improving upper limb motor functions in stroke patients. An imbalance in inter-hemispheric inhibition occurred after stroke and this imbalance could be reduced by increasing the cortical excitability in the lesioned hemisphere by HF-rTMS and anodal tDCS, which in turn may promote motor recovery [146, 147]. The results are in line with the previous reviews which assessed the effect of anodal tDCS and rTMS on upper limb motor function and included both RCTs, non-RCTs and pre-post trials [143, 148]. They reported significant beneficial effect of anodal tDCS (SMD:0.49; 95%CI (0.18-0.81, 7 studies, 168 participants) and HF-rTMS (ES:0.45; 95%CI (0.22 - 0.69, 8 studies, 335 participants) on upper limb motor function. Previous NMA also provide evidence in favor of anodal tDCS (MD: 5.23; 95%CI (2.45, 8.01, 16 studies, 514 participants) and reported that anodal tDCS is more effective than cathodal or dual tDCS in improving upper limb motor function after stroke[1]. Our result contradicts the analysis of Elsner et al., including 16 studies with 302 participants, who reported that active tDCS is not effective in improving upper limb motor function after stroke [44]. One reason for the discrepancy between their results and ours might be that the authors included few RCTs and the majority of the participants were treated with cathodal tDCS, therefore, masking the possible effect of anodal tDCS.

According to the stage of stroke, P-score revealed that taVNS and iTBS are most effective in improving upper limb motor function in acute/sub-acute and chronic stroke, respectively. In addition to taVNS and iTBS, excitatory stimulations (Hf-rTMS and anodal tDCS) are also effective in improving upper limb motor function in acute/sub-acute and chronic stroke. Dual tDCS is more effective than anodal tDCS in chronic stroke. The results are in line with previous meta-analysis which reported a large effect size for dual tDCS ((Hedge's g = 1.30, 95% CI = [−0.14,2.75]) as compared to anodal (Hedge's g = 0.21, 95% CI = [−0.72,1.14]) or cathodal tDCS (Hedge's g = 0.43, 95% CI = [−0.23,1.08]) in chronic stroke[149]. The reason for this might be that bi-hemispheric stimulation may cause downregulation of neural activity on the non-lesioned hemisphere and upregulation of neural activity on the lesioned hemisphere by cathodal and anodal stimulation, respectively[37, 149]. The re-balancing of inter-hemispheric competition may promote motor recovery after stroke.

Considering performance in ADLs, NMA revealed that taVNS and anodal tDCS are the best-ranked treatments with almost equal P-score in acute/sub-acute stroke. Our results are in line with previous review assessing the effect of VNS in improving the ADL[140]. Liu et al., reported that VNS is effective in improving upper limb ADLs (MD = 0.36; 95% CI, 0.02-0.70, 2 studies, 118 participants). Our result contradicts with previous analyses conducted by Elsner et al., which suggested a favorable effect of cathodal tDCS for improving upper limb ADLs after stroke (Elsner (2017); SMD: 0.42; 95%CI (0.15-0.69, 12 studies, 284 participants); Elsner (2016); SMD: 0.33; 95%CI (0.10-0.57, 6 studies, 301 participants)) [14, 44]. One reason for the discrepancy between their results and ours might be that the authors included few RCTs and the majority of the participants were treated with cathodal tDCS, therefore, masking the possible effect of anodal tDCS. The sensitivity analysis after removing taVNS and TBS revealed that anodal tDCS is the best-ranked treatment for improving upper limb performance in ADLs in stroke. The reason for this might be that tDCS can modulate

neuronal inhibitory and excitatory networks of the affected and the non-affected hemisphere post-stroke to enhance upper limb motor recovery resulting in improvement of ADL performance [44, 150]. It can also be hypothesized that tDCS might improve gait and balance disorders by modulating motor excitability [151], which leads to improvement in ADL performance. Since there is only a weak association between paresis of one upper limb after stroke and ADL scores [44], one could argue that the improvement in ADL performance maybe not be based on an improvement of the paretic arm itself, but rather on a generalized treatment effect, or on chance. Both low and high frequency were also effective in improving upper limb performance in ADLs in acute/sub-acute stroke. The results are in line with previous analysis which reported that rTMS is more effective in improving upper limb ADLs compared to sham rTMS (MD 5.13 [95% CI, 2.60 to 7.67, 2 studies, 128 participants)[39].

