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REVIEW

Nonpharmacological rehabilitation interventions for motor and cognitive outcomes following pediatric stroke: a systematic review

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Abstract
The aim of this review was to evaluate the evidence for nonpharmacological rehabilitation interventions for motor and cognitive impairment following pediatric stroke. A literature search was conducted using multiple scientific databases. Studies were included if (1) the study population was > 50% pediatric (< 18 years) stroke, (2) a diagnosis of stroke was explicitly stated, (3) there were ≥ 3 pediatric stroke participants included in the study sample, and (4) motor or cognitive outcome measures were used to assess effect of treatment. Levels of evidence were assigned to each study to determine the strength of the evidence for each intervention. A total of 18 articles met inclusion criteria. Most studies ($N = 14$) examined rehabilitation of the upper limb, with constraint-induced movement therapy (CIMT) as the most common intervention. Overall, the evidence supports the use of CIMT, forced use therapy, repetitive transcranial magnetic stimulation, functional electrical stimulation, and robotics, but suggests no beneficial effect of transcranial direct current stimulation. Very few studies assessed interventions for the lower limb ($N = 1$) or cognitive impairment ($N = 3$).

Conclusion: Effective rehabilitation approaches are important for optimizing outcomes in children who have had a stroke. Although the number of published clinical trials has increased in recent years, little evidence-based guidance exists for this clinical population.

What is Known:
- *Pediatric stroke is a significant cause of disability in children that is often associated with long-term motor and cognitive sequelae.*
- *There is a need to establish a knowledge base regarding available evidence-based rehabilitation therapies for this clinical population.*

What is New:
- *Most studies examining interventions for motor function focus on upper limb rehabilitation, whereas few studies have investigated interventions for improving lower limb or cognitive impairment.*
- *An important gap exists regarding evidence-based rehabilitative treatment approaches for pediatric stroke.*

Keywords Pediatric stroke · Stroke rehabilitation · Motor function · Cognitive function · Neurorehabilitation

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Abbreviations

AHA	Assisting Hand Assessment
BBT	Box and Blocks Test
CIMT	Constraint-induced movement therapy
COPM	Canadian Occupational Performance Measure
FES	Functional electrical stimulation
MA	Melbourne Assessment
PAFT	Pediatric Arm Function Test
PCT	Prospective controlled trial
PDMS	Peabody Developmental Motor Scale
PEDro	Physiotherapy evidence database
PMAL	Pediatric Motor Activity Log
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
WMTB-C	Working Memory Test Battery for Children

Introduction

Globally, the prevalence of pediatric stroke has increased by approximately 35% between 1990 and 2013 [29] and has been observed to occur at a rate as high as 1.6 per 100,000 children [32], placing it among the top ten causes of childhood mortality [33]. Although there are several distinct forms of pediatric stroke depending on mechanism and timing of injury, they can be broadly categorized into ischemic and hemorrhagic types [2]. While these same types of strokes are observed in the adult population, their underlying etiologies differ in the pediatric population. Traditional risk factors associated with adult stroke are related to lifestyle (e.g., atherosclerosis, hypertension, obesity) [3, 12], whereas congenital illnesses and cerebrovascular malformations, such as heart diseases and sickle cell disease, are the primary causes of pediatric stroke [3, 12, 30, 33].

Pediatric stroke often results in complications that lead to physical, cognitive, and psychosocial disability [19] and is associated with significant morbidity [44]. The clinical presentation of pediatric stroke varies based on the age of the child, with younger children typically presenting with motor deficits, while older children often demonstrate a combination of language and motor deficits [20]. Hemiparesis is one of the most common impairments post-stroke, being present in 50 to 80% of cases [8]. Cognitive impairment is also observed frequently following pediatric stroke, with long-term deficits occurring in up to half of child stroke survivors [18]. Of the various cognitive domains affected, such as intellectual functioning and memory, executive function (including attention and processing speed skills) is particularly vulnerable to impairment [18]. Importantly, deficits experienced post-stroke significantly impact children's independence, activities of daily living, and quality of life [31].

Compared to the adult stroke population, there is conflicting evidence regarding whether or not outcomes in children are more favorable and whether or not children recover better than adults after stroke [15, 23]. However, it has been suggested that recovery patterns and trajectories differ between children and adults [23]. Despite this difference, in addition to differing risk factors underlying stroke, current therapeutic management for children who have had a stroke continues to be mostly guided by extrapolation from the adult stroke literature [44]. Since appropriate treatment approaches and intervention protocols are informed by the combination of mechanisms underlying stroke as well as recovery trajectories [7, 25], there is a need for knowledge regarding pediatric-specific evidence-based interventions. Furthermore, current reviews and guidelines for pediatric stroke rehabilitation are often underpinned by studies that include mixed clinical populations (e.g., stroke, cerebral palsy, acquired brain injury) [19, 38]. Thus, greater and more accurate insight into pediatric stroke rehabilitation can be gained by limiting studies and reviews to stroke populations only.

To date, there has been no systematic review which comprehensively summarizes the state of the evidence regarding rehabilitation therapies for children post-stroke; much of the literature at present pertains to acute management, etiology, and outcomes. Therefore, the objective of this systematic review was to provide an overview of the evidence regarding effectiveness of nonpharmacological rehabilitation interventions for motor and cognitive impairment following pediatric stroke.

Methods

Literature search strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [34], a comprehensive literature search was conducted for articles published from January 1, 1980, to December 8, 2017, using the following scientific databases: PubMed, MEDLINE, CINAHL, and EMBASE. Pediatric stroke-related population key words were searched in combination with complication and intervention key words. Medical Subject Headings were used as available in each database. Variations of key words were used and were individualized for each database. The detailed search strategy is presented in Online Resource 1. Searches were limited to journal articles published in the English language.

Selection criteria

Articles which investigated nonpharmacological rehabilitation interventions for cognitive or motor outcomes post-pediatric stroke were included if they met the following four a priori inclusion criteria:

(1) The study population was composed of > 50% individuals who sustained a pediatric (28 weeks gestation to 18 years) stroke;
(2) A diagnosis of stroke was explicitly stated;
(3) There were ≥ 3 human pediatric (< 18 years) stroke participants included in the study sample;
(4) Motor or cognitive outcome measures were used to assess effect of treatment.

Stroke-induced conditions (i.e., cerebral palsy) were included if there was clear and explicit mention of stroke etiology. Articles were excluded if they were case studies/reports, study protocols, reviews, or used a qualitative research design.

Study selection

After removing duplicates, articles were screened for eligibility based on title and abstract by two independent reviewers (MM, AMc), according to inclusion criteria. The full text was retrieved if uncertainty remained or when more information was required to make a decision. Any discrepancies were resolved by a third reviewer (NS). Additionally, the reference lists of included articles as well as relevant published guidelines [19, 38] were screened for other articles which may have been missed by the computer search.

Methodological quality assessment

The methodological quality of randomized controlled trials (RCTs) was assessed by two independent reviewers (NS, MM) using the physiotherapy evidence database (PEDro) tool [35]. The PEDro tool assesses study quality and consists of 11 criteria that are answered with a “yes” (score = 1) or “no” (score = 0). The first item is not used in calculating the final score; thus, a maximum score of 10 can be achieved. PEDro scores were then used to categorize RCTs as poor (< 4), fair (4–5), good (6–8), or excellent (9–10) quality [11]. Levels of evidence were assigned to each study using a modified Sackett scale [40] (Table 1).

Data extraction and synthesis

The following data were extracted from each study by two independent reviewers (NS, MM): participant characteristics (age, gender, % stroke in study sample, stroke diagnosis, time post-stroke, stroke site, stroke side of pathology (as per reported hemispheric side or affected body side), and clinical presentation), study characteristics (author name, year and country of publication, article title, study design, sample size), treatment characteristics (intervention, comparator, concurrent therapy), outcome measures, assessment time points, and results. Extracted information from each study was organized into two tables whereby similar interventions for motor or cognitive outcomes, respectively, were grouped together. Levels of evidence assigned to each study were used to determine the strength of the evidence for each intervention.

