Stroke

CLINICAL AND POPULATION SCIENCES

Network Meta-Analysis of Non-Conventional Therapies for Improving Upper Limb Motor Impairment Poststroke

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BACKGROUND: Network meta-analysis is a method that can estimate relative efficacy between treatments that may not have been compared directly within the literature. The purpose of this study is to present a network meta-analysis of non-conventional interventions to improve upper extremity motor impairment after stroke.

METHODS: A literature search was conducted in 5 databases from their inception until April 1, 2021. Terms were used to narrow down articles related to stroke, the upper extremity, and interventional therapies. Randomized controlled trials written in English were eligible if; 50% poststroke patients; ≥18 years old; applied an intervention for the upper extremity, and/or used the Fugl-Meyer upper extremity scale as an outcome measure; the intervention had ≥3 randomized controlled trials with comparisons against a conventional care group; conventional care groups were dose matched for therapy time. A Bayesian network meta-analysis approach was taken to estimate mean difference (MD) and 95% CI.

RESULTS: One hundred seventy-six randomized controlled trials containing 6781 participants examining 20 non-conventional interventions were identified for inclusion within the final model. Eight of the identified interventions proved significantly better than conventional care, with modified constraint induced movement therapy (MD, 6.7 [95% CI, 4.3–8.9]), high frequency repetitive transcranial magnetic stimulation (MD, 5.4 [95% CI, 1.9–8.9]), mental imagery (MD, 5.4 [95% CI, 1.8–8.9]), bilateral arm training (MD, 5.2 [95% CI, 2.2–8.1]), and intermittent theta-burst stimulation (MD, 5.1 [95% CI, 0.62–9.5]) occupying the top 5 spots according to the surface under the cumulative ranking curve.

CONCLUSIONS: Overall, it would seem that modified constraint induced movement therapy has the greatest probability of being the most effective intervention, with high-frequency repetitive transcranial magnetic stimulation, mental imagery, and bilateral arm training all having similar probabilities of occupying the next spot in the rankings. We think this analysis can provide a guide for where future resources and clinical trials should be directed, and where a clinician may begin when considering alternative therapeutic interventions.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arm ■ motor impairment ■ network meta-analysis ■ transcranial magnetic stimulation ■ upper extremity

As it is currently understood, motor impairment after stroke and the subsequent neurological recovery is a distinct, independent process from functional gains that can be made through behavioral compensation and motor-relearning during rehabilitation.[1] Restitution of impairment is thought to be mainly attributed to a neurophysiological process of spontaneous neurobiological recovery that begins directly after neural insult.[2,3]

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Nonstandard Abbreviations and Acronyms

BAT	bilateral arm training
EMG-NMES	electromyography-triggered neuromuscular electrical stimulation
FMUE	Fugl-Meyer Upper Extremity Scale
HF-RTMS	high-frequency repetitive transcranial magnetic stimulation
MCID	minimal clinically important difference
mCIMT	modified constraint induced movement therapy
MD	mean difference
NMA	network meta-analysis
UE	upper extremity

Rehabilitation shortly after stroke is believed to enhance functional recovery by taking advantage of the increased neural plasticity after injury to learn new motor patterns or compensation techniques.[2,4] This initial period after injury is when stroke survivors see the greatest gains in motor function; the majority of functional gains (as well as neurological improvement) occur within the first 3 months after stroke[5,6] and essentially plateau by 6 months.[2,4,7] It has been argued that rehabilitative intervention may not contribute, or have limited contribution, to this spontaneous restitution of the underlying impairment.[1–3,6] Great efforts have been made over the past few decades to deliver early,[8,9] intensive,[3,10–12] and task-specific training[13] on dedicated stroke units as part of standard care to ensure that patients are able to maximize the therapeutic benefit of rehabilitation interventions, primarily by enhancing functional recovery.[5] Although many individuals participate in stroke rehabilitation, roughly 36% of survivors continue to have significant upper limb disabilities 5-year poststroke,[14] and >40% of individuals require some form of assistance with activities of daily living.[15]

While clinically there has been a greater emphasis on delivering standardized care, at the same time, there has been an unprecedented expansion of research into studying the efficacy of non-conventional therapies, which are traditionally not part of standard care regimes, and their role in furthering recovery poststroke. Nowhere is this more apparent than in therapeutic interventions designed to improve functional motor recovery of the upper extremity (UE), with 1307 randomized controlled trials (RCTs) investigating over 50 different non-conventional UE rehabilitation interventions poststroke published up until April 1, 2021.[16] While the evidence-base for individual therapies targeting recovery from UE hemiparesis after stroke is impressive, there is limited information on how these treatments compare in efficacy. Given the wide range of treatment options available for the hemiplegic UE, it has become difficult for clinicians and most researchers to be adequately informed and/or able to compare them all.

Network meta-analysis (NMA) is a relatively new statistical technique, which aims to compare the efficacy of a number of different interventions against one another to synthesize the results in a single analysis, for what would otherwise require a number of traditional pair-wise comparisons. Importantly, NMA uses both direct evidence provided within trials and indirect evidence estimated via common comparisons between the network of trials, to produce rankings for the most effective interventions. There are a number of standard meta-analysis for UE motor interventions in stroke rehabilitation that have been published to date,[17] but few NMA have been performed.[18–21] Further, those NMA that have been published focus on different applications or modifications on a single category of intervention and do not make relative effect estimates between different interventions used in motor rehabilitation.[18–21] These analyses are valuable when evaluating the most effective application of a therapy, but do not aid in evaluating which therapy should be applied. Therefore, in both primary (RCTs) and secondary (reviews and meta-analysis) research, there is limited evidence on the best therapeutic intervention for improving motor impairment poststroke.

