Physiotherapy interventions may relieve pain in individuals with central neuropathic pain: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Objectives: To evaluate the effectiveness of any form of physiotherapy intervention for the management of central neuropathic pain (cNeP) due to any underlying cause.

Methods: Multiple databases were searched from inception until August 2021. Randomised controlled trials evaluating physiotherapy interventions compared to a control condition on pain among people with cNeP were included. Methodological quality and the quality of evidence were assessed using the Physiotherapy Evidence Database Scale and the Grading of Recommendations, Assessment, Development, and Evaluation tool, respectively.

Results: The searches yielded 2661 studies, of which 23 randomised controlled trials met the inclusion criteria and were included in the meta-analyses. Meta-analyses of trials examining non-invasive neurostimulation revealed significant reductions in pain severity due to spinal cord injury (SCI; standardised mean difference (SMD): −0.59 (95% confidence interval [CI]: −1.07, −0.11), $p = 0.02$) and phantom limb pain (weighted mean difference (WMD): −1.57 (95% CI: −2.85, −0.29), $p = 0.02$). The pooled analyses of trials utilising acupuncture, transcutaneous electrical nerve stimulation (TENS), and mirror therapy showed significant reductions in pain severity among individuals with stroke (WMD: −1.46 (95% CI: −1.97, −0.94), $p < 0.001$), multiple sclerosis (SMD: −0.32 (95% CI: −0.57, −0.06), $p = 0.01$), and phantom limb pain (SMD: −0.74 (95% CI: −1.36, −0.11), $p = 0.02$), respectively. Exercise was also found to significantly reduce pain among people with multiple sclerosis (SMD: −1.58 (95% CI: −2.85, −0.30), $p = 0.02$).

Conclusion: Evidence supports the use of non-invasive neurostimulation for the treatment of pain secondary to SCI and phantom limb pain. Beneficial pain management outcomes were also identified for acupuncture in stroke, TENS in multiple sclerosis, and mirror therapy in phantom limb pain.

Keywords: physiotherapy, neuropathy, pain, central neuropathic pain

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Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by lesions or diseases of the somatosensory system.[1] Neuropathic pain describes the continuous shooting pains caused by endogenous chemicals in the body.[2] Pain initiated by lesions of the central nervous system, including the brain, brainstem, and spinal cord, has been categorised as central neuropathic pain (cNeP),[3] which is characterised by a throbbing clinical presentation and sensory impairments, manifested as the absolute or partial decline in sensory responses, resulting in pain, paraesthesia, and dysesthesia.[4] Stroke, traumatic brain injury, spinal cord injury (SCI),[5] and multiple sclerosis are common causes of cNeP.[6] cNeP is not uncommon, with 8% of stroke patients,[7] 65% to 80% of individuals with SCI,[3] and 50% of multiple sclerosis patients[8] reporting pain. Due to the chronic nature of cNeP, those

individuals diagnosed with neuropathic pain are among the most frequent consumers of health-care services.[9] The annual per-patient indirect medical costs associated with neuropathic pain have been estimated at USD 19,000.[10] In addition, individuals with neuropathic pain experienced a decline in quality of life due to the necessity of increased drug prescriptions and regular visits to healthcare providers.[10]

cNeP is commonly managed by pharmacotherapy, surgery, and non-surgical interventions.[3] Among existing non-surgical interventions, motor cortex stimulation, deep brain stimulation, and repetitive transcranial magnetic stimulation (rTMS) have gained interest.[11,12] These neuromodulation techniques are thought to increase blood flow to the cingulate gyrus, reducing emotional affective pain,[13] increase the release of endogenous opioids,[13] and activation of pain inhibitory pathways.[14] Physiotherapy modalities used to manage cNeP include the application of heat and cold, massage, high-frequency currents (short-wave diathermy), low-frequency currents (such as transcutaneous electrical nerve stimulation (TENS)), high-voltage galvanic currents, and laser therapy.[12] These interventions have been tested across a spectrum of conditions associated with cNeP; however, the results remain inconclusive.[15] Rehabilitative interventions, such as psychotherapy,[16] relaxation therapy,[17] mirror therapy,[18] and graded motor imagery[19,20] are considered to be useful adjuncts to pharmacotherapy, aiming to address the emotional, behavioural, and mental domains associated with pain. Unlike pharmacotherapeutic interventions, physiotherapy and rehabilitation interventions for neuropathic pain are less toxic and are often easily accessible.

Previously published reviews examining this field of research have restricted their focus to either one specific disease condition,[21,22] or one specific treatment modality for the management of neuropathic pain.[23,24] To the best of our knowledge, there are no previous systematic or Cochrane reviews on the efficacy of physiotherapy interventions for the management of cNeP due to any underlying cause. In 2020, a systematic review evaluated the effectiveness of pharmacological and non-pharmacological interventions, including non-invasive brain stimulation, TENS, invasive neurostimulation psychotherapy, and hypnosis, for the treatment of central and peripheral neuropathic pain. However, this review did perform any

meta-analysis.[25] Therefore, the objective of the current systematic review and meta-analysis was to evaluate the effectiveness of any form of physiotherapy intervention for the management of cNeP due to any underlying cause.

Materials and methods

Search strategy

This systematic review was developed and is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.[26] The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) before the search was initiated (CRD42020175111). The following databases were searched, from database inception to August 2021: Web of Science, Embase, EBSCO, MEDLINE, and CINAHL. Search terms were constructed as four themes, which included (1) diseases associated with neuropathic pain, (2) physiotherapy interventions, (3) outcome measures evaluating pain, and (4) randomised, controlled trial (RCT). The disease conditions that were included in the searches were based on the current grading system for neuropathic pain.[27] The search strategy for Medline is presented in Supplementary Appendix 1. The reference lists of all included studies and relevant systematic reviews were also manually searched. RCTs, pilot, cluster RCTs, cross-over trials (providing data prior to cross-over), and unpublished theses that compared any form of physiotherapy interventions against a control condition (no treatment, placebo, sham, or active control) for the management of cNeP associated with any underlying cause were included in the review. Trials that utilised the visual analogue scale (VAS) or numerical rating scale (NRS) to measure pain were included in the review. Trials published in languages other than English were also included in the review. Conference abstracts without full-text and quasi-experimental designs were excluded. Trials in which physiotherapy interventions were not delivered or supervised by physiotherapists were excluded. In this review, the usual care control was considered an active control.

Screening process

All identified trials were subjected to a four-step screening process. Duplicates were removed and titles were screened by one reviewer (UB).

The abstract and full-text screening was conducted by two reviewers (SW and UB). Discrepancies were resolved by discussion until consensus was reached. If consensus was not reached between the two reviewers (SW and UB), a third reviewer (PK) was consulted. At the full-text screening level, we used the International Classification of Diseases (ICD)-11 classification model for cNeP to categorise the studies into central and peripheral neuropathic pain.[6] In this review, we considered cNeP secondary to SCI, post-stroke pain, and multiple sclerosis. We have included interventions for phantom limb pain, which is categorised as a type of neuropathic pain,[27–29] with a strong inclination towards central pain components.[30] The authors of the included trials were approached to obtain additional information if not reported in the publication.

Methodological quality and the quality of evidence

The methodological quality of all included trials was assessed using the Physiotherapy Evidence Database scale, and the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool. PEDro scores for the included trials were obtained from the PEDro website (https://www.pedro.org.au/). If the score was not available, two independent reviewers (PK and UB) scored the methodological quality across the 10 items of the PEDro scale. Studies scoring 6 or above were considered high-quality studies, whereas studies scoring less than or equal to 5 were considered low-quality.[31]

The GRADE quality of evidence was rated using the GRADE profiler software 3.6.1 (http://tech.cochrane.org/revman/other-resources/gradepro/download), for each intervention specific to the outcome measure, and was completed by one reviewer (PK). The quality of evidence was classified according to four levels: 'very low', 'low', 'moderate', or 'high'.[32] The overall quality of evidence was based on the lowest quality of evidence for the outcome.[33] According to the GRADE system, evidence derived from RCTs is considered high-quality; however, the quality was downgraded for several reasons, including study limitations (risk of bias); the inconsistency of findings; the indirectness of evidence; imprecision; and reporting or publication bias.[32]

Data extraction and analysis

Two independent reviewers (SW and PK) were involved in data extraction. Discrepancies were resolved by discussion. The following data were extracted from all included studies: (1) author and year of publication; (2) population, recruitment setting, country, language, and sample size;[34] (3) intervention(s) and the intervention dosage; (4) assessment time points; and (5) pre- and post-treatment means.