Table 1 Modified Sackett scale

Level	Description
1a	More than one RCT (PEDro score ≥ 6)
1b	One RCT (PEDro score ≥ 6)
2	RCT (PEDro score < 6), prospective controlled trial, cohort
3	Case-control
4	Case series, pre-post test, post-test
5	Observational, case report, clinical consensus

PEDro Physiotherapy evidence database, *RCT* randomized controlled trial

Results

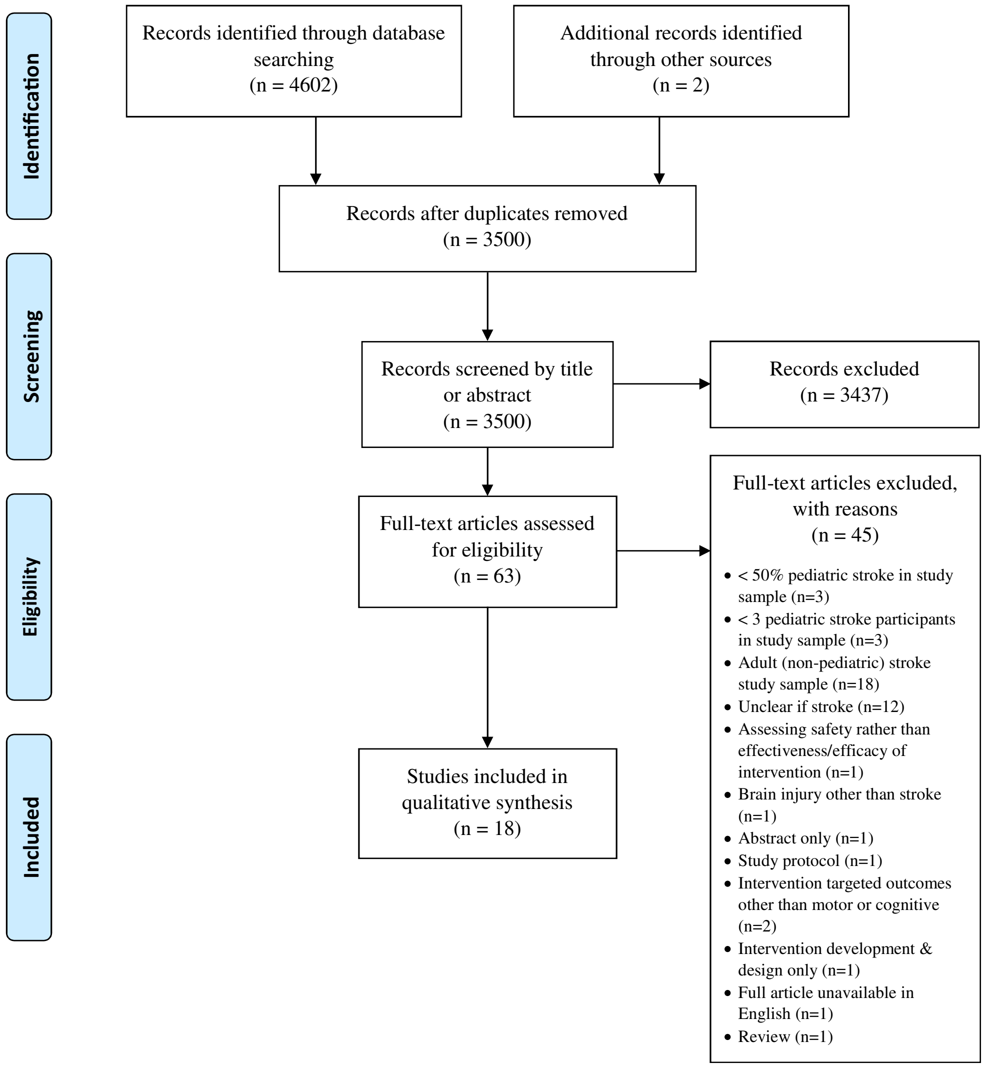
Study selection

The literature search yielded a total of 4602 citations, 16 of which met inclusion criteria and were suitable for qualitative analysis. Two additional articles were added after reviewing the reference lists of the included studies and relevant guidelines (Fig. 1).

Participant and study characteristics

Studies examining interventions for motor outcomes Fifteen studies investigated nonpharmacological rehabilitation interventions for motor outcomes. Participant and study characteristics are summarized in Table 3. Seven studies [13, 14, 26–28, 43, 45] were RCTs, two of which included a crossover component. Methodological quality of RCTs was fair for two studies [43, 45], good for four studies [13, 14, 26, 27], and excellent for one study [28] (Table 2). Two studies were conducted as secondary analyses in follow-up to RCTs, with quality ratings of fair [36] and good [4]. Six studies [10, 16, 21, 22, 37, 47] were pre-post studies. Individual total sample sizes ranged from 4 to 45 participants, generating a pooled sample of 200 participants among all studies. Mean ages ranged from 1.5 to 16.9 years, with a pooled mean age of 9.8 years. Most studies recruited pediatric stroke participants who were still pediatric (< 18 years) patients at the time of enrollment; the

Fig. 1 PRISMA flow diagram



remaining seven studies [4, 14, 21, 26–28, 36] recruited pediatric stroke participants of which a subset had become adults (> 18 years) by the time of enrollment. There were 91 male and 84 female participants overall across studies with the exception of one study [45] which did not report on gender. The majority of study populations were all stroke; the remaining studies [10, 13, 45] ranged from 52 to 95% stroke overall, and the percentage of stroke in one study [36] could only be identified as > 50%. Stroke diagnoses included arterial ischemic stroke, periventricular venous infarction, childhood, prenatal, perinatal, or very early antenatal stroke, or stroke without further description. Six studies [10, 16, 22, 26, 45, 47] reported on time post-stroke, which ranged from > 0.5 years to a mean of 8.1 years; the remaining studies did not report on time post-stroke. The location of stroke varied and included regions of the cerebral cortex, middle cerebral artery territory, basal ganglia, internal capsule, corona radiata, periventricular area, and other undefined subcortical areas; however, this information was not reported by the majority of studies. There were 63 right-sided and 100 left-sided strokes across the majority of studies; two studies [10, 45] did not report on stroke side. All but one study focused on exclusively upper extremity motor impairment; the majority of participants (N = 140) had hemiparesis, and smaller subsets of participants had hemiparesis with spasticity or dystonia, hemiparetic cerebral palsy, or hemiplegia. The remaining study [47] targeted lower extremity motor impairment in the form of hemiparesis (Table 3).

Studies examining interventions for cognitive outcomes Three studies investigated nonpharmacological rehabilitation interventions for cognitive outcomes. Participant and study characteristics are summarized in Table 4. One study [24] was a RCT of poor quality (Table 2). One study was a prospective controlled trial (PCT) [48], and one was a pre-post study [9]. Individual total sample sizes ranged from 6 to 9 participants, generating a pooled sample of 22 of which there were 10 males and 12 females. Mean ages ranged from 11.3 to

Table 2 Methodological quality assessment of included randomized controlled trials using the physiotherapy evidence database tool

Study	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Total
Carlson et al. 2018	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	7
Gillick et al. 2014	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	7
Gillick et al. 2015	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	7
King et al. 2007	Y	Y	N	N	N	N	N	N	N	Y	N	2
Kirton et al. 2008	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	6
Kirton et al. 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Kirton et al. 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Rich et al. 2016	Y	Y	N	Y	Y	N	Y	N	N	N	N	4
Taub et al. 2011	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Willis et al. 2002	Y	Y	N	N	N	N	N	Y	N	Y	Y	4

C criterion, *C1* eligibility criteria, *C2* random allocation, *C3* concealed allocation, *C4* group similarity at baseline, *C5* blinding of subjects, *C6* blinding of therapists, *C7* blinding of assessors, *C8* measures of key outcome(s) obtained from ≥ 85% of subjects, *C9* intention to treat analysis, *C10* between-group statistical comparisons, *C11* point measures and measures of variability, *N* no, *Y* yes

14.3 years, with a pooled mean age of 12.7 years. All three studies recruited pediatric stroke participants who were still pediatric (< 18 years) patients at the time of enrollment, and all had study populations that were 100% stroke, comprising various stroke diagnoses including silent and/or overt infarcts, sickle cell disease-related infarcts, and childhood arterial ischemic stroke. Only one study [9] reported on time post-stroke, with a mean of 7.3 years. Stroke site or side was not reported by one study [24]; the location of stroke across the remaining two studies was not described in detail, but included the frontal lobe and related areas, as well as subcortical involvement or lack thereof. There were two right-sided, four left-sided, and seven bilateral strokes. The cognitive clinical presentation of participants differed and included memory impairment, learning disabilities, dysarthria, attention deficits, or unremarkable deficits.

Interventions for motor outcomes

Constraint-induced movement therapy, forced use therapy

Five studies examined the effect of constraint-induced movement therapy (CIMT), and one study examined the effect of forced use therapy, on upper limb motor impairment, including three RCTs and three pre-post studies.

One RCT [27] compared CIMT combined with motor learning therapy to motor learning therapy alone in a subset of 23 children with hemiparesis due to stroke. Treatment was delivered over 10 consecutive weekdays. Children receiving CIMT improved on the Assisting Hand Assessment (AHA) at 1 week ($p = 0.0003$) and 2 months ($p = 0.0004$) following treatment compared to the control group, but this effect was not maintained at 6-month follow-up. Improvement was also noted for the Melbourne Assessment (MA) at 1-week follow-up; however, this did not reach statistical significance compared to the control group and was unchanged at 6-month follow-up. ABILHAND-Kids scores did not change following treatment.