An analysis of multiple interventions can provide a guide for where future resources and clinical trials should be directed and offer insight to clinicians looking to integrate alternative therapeutic interventions into practice. Therefore, the objective of this study was to perform a systematic review incorporating a NMA of all eligible interventions for UE impairment poststroke in an attempt to clarify which intervention is the most effective, based on published data. To specifically examine impairment, the Fugl-Meyer Upper Extremity Scale (FMUE) was chosen for this analysis as it is the most well-regarded measure for assessing neurological recovery at the level of impairment.[22] It was hypothesized that some non-conventional interventions would significantly improve motor impairment when compared with usual or conventional care, and some interventions would demonstrate a greater magnitude of improvement relative to others.

METHODS

This NMA was reported in adherence with the Preferred Reporting Items for Systematic reviews and Meta Analyses extension statement for NMA.[23] A protocol was registered with Open Science Framework (10.17605/OSF.IO/YFKAU). The data that support the findings of this study are available from the corresponding author upon reasonable request. To identify the studies required for inclusion in the NMA, a systematic search of the literature was conducted.

Literature Search Strategy and Eligibility Criteria

A literature search was performed in 5 scientific databases: PubMed, Scopus, Web of Science, Embase and CINAHL from database inception to April 1, 2021. The following search string was used: (Stroke OR Cerebrovascular Accident OR CVA) AND (upper extremity OR upper limb OR arm OR hand OR shoulder) AND (Remediation OR Therapy OR Intervention OR Stimulation OR Exercise OR Pharmaco* OR Medications OR Drug OR Pharmaceutical). For PubMed, Embase, and CINAHL a randomized controlled trial filter was applied. For Scopus and Web of Science, the search string was modified to include: AND randomized controlled trial. Databases were additionally filtered for English and Human where available. The Evidence Based Review of Stroke Rehabilitation was cross-referenced to ensure no articles were missed in the original search (www.ebrsr.com). Inclusion criteria for article selection were (1) RCTs, or randomized crossover trials published in English; (2) patients were ≥18 years old; (3) ≥50% of study subjects were individuals who had previously experienced a stroke; (4) the study used the primary outcome measure (FMUE) to assess UE impairment across time points; and (5) therapy dosage was time matched for intervention groups and control groups.

All possible interventions used for the remediation of UE impairment were eligible for inclusion. Interventions were specifically included in the model if there were at least 3 unique RCTs where the intervention was compared with conventional therapy. This was to ensure a more valid and robust estimate for each intervention node. Conventional therapy is a heterogenous term and often poorly described in published RCTs.[24,25] For this review, conventional therapy was defined as any intervention described by the study as usual care, standard rehabilitation, occupational therapy, physiotherapy, sham, or placebo. Descriptors such as task-specific training, range of motion exercises, Bobath training, or proprioceptive neuromuscular facilitation were also considered conventional care. Additionally, RCTs that directly compared eligible interventions head-to-head were included for the formation of direct evidence loops within the network.

Reasons for exclusion were (1) a secondary analysis or long-term follow-up of an original trial that did not present new or unique data; (2) the intervention was performed during one session only; (3) <2 subjects were analyzed in any trial arm; and (4) Fugl-Meyer data was not reported in an extractable format appropriate for NMA; studies, which only reported partial subscale scores or combined upper/lower scores were excluded.

Outcome Measure of Interest

The outcome measure of interest was the FMUE. The FMUE assesses shoulder, elbow, forearm, wrist, finger, and reflexive movements to measure impairment from proximal to distal, and synergistic to isolated voluntary movement.[26] It is comprised of 33 items, each scored on a 3-point ordinal scale (0=cannot perform, 1=performs partially, 2=performs fully) and has a total score of 66 points; higher scores are indicative of better performance.[22] The FMUE demonstrates excellent intra- and interrater reliability at >79% and 90% to 100% percent agreement, respectively.[27] The FMUE also demonstrates moderate to strong concurrent validities with the Jebsen-Taylor Hand Function test, grip power test, and modified Ashworth scale.[28] At 5 days poststroke, the total motor Fugl-Meyer has been shown to be a strong predictor of motor recovery at 6 months.[29] The total motor Fugl-Meyer can also effectively distinguish between levels of self-care in acute stroke survivors.[29] Due to its strong test-retest ability, construct validity, and pervasiveness in literature, the FMUE was selected as the outcome measure for the NMA. To interpret the clinical significance of each intervention, estimated mean differences (MDs) for each intervention were compared with the FMUE's lower published minimal clinically important difference (MCID) of 4.25 to 7.25,[30] and higher published MCID of 9 to 10.[31]

Article Screening and Data Extraction

Covidence software was used to manage all aspects of screening, review, and extraction (www.covidence.org). Articles identified from the literature search were imported into Covidence, and duplicates were automatically removed. Two independent reviewers screened each article based on title and abstract and subsequently performed full-text review. Any conflicts during the screening phases were resolved by a third independent reviewer. Data extraction was also performed by 2 independent reviewers using a pre-determined template created in Covidence. Data extraction included study characteristics (author, year, title), patient demographics (number of participants at start and finish, age, sex, stroke type, affected side of body, time poststroke), details of the intervention and control protocols, and Fugl-Meyer outcome measure data. Point measures and variability estimates for outcome data were taken at baseline, and either post-intervention and/or the change from baseline scores. Where available, intention-to-treat data was taken over pre-protocol analyses, and change scores from baseline were selected over pre- and postintervention scores. MDs were calculated when necessary, according to the formula provided by the Cochrane Handbook V6.2.[32] Point measures and variability estimates were converted into means and SDs, where possible, with the formulae set given by Wan et al.[33] Methodological quality and risk of bias for each individual randomized controlled trial was assessed using the Physiotherapy Evidence Database scale based on details reported and published within the study.[34] One reviewer scored each of the articles that were not already scored and present online in the Physiotherapy Evidence Database database (https://search.pedro.org.au/advanced-search). Specifically, we focused on items 3 (concealed allocation), 7 (blind assessor), 8 (study attrition), and 9 (intention-to-treat analysis). These were chosen as the most relevant methodological quality indicators and are applicable to all interventions.[16] Risk of bias appraisals were summarized on an item-by-item basis. All data processing and formatting was performed with Python Version 3.6 in combination with Microsoft Excel for preparation to perform NMA in R version 4.0.3 (R Core Team) using the gemtc and netmeta packages.