Meta-analyses were conducted using the Comprehensive Meta-Analysis (CMA) software version 3.0 (Biostat Inc., Englewood, New Jersey, USA). Trials of similar underlying causes for cNeP, interventions, outcome measures, and time points were grouped for pooling. A meta-analysis was planned if at least two trials evaluated an intervention for cNeP of a similar underlying cause. Pre- and post-intervention data were used to obtain the pooled estimates of differences between groups. Study authors were contacted in an attempt to obtain any missing data for the included studies. Data presented in graphical formats were extracted using the GetData Graph Digitizer 2.26 (http://getdata-graph-digitizer.com/).[35] Data reported as the median and range were converted to the mean and standard deviation, as described elsewhere.[36] To obtain pooled estimates of the differences between groups and associated 95% confidence intervals (CIs), the bias-adjusted, standardised, mean difference (SMD; Hedges's g) or differences in means (weighted mean difference, WMD) were analysed. WMD was used to pool the effect of homogeneous studies that adopted similar outcome measures. The chi-square test (I^2 statistics) was used to determine the degree of variance across studies.[37] A random-effects model was used for all meta-analyses. A *p* value of ⩽0.05 indicated significance.

Results

Figure 1 provides an overview of the search and selection process. The searches yielded 2661 studies. Twenty-three randomised controlled trials met the inclusion criteria and were included in the meta-analyses.

Characteristics of the included studies

The characteristics of each included study are presented in Table 1. The trials included in the
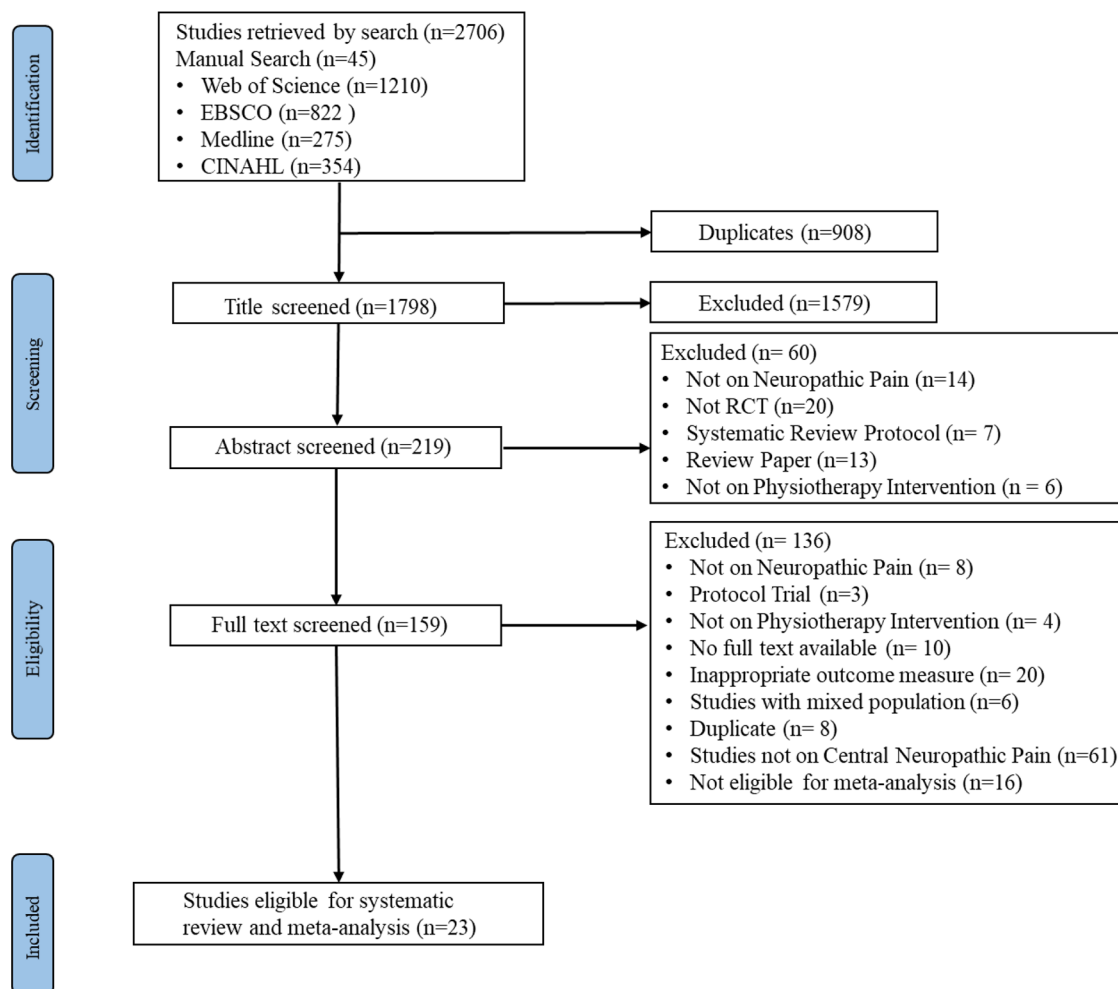
Figure 1. Flow of study process.

review were published between 2003 and 2021. Among the included trials, cNeP was secondary to SCI $(n=8)$,[38–45] multiple sclerosis $(n=7)$,[46–52] stroke $(n=4)$,[53–56] or phantom limb pain $(n=4)$.[57–60] The interventions evaluated by the included trials for the treatment of pain were TENS $(n=4)$,[46–49] rTMS $(n=6)$,[38,41,43,53,54,59] transcranial direct current stimulation (tDCS, $n=5$),[39,40,44,45,60] mirror therapy $(n=2)$,[57,58] exercise $(n=3)$,[50–52] acupuncture $(n=2)$,[55,56] and spinal cord stimulation $(n=1)$.[42]

Quality

The GRADE qualities of the 23 trials included in the meta-analyses ranged from 'very low' to 'moderate' (Table 2). The mean PEDro score of the trials included in the meta-analysis was 7,

with scores ranging from 4 to 9. The PEDro quality scores of all included trials are reported in Table 3.

Effectiveness of interventions

Non-invasive neurostimulation for cNeP, secondary to SCI

Eight trials evaluated the effectiveness of non-invasive neurostimulation on cNeP secondary to SCI. Neurostimulation was provided through 5–20 sessions of rTMS at a frequency of 5–10 Hz,[38,41,43] tDCS at an intensity of 2 mA,[39] with a ramp on for 30 s and ramp off for 8 s;[40] and cranial electrotherapy, with a current intensity of 100 mA.[42] The methodological quality of the eight trials ranged from low to high and the

Table 1. Summary of the included studies (*n* = 23).