One RCT [43] examined the effect of CIMT compared to usual care (occupational and physical therapy) in 20 children with hemiparesis due to stroke over 15 consecutive weekdays. Immediately following treatment and at 6-month follow-up, children who received CIMT demonstrated significant improvement on the Pediatric Motor Activity Log (PMAL), Inventory of New Motor Activities and Patterns, and Pediatric Arm Function Test (PAFT) and showed significantly improved active range of motion, compared to the control group ($p < 0.05$ for all). Nine children who were randomized to the control group initially were treated with CIMT after a period of 6 months and performed significantly better on all measures ($p < 0.005$ for all) after crossover compared to baseline.

Three studies utilized a pre-post design [16, 21, 37]. Among these studies, the effect of CIMT was examined in children with hemiparetic cerebral palsy, or hemiparesis with or without spasticity or dystonia, due to stroke. CIMT duration ranged from 12 days to 4 weeks. Assessment scores before and after intervention demonstrated improved upper limb function as per the PMAL ($p < 0.001$), PAFT ($p < 0.001$) [37], and Wolf Motor Function Test time ($p = 0.052$) and quality ($p = 0.005$) scores [21]. The remaining study [16] reported improved motor function in one of six participants and no improvement in quality of movement among any participants following intervention, although the results of statistical analyses were not provided.

One RCT [45] compared forced use therapy to no intervention in 25 children with hemiparesis over the course of 1 month. Of the total study sample, 13 of 25 (52%) children had a stroke, while the other participants had cerebral malformations, trauma, or unknown diagnoses. All children continued to receive routine occupational and physical therapy throughout the duration of the study. Compared to the control group, the children receiving forced use therapy

Table 3 Study, participant, and treatment characteristics and results of included studies examining rehabilitation interventions for motor outcomes

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
Constraint-Induced Movement Therapy				
[a]Kirton et al. 2016, Brain stimulation and constraint for perinatal stroke hemiparesis: The PLASTIC CHAMPS trial, Canada, RCT, PEDro = 8, $N_{Initial} = 45$, $N_{Final} = 45$, Level 1b	*Treatment Group 1 (CIMT) (n = 11)*: 10.57 (3.7) yr., 6.23–17.63 yr., males = 6, females = 5, 100% stroke, Perinatal arterial ischemic stroke (*n* = 5), periventricular venous infarction (*n* = 6), NR, NR; R = 3, L = 8, Symptomatic hemiparesis with perceived functional limitations	CIMT (cast 90% of waking hours) and motor learning therapy (2 h/d of individualized therapy, 5.5 h/d of group therapy) for 10 consecutive weekdays. Additionally, 60 min/evening of upper limb activity homework during the treatment period, and 15 min/d of home bimanual therapy following the treatment period.	AHA[1], COPM[1], MA[2], PedsQL in CP[2], ABILHAND-Kids[2], grip strength[2], BBT[2]	1. The CIMT group improved on the AHA at 1 wk. ($p = 0.0003$) and 2 months ($p = 0.0004$), but not at 6 months ($p = 0.11$) post intervention compared to the control group. 2. A clinically significant improvement was achieved on the AHA in 52% of the CIMT group vs. 32% of the control group ($p = 0.10$).
	Control Group (no CIMT or rTMS) (n = 12): 10.34 (3.5) yr., 6.32–18.22 yr., males = 7, females = 5, 100% stroke, Perinatal arterial ischemic stroke (*n* = 10), periventricular venous infarction (*n* = 2), NR, NR; R = 7, L = 5, Symptomatic hemiparesis with perceived functional limitations	Motor learning therapy without CIMT. None.	Outcomes were assessed at baseline, and 1 wk., 2 months, and 6 months post intervention.	3. Treatment with CIMT was associated with clinically significant gains on the COPM at 6 months. 4. Treatment with CIMT was associated with significant gains in satisfaction ($p = 0.04$) but not performance ($p = 0.21$) on the COPM. 5. Mean MA scores increased from baseline at 1 wk. in the CIMT group, but were unchanged at 6 months. 6. PedsQL in CP parent scores for child daily activity and school activity increased at 6 months in the CIMT group compared to the control group ($p < 0.05$). 7. There were no changes in ABILHAND-Kids scores. 8. Results were not reported for BBT or grip strength for the affected extremity.
Rickards et al. 2014, Diffusion tensor imaging study of the response to constraint-induced movement therapy of children with hemiparetic cerebral palsy and adults with chronic stroke, USA, Pre-Post, N/A, $N_{Initial} = 10$, $N_{Final} = 10$, Level 4	*Total Study Sample (n = 10)*: 3.2 (1.7) yr., 2.1–7.6 yr., males = 7, females = 3, 100% stroke, Prenatal, perinatal, or very early antenatal stroke, NR, NR; R = 2, L = 8, Hemiparetic CP	CIMT 3 h/d for 15 consecutive weekdays. On the final 2 days, the cast was removed, and bilateral activity training was performed. Childrens' caregivers facilitated transfer of therapeutic gains for an additional 0.5 h/treatment day.	PMAL-R, PAFT	1. Scores on the PMAL-R increased significantly ($p < 0.001$), indicating improved real-world arm use. 2. Scores on the PAFT increased significantly ($p < 0.001$) indicating improved limb preference in the lab.

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
		None. None.	Outcomes were assessed before and after intervention.	
Taub et al. 2011, Treatment of congenital hemiparesis with pediatric constraint-induced movement therapy, USA, RCT with crossover, PEDro = 5, $N_{Initial} = 20$, $N_{Final} = 9$, Level 2	*Treatment Group (n = 10)*: 4.0 (1.2) yr., 2.0–6.0 yr., males = 2, females = 8, 100% stroke, Prenatal, perinatal, or very early antenatal stroke, NR, NR; R = 2, L = 8, Upper extremity hemiparesis	CIMT 6 h/d for 15 consecutive week-days. On the final 2 days, the cast was removed, and bilateral activity training was performed. Usual and customary care (1–2 h PT or OT/wk). None.	PMAL, INMAP, PAFT, PROM, AROM Outcomes were assessed at baseline, and immediately, 6 months, and 1 yr. post intervention.	1. PMAL, INMAP, PAFT (affected arm use, functional ability), and AROM scores increased significantly in the immediate CIMT group compared to the control group immediately post intervention ($p < 0.0001$, $p < 0.0001$, $p = 0.01$, $p = 0.03$, and $p < 0.0001$, respectively).
	Control Group (n = 10): 3.3 (1.6) yr., 2.0–6.0 yr., males = 2, females = 8, 100% stroke, Prenatal, perinatal, or very early antenatal stroke, NR, NR; R = 4, L = 6, Upper extremity hemiparesis	After 6 months, 9 control group participants received CIMT.		2. At 6-month follow-up, the immediate CIMT group continued to show larger gains compared to the control group ($p < 0.05$ for all measures). 3. The control group performed significantly better on PMAL, INMAP, PAFT (affected arm use, functional ability), and AROM after crossing over to CIMT treatment ($p < 0.0001$, $p < 0.0001$, $p = 0.004$, $p < 0.0001$, and $p < 0.0001$, respectively). 4. For both immediate and crossover CIMT groups, there was no significant decrease in INMAP, PAFT, or AROM from post-treatment scores to 6 months follow-up, or at 1 yr. follow-up for the immediate CIMT group ($p > 0.09$ for all measures).
Gordon et al. 2007, Modified constraint-induced movement therapy after childhood stroke, UK, Pre-Post, N/A, $N_{Initial} = 8$, $N_{Final} = 6$, Level 4	*Total Study Population (n = 6)*: 11.6 yr., 6.83–15.17 yr., males = 1, females = 5, 100% stroke, Arterial ischemic stroke, 8.1 yr., Various locations by patient, including cerebral cortex, basal ganglia, and internal capsule; R = 4, L = 2, Chronic hemiparesis and impaired	Modified CIMT 2 h/d, 5×/wk. for 4 wks. None. One child received no community therapy while the other participants received periodic PT and/or OT.	MAS, grip strength, Annett pegs, tapping with a stylus, MA, COPM, GAS Outcomes were assessed 4 wks prior to intervention, at baseline,	1. Level of motor impairment improved in only 1 participant (severe impairment at baseline, moderate impairment immediately after and 4 wks post intervention; significant improvement on MA).