Statistical Analysis and Network Model Generation

A Bayesian inference random effects approach was chosen to create the NMA model, using the Markov chain Monte Carlo method. There were 4 chains fitted, that had a burn-in phase of 5000 iterations with a simulation of 100 000 iterations. FMUE scores were treated as continuous and are presented as mean difference (MD) and 95% CIs. The treatment ranking probabilities were calculated using the surface under the cumulative ranking curve. This provides a ranked list based on which interventions have the highest probability of being the most effective.

Clinical heterogeneity was assessed and discussed by all members of the review team. Intervention protocols within each node were compared to ensure there was sufficient homogeneity. Any protocols that were deemed too clinically distinct from the rest were removed from the node. Conventional care protocols were also reviewed to ensure they did not contain any of the other intervention's being compared. Consistency was statistically assessed globally through the I^2 statistic under the assumption of a full design-by-treatment interaction random effects model. A random effects model has been chosen a priori as the more appropriate option for this patient population and evidence base, as it will better account for between trial heterogeneity.[32] Consistency was also assessed locally with a node splitting analysis to assess discrepancies between direct evidence and estimated indirect evidence. In addition, Egger's test with a comparison adjusted funnel plot was used to test for small-study effects. Network meta-regression was performed to investigate possible effect modifiers such as patient demographics (ie, age, sex, stroke type, affected hemisphere, time poststroke and baseline FMUE) and protocol characteristics (ie, intensity, follow-up length) under a shared interaction model. Guidance on statistical programming and analysis methods for this review closely followed the tutorial provided by Harrer et al[35] for using R to perform NMA, as well the Cochrane Handbook.[32]

RESULTS

Study Characteristics and Network Geometry

In total, 176 RCTs met the inclusion criteria and were included in the final analysis (Figure 1). Table S1 provides a description of the included intervention nodes and outlines important protocol details used to ensure homogenous protocols within unique nodes. Table S1 also displays the number of trial arms contained within each node and the total number of patients included in each intervention node. The network contained 13 multi-arm trials. One trial[36] had 2 randomization procedures based on baseline severity and was split into 2 separate studies for the purpose of the analysis. The geometry of the network is displayed graphically in Figure 2. The width of the line corresponds to the number of RCTs for that comparison. Shaded blue areas represent multi-arm trials that link 3 or more nodes together. The data extracted for all trials is outlined in Table S2, and references for the articles are also found in the supplementary material. Summary statistics for the covariate distributions by intervention node are displayed in Figure 3A through 3F (excluding age and ratio of males, which were similar across all groups).

Risk of Bias

A breakdown of the adherence to Physiotherapy Evidence Database scale items for each study is provided in Table S3 and summarized in Figure S1A and S1B. Overall, 39% of RCTs reported concealed allocation, 61% of RCTs reported blinding of the outcome assessor, 77% of RCTs reported a study attrition of < 15%, and 45% of RCTs reported the use of an intention-to-treat analysis. Among all RCTs, 6% reported none of these items, 20% reported only one, 30% reported 2, 33% reported 3, and 11% reported all 4 items. Egger's Test revealed a significant small-sample bias effect (P=0.0014), as shown in the comparison adjusted funnel plot (Figure S2).

Assessing Inconsistency, Heterogeneity, and Model Fit

With all nodes included in the model, node splitting analysis of direct versus indirect evidence indicated a significant inconsistency between the robotic bilateral am end effector group and conventional care comparison (P<0.05), as well between the robotic bilateral arm end effector group and electromyography-triggered neuromuscular electrical stimulation (EMG-NMES; P<0.05; Figure S3). The I^2 statistic was equal to 0%, and deviance information criterion value was equal to 642.12. There was no obvious determinant from any individual study responsible for this inconsistency; thus, it was decided to remove robotic bilateral arm training (BAT). The revised model was re-tested for inconsistency and none remained afterward (Figure S4). After node-removal, 169 RCTs remained, the I^2 statistic was equal to 0%, and deviance information criterion value was equal to 614.23, implying no detectable heterogeneity in the estimated effect sizes.

Network-Meta Regression

Regression models were run to test for any influence of covariates of the estimated MDs. Each covariate described in the methods was run in an independent regression model. All of these variables were found not to have a significant influence as determined by the 95% CIs: sex (RCTs n=160, Beta=−1.08 [95% CI, −2.54 to 0.40]); proportion of left hemisphere strokes (RCTs n=149, Beta=0.52 [95% CI, −0.96 to 2.00]); proportion of ischemic strokes (RCTs n=124, Beta=0.51 [95% CI, −1.39 to 2.45]), and the proportion of hemorrhagic strokes (RCTs n=123, Beta=−0.85 [95% CI, −2.85 to 1.135]; both the ischemic and hemorrhagic models did not contain the mental imagery node, as there were insufficient trials in this node which reported stroke type); age of participants (RCTs n=161, Beta=−0.18 [95% CI, −1.73 to 1.40]); days poststroke (RCTs n=144, Beta=−1.03 [95% CI, −2.51 to 0.46]); baseline FMUE score (RCTs n=166, Beta=−1.40 [95% CI, −3.00 to 0.25]); the total number of intervention sessions (RCTs n=158, Beta=−0.55 [95% CI, −2.77 to 1.70]).