Study (first author, country of publication)	Participants (condition, sample size, gender, and age)	Intervention	Outcome measurement(s)	Results (time points of assessment): mean (SD)
Bolognini *et al.*[60] Italy	Phantom limb pain *n* = 8 M/F ratio: 3/5 Age (mean ± SD): n/s	Exp 1 = transcranial direct current stimulation of the primary motor cortex with an intensity of 2 mA for 15 minutes × 2 sessions Exp 2 = sham (15 minutes × 2 sessions)	Pain severity: VAS Follow-up: n/s	Pre (mean (range)) Exp 1: 2.66 (1.52–3.71) Exp 2: 3.31 (2.46–4.10) Post Exp 1: 0.77 (0.48–0.97) Exp 2: 2.65 (1.51–3.75)
Castro-Sanchez *et al.*[51] Spain	Multiple sclerosis *n* =: 73 M/F ratio: n/s Age (mean ± SD): n/s	Exp (*n* = 36) = Ai-Chi exercise for 80 minutes, twice per week × 20 weeks (36°C water temperature, 20–25°C air temperature) Con (*n* = 37) = relaxation exercise for 80 minutes, twice per week × 20 weeks (26°C air temperature)	Pain severity: VAS Follow-up: 4 and 20 weeks	Pre (median (SD)) Exp: 7 (2.1) Con: 7 (1.9) Post (20 weeks) Exp: 3 (2.3) Con 6 (2.3)
Chitsaz *et al.*[48] Iran	Multiple sclerosis *n* =: 59 M/F ratio: Exp 1: 6/23 Exp 2: 9/21 Age (mean ± SD): Exp 1: 34.3 ± 6.9 Exp 2: 30.5 ± 8.7	Exp 1 (*n* = 29) = transcutaneous electrical nerve stimulation (60 Hz, 40 µs, 20–30 minutes, 3/day × 8 weeks) Exp 2 (*n* = 30) = Nortriptyline (10 mg daily for 3 days, then 25 mg daily for 4 days, then 50 mg for the rest of the study period)	Pain severity: VAS Follow-up: 2, 4, and 8 weeks	Pre Exp 1: 5.3 (1.6) Exp 2: 4.9 (1.9) Post (8 weeks) Exp 1: 2.8 (1.5) Exp 2: 3.3 (2.1)
Choi and Chang[53] Korea	Chronic stroke with chronic hemiplegic shoulder pain *n* = 24 M/F ratio: n/s Age (mean ± SD): n/s	Exp 1 (*n* = 12) = repetitive transcranial magnetic stimulation at a frequency of 10 Hz for 5 seconds, for a total of 20 trains, with 55-second pauses (5 times per week × 2 weeks) Exp 2 (*n* = 12) = sham (5 times per week × 2 weeks)	Pain severity: NRS Follow-up: 1 day, 1, 2, and 4 weeks	Pre Exp 1: 6.3 (1.3) Exp 2: 5.8 (1.5) Post (4 weeks) Exp 1: 4.7 (1.7) Exp 2: 5.8 (1.4)
De Oliveira *et al.*[54] Brazil	Central post-stroke pain *n* =: 21 M/F ratio: 11/10 Age (mean ± SD): Exp: 55 ± 9.6 Con: 57.8 ± 11.8	Exp (*n* = 11) = repetitive transcranial magnetic stimulation of the left premotor cortex/dorsolateral prefrontal cortex at a frequency of 10 Hz, 1250 pulses per day (10-day sessions × 2 weeks) Con (*n* = 10) = sham repetitive transcranial magnetic stimulation (10-day sessions × 2 weeks)	Pain severity: VAS Follow-up: 1, 2, and 4 weeks	Pre (mean (range)) Exp: 6.8 (5.07–8.68) Con: 6.8 (4.58–9.03) Post (4 weeks) Exp: 7.5 (6.14–9.29) Con: 8.2 (5.61–10.14)

(Continued)

Table 1. (Continued)

Study (first author, country of publication)	Participants (condition, sample size, gender, and age)	Intervention	Outcome measurement(s)	Results (time points of assessment): mean (SD)
Defrin et al.[43] Israel	Spinal cord injury paraplegic n=: 11 M/F ratio: Exp: 4/2 Con: 3/2 Age (mean ± SD): 54 ± 6	Exp (n=6)=repetitive transcranial magnetic stimulation at a frequency of 5 Hz for 10 second, 500 trains, for a total of 500 pulses at 115% intensity (10 sessions × 15–30 minutes × 2 weeks) Con (n-5)=sham repetitive transcranial magnetic stimulation (10 sessions × 15–30 minutes × 2 weeks)	Pain severity: VAS Follow-up: 2 to 6 weeks	Pre (mean (range)) Exp: 4.6 (4.4–4.8) Con: 3.5 (3.2–3.8) Post (10 session) Exp: 3.9 (3.7–4.1) Con: 2.5 (2.2–2.8)
Finn et al.[57] United States	Phantom limb pain n=: 15 M/F ratio: n/s Age (mean ± SD): n/s	Exp (n=9)=mirror therapy (15 minutes per day for 5 days per week for 4 weeks) Con (n=6)=covered mirror or mental visualisation therapy (15 minutes per day for 5 days per week for 4 weeks)	Pain severity: VAS Follow-up: 4 weeks (lack of treatment efficacy or increased pain, all subjects assigned to the control group switched after 11 treatment sessions.)	Pre Exp: 41.4 (17.6) Con: 35.2 (25.5) Post (4 weeks) Exp: 27.5 (17.2) Con: 48.5 (29.0)
Fregni et al.[39] Brazil	Spinal cord injury n=: 17 M/F ratio: Exp: 9/2 Con: 5/1 Age (mean ± SD): Exp: 36.6 ± 12.6 Con: 34.2 ± 15.8	Exp (n=11)=transcranial direct current stimulation with an intensity of 2 mA for 20 minutes × 5 consecutive days Con (n=6)=sham transcranial direct current stimulation with an intensity of 2 mA for 20 minutes × 5 consecutive days	Pain severity: VAS Follow-up: 16 days	Pre Exp: 6.2 (1.5) Con: 6 (2) Post (16 days) (mean (SEM)) Exp: 3.9 (3.3) Con: 7.2 (7.9)
Kang et al.[41] South Africa	Spinal cord injury n=: 11 M/F ratio: 6/5 Age (mean ± SD): 54.8 ± 13.7	Separated by 12 weeks Exp=repetitive transcranial magnetic stimulation at a frequency of 10 Hz for 5 second with an intensity of 80%, 20 trains with 55 second interval × 5 consecutive days Con=sham stimulation	Pain severity: NRS Follow-up: 1 week	Pre Exp: 6.45(2.25) Con: 6.18 (1.83) Post (1 week) Exp: 5.45 (1.81) Con: 5.91 (2.07)
Lee et al.[55] Korea	Post-stoke n=: 53 M/F ratio: Exp: 15/12 Con: 20/6 Age (mean ± SD): Exp: 56.81 ± 10.23 Con: 58.38 ± 12.38	Exp (n=27)=acupuncture, stainless steel needles (length 40 mm, diameter 0.25 mm) inserted in 10 body points of the unilateral (LI15, LI16, LI14, LI4, TE14, TE3, SI10, SI13, GB20, and ST36) for 3 times per week, a total of 9 sessions × 3 weeks Con (n=26)=sham acupuncture for 3 times per week, a total of 9 sessions × 3 weeks	Pain severity: VAS Follow-up: 1 week	Pre Exp: 7.15 (1.85) Con: 6.54 (2.16) Post (1 week) Exp: 3.00 (3.28) Con: 1.65 (2.50)

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Table 1. (Continued)

Study (first author, country of publication)	Participants (condition, sample size, gender, and age)	Intervention	Outcome measurement(s)	Results (time points of assessment): mean (SD)
Li *et al.*[44] China	Spinal cord injury *n* =: 12 M/F ratio: 7/5 Age (mean ± SD): n/s	Crossover study Exp = transcranial direct current stimulation for 20 minutes, followed by 20 minutes breathing-controlled electrical stimulation Con = sham transcranial direct current stimulation for 20 minutes, followed by 20 minutes breathing-controlled electrical stimulation	Pain severity: VAS Follow-up: n/s	Pre (mean [SEM]) Exp: 5.7 (6.2) Con: 5.9 (6.6) Post Exp: 5.0 (5.6) Con: 5.4 (6.1)
Malavera *et al.*[59] United States	Phantom limb pain *n* = 54 M/F ratio: Exp: 25/2 Con: 25/2 Age (mean ± SD): Exp: 33.1 ± 6.6 Con: 34.7 ± 9.9	Exp (*n* = 27) = repetitive transcranial magnetic stimulation at a frequency of 10 Hz with an intensity of 90%, 20 trains of 6 second duration, with 54 second interval (5 days per week × 2 weeks) Con (*n* = 27) = sham stimulation (5 days per week × 2 weeks)	Pain severity: VAS Follow-up: 15 and 30 days	Pre Exp: 4.9 (1.9) Con: 4.8 (1.9) Post (30 days) Exp: 3.02 (2.64) Con: 3.88 (2.68)
Masoudi *et al.*[50] Iran	Multiple Sclerosis *n* =: 70 M/F ratio: Exp: 13/22 Con: 12/23 Age (mean ± SD): n/s	Exp (*n* = 35) = progressive muscle relaxation technique for 90 sessions (a total of 3 months) Con (*n* = 35) = single session on relaxation technique, along with a cassette tape for home practicing (once a day for a total of 3 months)	Pain severity: VAS Follow-up: 3 months	Pre Exp: 8.02 (1.70) Con: 7.94 (1.28) Post (3 months) Exp: 3.97 (1.72) Con: 8.14 (0.94)
Miller *et al.*[49] United Kingdom	Multiple sclerosis *n* =: 32 M/F ratio: 15/17 Age (mean ± SD): Exp 1: 46.8 ± 9.9 Exp 2: 47.1 ± 9.8	Wash-out: 2 weeks Exp 1 (*n* = 16) = transcutaneous electrical nerve stimulation at a frequency of 100 Hz with an intensity of 0.125 ms pulse width for 60 minutes per day for 2 weeks Exp 2 (*n* = 16) = transcutaneous electrical nerve stimulation at a frequency of 100 Hz with an intensity of 0.125 ms pulse width for 8 hours daily for 2 weeks	Pain severity: VAS Follow-up: n/s	Pre (mean [range]) Exp 1: 2.8 (0.8–4.9) Exp 2: 3.1 (0.9–5.3) Post Exp 1: 2.5 (0–4.6) Exp 2: 2.1 (0–4.2)
Nardone *et al.*[38] Austria	Spinal cord injury *n* =: 12 M/F ratio: Exp: 4/2 Con: 5/1 Age (mean ± SD): n/s	Exp (*n* = 6) = repetitive transcranial magnetic stimulation at a frequency of 10 Hz with an intensity of 1,250 pulses, separated by 25 second interval for 5 per week × 10 sessions × 2 weeks) Con (*n* = 6) = sham stimulation	Pain severity: VAS Follow-up: 1 month	Pre Exp: 6.67 (1.75) Con: 6.83 (1.47) Post (1 month) Exp: 6.5 (1.52) Con: 6.83 (1.47)