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
	upper limb function, including dystonia or spasticity		immediately after intervention, and 4 wks post intervention.	2. There were no significant changes in quality of movement post intervention. 3. All participants improved by at least 1 increment in each of their 3 goals on the COPM.
Juenger et al. 2007, Cortical neuromodulation by constraint-induced movement therapy in congenital hemiparesis: An fMRI study, Germany, Pre-Post, N/A, $N_{Initial}$ = 10, N_{Final} = 10, Level 4	*Total Study Population (n = 10)*: 15.8 yr., 10.0–30.0 yr., males = 5, females = 5, 100% stroke, Stroke (not specified further), NR, Cortico-subcortical infarction in MCA territory including the frontal, temporal, and/or parietal lobes; R = 4, L = 6, Congenital hemiparesis with significant motor impairment of the paretic hand but preserved active grasp	CIMT 2 h/d (individual therapy) in combination with group therapy CIMT for 12d. None. None.	WMFT Outcomes were assessed before and after intervention.	1. Following CIMT, participants demonstrated a significant functional improvement in the paretic hand, as measured by WMFT time (reduced time median in 8/10 participants) ($p = 0.052$) and quality (increased quality score in 10/10 participants) ($p = 0.005$) scores.
Forced Use Therapy				
Willis et al. 2002, Forced use treatment of childhood hemiparesis, USA, RCT with crossover, PEDro = 4, $N_{Initial}$ = 25, N_{Final} = 17, Level 2	*Treatment Group (n = 12)*: 4.7 yr., 3.0–6.0 yr., NR, NR, Stroke (not specified further), ≥ 1 yr., NR; NR, Hemiparesis of at least 1 yr *Control Group (n = 13)*: 3.5 yr., 1.0–8.0 yr., NR, NR, Stroke (not specified further), ≥ 1 yr., NR; NR, Hemiparesis of at least 1 yr., Overall: 52% (13/25) stroke	Forced use therapy for 1 month. No intervention. During the study period, all participants continued routine visits to OT and PT (30-60 min/visit). After 6 months, 10 control group participants received forced use therapy for 1 month and 7 treatment group participants received no intervention.	PDMS Outcomes were assessed at baseline and immediately after intervention, both before and after crossover.	1. The treatment group improved significantly compared with controls during the first set of treatment ($p < 0.0001$). 2. For initial treatment group participants, the effect of casting persisted 6 months later. 3. For initial control group participants who returned for casting 6 months later, score differences before and after casting were significant ($p = 0.005$).
Transcranial Direct Current Stimulation				
Gillick et al. 2015, Safety and feasibility of transcranial direct current stimulation in pediatric hemiparesis: Randomized controlled preliminary study, USA, RCT, PEDro = 7, $N_{Initial}$ = 13, N_{Final} = 11, Level 1b	*Treatment Group (n = 5)*: 10.7 (3.2) yr., 7.8–15.2 yr., males = 3, females = 2, 100% stroke, Hemispheric stroke (not specified further), NR, NR; R = 4, L = 1, Congenital hemiparesis	1 10 min session of tDCS (0.7 mA, anodal over ipsilesional M1 and cathodal over contralesional M1). Sham tDCS. None.	BBT-A, grip strength Outcomes were assessed at baseline, immediately post intervention, and at 7 days follow-up.	1. BBT-A scores demonstrated stability or slight improvement in the treatment and control groups. 2. There was a small decline in some grip strength values in the control group at follow-up.

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
	Control Group (n = 6): 16.9 (2.6) yr., 11.8–18.5 yr., males = 1, females = 5, 100% stroke, Hemispheric stroke (not specified further), NR, NR; R = 1, L = 5, Congenital hemiparesis			3. Overall, there were no significant differences between groups on all outcome measures.
Kirton et al. 2017, Transcranial direct current stimulation for children with perinatal stroke and hemiparesis, Canada, RCT, PEDro = 10, $N_{Initial} = 24$, $N_{Final} = 23$, Level 1b	*Treatment Group (n = 12)*: 12.20 (3.08) yr., 6.23–18.34 yr., males = 8, females = 4, 100% stroke, Perinatal arterial ischemic stroke (*n* = 7), periventricular venous infarction (*n* = 5), NR, NR; R = 8, L = 4, Symptomatic, non-severe hemiparetic CP *Control Group (n = 11)*: 10.89 (3.71) yr., 5.80–16.06 yr., males = 7, females = 4, 100% stroke, Perinatal arterial ischemic stroke (*n* = 8), periventricular venous infarction (*n* = 3), NR, NR; R = 5, L = 6, Symptomatic, non-severe hemiparetic CP	20 min/d tDCS (1 mA cathodal over contralesional M1) followed by motor learning therapy (90 min/d individualized therapy, 30 min/d group therapy) for 10 consecutive weekdays, including CIMT training during the first 5 weekdays and bi-manual training during the second 5 weekdays. 120 min/session of group therapy was provided on weekends (3 sessions total). Additionally, participants were given 15 min/evening of upper limb activity homework during the treatment period, and 15 min/d home therapy program from 2 wks to 2 months post intervention. Sham tDCS and motor learning therapy. None.	AHA[1], COPM[1], MA[2], PedsQL in CP[2], ABILHAND-Kids[2], bilateral grip and pinch strength[2], BBT[2] Outcomes were assessed at baseline, and 1 wk. and 2 months post intervention.	1. AHA scores increased significantly in all patients after 1 wk. ($p = 0.002$). 2. There was no significant difference in AHA scores between treatment and control groups at 2 months ($p = 0.69$). 3. COPM performance and satisfaction scores increased in all participants over time. 4. At 1 wk. and 2 months, significantly more tDCS participants had achieved a clinically significant improvement (≥ 2 point increase) in performance and satisfaction scores on the COPM ($p = 0.005$, $p < 0.001$ and $p = 0.02$, $p < 0.001$, respectively) compared to controls. 5. The increase in mean COPM performance and satisfaction scores from baseline to 2 months was greater in tDCS participants ($p = 0.001$, $p = 0.02$, respectively) compared to controls. 6. PedsQL in CP parent scores were significantly associated with tDCS treatment for child daily activity ($p = 0.06$) and school activity ($p = 0.02$). 7. There were no treatment effects for the MA, BBT, ABILHAND-Kids, grip, or pinch strength.
			COPM, AHA, MA, BBT-A	

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
Carlson et al. 2018, Changes in spectroscopic biomarkers after transcranial direct current stimulation in children with perinatal stroke, Canada, RCT (Follow-up to Kirton et al. 2017), PEDro = 7, $N_{Initial} = 23$, $N_{Final} = 15$, Level 1b	*Total Study Population (Treatment Group (n = 7), Control Group (n = 8))*: 12.1 (3.0) yr., 6.6–18.3 yr., males = 11, females = 4, 100% stroke, Perinatal arterial ischemic stroke (*n* = 9), periventricular venous infarction (*n* = 6), NR, NR; R = 8, L = 7, Symptomatic hemiparetic CP with perceived functional limitations	20 min/d tDCS (1 mA cathodal over contralesional M1) followed by motor learning therapy (90 min/d individualized therapy, 30 min/d group therapy) for 10 consecutive weekdays, including CIMT training during the first 5 weekdays and bi-manual training during the second 5 weekdays. 120 min/session of group therapy was provided on weekends (3 sessions total). Additionally, participants were given 15 min/evening of upper limb activity homework during the treatment period, and 15 min/d home therapy program from 2 wks to 2 months post intervention. Sham tDCS and motor learning therapy. None.	 Outcomes were assessed at baseline, and 1 and 8 wks post intervention.	1. Mean motor function improved in all participants post intervention. 2. Individual clinically significant improvements (≥ 2 point increase) were seen in performance and satisfaction scores on the COPM, with tDCS being significantly associated with larger improvements at 1 wk. and 2 months. 3. No effect of tDCS was demonstrated on the AHA.
Repetitive Transcranial Magnetic Stimulation				
Kirton et al. 2008, Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical pediatric stroke: a randomized trial, Canada, RCT, PEDro = 6, $N_{Initial} = 10$, $N_{Final} = 10$, Level 1b	*Treatment Group (n = 5)*: 14.1 yr., 10.0–20.2 yr., males = 3, females = 2, 100% stroke, Subcortical arterial ischemic stroke, 7.6 yr., Basal ganglia, PLIC (*n* = 4), corona radiata, PLIC (*n* = 1); R = 1, L = 4, Unilateral hand weakness with impaired function *Control Group (n = 5)*: 13.8 yr., 8.6–20.7 yr., males = 3, females = 2, 100% stroke, Subcortical arterial ischemic stroke, 5.0 yr., Basal ganglia, PLIC; R = 0, L = 5, Unilateral hand weakness with impaired function	20 min treatments of rTMS (1 Hz over contralesional motor cortex) 1x/d for 8 days. Sham rTMS. None.	MA[1], grip strength[1], PPT[2], HRFT[2], IHM[2] Outcomes were assessed at baseline, day 5 (within 1 h post 4th treatment), day 10 (24 h post 8th treatment), and day 17 (1 wk. post 8th treatment).	1. Significant improvements in MA scores were noted in the rTMS group at day 10 ($p = 0.002$), but not at day 5 ($p = 0.65$) or day 17 ($p = 0.32$), compared to the sham rTMS group. 2. MA scores improved between baseline and day 10 ($p = 0.07$) within the rTMS group. 3. Significant improvements in grip strength were noted in the rTMS group at day 10 ($p = 0.009$) and day 17 ($p = 0.01$), but not at day 5 ($p = 0.19$), compared to the sham rTMS group. 4. Grip strength improved between baseline and day 10 ($p = 0.07$) as well as day 17 ($p = 0.05$), within the rTMS group.