Treatment Rankings and Relative Effectiveness

The relative effectiveness of each intervention comparison is reported in Table S4. Significant results as

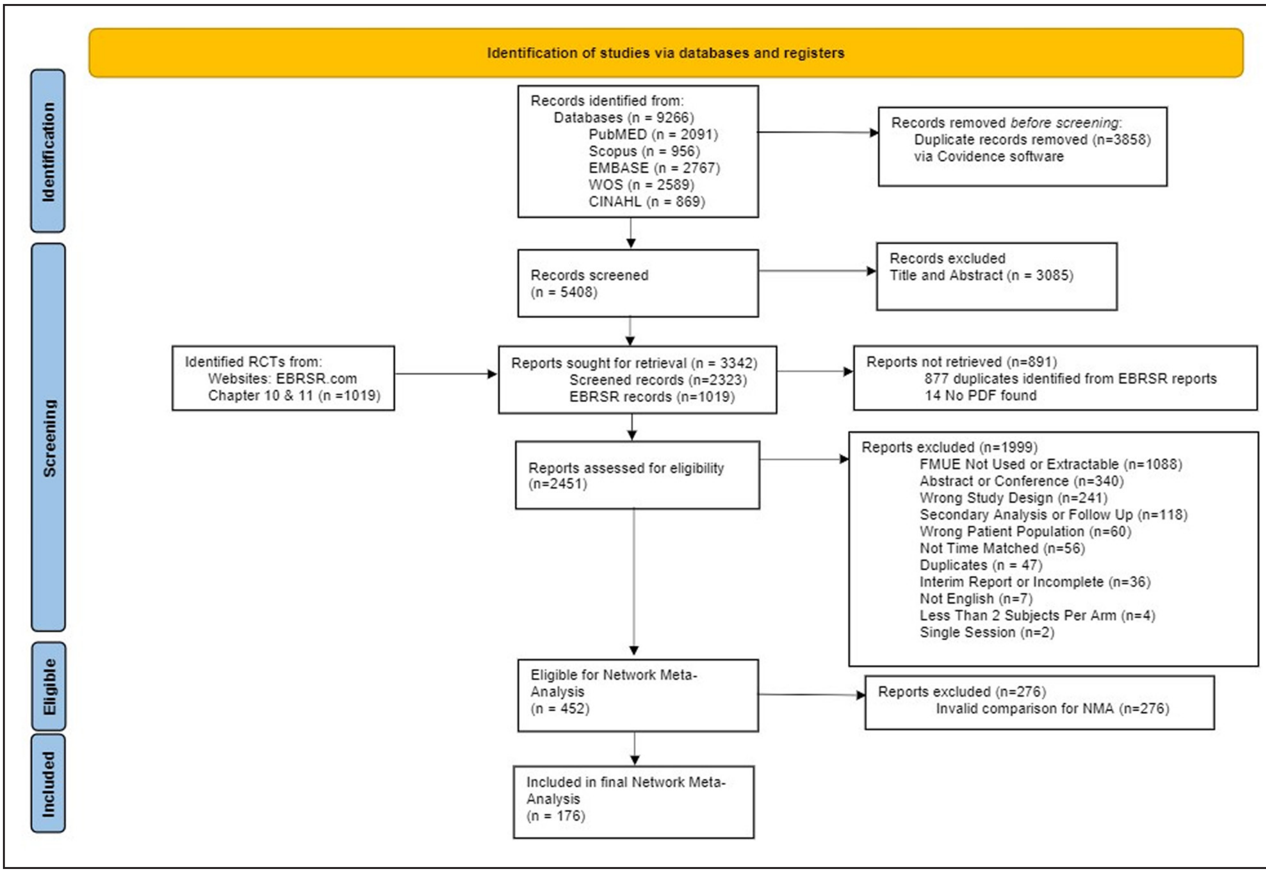

Figure 1. PRISMA flow diagram.
FMUE indicates Fugl-Meyer Upper Extremity Scale.

determined by the 95% CI are bolded. Figure 4 displays a forest plot of estimated MD and 95% CI between each node and the conventional care node. The full rankogram plot can be found in the Figure S5. Figure 5 shows the surface under the cumulative ranking plot for all adjunct interventions.

To summarize, just over half (11/20) of all interventions were found to be significantly more effective than conventional care. These were modified constraint induced movement therapy (mCIMT; 6.7 [4.3–8.9]), high frequency repetitive transcranial magnetic stimulation (HF-rTMS; 5.4 [1.9–8.9]), mental imagery (5.4 [1.8–8.9]), BAT (5.2 [2.2–8.1]), intermittent theta-burst stimulation (5.1 [0.62–9.5]), cathodal transcranial direct current stimulation (4.8 [1.1–8.4]), action observation (4.0 [0.76–7.3]), low-frequency repetitive transcranial magnetic stimulation (3.5 [1.6–5.5]), mirror therapy (3.2 [1.2–5.2]), neuromuscular electrical stimulation (4.4 [0.82–7.9]), and custom virtual reality (2.9 [1.0–4.6]). The majority of comparisons between non-conventional intervention nodes found no statistically significant difference between intervention efficacies. However, 12 of 190 non-conventional comparisons did produce a significant difference, with mCIMT showing a greater MD than 8 other interventions, with the others favoring; mental imagery over arm exoskeleton robotics, BAT over arm exoskeleton and unilateral arm end-effector robotics, and HF-rTMS over arm exoskeleton robotics. As demonstrated by Figure 4, mCIMT had the highest probability of occupying the first ranked intervention, indicating it to be potentially the most effective intervention when compared with conventional care for improving the FMUE measure. HF-RTMS, mental imagery, and BAT all have a similar surface under the cumulative ranking curve value occupying the next 3 ranks. However, these interventions all had highly overlapping confidence intervals as compared with conventional care.