(Continued)

Table 1. (Continued)

Study (first author, country of publication)	Participants (condition, sample size, gender, and age)	Intervention	Outcome measurement(s)	Results (time points of assessment): mean (SD)
Negahban et al.[52] Iran	Multiple sclerosis n=: 48 M/F ratio: n/s Age (mean ± SD): Exp 1: 36.33 ± 7.62 Exp 2: 36.67 ± 6.69 Exp 3: 36.67 ± 7.63 Con: 36.83 ± 8.74	Exp 1 (n = 12) = standard Swedish massage therapy for 3 times per week, 30 minutes per session, for a total of 15 sessions × 5 weeks Exp 2 (n = 12) = a combination of strength, stretch, endurance and balance exercises for 3 times per week, 30 minutes per session, for a total of 15 sessions × 5 weeks Exp 3 (n = 12) = a combination of massage therapy for 15 minutes and exercise for 15 minutes × 5 weeks Con(n = 12) = continue standard medical care (avoid participation in exercise programme)	Pain severity: VAS Follow-up: 5 weeks	Pre Exp 1: 4.91 (2.02) Exp 2: 1.83 (1.85) Exp 3: 4.75 (1.54) Con: 4.25 (2.56) Post (5 weeks) Exp 1: 1.75 (1.95) Exp 2: 1.41 (1.24) Exp 3: 2.66 (1.61) Con: 4.83 (2.69)
Soler et al.[45] Spain	Spinal cord injury n=: 39 M/F ratio: Exp 1: 8/2 Exp 2: 9/1 Exp 3: 6/3 Exp 4: 7/3 Age (mean ± SD): n/s	Exp 1 (n = 10) = transcranial direct current stimulation with walking visual illusion (20 minutes per session, for a total of 10 sessions, 5 times per week × 2 weeks) Exp 2 (n = 10) = transcranial direct current stimulation with control illusion (20 minutes per session, for a total of 10 sessions, 5 times per week × 2 weeks) Exp 3 (n = 9) = sham stimulation with walking visual illusion (20 minutes per session, for a total of 10 sessions, 5 times per week × 2 weeks) Exp 4 (n = 10) = sham stimulation with control illusion (20 minutes per session, for a total of 10 sessions, 5 times per week × 2 weeks)	Pain severity: NRS Follow-up: 2, 4, and 12 weeks	Pre Exp 1: 7.5 (1.2) Exp 2: 6.3 (2.0) Exp 3: 7.2 (1.6) Exp 4: 7.1 (1.5) Post (12 weeks) Exp 1: 5.5 (1.8) Exp 2: 5.9 (2.3) Exp 3: 7.1 (1.4) Exp 4: 6.6 (1.8)
Tan et al.[42] United States	Spinal cord injury n=: 38 M/F ratio: Exp: 20/0 Con: 18/0 Age (mean ± SD): Exp: 56.0 ± 8.3 Con: 56.6 ± 10.9	Exp (n = 18) = cranial electrotherapy stimulation with a stimulation rate of 100 µA for 1 hour per day × 21 days, consecutively Con (n = 20) = sham stimulation with a stimulation rate of 100 µA for 1 hour per day × 21 days, consecutively	Pain severity: NRS Follow-up: 21 days	Pre Exp: 6.46 (1.95) Con: 6.08 (2.42) Post (21 days) Exp: 5.73 (2.56) Con: 6.00 (2.41)
Tilak et al.[58] India	Phantom limb pain n=: 26 M/F ratio: Exp 1: 12/1 Exp 2: 11/2 Age (mean ± SD): Exp 1: 42.62 ± 10.69 Exp 2: 36.38 ± 9.55	Exp 1 (n = 13) = mirror therapy for 20 minutes × 4 consecutive days Exp 2 (n = 13) = transcutaneous electrical nerve stimulation for 20 minutes × 4 consecutive days	Pain severity: VAS Follow-up: 4 days	Pre Exp 1: 5.46 (1.671) Exp 2: 5 (1.63) Post (4 days) Exp 1: 2.08 (1.621) Exp 2: 2.46 (1.561)

(Continued)

Table 1. (Continued)

Study (first author, country of publication)	Participants (condition, sample size, gender, and age)	Intervention	Outcome measurement(s)	Results (time points of assessment): mean (SD)
Wang *et al.*[56] China	Stroke n=: 96 M/F ratio: Exp: 33/15 Con: 35/13 Age (mean ± SD): Exp: 60 ± 9 Con: 61 ± 9	Exp (n=48)=Xingnao Kaiqiao acupuncture (0.25 mm×40 mm disposable acupuncture needle at Neiguan, Shuigou and Sanyinjiao, 6 sessions/week, 3 weeks) + Jingu three-needle therapy (0.40 mm×50 mm disposable acupuncture needle at coracoid, greater tuberosity of humerus and infraglenoid tubercle, 2 sessions/day, 3 times/weeks, 3 weeks) + basic treatment Con (n=48)=basic treatment and Xingnao Kaiqiao acupuncture	Pain severity: VAS Follow-up: 40 days	Pre Exp: 5.79 (1.25) Con: 5.35 (1.30) Post (40 days) Exp: 3.06 (1.55) Con: 4.06 (1.48)
Warke *et al.*[47] Northern Ireland	Multiple sclerosis n=: 15 M/F ratio: n/s Age (range): 18–65	Exp 1 (n=5)=transcutaneous electrical nerve stimulation at a frequency of 4 Hz with an intensity of 200 µs for 45 minutes, 2 times per day×6 weeks Exp 2 (n=5)=transcutaneous electrical nerve stimulation at a frequency of 110 Hz with an intensity of 200 µs for 45 minutes, 2 times per day×6 weeks Con (n=5)=sham stimulation	Pain severity: VAS Follow-up: 10 and 32 weeks	Pre (mean (SE)) Exp 1: 62.40 (5.28) Exp 2: 41.50 (16.79) Con: 66.80 (8.70) Post (32 weeks) Exp 1: 24.6 (13.21) Exp 2: 39.33 (13.12) Con: 28.33 (17.40)
Warke *et al.*[46] Northern Ireland	Multiple sclerosis n=: 90 M/F ratio: Exp 1: 6/24 Exp 2: 7/23 Con: 8/22 Age mean (SEM): Exp 1: 45.6 (1.7) Exp 2: 47.8 (2.2) Con: 48.7 (2.6)	Exp 1 (n=30)=transcutaneous electrical nerve stimulation at a frequency of 4 Hz (low-frequency), with an intensity of 200 µs for 45 minutes, 2 times per day×6 weeks Exp 2 (n=30)=transcutaneous electrical nerve stimulation at a frequency of 110 Hz (high-frequency), with an intensity of 200 µs for 45 minutes, 2 times per day×6 weeks Con (n=30)=sham stimulation	Pain severity: VAS Follow-up: 1, 6, 10, and 32 weeks	Pre (mean (SEM)) Exp 1: 54.17 (58.58) Exp 2: 53.43 (57.35) Con: 57.60 (61.03) Post (32 weeks) Exp 1: 33.33 (38.24) Exp 2: 40.20 (45.34) Con: 44.85 (49.02)
Wrigley *et al.*[40] Australia	Spinal cord injury n=: 10 M/F ratio: 8/2 Age (mean ± SD): 56.1 ± 14.9	Exp 1 (n=5)=transcranial direct current stimulation followed by Sham stimulation (20 minutes per session, 5 consecutive days×4 weeks) Exp 2 (n=5)=sham stimulation followed by transcranial direct current stimulation (20 minutes per session, with 30 second ramp on and 8 second ramp off, 5 consecutive days×4 weeks)	Pain severity: NRS Follow-up: 4 weeks and 6 months	Pre Exp 1: 5.4 (1.96) Exp 2: 5.8 (1.17) Post (6 months) Exp 1: 5.4 (2.06) Exp 2: 6.4 (0.8)

Con, control; Exp, experimental; F, female; M, male; n/s, not stated; NRS, numerical rating scale; SD, standard deviation; SE, standard error; SEM, standard error of the mean; VAS, visual analogue scale.