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
				5. Accurate data was only available for all participants for the two primary outcome measures.
[a]Kirton et al. 2016, Brain stimulation and constraint for perinatal stroke hemiparesis: The PLASTIC CHAMPS trial, Canada, RCT, PEDro = 8, $N_{Initial} = 45$, $N_{Final} = 45$, Level 1b	*Treatment Group 2 (rTMS) (n = 10)*: 12.20 (4.2) yr., 6.32–18.48 yr., males = 5, females = 5, 100% stroke, Perinatal arterial ischemic stroke ($n = 7$), periventricular venous infarction ($n = 3$), NR, NR; R = 6, L = 4, Symptomatic hemiparesis with perceived functional limitations	20 min treatments of rTMS (1 Hz over contralesional M1) 1x/d and motor learning therapy (2 h/d of individualized therapy, 5.5 h/d of group therapy) for 10 consecutive weekdays. Additionally, 60 min/evening of upper limb activity homework during the treatment period, and 15 min/d of home bimanual therapy following the treatment period.	AHA[1], COPM[1], MA[2], PedsQL in CP[2], ABILHAND-Kids[2], grip strength[2], BBT[2]	1. The rTMS group improved on the AHA at 1 wk. ($p = 0.005$), but not at 6 months ($p = 0.09$) post intervention compared to the control group. 2. A clinically significant improvement was achieved on the AHA in 52% of the rTMS group vs. 33% of the control group ($p = 0.13$).
	Control Group (no CIMT or rTMS) (n = 12): 10.34 (3.5) yr., 6.32–18.22 yr., males = 7, females = 5, 100% stroke, Perinatal arterial ischemic stroke ($n = 10$), periventricular venous infarction ($n = 2$), NR, NR; R = 7, L = 5, Symptomatic hemiparesis with perceived functional limitations	Sham rTMS and motor learning therapy without CIMT. None.	Outcomes were assessed at baseline, and 1 wk., 2 months, and 6 months post intervention.	3. Treatment with rTMS was associated with clinically significant gains on the COPM at 6 months. 4. Treatment with rTMS was associated with significant gains in satisfaction ($p = 0.01$) and performance ($p = 0.02$) on the COPM. 5. Mean MA scores significantly increased from baseline at 1 wk. in the rTMS group compared to the control group ($p = 0.003$), but were unchanged at 6 months. 6. PedsQL in CP parent scores for child daily activity and school activity increased at 6 months in the rTMS group compared to the control group ($p < 0.05$). 7. There were no changes in ABILHAND-Kids scores. 8. Results were not reported for BBT or grip strength for the affected extremity.
[a]Kirton et al. 2016, Brain stimulation and constraint for perinatal stroke hemiparesis: The PLASTIC	*Treatment Group 3 (CIMT + rTMS) (n = 12)*: 13.23 (3.7) yr., 8.26–19.79 yr., males = 10,	20 min treatments of rTMS (1 Hz over contralesional M1) 1x/d, CIMT (cast 90% of waking hours), and motor	AHA[1], COPM[1], MA[2], PedsQL in CP[2], ABILHAND-Kids[2], grip strength[2], BBT[2]	1. The CIMT+rTMS group improved on the AHA at 1 wk. ($p = 0.02$), 2 months ($p = 0.0002$), and 6 months

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
CHAMPS trial, Canada, RCT, PEDro = 8, $N_{Initial} = 45$, $N_{Final} = 45$, Level 1b	females = 2, 100% stroke, Perinatal arterial ischemic stroke (*n* = 7), periventricular venous infarction (*n* = 5), NR, NR; R = 4, L = 8, Symptomatic hemiparesis with perceived functional limitations *Control Group (no CIMT or rTMS) (n = 12)*: 10.34 (3.5) yr., 6.32–18.22 yr., males = 7, females = 5, 100% stroke, Perinatal arterial ischemic stroke (*n* = 10), periventricular venous infarction (*n* = 2), NR, NR; R = 7, L = 5, Symptomatic hemiparesis with perceived functional limitations	learning therapy (2 h/d of individualized therapy, 5.5 h/d of group therapy) for 10 consecutive weekdays. Additionally, 60 min/evening of upper limb activity homework during the treatment period, and 15 min/d of home bimanual therapy following the treatment period. Sham rTMS and motor learning therapy without CIMT. None.	Outcomes were assessed at baseline, and 1 wk., 2 months, and 6 months post intervention.	($p = 0.0004$) post intervention compared to the control group. 2. Treatment with CIMT+rTMS was associated with clinically significant gains on the COPM at 6 months. 3. Mean MA scores increased from baseline at 1 wk. in the CIMT+rTMS group, but were unchanged at 6 months. 4. PedsQL in CP parent scores for child daily activity and school activity increased at 6 months in the CIMT+ rTMS group compared to the control group ($p < 0.05$). 5. There were no changes in ABILHAND-Kids scores. 6. Results were not reported for BBT or grip strength for the affected extremity.
Gillick et al. 2014, Primed low-frequency repetitive transcranial magnetic stimulation and constraint-induced movement therapy in pediatric hemiparesis: a randomized controlled trial, USA, RCT, PEDro = 7, $N_{Initial} = 19$, $N_{Final} = 19$, Level 1b	*Treatment Group (n = 10)*: 10.75 (2.7) yr., 8.0–15.0 yr., males = 6, females = 4, 100% stroke, Stroke (not specified further), NR, Various locations by patient, including cortical and subcortical areas; R = 2, L = 8, Hemiparesis *Control Group (n = 9)*: 10.8 (3.1) yr., 8.0–16.0 yr., males = 4, females = 5, 89% (8/9) stroke, Stroke (not specified further), NR, Various locations by patient, including cortical and subcortical areas; R = 4, L = 5, Hemiparesis	5 10 min treatments of rTMS (1 Hz over contralesional M1) and 5 2 h CIMT treatments on alternating days for 2 wks. Sham rTMS and CIMT. None.	AHA[1], COPM[2], finger extension force[2] Outcomes were assessed at baseline and 2 days after intervention.	1. Improvement in hand function as measured by AHA scores was significantly higher in the treatment group compared to the control group ($p = 0.008$). 2. 8/10 participants in the treatment group showed an improvement greater than the smallest detectable difference on AHA raw scores, compared to 2/9 participants in the control group ($p = 0.023$). 3. There were no significant pre-post between-group differences in secondary outcome measures. 4. For COPM participation and satisfaction subsections, the mean change was large enough to be

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
				clinically important (> 2.0 points) in both groups.
Rich et al. 2016, Repetitive transcranial magnetic simulation/behavioral intervention clinical trial: Long-term follow-up of outcomes in congenital hemiparesis, USA, RCT (Follow-up to Gillick et al. 2014), PEDro = 4, $N_{Initial}$ = 19, N_{Final} = 14, Level 2	*Treatment Group (n = 8)*: 13.4 yr. (median), 12.8–16.4 yr., males = 4, females = 4, > 50% stroke, Stroke (not specified further), NR, NR; R = 1, L = 7, Hemiparesis *Control Group (n = 6)*: 13.0 yr. (median), 11.6–19.9 yr., males = 3, females = 3, > 50% stroke, Stroke (not specified further), NR, NR; R = 3, L = 3, Hemiparesis	5 10 min treatments of rTMS (1 Hz over contralesional M1) and 5 2 h CIMT treatments on alternating days for 2 wks. Sham rTMS and CIMT. None.	AHA[1], COPM[2] Outcomes were assessed once at various time points depending on when participants entered the initial trial, and ranged from 21 to 57 months (median = 47.5) post intervention.	1. AHA scores improved or were maintained in 7/8 rTMS participants and 5/6 sham rTMS participants. 2. Both COPM and AHA scores improved in 50% of rTMS and sham rTMS participants. 3. Participants displayed an increase in satisfaction on the COPM despite no change in performance, as their goal areas changed over time.
Functional Electrical Stimulation				
Kapadia et al. 2014, Functional electrical stimulation therapy for recovery of reaching and grasping in severe chronic pediatric stroke patients, Canada, Pre-Post, N/A, $N_{Initial}$ = 4, N_{Final} = 4, Level 4	*Total Study Population (n = 4)*: 13 yr., 13–13 yr., males = 2, females = 2, 100% stroke, Stroke (not specified further), 4.5 yr., Stroke in various locations by patient, including cortical and subcortical areas; R = 1, L = 3, Hemiplegia and severely impaired motor function with inability to use arm/hand for functional activities	1 h of FES therapy (40 Hz) 3×/wk. for 16 wks, delivered during functional reaching and grasping movements. None. None.	RELHFT, QUEST, PEDI, AHA Outcomes were assessed at baseline and discharge (upon completion of 48 sessions).	1. All participants improved in hand function on the RELHFT, with statistically significant improvement on the itemized objects subtest ($p = 0.042$) but no significant improvement on the other subtests. 2. All participants improved on all domains of the remaining outcome measures, however none reached statistical significance apart from the grasp subcomponent of the QUEST.
Robotics				
Fasoli et al. 2008, Upper limb robotic therapy for children with hemiplegia, USA, Pre-Post, N/A, $N_{Initial}$ = 12, N_{Final} = 12, Level 4	*Total Study Population (n = 12)*: 9.2 yr., 4.9–12.5 yr., males = 7, females = 5, 92% (11/12) stroke, Perinatal stroke ($n = 10$), childhood stroke ($n = 1$), ≥ 0.5 yr. (6.4 yr. for childhood stroke participant), NR; unclear, Upper limb hemiplegia, upper limb spasticity	Robotic therapy with the InMotion2 robot in 1 h sessions 2×/wk. for 8 wks. None.	QUEST[1], FMA upper limb subtest[1], MAS[2], peak isometric shoulder/elbow flexor/extensor strength[2], parent questionnaire[2] Outcomes were assessed at baseline, 4 wks (interim),	1. Statistically significant improvements with moderate-large effect sizes were found for FMA total score as well as the dissociated movements and weight bearing QUEST subscores at 4, 8, and 12 wks. QUEST total scores improved significantly at 8 and 12 wks. 2. MAS and isometric elbow strength as measured using a dynamometer had statistically significant improvements