Limitations

There were several limitations to our study that need to be considered. First, this study cannot draw conclusions about the mechanisms underpinning motor recovery of these stimulation modalities because there was methodological and clinical heterogeneity among the included studies regarding the dosage of stimulation, concurrent rehabilitation treatment, level of initial severity, and presence/absence of concomitant aphasia. This may be due to the fact that the optimal stimulation paradigm still has to be established and different methods and treatment duration of rehabilitation may produce some bias. Second, some unpublished and missing data may lead to some bias for the pooled effect. Third, although this NMA suggests that taVNS is the best possible treatment for promoting upper limb motor function and performance in ADLs, an NMA is not adequate to inform treatment and further larger multicenter clinical trials need to be conducted to determine the effect of taVNS on upper limb motor function in stroke. Finally, this NMA could not include all NiBS protocols because no

studies were found investigating the effects of tRNS and tACS on upper extremity motor function and performance in ADLs in stroke patients.

Conclusions

This systematic review with NMA revealed that taVNS is the most effective intervention in improving upper limb motor function and performance in ADLs after acute/sub-acute stroke whereas, iTBS is most effective in improving upper limb motor function in chronic stroke. After taVNS, excitatory stimulation protocols (iTBS, anodal tDCS, and HF-rTMS) are most effective in improving upper limb motor function and performance in ADLs after acute/sub-acute and chronic stroke. The taVNS has the good effect on upper limb stroke rehabilitation, but the taVNS is comparatively new investigational treatment and early-phase positive findings of studies may likely to be biased in favor of pilot interventions. Therefore, giving precise recommendation/conclusion seems difficult. Our NMA analysis provided favorable evidence for taVNS, and further large sample, multi-center clinical trials are needed in future to confirm the relative superiority of taVNS.

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Tables and figures

Table captions

Table 1: League table showing the result of network meta-analysis comparing the effect of all intervention on motor function including standard mean difference (SMD) and 95% CI. Comparisons between treatments should be read from left to right. Their SMD and corresponding 95% CI can be obtained from the cell shared by the column defining treatment and the row defining treatment. The direct estimates are reported in the upper right portion of the table, while the network estimates (indirect and mixed) are shown in lower left portion. Moving along the diagonal line from upper left to bottom right, the green cells contain all possible intervention procedure. Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation. Bold denotes significance.

Table 2: League table showing the result of network meta-analysis comparing the effect of all intervention on performance in activity of daily livings including standard mean difference (SMD) and 95% CI. Comparisons between treatments should be read from left to right. Their SMD and corresponding 95% CI can be obtained from the cell shared by the column defining treatment and the row defining treatment. The direct estimates are reported in the upper right portion of the table, while the network estimates (indirect and mixed) are shown in lower left portion. Moving along the diagonal line from upper left to bottom right, the blue cells contain all possible intervention procedure. Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation. Bold denotes significance.

Figure legends

Figure 1. PRISMA Flow Diagram demonstrating the search process and study selection through the review.