Table 2. Summary of the findings for the effectiveness of interventions compared to control.

Quality assessment							No. of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute	
Non-invasive neurostimulation for cNeP* in spinal cord injury											
8 Nardone et al.[38] Fregni et al.[39] Wrigley et al.[40] Kang et al.[41] Tan et al.[42] Defrin et al.[43] Li et al.[44] Soler et al.[45]	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	79	73	–	The mean cNeP in the intervention group was 0.59 lower (1.07 lower to 0.11 higher)	⊕⊖⊖⊖[a,b] Very low
Non-invasive neurostimulation for cNeP* secondary to stroke											
2 Choi and Chang[53] De Oliveira et al.[54]	Randomised trials	Very serious[c]	Serious[d]	No serious indirectness	Serious[b]	None	24	23	–	The mean cNeP in the intervention group was 0.70 lower (2.09 lower to 0.69 higher)	⊕⊖⊖⊖[b,c,d] Very low
Acupuncture for cNeP* secondary to stroke,											
2 Lee et al.[55] Wang et al.[56]	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association[f]	75	74	–	The mean cNeP in the intervention group was 1.46 lower (1.97 lower to 0.94 higher)	⊕⊕⊕⊕ Moderate[e,f]
TENS for cNeP* in multiple sclerosis											
4 Warke et al.[46] Warke et al.[47] Chitsaz et al.[48] Miller et al.[49]	Randomised trials	Very serious[g]	No serious inconsistency	No serious indirectness	Serious[b]	None	131	81	–	The mean cNeP in the intervention group was 0.32 lower (0.57 lower to 0.06 higher)	⊕⊖⊖⊖[b,g] Very low

(Continued)

Table 2. (Continued)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute	Quality
Exercise in multiple sclerosis											
3 Masoudi et al.[50] Castro-Sanchez et al.[51] Negahban et al.[52]	Randomised trials	Serious[h]	Serious[d]	No serious indirectness	No serious imprecision	Strong association[f]	83	84	–	The mean cNeP in the intervention group was 1.58 lower (2.85 lower to 0.30 higher)	⊕⊕⊕⊖ Moderate[d,f,h]
Non-invasive neurostimulation effect on cNeP in phantom limb pain											
2 Malavera et al.[59] Bolognini et al.[60]	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious[b]	Strong association[f]	35	35	–	The mean cNeP in the intervention group was 1.57 lower (2.85 lower to 0.29 higher)	⊕⊕⊖⊖ Low[b,f,i]
Mirror therapy for in phantom limb pain											
2 Finn et al.[57] Tilak et al.[58]	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness	Serious[b]	None	22	19	–	The mean cNeP in the intervention group was 0.74 lower (1.36 lower to 0.11 higher)	⊕⊕⊖⊖ Low[b,j]

CI, confidence interval; cNeP, central neuropathic pain; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NRS, numerical rating scale; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale.

*Pain measured with 0–10 VAS or NRS, with lower scores indicating a better outcome.

The corresponding risk (and 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

GRADE Working Group grades of evidence

High-quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate-quality: Further research is likely to have an important impact on our confidence in the estimated effect and may change the estimate.

Low-quality: Further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate.

Very-low-quality: We are very uncertain about the estimated effect.

[a]Lack of allocation concealment in six[38–42,45] out of seven studies pooled in the meta-analysis; lack of therapist blinding;[43,45] and lack of assessor blinding.[39]

[b]Wide CI/ no overlap in CI

[c]Lack of allocation concealment, lack of intention-to-treat (ITT)-based analysis, and loss to follow-up >15%;[53] lack of therapist blinding;[53,54] lack of assessor blinding.[54]

[d]Evidence of clinical/methodological heterogeneity (I² > 50%)

[e]Lack of random allocation,[55] insufficient information about the allocation concealment and lack of therapist and assessor blinding.[56]

[f]Strength of association

[g]Lack of allocation concealment in all four studies pooled in the meta-analysis;[46–49] lack of therapist blinding[47–49] and assessor blinding;[49] and analysis not based on ITT.[46,47,49]

[h]Lack of allocation concealment in two[50,52] out of three studies pooled in the meta-analysis; lack of subject blinding,[50–52] therapist blinding[50,51] and accessor blinding.[50]

[i]Lack of allocation concealment and assessor blinding in both studies pooled in the meta-analysis.[59,60]

[j]Lack of allocation concealment;[57] lack of subject blinding,[58] therapist blinding and accessor blinding.[57]

Table 3. Summary of methodological quality of the included studies according to the PEDro scale ($n = 23$).

PEDro Scale	Random allocation	Concealed allocation	Baseline similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between group comparison	Points estimate	Total Score/10
Bolognini et al.[60]	Y	N	N	Y	Y	N	Y	N	Y	Y	6
Castro-Sanchez et al.[51]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Chitsaz et al.[48]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Choi and Chang[53]	Y	N	Y	N	N	Y	N	N	Y	Y	5
De Oliveira et al.[54]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Defrin et al.[43]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Fregni et al.[39]	Y	N	Y	Y	Y	N	Y	Y	Y	Y	8
Finn et al.[57]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Kang et al.[41]	Y	N	Y	N	Y	Y	Y	Y	Y	Y	8
Lee et al.[55]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	8
Li et al.[44]	N	N	Y	Y	N	N	N	N	Y	Y	4
Malavera et al.[59]	Y	N	Y	Y	Y	N	Y	Y	Y	Y	8
Masoudi et al.[50]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Miller et al.[49]	Y	N	Y	Y	N	N	Y	N	Y	Y	6
Nardone et al.[38]	Y	N	Y	N	Y	Y	Y	N	Y	Y	7
Negahban et al.[52]	Y	N	N	N	Y	Y	Y	Y	Y	Y	7
Soler et al.[45]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Tan et al.[42]	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8
Tilak et al.[58]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	9
Wang et al.[56]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Warke et al.[47]	Y	N	N	Y	N	Y	N	N	Y	Y	5
Warke et al.[46]	Y	N	Y	N	Y	Y	Y	N	Y	Y	7
Wrigley et al.[40]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
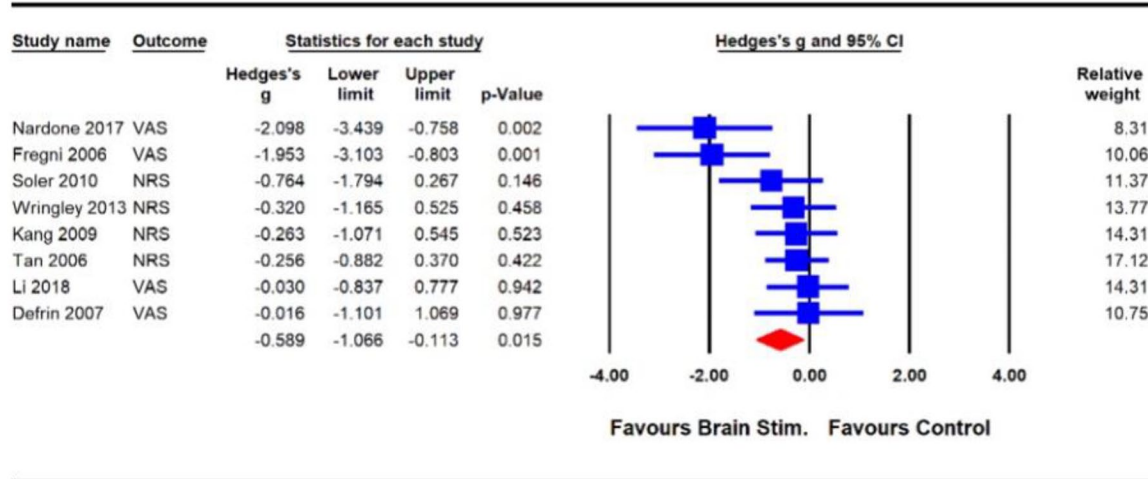
Figure 2. Effects of non-invasive neurostimulation on pain severity in individuals with spinal cord injury.
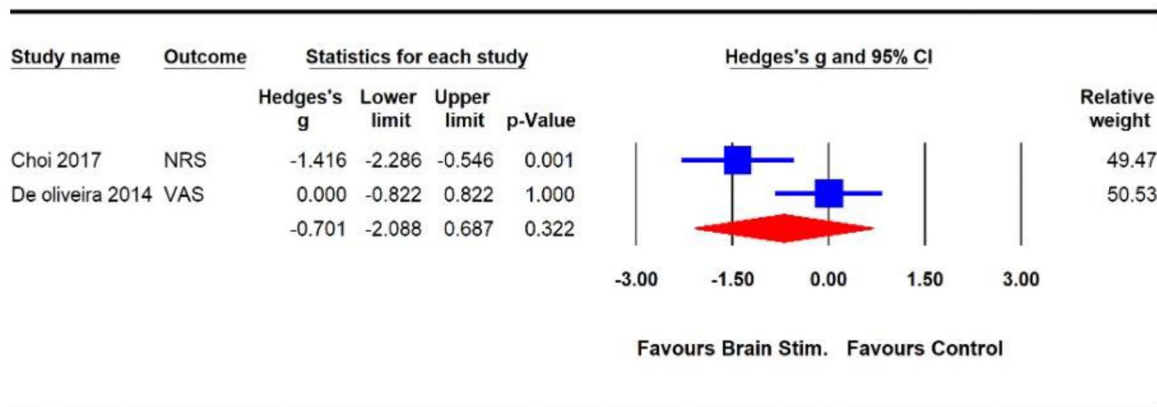
Figure 3. Effects of non-invasive neurostimulation on pain severity in individuals with stroke.