Table 3 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range), gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/outcomes Assessment time points	Results
			discharge (8 wks), and 12 wks (1 month post intervention).	with small-moderate effect sizes, although inconsistently at 8 and 12 wks.
		During the study period, 8 children continued to receive community-based therapy (OT), and 4 children did not receive any OT or PT.		3. Parent questionnaire evaluated using Friedman tests for related samples showed significance for "how much" ($p = 0.001$) and "how well" ($p < 0.0005$) the child used the arm at 8 wks.
Walking Training				
Yang et al. 2013, Training to enhance walking in children with cerebral palsy: Are we missing the window of opportunity?, Canada, Pre-Post, N/A, $N_{Initial} = 5$, $N_{Final} = 5$, Level 4	*Total Study Population (n = 5)*: 1.5 (0.4) yr., 1.0–1.9 yr., males = 2, females = 3, 100% stroke, Ischemic stroke (*n* = 4), periventricular venous infarction (*n* = 1), ≥ 1 yr., MCA or periventricular area; R = 1, L = 4, Upper and lower extremity hemiparesis	Intensive walking exercise training program, ~ 1 h/d, 4d/wk. for 2–3 months. None. None.	GMFM-66, Step length symmetry, Weight-bearing during supported stepping, Outcomes were assessed before and after intervention (GMFM-66), or approximately every 2 wks (remaining measures).	1. In 4 of 5 participants, effect sizes for the total GMFM-66 score, standing subscore, and walking, running, jumping subscore were 1.09, 0.91, and 1.21, respectively. 2. In 4 of 5 participants who showed step length asymmetry, this reduced with training. 3. Weight-bearing asymmetry improved in all children in the total weight applied to the force plate during the stance phase of walking.

[a] Kirton et al. 2016 appears more than once throughout the table since multiple treatment comparisons were performed

[1] Primary outcome measure

[2] Secondary outcome measure, as identified in each study

AHA Assisting Hand Assessment, *AROM* active range of motion, *BBT* Box and Blocks Test, *BBT-A* Box and Blocks Test for affected hand, *CIMT* constraint-induced movement therapy, *COPM* Canadian Occupational Performance Measure, *CP* cerebral palsy, *d* day, *FES* functional electrical stimulation, *FMA* Fugl-Meyer Assessment, *GAS* Goal Attainment Scaling, *GMFM-66* Gross Motor Function Measure with 66 items, *h* hour(s), *HRFT* Halstead-Reitan finger tapping, *IHM* in-hand manipulation, *INMAP* Inventory of New Motor Activities and Programs, *L* left, *M1* primary motor cortex, *MA* Melbourne Assessment, *MAS* Modified Ashworth Scale, *MCA* middle cerebral artery, *N/A* not applicable, *NR* not reported, *OT* occupational therapy, *PAFT* Pediatric Arm Function Test, *PDMS* Peabody Developmental Motor Scale, *PEDI* Pediatric Evaluation of Disability Inventory, *PEDro* Physiotherapy evidence database, *PedsQL* Pediatric Quality of Life Inventory, *PLIC* posterior limb of the internal capsule, *PMAL-R* Pediatric Motor Activity Log-Revised, *PPT* Perdue peg board test, *PROM* passive range of motion, *PT* physiotherapy, *QUEST* Quality of Upper Extremity Skills Test, *R* right, *RCT* randomized controlled trial, *RELHFT* Rehabilitation Engineering Laboratory Hand Function Test, *rTMS* repetitive transcranial magnetic stimulation, *SD* standard deviation, *tDCS* transcranial direct current stimulation, *wk.* week, *WMFT* Wolf Motor Function Test, *yr.* year

Table 4 Study, participant, and treatment characteristics and results of included studies examining rehabilitation interventions for cognitive outcomes

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range). gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/ outcomes Assessment time points	Results
Memory Training				
Eve et al. 2016, Computerized working-memory training for children following arterial ischemic stroke: A pilot study with long-term follow-up, UK, Pre-Post, N/A, $N_{Initial} = 9$, $N_{Final} = 7$, Level 4	*Total Study Population (n = 7)*: 12.8 (2.2) yr., 10.5–16.17 yr., males = 3, females = 4, 100% stroke, Childhood arterial ischemic stroke, 7.3 yr., Subcortical involvement ($n = 1$), no subcortical involvement ($n = 6$); R = 2, L = 2, Bilateral = 3, Hemiparesis, attention deficits, average or below average working memory	25 30–40 min sessions of Cogmed Working Memory Training program over 5-7wks. None. None.	WMTB-C, TEA-Ch, WRAT-4 Outcomes were assessed at baseline, and 1–2 wks and 12 months post intervention.	1. At 1–2wks following intervention, the mean group score for phonological-loop working memory increased significantly ($p = 0.046$). 2. At 1–2 wks, visuospatial sketchpad, central executive, and WRAT-4 mathematics scores did not change significantly. 3. At 12 months post intervention, the mean group improvement in phonological-loop working memory was no longer significantly different from baseline. 4. At 12 months, there continued to be no change in visuospatial sketchpad or central executive scores. WRAT-4 mathematics group mean scores decreased but did not reach statistical significance. 5. At 1–2 wks and 12 months post intervention, group means for attention tasks did not change following intervention and continued to reflect deficits noted at baseline. 6. Increases and decreases in test scores were noted across participants for all outcome measures at both 1–2 wks and 12 months post intervention, with the exception of the response inhibition measure, for which no declines were observed.
King et al. 2007, A pilot randomized education rehabilitation trial is feasible in sickle cell and strokes, USA, RCT, PEDro = 2, $N_{Initial} = 11$, $N_{Final} = 9$, Level 2	*Treatment Group (n = 5)*: 12.2 yr., 9.0–16.0 yr., males = 3, females = 2, 100% stroke, Silent infarct ($n = 2$), overt infarct ($n = 2$), silent + overt infarct ($n = 1$), NR, NR; NR, Memory impairment *Control Group (n = 4)*: 11.3 yr., 8.0–13.0 yr., males = 1, females = 3, 100% stroke, Silent infarct ($n = 3$), overt infarct ($n = 1$), NR, NR; NR, Memory impairment	40 min general academic tutoring followed by 20 min memory rehabilitation training, 1×/wk. for the 1st yr. and 2×/wk. for the 2nd yr. Parents reviewed homework assignments with participants for at least 1 h/wk. 1 h general academic tutoring, 1×/wk. for the 1st yr. and 2×/wk. for the 2nd yr. Parents reviewed homework assignments with participants for at least 1 h/wk. None.	CVLT-C, CMS Digit Span subtest, WIAT-II reading, math, spelling subtests Outcomes were assessed at baseline and at 1 and 2 yrs.	1. Memory measures increased in the treatment group compared to the control group overall. 2. The treatment group had significant improvement in the delayed cue recall of the CVLT-C compared to the control group ($p = 0.02$). 3. Both the treatment and control groups improved on the backward recall component of the Digit Span subtest, although the treatment group had a

Table 4 (continued)