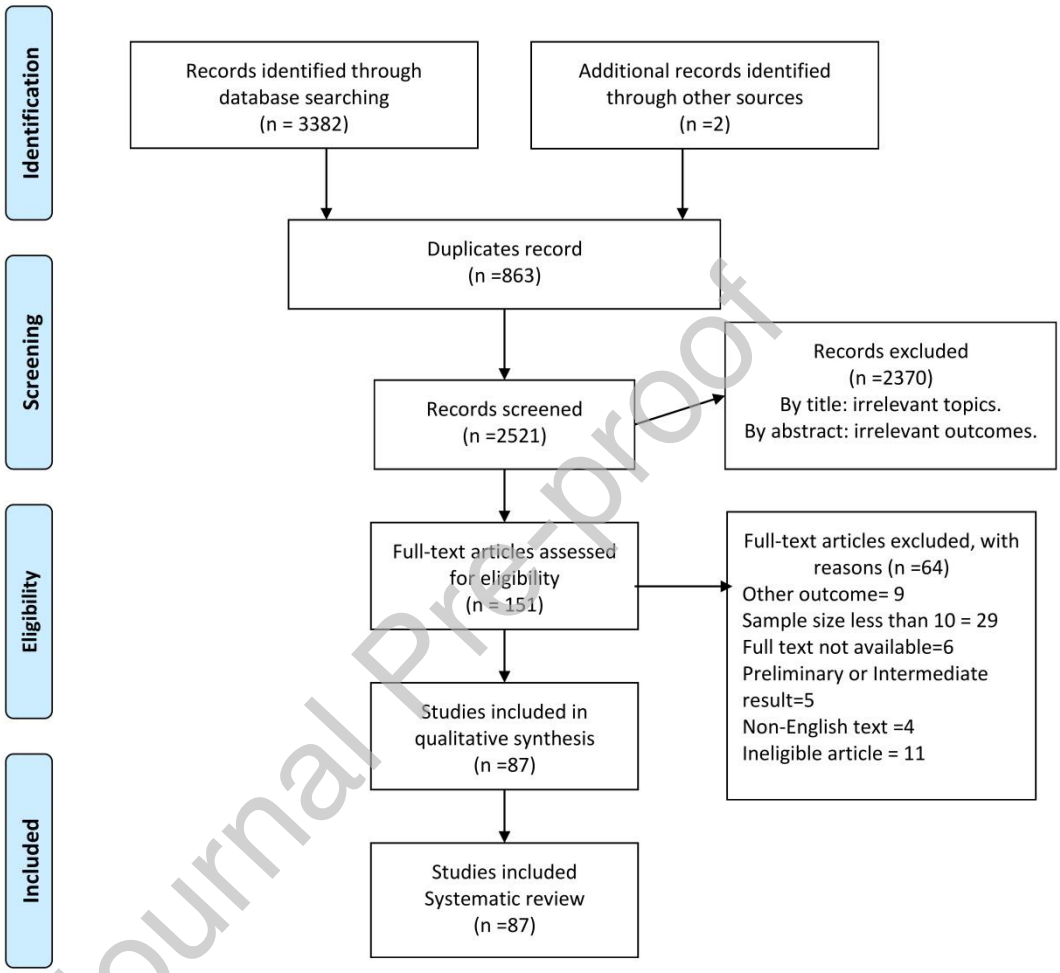

Figure 1: PRISMA flow diagram demonstrating the search process and study selection through the review.