GRADE quality of the evidence was very low. Pooled analysis of the eight trials (n = 152) showed a significant benefit of non-invasive neurostimulation for reducing pain severity compared to control (SMD −0.59 (95% CI: −1.07 to −0.11); p = 0.02; Figure 2).

Non-invasive neurostimulation for cNeP secondary to stroke

Two trials[53,54] evaluated the effectiveness of non-invasive neurostimulation on cNeP secondary to stroke. Both trials used rTMS to treat pain following stroke. rTMS was provided for 10 treatment sessions at a frequency of 10 Hz.[53,54] Intensity of rTMS was set at 90%[53]% and 120%[54] of the resting motor threshold. Each train of

stimulation lasted for 5 s, for a total of 20[53] and 25[54] trains of stimulation. The methodological quality of the two trials ranged from low to high and GRADE quality of evidence was very low. Pooled analysis of the two trials (n = 47) showed a non-significant effect of non-invasive neurostimulation (rTMS) for reducing pain compared to control (SMD −0.7 (95% CI: −2.09 to 0.69); p = 0.32; Figure 3).

Acupuncture for cNeP secondary to stroke

Two trials[55,56] evaluated the effectiveness of acupuncture for cNeP secondary to stroke. Both trials used acupuncture to treat shoulder pain following stroke. Acupuncture was provided in 9[55] and 18[56] treatment sessions using ten stainless
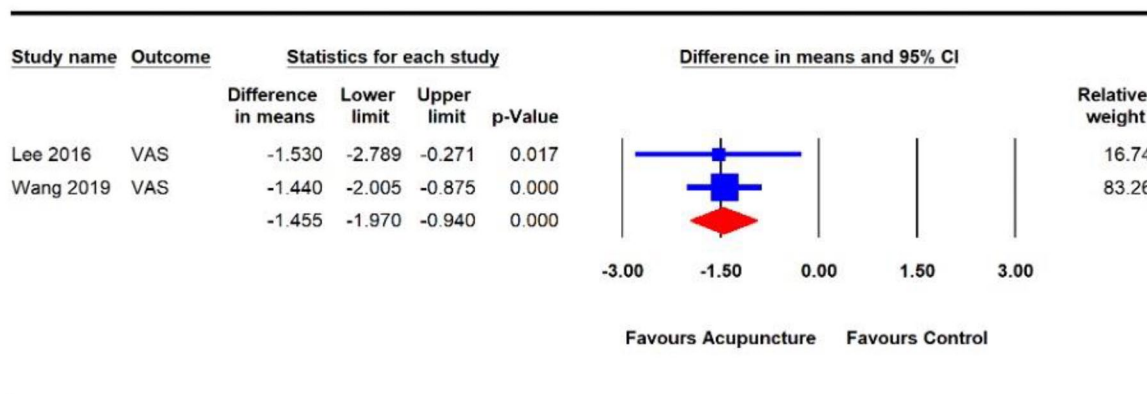
Figure 4. Effects of acupuncture on pain severity in people with stroke.
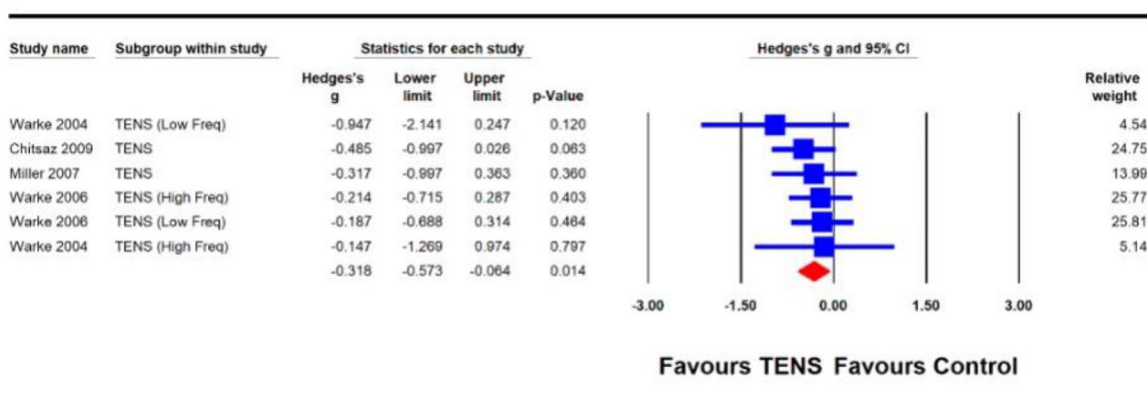

Figure 5. Effects of TENs on pain severity in individuals with multiple sclerosis.

steel needles (40 mm length and 0.25 mm diameter) to various acupoints (LI15, LI14, LI16, LI4, TE14, TE3, SI10, SI13, GB20, and ST36). Needles were inserted to a depth of 15–35 mm, retained for over 15 minutes during each treatment session, and manipulated until De Qi was elicited. The methodological quality of the two trials was high and the GRADE quality of the evidence was moderate. Pooled analysis ($n = 149$) revealed a significant benefit of acupuncture for reducing pain severity compared with sham acupuncture (WMD −1.46 (95% CI: −1.97 to −0.94); $p < 0.01$; Figure 4).
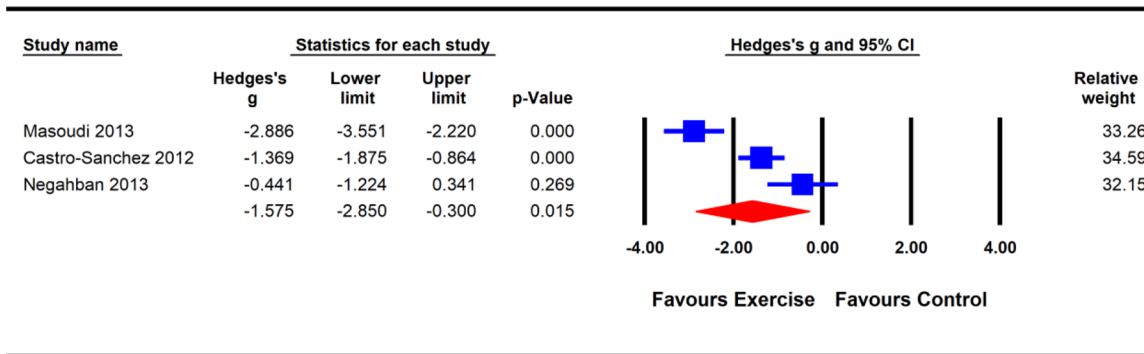
TENS for cNeP, secondary to multiple sclerosis
The effectiveness of TENS for cNeP secondary to multiple sclerosis was evaluated in four trials[46–49] (including six comparisons). In the four trials, TENS was delivered at frequencies of
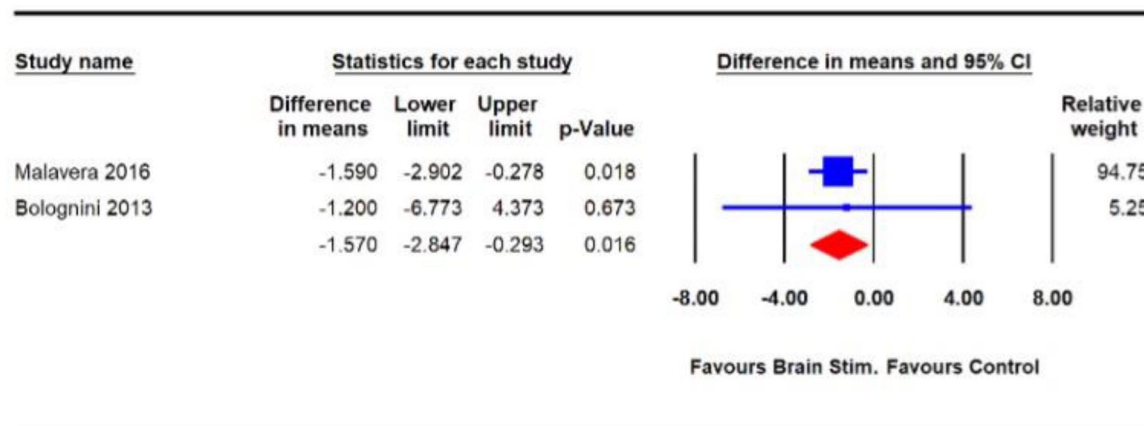
4–110 Hz, with intensity ranging between 40 µs and 0.125 ms, for 20–60 mins over 12–24 treatment sessions.[46–49] The methodological quality of the four trials ranged from low to high and the GRADE quality of the evidence was very low. Pooled analysis ($n = 212$) showed a significant effect of TENS on the reduction of pain severity compared with placebo or pharmacological intervention (SMD −0.32 (95% CI: −0.57 to −0.06); $p = 0.01$; Figure 5).