Author, year, title, country, study design, PEDro score, sample size, level of evidence	Age (mean (SD), range). gender, % stroke in study sample, stroke diagnosis, time post stroke (mean), stroke site; stroke side, clinical presentation	Intervention Comparator Concurrent therapy	Clinical outcome measures/ outcomes Assessment time points	Results
				statistically significant improvement compared to the control group ($p = 0.04$). 4. Both the treatment and control groups improved on the forwards test of the Digit Span subtest, and there was no significant difference between groups ($p = 0.9$). 5. All students improved in reading over the 2 yr. period ($p = 0.046$ overall). 6. The treatment group improved in math, but there was no significant difference between groups ($p = 0.4$). 7. The control group improved in spelling, but there was no significant difference between groups ($p = 0.1$).
Yerys et al. 2003, Memory strategy training in children with cerebral infarcts related to sickle cell disease, USA, PCT, N/A, $N_{Initial} = 6$, $N_{Final} = 6$, Level 2	*Treatment Group (n = 3)*: 14.3 yr., 13.0–15.0 yr., males = 2, females = 1, 100% stroke, SCD-related infarct, NR, Frontal lobe or related brain region; Bilateral = 3, Learning disability, or motor seizures, hemiparesis, and dysarthria, or unremarkable presentation *Control Group (n = 3)*: 13 yr., 11.0–15.0 yr., males = 1, females = 2, 100% stroke, SCD-related infarct, NR, Frontal lobe or related brain region; L = 2, Bilateral = 1, Hemiparesis and/or dysarthria	40 min academic tutoring followed by 20 min memory strategy training, 1×/wk. for 6wks. 1 h academic tutoring 1×/wk. for 6 wks. None.	CMS Numbers subtest, CVLT Outcomes were assessed at baseline and 1wk post intervention.	1. Two children in the treatment group improved markedly on the Numbers subtest, whereas there was no change in the performance of one child. 2. Little change was noted on the Numbers subtest for children in the control group. 3. Performance of children in the treatment group improved on the word-list learning aspect of the CVLT, but there was little change in the performance of children in the control group. The most dramatic result was the change in semantic clustering. 4. Performance on the free recall aspect of the CVLT was comparable for both groups.

CMS Children's Memory Scale, *CVLT-C* California Verbal Learning Test–Children's Version, *h* hour(s), *L* = left, *N/A* not applicable, *NR* not reported, *PCT* prospective controlled trial, *PEDro* Physiotherapy evidence database, *R* right, *RCT* randomized controlled trial, *SCD* sickle cell disease, *SD* standard deviation, *TEA-Ch* Test of Everyday Attention for Children, *WIAT-II* Wechsler Individual Achievement Tests–Second Edition, *wk.* week, *WMTB-C* Working Memory Test Battery for Children, *WRAT-4* Wide Range Achievement Test-4, *yr.* year improved significantly on the Peabody Developmental Motor Scale (PDMS) following 1 month of treatment ($p < 0.0001$), and this effect was maintained 6 months later. Ten children who were randomized to the control group initially were treated with forced use therapy 6 months after the initial treatment course and demonstrated improved PDMS scores following treatment compared to baseline ($p = 0.005$).

Levels of Evidence:

There is level 1b evidence that CIMT in combination with motor learning therapy may improve upper limb function compared to motor learning therapy alone in children with hemiparesis following pediatric stroke.

There is level 2 evidence that CIMT improves upper limb function compared to usual care in children with hemiparesis following pediatric stroke.

There is level 2 evidence that forced use therapy improves upper limb function compared to no intervention in children with hemiparesis following pediatric stroke.

Transcranial direct current stimulation One RCT [14] examined the effect of 1 session of transcranial direct current stimulation (tDCS) compared to sham tDCS in 11 children with upper limb hemiparesis due to stroke. Participants in both groups demonstrated stability or slight improvement on the Box and Blocks Test (BBT) for the affected hand following treatment, although there were no significant differences between groups for any outcomes.

One RCT [28] compared the combined effect of tDCS and motor learning therapy to sham tDCS combined with motor learning therapy for 2 weeks in 23 children with hemiparetic cerebral palsy due to stroke. Motor learning therapy included both CIMT and bimanual training. Although there was a significant increase in AHA scores ($p = 0.002$) across all participants at 1 week following intervention, there were no between-group differences at 2-month follow-up. No treatment effects were found for other motor outcome measures, including the MA, BBT, ABILHAND-Kids, or for grip or pinch strength. A follow-up study [4] was conducted using a subset of 15 children primarily to investigate metabolic changes in the motor cortex associated with the intervention. Clinical outcomes were also reported, although between-group analyses were not performed. All children improved in terms of motor function, but there was no effect of tDCS treatment on AHA scores.

Levels of Evidence:

There is level 1b evidence that tDCS does not improve upper limb function compared to sham tDCS in children with hemiparesis following pediatric stroke.

There is level 1b evidence that tDCS in combination with motor learning therapy does not improve upper limb function compared to sham tDCS in combination with motor learning therapy in children with hemiparetic cerebral palsy following pediatric stroke.

Repetitive transcranial magnetic stimulation One RCT [26] examined the effect of repetitive transcranial magnetic stimulation (rTMS) compared to sham rTMS over the course of 8 days in 10 children with hand weakness due to stroke. Children who received rTMS demonstrated significant improvements in MA scores 24 h following treatment completion ($p = 0.002$) compared to those receiving sham rTMS, but the difference was not maintained at 1-week follow-up. Significant between-group differences were noted for grip strength for both time points in favor of rTMS ($p = 0.009$ and $p = 0.01$, respectively).

Three studies examined the effect of rTMS in combination with a form of motor learning therapy. One RCT [27] assessed multiple treatment pairings, comparing rTMS plus motor learning therapy, or rTMS plus CIMT and motor learning therapy, to sham rTMS in combination with motor learning therapy without CIMT. Subsets of 22 and 24 children, respectively, who had upper limb hemiparesis due to stroke, were studied. Treatment was delivered over 10 consecutive weekdays. The former treatment comparison resulted in improvement on the AHA at 1 week ($p = 0.005$) but not at 6 months ($p = 0.09$) post-intervention for children receiving rTMS with motor learning therapy. Improvement was also noted for the MA at 1-week follow-up compared to the control group ($p = 0.003$). The latter treatment comparison resulted in improvement on the AHA at 1 week ($p = 0.02$), 2 months ($p = 0.0002$), and 6 months ($p = 0.0004$) following intervention for children receiving rTMS with CIMT and motor learning therapy. Improvement was also noted for the MA at 1-week follow-up; however, this did not reach statistical significance when compared to the control group. For both treatment comparisons, there were no changes in ABILHAND-Kids scores, and both treatment groups had unchanged AHA scores from baseline to 6-month follow-up.

One RCT [13] compared the combined effect of rTMS and CIMT to sham rTMS in combination with CIMT over the course of 2 weeks in children with upper limb hemiparesis. Of the total study sample, 18 of 19 children (95%) had a stroke. Two days following treatment completion, children receiving rTMS demonstrated significantly better improvement on the AHA compared to the control group ($p = 0.008$), although there were no significant between-group differences for finger-extension force. A follow-up study [36] was conducted to assess long-term treatment effects using a subset of 14 children. More than half of these children had a stroke, although the exact percentage could not be determined. Eighty-six percent of the total follow-up study sample demonstrated improved or maintained treatment effects on the AHA, including children from both treatment groups, at a median of 47.5 months following intervention.

Levels of Evidence:

There is level 1b evidence that rTMS may improve upper limb function compared to sham rTMS in children with hand weakness following pediatric stroke.

There is level 1b evidence that rTMS in combination with either motor learning therapy or both CIMT and motor learning therapy may improve upper limb function compared to sham rTMS in combination with motor learning therapy without CIMT in children with hemiparesis following pediatric stroke.

There is level 1b evidence that rTMS in combination with CIMT may improve upper limb function compared to sham rTMS in combination with CIMT in children with hemiparesis following pediatric stroke.

Functional electrical stimulation One pre-post study [22] examined the effect of 48 1-h sessions of functional electrical stimulation (FES) in 4 children with upper limb hemiplegia due to stroke over the course of 16 weeks and found a statistically significant improvement ($p = 0.042$) on the itemized objects subtest of the Rehabilitation Engineering Laboratory Hand Function Test upon treatment completion. No other significant improvements were found for the other subtests or for other outcome measures, although all participants demonstrated improved motor function following intervention.

Levels of Evidence:

There is level 4 evidence that FES may improve upper limb function in children with hemiplegia following pediatric stroke.

Robotics One pre-post study [10] examined the effect of 16 1-h sessions of robotic therapy in 12 children with upper limb hemiplegia and spasticity over the course of 8 weeks. Of the total study sample, 11 children (92%) had a stroke, and 8 children continued to receive community-based concurrent occupational therapy. After 8 weeks of treatment, total scores on the Fugl-Meyer Assessment and Quality of Upper Extremity Skills Test improved significantly ($p < 0.0005$ and $p = 0.001$, respectively) and were maintained at 1 month post-intervention. Significant improvements were also noted on the Modified Ashworth Scale as well as for isometric elbow strength, although inconsistently at 8 and 12 weeks.

Levels of Evidence:

There is level 4 evidence that robotics may improve upper limb function in children with hemiplegia and spasticity following pediatric stroke.

Walking training One pre-post study [47] examined the effect of an exercise training program on walking ability in five children with hemiparesis due to stroke over the course of 2–3 months. Large effect sizes were demonstrated by four of five children for the total score (1.09) and two subscores (0.91 and 1.21, respectively) of the Gross Motor Function Measure following intervention, although no statistical analyses were reported. Additionally, during the course of treatment, step length and weight-bearing asymmetry improved in all children who showed these impairments at baseline.