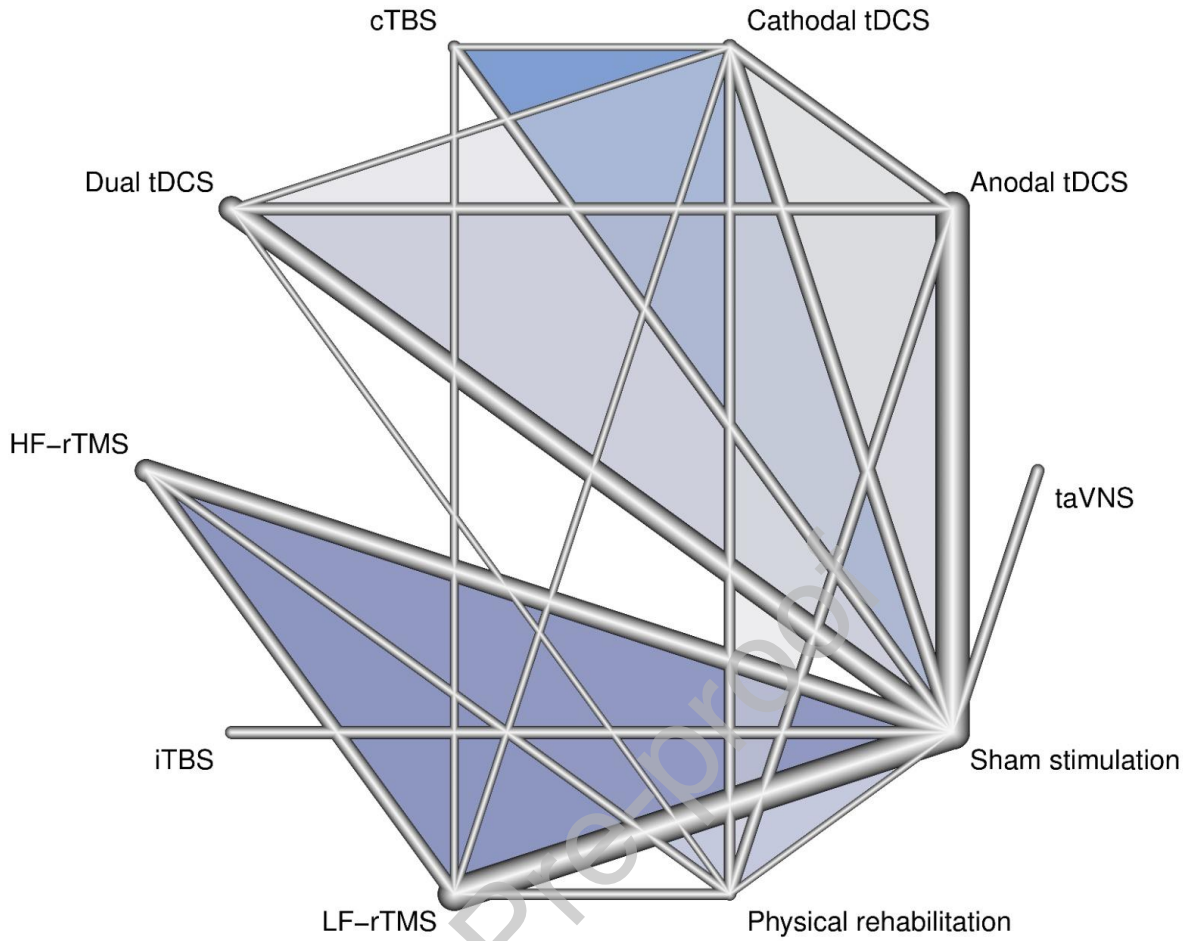

Figure 2: Network graph of NiBS for improving upper limb motor function (FMA-UL) after stroke.

Abbreviations: Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation.

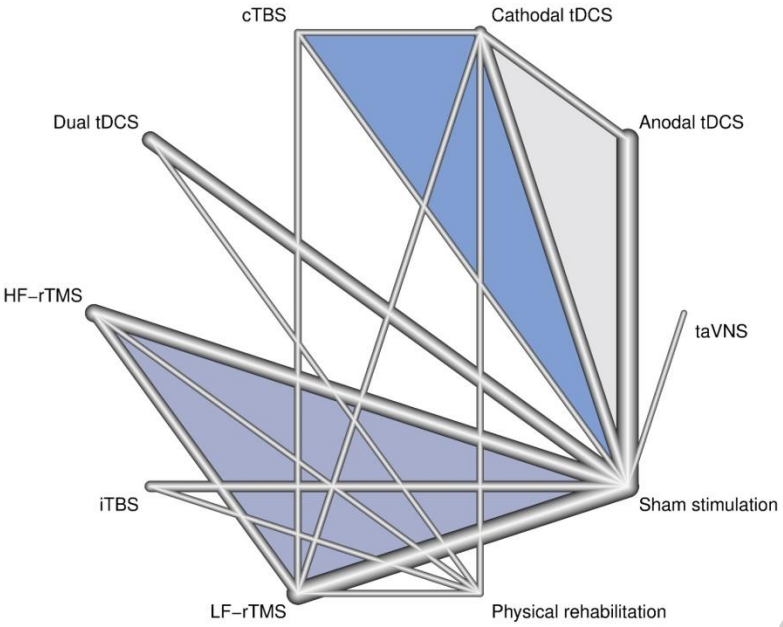

Figure 3: Network graph of NiBS for improving upper limb upper limb performance in activity of daily livings (ADLs) after stroke.

Abbreviations: Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation.