Exercise for cNeP, secondary to multiple sclerosis
The effects of different forms of exercise on cNeP secondary to multiple sclerosis was evaluated in three trials.[50–52] Among these three trials, exercises were delivered for 3 months (90 sessions of progressive muscle relaxation),[50] 20 weeks (40 sessions of Ai-chi: Hydrotherapy)[51] or 5 weeks

Study name	Statistics for each study				Hedges's g and 95% CI	Relative weight
	Hedges's g	Lower limit	Upper limit	p-Value		
Masoudi 2013	-2.886	-3.551	-2.220	0.000		33.26
Castro-Sanchez 2012	-1.369	-1.875	-0.864	0.000		34.59
Negahban 2013	-0.441	-1.224	0.341	0.269		32.15
	-1.575	-2.850	-0.300	0.015		

Favours Exercise   Favours Control

Figure 6. Effects of exercise on pain severity in individuals with multiple sclerosis.

Study name	Statistics for each study				Difference in means and 95% CI	Relative weight
	Difference in means	Lower limit	Upper limit	p-Value		
Malavera 2016	-1.590	-2.902	-0.278	0.018		94.75
Bolognini 2013	-1.200	-6.773	4.373	0.673		5.25
	-1.570	-2.847	-0.293	0.016		

Favours Brain Stim. Favours Control

Figure 7. Effects of non-invasive neurostimulation on pain severity in individuals with phantom limb pain.

(15 sessions of strengthening, stretching, endurance, and balance exercises for 30 minutes each session).[52] The methodological quality of the three trials was high, and the GRADE quality of the evidence was moderate. The pooled analysis ($n=167$) showed a significant effect of exercise on reductions in pain severity compared with control conditions (single or multiple sessions of relaxation exercises,[50,51] and continued standard medical care[52] (SMD –1.58 (95% CI: –2.85 to –0.30); $p=0.02$; Figure 6).
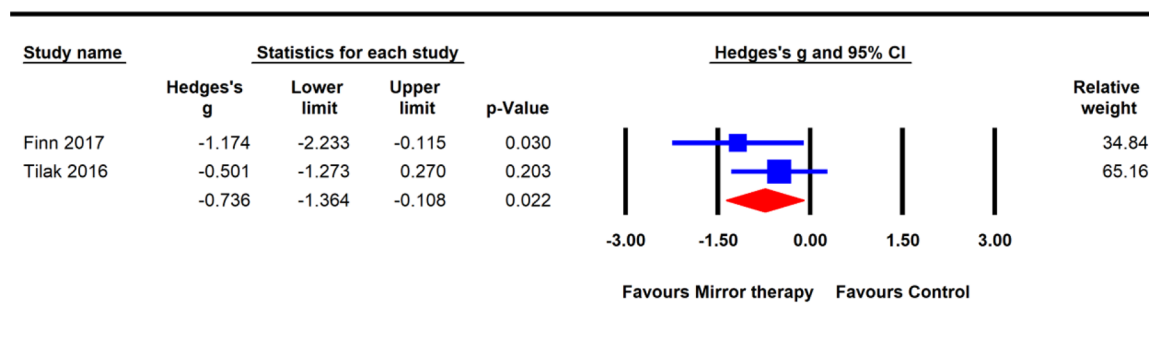
Non-invasive neurostimulation for phantom limb pain

Two trials[59,60] evaluated the effectiveness of non-invasive neurostimulation for phantom limb pain. The trials delivered rTMS at a frequency of 10 Hz,[59] and tDCS, at an intensity of 2 mA.[60] The methodological quality of the two trials was high and the GRADE quality of the evidence was low.

The pooled analysis showed a significant benefit of non-invasive neurostimulation for reducing pain compared with controls (WMD –1.57 (95% CI: –2.85 to –0.29); $p=0.02$; Figure 7).

Mirror therapy for phantom limb pain

The effect of mirror therapy on cNeP among people with phantom limb pain was evaluated in two trials.[57,58] One[57] of the two trials delivered mirror therapy in 15-minute sessions for a total of 20 sessions over the course of 4 weeks. The other trial[58] provided mirror therapy in 20-minute sessions for 4 consecutive days. The methodological quality of the two trials was high, and the GRADE quality of evidence was low. The pooled analysis ($n=41$) showed a significant effect of mirror therapy on reductions in pain severity compared with control conditions (covered mirror[57] and TENS[58] (SMD: –0.74 (95% CI: –1.36 to –0.11); $p=0.02$; Figure 8).

Study name	Statistics for each study				Hedges's g and 95% CI	Relative weight
	Hedges's g	Lower limit	Upper limit	p-Value		
Finn 2017	-1.174	-2.233	-0.115	0.030		34.84
Tilak 2016	-0.501	-1.273	0.270	0.203		65.16
	-0.736	-1.364	-0.108	0.022		

-3.00 -1.50 0.00 1.50 3.00

Favours Mirror therapy   Favours Control

Figure 8. Effects of mirror therapy on pain severity in individuals with phantom limb pain.

Discussion

The current review identified significant reductions in pain severity in response to several physiotherapy interventions among individuals with cNeP resulting from various neurological conditions. Whether the meta-analysis-derived estimates for the average effects on pain and their confidence intervals represent clinically insignificant or clinically important effects must be carefully interpreted for each specific intervention, depending on the precise conditions to which they were applied, due to variations in the sizes and quality of trials and the parameters of the various interventions.

Different forms of non-invasive neurostimulation, including rTMS, tDCS, and cranial electrotherapy stimulation, were found to be beneficial for the treatment of pain in individuals with SCI and phantom limb pain. The meta-analysis of eight trials examining non-invasive neurostimulation identified significant effects for the relief of pain secondary to SCI. Although the mean estimate of the effect of the intervention (0.59) was small and the CI surrounding these estimates (1.07, 0.11) did not exclude the possibility that the effect was clinically trivial, the extent and quality of the obtained evidence and the minimal potential for a placebo effect suggested that non-invasive neurostimulation may be considered effective for the treatment of SCI-associated pain. Non-invasive neurostimulation has been proposed to reduce pain perception, *via* an indirect influence on pain modulation areas, such as the thalamic nuclei.[39] These alterations entail either the inhibition or interference with thalamic nociceptive afferents in neural pain pathways, through the transcranial stimulation of the primary motor cortex or the dorsolateral prefrontal cortex, leading to a decrease in the 'somatosensory-discriminative aspect of pain' or the modulation of the 'affective-emotional aspect of pain', respectively.[61,62] However, the generalisability of non-invasive neurostimulation across different stages of SCI remains unclear. Future studies remain necessary to evaluate the benefits of non-invasive neurostimulation across different stages and levels of SCI.