Levels of Evidence:

There is level 4 evidence that walking training may improve walking ability in children with hemiparesis following pediatric stroke.

Interventions for cognitive outcomes

Memory training Three studies examined the effect of memory training on cognitive outcomes.

One RCT [24] and one PCT [48] compared the combined effect of memory training with academic tutoring to academic tutoring alone in children with memory impairment, learning disabilities, dysarthria, or unremarkable deficits. Children receiving memory training and tutoring for 2 years demonstrated significantly improved memory function compared to the control group in terms of the California Verbal Learning Test delayed cue recall ($p = 0.02$) and the Children's Memory Scale backward recall digit span subtest ($p = 0.04$). There were no between-group differences on the forwards test of the digit span subtest. The PCT [48] reported improved short- and long-term memory function in children receiving memory training and tutoring for 6 weeks, compared to little change in the control group; however, the results of statistical analyses were not provided.

One pre-post study [9] examined the effect of a computerized working memory training program in seven children with attention deficits and average or below average working memory over the course of 5–7 weeks. At 1–2 weeks following treatment, there was a significant improvement on the phonological loop subtest of the Working Memory Test Battery for Children (WMTB-C); however, this effect was not maintained at 12-month follow-up. No other WMTB-C or Wide Range Achievement Test-4 subtest scores changed significantly from baseline at either time point. Mean scores on attention tasks also did not change following intervention.

Levels of Evidence:

There is level 2 evidence that memory training in combination with academic tutoring may improve memory compared to academic tutoring alone in children following pediatric stroke.

There is level 4 evidence that computerized memory training may improve working memory but not attention in children following pediatric stroke.

Discussion

This systematic review aimed to summarize and assess the available evidence for nonpharmacological motor and cognitive rehabilitation interventions in the pediatric stroke population. This review is unique in that it used a narrowly defined clinical population such that the evidence statements are specifically relevant to both clinical and non-clinical settings. The authors were able to identify just 18 studies that met inclusion criteria.

It is important to consider the relative dearth of studies in this field as reflective of the low incidence of pediatric stroke relative to its occurrence among adults. While there is a large discrepancy in incidence rates between these populations, it does not diminish the importance or necessity of conducting interventional trials specifically within the pediatric population. The extrapolation of treatment recommendations from the adult literature has limitations due to developmental differences between coagulation, cerebrovascular, and neurological systems in adults and children [7, 33], and potential differences in eventual outcomes as well. There are also significant differences between the adult and pediatric populations in terms of the type of stroke sustained, underlying risk factors [30], and the long-term sequelae experienced. Mortality and long-term morbidity following pediatric stroke are highly variable and are influenced by many factors, including lesion location [42], age, developmental level, family environment, and resource acquisition [17]. It has been reported that children will experience a spectrum of difficulties across several domains of the International Classification of Function [46] and that the extent and severity of these problems may not present themselves right away but rather they may "grow into" their problems as they gain new skills [17] and attempt new developmental milestones. As was demonstrated by the current review, few studies are available to guide clinical practice for the rehabilitation or habilitation of these deficits, despite the high prevalence of disability incurred by children post-stroke. Although the increase in the number of clinical trials and published protocols in recent years is encouraging, there remains an important gap in the literature pertaining to pediatric stroke rehabilitation.

In terms of motor studies, most have focused on the rehabilitation of upper limb motor deficits, with CIMT being the most commonly investigated intervention, and forced use therapy, FES, and robotics being the least commonly investigated interventions. CIMT, forced use therapy, rTMS, FES, and robotics generally demonstrated improvements on all or some motor outcomes among children with hemiparesis or hemiplegia post-stroke, supported by varying levels of evidence (Online Resource 2). In contrast, the application of tDCS was not shown to result in improvements in upper limb hemiparesis among children post-stroke. Studies investigating therapies for upper limb motor impairment which utilized the Canadian Occupational Performance Measure (COPM) [5] in addition to motor outcomes generally reported improved COPM scores alongside improved motor function, indicating self-perceived improvement with performance on everyday living tasks. Interestingly, although tDCS did not demonstrate favorable outcomes for motor function, tDCS treatment was associated with improvement in COPM scores, signifying the importance of appropriate outcome measure selection and use to detect improved function. Only walking training has been studied for lower limb rehabilitation, demonstrating potential therapeutic benefit for walking ability. Finally, among the cognitive studies, memory training with or without academic tutoring, as well as computerized memory training, demonstrated improvements on some memory and attention measures among study participants, but not all.

The evidence identified and presented here is partly in line with published Canadian Best Practice Guidelines for Stroke Care [19]. The evidence statements reported by Hebert et al. [19] indicate strong support (level A) for CIMT or modified CIMT but not any other type of intervention. It is important to note that the pediatric guidelines mentioned above were often based on research studies with heterogeneous stroke populations inclusive of cerebral palsy or clinical presentations where diagnosis of stroke was not specified. The advantage of the current systematic review is that it offers both pediatric-specific and stroke-specific implications for rehabilitation. It is possible that combining various aetiologies within a single-study sample may lead to large variances in results which can mask the magnitude of the treatment effect, potentially leading to incorrect conclusions or conclusions that are not generalizable to all diagnoses [43]. Therefore, it is imperative that effectiveness of interventions for various neurological populations should be established separately. Future studies should, at the very least, specifically identify the etiology of stroke-induced conditions or recruit a homogenous population such that treatment effectiveness can be comprehensively evaluated for the pediatric stroke clinical population.

It should be noted that the studies included in this review varied in terms of reporting on the chronicity of stroke. Overall, seven studies reported the time post-stroke onset of their participant sample, which ranged from greater than 6 months to a mean of 8.1 years. Although the remaining studies did not provide this information, most presumably also had chronic stroke participant samples based on ages at the time of study enrollment along with the fact that the strokes occurred prenatally or perinatally or resulted in congenital effects (i.e., hemiparesis), or that the study was investigating long-term outcomes in follow-up to another included study. Three studies were of unknown stroke chronicity. Taken together, the majority of studies were conducted during the chronic phase of pediatric stroke, highlighting the need for future studies to examine the effect of rehabilitation interventions during the acute phase.

It is important to recognize the unique situation presented by pediatric stroke in terms of overall rehabilitation. The term habilitation is often used in lieu of rehabilitation because children must often relearn previously developed skills and abilities, as well as learn to develop new skills and cope with missing ones. Regardless of the interventions applied, rehabilitation as a whole occurs within the context of a family and the child's parents and/or caregivers; as such, the needs of not only the child, but also the child's family should be prioritized. The delivery of care in terms of methods of rehabilitation, intensity, duration, and environment should be individualized to the child and family and tailored to meet their unique needs [38] and provided by a multidisciplinary team given the complex and diverse types, and number, of issues a child may experience [1].

There is substantial heterogeneity in the pediatric stroke population and the diversity of issues experienced by these individuals; therefore, identification of the most useful trials for interventional study is imperative. A recent study by Steinlin et al. [41] has shown how the use of a Delphi process, which seeks to obtain consensus among clinicians on a specific topic of interest in health care [6, 39], can identify critical areas for interventional study in pediatric stroke. Given the considerable difficulty in designing and recruiting patients for pediatric stroke rehabilitation trials, the Delphi method should be considered as a foundation for the development of these trials as well. This may assist in designing a highly feasible study with equally high clinical utility.

Limitations

A limitation of this review is that a number of relevant studies may have been excluded, such as studies evaluating the effects of various motor and cognitive treatments on children with cerebral palsy or congenital hemiparesis/hemiplegia, due to a lack of explicit description or mention of stroke etiology. Additionally, as our search criteria were limited to English publications, this review is not representative of findings from studies published in other languages.

Conclusion

Pediatric stroke is a significant contributor to childhood mortality, morbidity, and disability. Although effective rehabilitative treatment approaches for pediatric stroke are important, little evidence-based guidance exists. Of the available studies to date, most have focused on the rehabilitation of upper limb motor deficits. There is still a lack of evidence at present for interventions for improving lower limb or cognitive impairment in children who have had a stroke. Although the increase in the number of clinical trials and published protocols in recent years is encouraging, there remains an important gap in the literature pertaining specifically to pediatric stroke rehabilitation. There is a need to address this gap in order to effectively guide rehabilitative management and meet the ongoing needs of the pediatric stroke population.

Authors' contributions MM was responsible for manuscript conceptualization, literature search, article selection, quality assessment, data extraction, table and figure creation, manuscript drafting and editing, and preparation of the final manuscript for submission; MM wrote the abstract, methods, and results, and contributed to the introduction and discussion. AMc assisted with article selection and wrote the discussion. PF contributed to writing the introduction. NS assisted with article selection, quality assessment, and data extraction. CC and RT provided clinical expertise about stroke rehabilitation throughout the manuscript. AMc, PF, NS, CC, and RT all contributed to manuscript editing.

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Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

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