DISCUSSION

Summary of Findings

The NMA found that 11 non-conventional interventions were significantly more effective than conventional care (mCIMT, HF-rTMS, mental imagery, BAT, intermittent theta-burst stimulation, cathodal transcranial direct current stimulation, EMG-NMES, action observation, low-frequency repetitive transcranial magnetic stimulation, mirror therapy, and neuromuscular electrical stimulation) as measured by the FMUE outcome. Of these 11 therapies, 6 therapies (mCIMT, HF-rTMS, mental imagery, BAT, intermittent theta-burst stimulation, cathodal transcranial

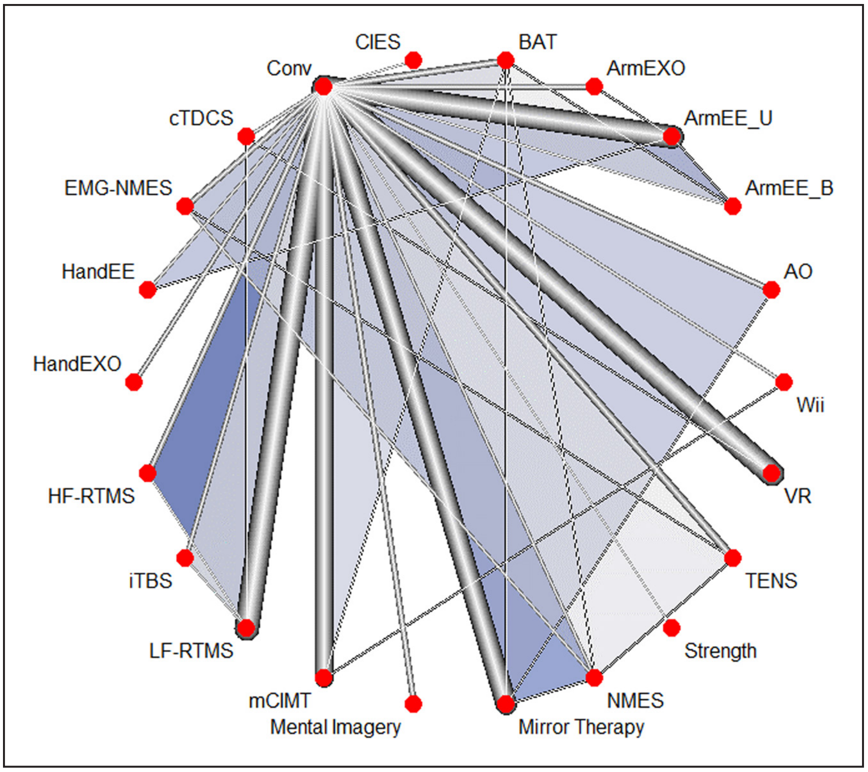

Figure 2. Network graph.
Thicker lines indicate more trials per comparison, and shaded blue triangles indicate connections formed through multi-arm trials. AO indicates action observation; ArmEE_B, bilateral arm end-effector robotics; ArmEE_U, unilateral arm end-effector robotics; ArmEXO, arm exoskeleton robotics; BAT, bilateral arm training.; CIES, cortically implanted electrical stimulation; Conv, conventional therapy; c-TDCS, cathodal transcranial direct current stimulation; EMG-NMES, electromyographically triggered NMES; HandEE, hand end-effector robotics; HandEXO, hand exoskeleton robotics; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; mCIMT, modified constraint induced movement therapy; NMES, neuromuscular electrical stimulation; Strength, strength training; TENS, transcutaneous electrical nerve stimulation; VR, custom virtual reality training; and Wii, Nintendo Wii training.

direct current stimulation, EMG-NMES) were found to produce gains within the lower FMUE MCID (4.25–7.25),[30] with some upper CIs reaching the higher reported MCID (9–10).[31] For comparisons between adjunct (nonconventional) therapies, mCIMT was significantly better than 8 of the other 19 interventions, with a few other instances of significance indicated in the results. Overall, the NMA has shown that, among all interventions considered, mCIMT, HF-rTMS, mental imagery, and BAT seem to be the most effective at improving impairment when compared with conventional care, as measured by the FMUE. It is important to note, however, that the 95% CI for all of the top therapies have considerable overlap. Therefore, the relative difference between the top interventions should be interpreted with caution. The Fugl-Meyer scale has subsequently been shown to correlate well with functional measures such as the Action Research Arm Test.[37,38] Given that 6 interventions had estimated MDs above the lowest reported MCID, the results of this analysis support the assumption that these particular adjunct therapies could make a noticeable difference in the functional capacity of stroke survivors.

Comparison to the Literature

mCIMT

One standard pairwise meta-analysis examining mCIMT versus a traditional rehabilitation group reported a MD of 7.8 on the FMUE,[39] while another analysis combining both CIMT and mCIMT reported a MD of 10.8.[40] These values are both slightly higher than the reported value in our NMA (6.7). This could be due to the increased number of RCTs contained within our mCIMT node as compared with Yue et al (2011; 17 versus 6, respectively), and the fact that CIMT is a more intensive protocol and its inclusion may lead to greater MDs due to increased therapy time.[39,40] This would imply our more conservative estimate of 6.7 may be more reflective of the true effect size for mCIMT specifically.