The pooled analysis of two trials of high methodological quality and very-low-GRADE evidence, examining non-invasive neurostimulation for the treatment of phantom limb pain identified a significant benefit of the intervention for reducing pain compared with the control, with a mean estimate of 1.57 (95% CI: 2.85, 0.29). Both phantom limb pain trials lacked allocation concealment and assessor blinding. Because these results were derived from two small, very-low-grade trials, other high-quality trials examining non-invasive neurostimulation remain necessary to confirm the effects of non-invasive neurostimulation and to narrow the CI obtained in this review.

Among the studies included in the meta-analysis that evaluated individuals with stroke, one study included participants with shoulder pain alone[53] whereas the other included cNeP that spread across the involved side.[54] Both studies used rTMS, and the technique was found to be effective for reducing shoulder pain alone. Because the cumulative effect of non-invasive neurostimulation was insignificant, we are unable to make a recommendation. Further studies that include a large sample are necessary to better evaluate the benefits of non-invasive neurostimulation for cNeP following stroke.

The pooled analysis of data from two[55,56] methodologically high-quality, moderate-grade trials evaluating the effects of acupuncture revealed a significant reduction in pain in individuals with stroke. The 1.5 point reduction in pain approaches the MCID of 2 for the 0–10-point VAS.[63] Future research in this area would be useful to narrow the 95% CI, which currently extends up to 1.97 and down to 0.94 on the 0–10-point VAS. Both studies included in the meta-analysis used acupuncture to treat shoulder pain following stroke. Among the many theories postulated to explain the benefits of acupuncture, the included studies reported pain relief due to the closure of the pain gate, the release of endorphins,[55] and the adjustment of the primordial spirit that allows the flow of Qi energy.[56] The central phenomenon underlying pain relief mediated by acupuncture remains inconclusive and requires further exploration. Evoking de qi is considered to be the key to achieving desired therapeutic effects[64] and might represent a critical factor in the success of acupuncture-based analgesia.[65] De qi is a sensory response that occurs during acupuncture and is described as a sensation of warmth and tightening or deep soreness. Acupuncture needle manipulations that evoke de qi have been found to induce anti-nociceptive effects in both humans and animal models.[66–68] In both of the included acupuncture trials, de qi was reported to be evoked in the experimental groups but not in the control groups. Therefore, the control group participants may have been aware that they were receiving sham acupuncture, resulting in the biased reporting of outcomes. Because de qi is closely related to treatment efficacy,[65] future acupuncture trials should also include quantitative measurements of de qi using validated and standardised tools, such as the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) or the Southampton Needle Sensation Questionnaire.

Mirror therapy, or mirror-induced visual illusion, entails the use of a mid-sagitally placed mirror to create the illusion of moving a hidden limb through the complete mirror inversion of the opposite limb.[30,69] Although the neural mechanisms underpinning the analgesic effects of mirror therapy for central pain remain unclear, the restoration of mismatch between motor and sensory mechanisms mediated by the mirror illusion has been postulated as a potential explanation for this phenomenon.[70] The results obtained for mirror therapy in the treatment of phantom limb pain in the current review were obtained from two trials of high methodological quality and low-GRADE quality of evidence. We recommend the performance of further studies to substantiate these findings due to the limited number of studies that were included in the pooled analysis ($n = 2$) and the low quality of evidence. Similarly, well-designed brain imaging studies remain necessary to identify the neural underpinnings of the reported analgesic effects.

Meta-analysis of data from four TENS trials[46–49] for multiple sclerosis, of low to high methodological quality, very-low-GRADE evidence revealed a significant effect on cNeP and agree with the findings of a previous systematic review.[22] However, the mean estimate of the effect (0.32) was small and the 95% CI (0.57 to 0.06) does not exclude a clinically trivial effect. Due to the small effect size and quality of the included studies of TENS, we are unable to make any recommendations regarding the efficacy of TENS for the treatment of cNeP secondary to multiple sclerosis. Replication of this result in other methodologically high-quality studies of TENS should be sought. TENS parameters in the included trials of the current review varied greatly, which minimised the applicability of the review findings to clinical settings. Future studies and reviews are warranted to determine the optimal parameters for pain relief using TENS in individuals with cNeP.

Analgesic effects evoked by high-frequency, low-intensity TENS delivered via surface electrodes placed over the painful area or the innervating nerve have been proposed to be associated with a pain gating mechanism mediated by the intense activation of Aβ afferent fibres.[71] All four TENS trials[46–49] that were included in the review delivered TENS using surface electrodes placed over the painful area and delivered TENS at a high frequency and low intensity. However, one[46] of the four trials also provided low-frequency TENS (4 Hz) to one of three study groups and found that a greater number of participants in the high-frequency TENS group reported clinically significant effects compared with the low-frequency TENS group. The TENS intervention parameters in the trials included in the review varied greatly, which minimises the applicability of these findings to clinical settings. Future studies remain

necessary to determine the optimal TENS parameters for improving pain severity in people with cNeP secondary to multiple sclerosis.

The pooled analysis of data from three exercise trials of high methodological quality and moderate quality of evidence showed the significant effects of exercise interventions on pain severity compared with control conditions among people with cNeP due to multiple sclerosis. The mean estimate of 1.6 reported in the meta-analysis approaches the clinically significant difference of 2 on the 0–10 VAS scale; however, the confidence interval extends below this threshold, indicating a clinically trivial effect. The proposed mechanisms underlying the beneficial effects of exercise interventions on central pain include altered serotonin transporter expression, increases in serotonin levels, increases in the opioid levels in central inhibitory pathways, and the facilitation of inherent inhibitory systems to modulate pain'.[72] Specific reductions in multiple sclerotic pain have been attributed to the physical and psychological health benefits of exercise and associated influences on strength and endurance.[51,52] Although the analgesic benefits of exercise were significant, the evidence associated with this intervention modality must be interpreted with caution. The mean estimate was provided by a small number of studies, and the confidence interval did not exclude the possibility that the effect was clinically insignificant. The exercise interventions and parameters in the included trials varied greatly, minimising the applicability of these findings to clinical settings. Future studies remain necessary to substantiate the analgesic effects obtained in response to exercise interventions in the current review and to determine the optimal exercise types and parameters for the treatment of cNeP due to multiple sclerosis.

Significant benefits have been identified for several physiotherapy interventions, including non-invasive neurostimulation (for SCI and phantom limb pain), mirror therapy (for phantom limb pain), acupuncture (for stroke), and TENS and exercises (for multiple sclerosis). These results may potentially indicate useful approaches for the treatment of pain in neurological disorders. The other strengths of the review are as follows: (1) the comprehensive search strategy used to identify physiotherapy intervention trials for the treatment of cNeP; (2) this review is the most

comprehensive review, to date, including all neurological disorders resulting in cNeP; and (3) language barriers were eliminated by the inclusion of studies published in all languages. A possible limitation of this systematic review was that heterogeneity and the limited number of studies for certain health conditions prevented the performance of meta-analysis for at least half of the identified interventions. Finally, we restricted our review to RCTs. Although systematic reviews of RCTs are considered to represent the highest level of evidence for investigating the efficacy of interventions, we excluded studies on pain management for cNeP beyond the five included health conditions due to the study design.

Conclusion
We identified five physiotherapy interventions for the management of cNeP secondary to SCI, multiple sclerosis, stroke, and phantom limb pain. Our meta-analysis provided evidence for the use of non-invasive neurostimulation to manage cNeP secondary to SCI and phantom limb pain, the use of mirror therapy to manage phantom limb pain, the use of acupuncture to manage cNeP secondary to stroke, and the use of TENS and exercises to manage cNeP secondary to multiple sclerosis. Further studies should include larger sample sizes to validate the benefits of non-invasive neurostimulation for the treatment of patients who require pain management following stroke and various stages of SCI. Because the treatment efficacy of acupuncture therapy depends on eliciting de qi, future acupuncture trials must utilise valid and standardised tools capable of performing quantitative measurement of de qi. Further studies also remain necessary to determine the optimal parameters for exercise and TENS interventions, including the most beneficial exercise types for improving pain severity in cNeP secondary to multiple sclerosis.

Author contributions
Priya Kannan: Conceptualisation; Methodology; Supervision; Writing – original draft; Writing – review & editing.
Umar Muhammad Bello: Methodology; Software; Writing – review & editing.
Stanley John Winser: Conceptualisation; Funding acquisition; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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