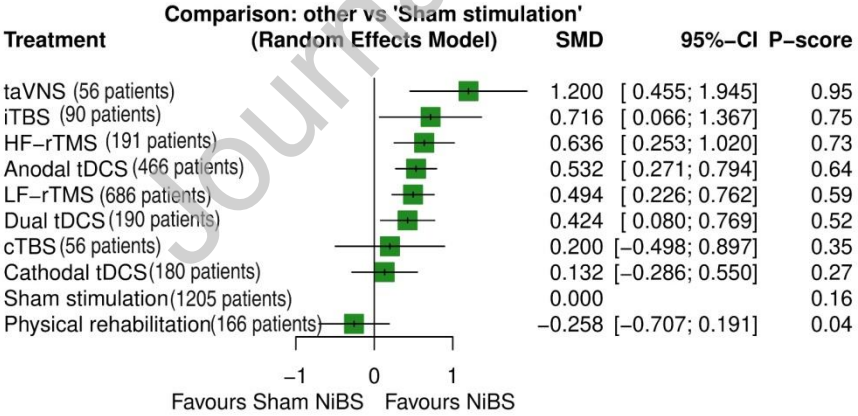

Figure 4: Forest plot of NiBS for improving upper limb motor function (FMA-UL) after stroke. Treatments are listed in order of relative ranking. The P-Score, ranging from 0 to 1, describes the mean degree of certainty about a particular treatment being better than another treatment

Abbreviations: SMD = standardized mean difference, CI = confidence interval. Sham stimulation is the reference treatment.

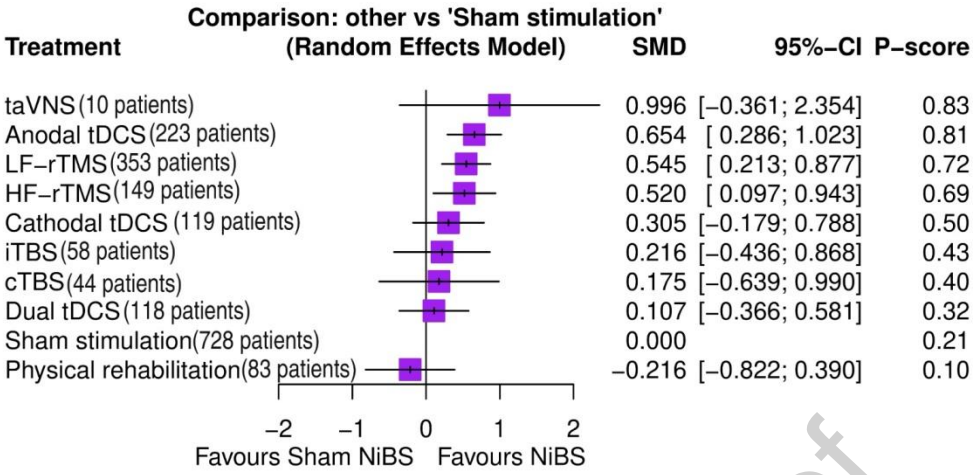

Figure 5: Forest plot of NiBS for improving upper limb limb performance in activity of daily livings (ADLs) after stroke. Treatments are listed in order of relative ranking. The P-Score, ranging from 0 to 1, describes the mean degree of certainty about a particular treatment being better than another treatment

Abbreviations: SMD = standardized mean difference, CI = confidence interval. Sham stimulation is the reference treatment.