HF-rTMS

After mCIMT, our NMA found that the second, third, and fourth ranked interventions all had comparable surface under the cumulative ranking curve scores. These were (1) HF-rTMS, (2) mental imagery, and (3) BAT. Although there are several previous standard meta-analyses performed on rTMS, to our knowledge, none have reported the FMUE MD for HF-rTMS specifically.[41–43] One meta-analysis reported a standardized MD including the FMUE that was of moderate effect (0.762); similar to our NMA, He et al[41] reported HF-rTMS to be more effective than low-frequency repetitive transcranial magnetic stimulation. Another meta-analysis did not however find any noticeable difference between LF- and HF-rTMS standardized MDs (0.42–0.45) but included mostly studies that were not included for this analysis based on our inclusion or exclusion criteria, and protocol homogeneity.[43]

Mental Imagery

Regarding mental imagery, published meta-analysis have reported MDs of 3.94[44] and 4.43.[45] This is in

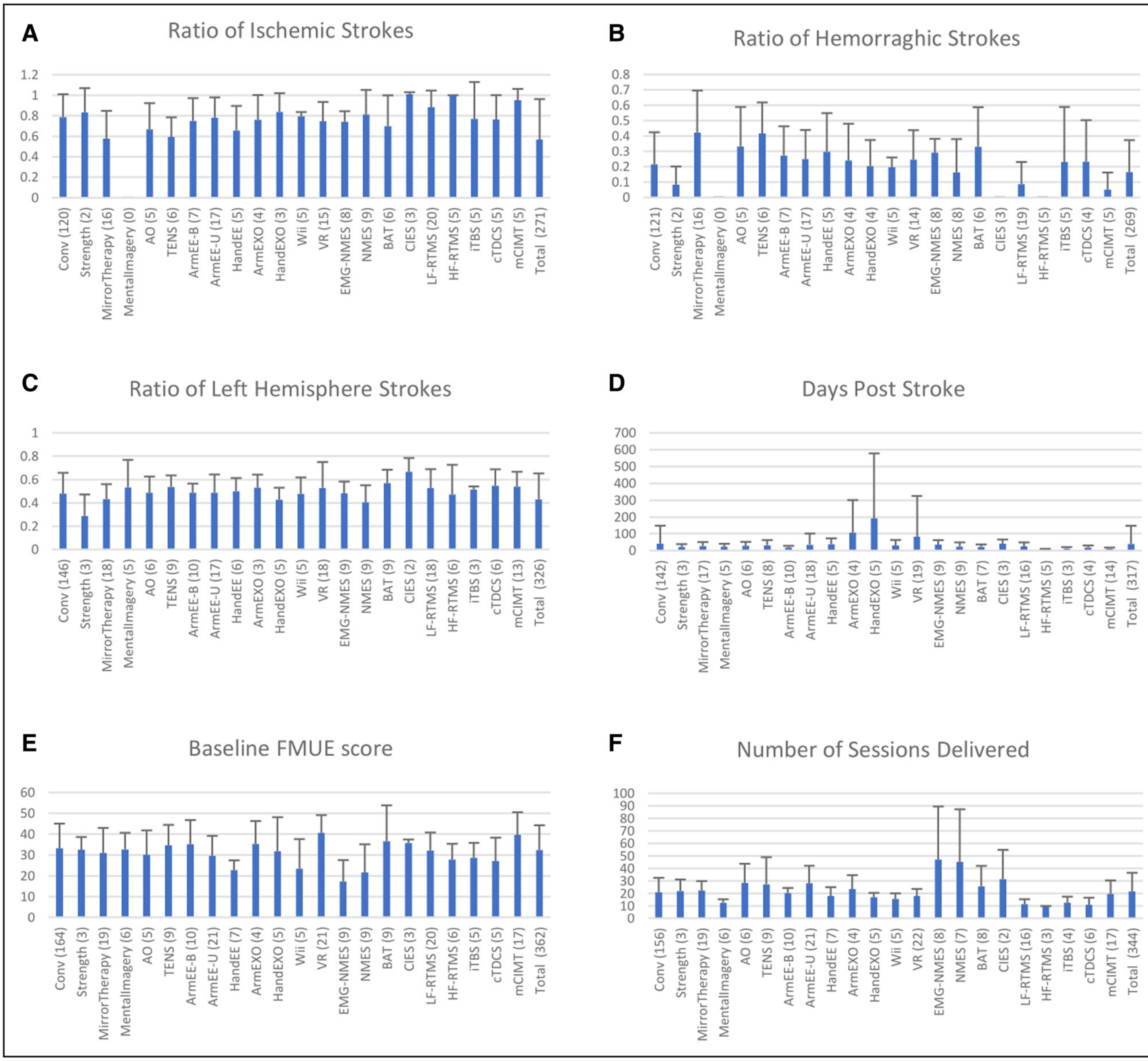

Figure 3. Mean and SD of the trial arms for each intervention node with respect to A, ratio of ischemic strokes; (B) ratio of hemorrhagic strokes; (C) ratio of left hemisphere strokes; (D) time poststroke (days); (E) baseline FMUE score; (F) total number of sessions delivered.

The number of trial arms included in each node are in brackets. AO indicates action observation; ArmEE_B, bilateral arm end-effector robotics; ArmEE_U, unilateral arm end-effector robotics; ArmEXO, arm exoskeleton robotics; BAT, bilateral arm training; CIES, cortically implanted electrical stimulation; Conv, conventional therapy; c-TDCS, cathodal transcranial direct current stimulation; EMG-NMES, electromyographically triggered NMES; HandEE, hand end-effector robotics; HandEXO, hand exoskeleton robotics; HF-rTMS, high frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; mCIMT, modified constraint induced movement therapy; NMES, neuromuscular electrical stimulation; Strength, strength training; TENS, transcutaneous electrical nerve stimulation; VR, custom virtual reality training; and Wii, Nintendo Wii training.

line with our findings and although slightly below our estimated MD of 5.4, all estimates had highly overlapping confidence intervals. Our mental imagery node of 7 RCTs contained many of the same publications as the previously published meta-analyses (5/8 and 4/5 respectively); however; those that differed we had excluded based on non-time matched controls or protocols that involved a combination with another intervention node.