taVNS								1.20 (0.46 - 1.95)	
0.48 (-0.51 - 1.47)	**iTBS**							0.72 (0.07 - 1.37)	
0.56 (-0.27 - 1.40)	0.08 (-0.68 - 0.84)	**HF-rTMS**		0.01 (-0.62 - 0.64)				0.75 (0.32 - 1.17)	0.84 (-0.10 - 1.79)
0.67 (-0.12 - 1.46)	0.18 (-0.52 - 0.89)	0.10 (-0.35 - 0.56)	**Anodal tDCS**		0.12 (-0.61 - 0.85)		0.12 (-0.55 - 0.79)	0.50 (0.21 - 0.78)	1.03 (0.26 - 1.79)
0.71 (-0.09 - 1.50)	0.22 (-0.48 - 0.93)	0.14 (-0.28 - 0.56)	0.04 (-0.33 - 0.40)	**LF-rTMS**		0.17 (-0.99 - 1.33)	-0.08 (-1.26 - 1.10)	0.51 (0.22 - 0.81)	0.96 (0.08 - 1.83)
0.78 (-0.04 - 1.60)	0.29 (-0.44 - 1.03)	0.21 (-0.30 - 0.72)	0.11 (-0.29 - 0.51)	0.07 (-0.36 - 0.50)	**Dual tDCS**		0.06 (-1.16 - 1.28)	0.42 (0.04 - 0.80)	0.60 (-0.79 - 1.99)
1.00 (-0.02 - 2.02)	0.52 (-0.44 - 1.47)	0.44 (-0.35 - 1.22)	0.33 (-0.40 - 1.07)	0.29 (-0.41 - 1.00)	0.22 (-0.55 - 1.00)	**cTBS**	0.12 (-1.16 - 1.40)	0.13 (-0.79 - 1.05)	
1.07 (0.21 - 1.92)	0.58 (-0.19 - 1.36)	0.50 (-0.05 - 1.05)	0.40 (-0.05 - 0.85)	0.36 (-0.10 - 0.83)	0.29 (-0.22 - 0.81)	0.07 (-0.70 - 0.83)	**Cathodal tDCS**	-0.05 (-0.67 - 0.56)	0.07 (-0.77 - 0.92)
1.20 (0.46 - 1.95)	**0.72 (0.07 - 1.37)**	**0.64 (0.25 - 1.02)**	**0.53 (0.27 - 0.79)**	**0.49 (0.23 - 0.76)**	**0.42 (0.08 - 0.77)**	0.20 (-0.50 - 0.90)	0.13 (-0.29 - 0.55)	**Sham stimulation**	-0.88 (-2.23 - 0.46)
1.46 (0.59 - 2.33)	**0.97 (0.18 - 1.76)**	**0.89 (0.36 - 1.43)**	**0.79 (0.32 - 1.26)**	**0.75 (0.28 - 1.23)**	**0.68 (0.15 - 1.22)**	0.46 (-0.35 - 1.27)	0.39 (-0.14 - 0.92)	0.26 (-0.19 - 0.71)	**Physical rehabilitation**

Table 1: League table showing the result of network meta-analysis comparing the effect of all intervention on motor function including standard mean difference (SMD) and 95% CI. Comparisons between treatments should be read from left to right. Their SMD and corresponding 95% CI can be obtained from the cell shared by the column defining treatment and the row defining treatment. The direct estimates are reported in the upper right portion of the table, while the network estimates (indirect and mixed) are shown in lower left portion. Moving along the diagonal line from upper left to bottom right, the green cells contain all possible intervention procedure. Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation. Bold denotes significance.

taVNS	.							1.00 (-0.36 - 2.35)	
0.34 (-1.07 - 1.75)	**Anodal tDCS**			-0.14 (-0.98 - 0.70)				0.69 (0.31 - 1.06)	
0.45 (-0.95 - 1.85)	0.11 (-0.38 - 0.60)	**LF-rTMS**	-0.12 (-0.83 - 0.59)	-0.27 (-1.43 - 0.88)		0.34 (-0.79 - 1.48)		0.59 (0.23 - 0.96)	1.05 (-0.16 - 2.26)
0.48 (-0.95 - 1.90)	0.13 (-0.42 - 0.69)	0.02 (-0.46 - 0.51)	**HF-rTMS**					0.58 (0.12 - 1.05)	0.05 (-1.22 - 1.33)
0.69 (-0.75 - 2.13)	0.35 (-0.21 - 0.91)	0.24 (-0.29 - 0.78)	0.22 (-0.41 - 0.84)	**Cathodal tDCS**		0.17 (-1.08 - 1.43)		0.05 (-0.56 - 0.66)	0.28 (-0.91 - 1.46)
0.78 (-0.73 - 2.29)	0.44 (-0.31 - 1.18)	0.33 (-0.39 - 1.05)	0.30 (-0.46 - 1.06)	0.09 (-0.70 - 0.88)	**iTBS**			0.07 (-0.67 - 0.82)	0.80 (-0.40 - 2.00)
0.82 (-0.76 - 2.40)	0.48 (-0.40 - 1.36)	0.37 (-0.44 - 1.18)	0.34 (-0.55 - 1.24)	0.13 (-0.73 - 0.99)	0.04 (-0.99 - 1.07)	**cTBS**		0.17 (-1.09 - 1.43)	
0.89 (-0.55 - 2.33)	0.55 (-0.05 - 1.15)	0.44 (-0.13 - 1.01)	0.41 (-0.21 - 1.04)	0.20 (-0.47 - 0.86)	0.11 (-0.68 - 0.90)	0.07 (-0.87 - 1.01)	**Dual tDCS**	0.07 (-0.42 - 0.57)	0.57 (-0.78 - 1.92)
1.00 (-0.36 - 2.35)	**0.65 (0.29 - 1.02)**	**0.55 (0.21 - 0.88)**	**0.52 (0.10 - 0.94)**	0.30 (-0.18 - 0.79)	0.22 (-0.44 - 0.87)	0.18 (-0.64 - 0.99)	0.11 (-0.37 - 0.58)	**Sham stimulation**	
1.21 (-0.27 - 2.70)	**0.87 (0.17 - 1.57)**	**0.76 (0.13 - 1.39)**	**0.74 (0.06 - 1.41)**	0.52 (-0.17 - 1.21)	0.43 (-0.34 - 1.20)	0.39 (-0.59 - 1.37)	0.32 (-0.39 - 1.03)	0.22 (-0.39 - 0.82)	**Physical rehabilitation**

Table 2: League table showing the result of network meta-analysis comparing the effect of all intervention on performance in activity of daily livings including standard mean difference (SMD) and 95% CI. Comparisons between treatments should be read from left to right. Their SMD and corresponding 95% CI can be obtained from the cell shared by the column defining treatment and the row defining treatment. The direct estimates are reported in the upper right portion of the table, while the network estimates (indirect and mixed) are shown in lower left portion. Moving along the diagonal line from upper left to bottom right, the blue cells contain all possible intervention procedure. Anodal, Cathodal and Dual tDCS. tDCS: transcranial Direct Current Stimulation; taVNS: transcutaneous Vagus Nerve Stimulation; HF-rTMS: High Frequency repetitive Transcranial Magnetic Stimulation; LF-rTMS: Low Frequency repetitive Transcranial Magnetic Stimulation; iTBS: intermittent Theta Burst Stimulation; cTBS: continuous Theta Burst Stimulation. Bold denotes significance.

Appendix 1

Search Strategy

The search of the databases was done by using the terms as follows:

(1) “Stroke” [Mesh][tiab]

(2) “Stroke” [tiab]

(3) “Cerebrovascular Accident” [tiab]

(4) “Brain Ischemia” [MESH][tiab]

(5) or/1–4

(6) “Transcutaneous Vagus Nerve Stimulation” [tiab]

(7) “Transcutaneous Auricular Vagus Nerve Stimulation” [tiab]

(8) “Non-invasive Vagus Nerve Stimulation” [tiab]

(9) “Non-invasive Cervical Vagus Nerve Stimulation” [tiab]

(10) “Transcranial Direct Current Stimulation” [MESH] [tiab]

(11) “Transcranial Magnetic Stimulation” [MESH] [tiab]

(12) “repetitive Transcranial Magnetic Stimulation” [MESH] [tiab]

(13) “Theta Burst Stimulation” [MESH] [tiab]

(14) “Transcranial Random Noise Stimulation” [MESH] [tiab]

(15) “Transcranial Alternating Current Stimulation” [MESH] [tiab]

(16) “Vagus Nerve Stimulation” [MESH] [tiab]

(17) “Non-invasive brain stimulation” [tiab]

(18) “Non-surgical brain stimulation” [tiab]

(19) or/6–18

(20) “upper extremity” [tiab]

(21) “upper limb” [tiab]

(22) or/20-21

(23) randomized controlled trial [pt]

(24) controlled clinical trial [pt]

(25) randomized controlled trials [mh]

(26) random allocation [mh]

(27) double-blind method [mh]

(28) single-blind method [mh]

(29) clinical trial [pt]

(30) clinical trials [mh]

(31) “clinical trial” [tw]

(32) or/23–32

(33) 5,19 and 22.