BAT

BAT has also shown efficacy in meta-analyses with one published analysis reporting a MD of 2.21 on the FMUE.[46] This is markedly lower than the MD of 5.2 estimated by our model. It is important to note however that this study performed by Chen et al[46] included robotic BAT, bimanual resistance training and rhythmic auditory cueing. Our analysis focused solely on manual, symmetrical or antiphase repetitive movements without the aid of

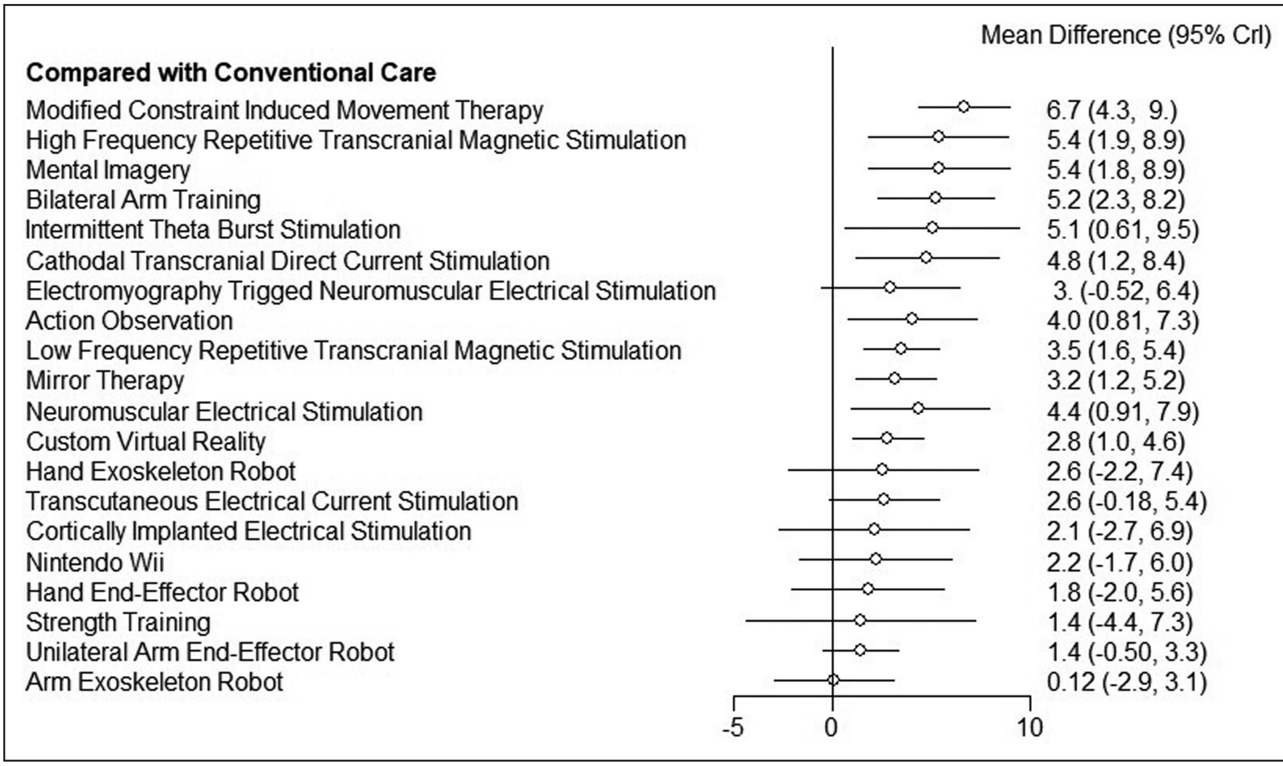

Figure 4. Forest plot of mead difference and 95% CIs for included interventions versus convectional care.

technologies, and so was not influenced by these other interventions.

Limitations

This study is not without limitations. First, the NMA did not include all possible intervention types that have been examined in the literature. Based on our inclusion criteria, many were excluded because they lacked at least 3 trials comparing them against our common comparator conventional care, or simply did not have enough trials reporting the FMUE scale in an appropriate manner for extraction. Therefore, the interventions included were not exhaustive and should be interpreted in conjunction with the literature surrounding the efficacy of non-included adjunct therapies. Second, the term conventional care is used frequently within the literature, but in a clinical context is heterogenous, ill-defined, and subject to site-specific differences. As such, the completeness of reporting on the conventional care group varied significantly in these trials. We made a concerted effort to review conventional care group protocols and ensure a relative degree of homogeneity in content of the reported therapy. Third, regression models in this study were subject to the reporting of covariates. All models were run with a lower number of trials than the full consistency model. This makes proper comparison of model fit difficult, but as reported, none proved to be of significant effect. Additionally, it is important to note that RCTs used in our NMA analysis were of moderate methodological quality. Therefore, some risk of bias may be present within the primary studies included in the NMA. In addition, the Egger's Test of funnel plot asymmetry found a significant small-study effect, furthering the risk of biased estimates. These 2 limitations should not be overlooked, and examination of the studies contained within each node is recommended for adequate interpretation of the results. Finally, this model did not consider trials where targeted combinations of interventions were applied, in order to maintain homogeneity of the intervention nodes. Importantly, there is evidence for the use of combinations of these non-conventional therapies, which should be considered when interpreting the findings of this study.[47]

Another limitation in extrapolating this data to UE rehabilitation in general is we limited our study to the FMUE. The FMUE has been chosen as one of the outcome measures, which should be included in all future clinical trials based on the work of the international Stroke Recovery and Rehabilitation Roundtable (SRRR2) group.[48] It is widely regarded as primarily a measure of impairment, and there may be treatments that impact function much more than impairment. This NMA could be repeated for other more function driven measures such as the Action Research Arm Test or the Wolf Motor Function Test. It should also be noted that the majority of patients included in this analysis (and RCTs in general) have mild-to-moderate impairment as determined by their baseline FMUE scores, and these results may not be generalizable to severely disabled patients.

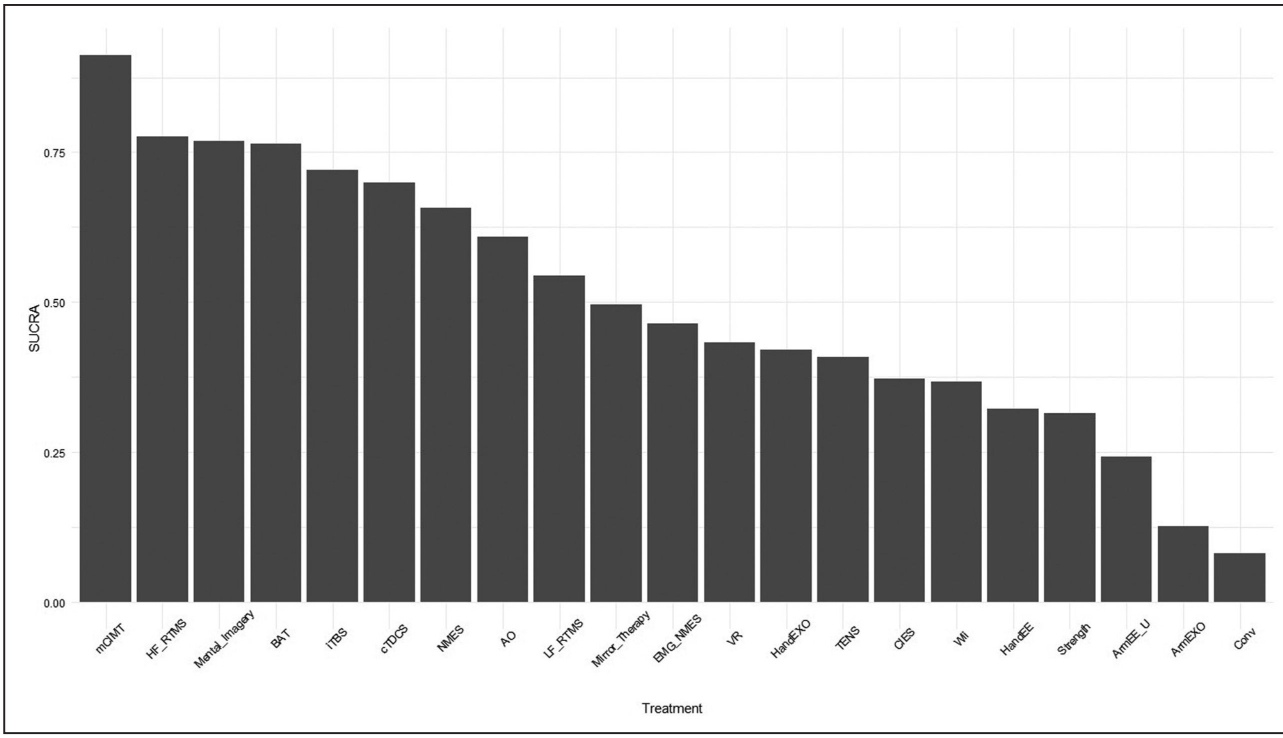

Figure 5. Surface under the cumulative ranking analysis plot.
AO indicates action observation; ArmEE_B, bilateral arm end-effector robotics; ArmEE_U, unilateral arm end-effector robotics; ArmEXO, arm exoskeleton robotics; BAT, bilateral arm training; CIES, cortically implanted electrical stimulation; Conv, conventional therapy; c-TDCS, cathodal transcranial direct current stimulation; EMG-NMES, electromyographically triggered NMES; HandEE, hand end-effector robotics; HandEXO, hand exoskeleton robotics; HF-rTMS, high frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; LF-rTMS, low frequency repetitive transcranial magnetic stimulation; mCIMT, modified constraint induced movement therapy; NMES, neuromuscular electrical stimulation; Strength, strength training; TENS, transcutaneous electrical nerve stimulation; VR, custom virtual reality training; and Wii, Nintendo Wii training.

Clinical Implications

Given the relative novelty and complexity of a NMA, we strongly encourage the reader to familiarize themselves with this technique and how to interpret the findings so that they can better understand the nuances of this study not covered within this article. Although this analysis should be interpreted carefully, there remains robust evidence to support the notion that a select number of non-conventional therapies are significantly more effective than conventional regimes at improving UE motor impairment. While many previous meta-analyses of stroke rehabilitation trials have come to the same conclusion, they were limited in that they could only compare 2 interventions at a time. This NMA has demonstrated the ability to simultaneously assess the effectiveness of multiple different interventions, in particular when compared with conventional rehabilitation therapy. It can begin to provide direction to rehabilitation providers on the available interventions with the greatest likelihood of success in improving UE motor impairment. Additionally, the results of this study may help to guide future research and funding allocation to ensure resources are directed towards treatments which are potentially more efficacious. For example, this NMA found that robotic interventions were relatively less effective in comparison to other options (mCIMT, mental imagery, BAT, HF-rTMS). Interestingly, they represent the largest group of trials in the UE stroke literature, with 181 RCTs having investigated some form of robotic therapy.[16] Although one cannot confidently advocate for one intervention over another owing to the observational nature of indirect comparisons, future clinical and research efforts can use these results to focus those interventions which seem to provide a greater improvement when investigating adjunct treatment options. These results can be expanded on in the future to answer more specific questions about who these therapies are most effective on (eg, age of patient, sex, chronicity) and how they may be best applied (eg, protocol variations, combination therapies).

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Disclosures

None.

Supplemental Material

Figures S1–S5
Tables S1–S4
References of studies included in the model

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