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SYSTEMATIC REVIEW

Cognitive approaches in the rehabilitation of upper limbs function in children with cerebral palsy: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Cerebral palsy (CP) is the predominant cause of children disability. It is characterized by motor, sensory, and postural deficits due to a non-progressive injury to the developing central nervous system. In recent years, new rehabilitation techniques targeting the central representations of motor patterns have been introduced: the most used are action observation therapy (AOT), motor imagery (MI), and mirror therapy (MT). Aim of this study is to assess the effectiveness of these cognitive strategies on the recovery of upper limb motor functions in children with CP.

EVIDENCE ACQUISITION: This study was designed as a systematic review and meta-analysis, registered in PROSPERO (CRD42023403794). For the report and methodological definitions of this study, the recommendations of the PRISMA protocol and the Cochrane collaboration, were followed. A total of 3 electronic databases (PubMed, Scopus, and Web of Science) were searched for relevant Randomized Control Trials (RCT) using the combinations of terms “cerebral palsy” AND “action observation” OR “motor imagery” OR “mirror therapy” OR “cognitive therapy.” A meta-analysis was carried out to compare cognitive and conventional approaches and combine direct and indirect effects. A random-effects meta-analysis model was used to derive pooled effect estimates.

EVIDENCE SYNTHESIS: Out of 328 records, 12 RCTs were analyzed in this systematic review published from 2012 to 2022, and included 375 children, of whom 195 received cognitive therapies, and 180 underwent conventional rehabilitation. AOT was the most investigated (RCTs N.=7), and showed significant results in the recovery of upper limb motor functions, albeit the meta-analysis demonstrated a non-significant difference in Melbourne Unilateral Upper limb Scale (MUUL) (95% CI: -7.34, 12); in Assisting Hand Assessment (AHA) (95% CI: -4.84, 10.74), and in AbilHand-Kids Questionnaire (95% CI: -1.12, 1.45). Five RCTs investigated MT showing significant improvements in grip and dexterity; none used MI as intervention therapy.

CONCLUSIONS: Cognitive therapies provided with encouraging results in the recovery of upper limb motor functions, although not a clinical effect in bimanual or unimanual performance; they could represent a valid therapeutic solution integrated to conventional rehabilitation in the treatment of upper limb motor impairment in children with CP.

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KEY WORDS: Neurological rehabilitation; Cerebral palsy; Movement disorders.

Introduction

Over the past 30 years, there has been a significant improvement in the knowledge about the motor system, no longer considered just as an executor of motor actions, but also involved in motor imagery, action recognition, and language processing.[1-3] Moreover, through observation and imitation of models, it is possible to acquire new skills and refine motor abilities based on self-evaluation of previous performance.[3]

This utilization of neural structures involved in action execution for cognitive strategies is referred to as action re-enactment. In details, this mechanism encompasses the capacity to activate motor representations for various cognitive functions, including motor imagery, action observation and recognition, imitation, social interactions, and language processing, thus strictly linking motor experience to cognition. This approach to cognition is known as embodiment.[4]

It is worth stressing that already in the early 90s Jeannerod[5] had postulated that the motor system is involved in all situations endowed with a motor content, what he called S states, situations when actions are not actually executed.[6]

The neural substrates involved in action re-enactment are fronto-parietal circuits, including ventral and dorsal premotor cortex, the inferior frontal gyrus as well as the inferior parietal lobule, known to be involved in sensorimotor transformations.[2]

Within this conceptual framework, novel approaches to rehabilitation have been introduced, referred to as cognitive-based strategies or mental simulation practices. These strategies have the potential to specifically address the central representation of motor patterns and stimulate action re-enactment, potentially improving motor performance in patients with neurological and non-neurological pathologies. These cognitive approaches include motor imagery (MI), action observation therapy (AOT) and mirror therapy (MT). These approaches aim to reinforce intact neural networks and reactivate damaged ones.[7, 8]

During MI, individuals are instructed to mentally rehearse a specific movement without physically executing it. This involves imagining to execute actions in a first person perspective while remaining physically still, without any subsequent motor output.

In AOT, patients are encouraged to observe everyday actions being performed by healthy individuals. This therapeutic approach involves the visual observation of actions without active physical involvement. By engaging in the process of observing actions, individuals may benefit from the activation and modulation of neural networks associated with action re-enactment ultimately facilitating improvements in motor function.[9, 10]

AOT not only activates higher-order visual areas but also engages motor areas. The neural coding of motor imitation involves a wide-ranging network that integrates sensory inputs with stored motor patterns, enabling the generation of required movements.

Moreover, when examined individually, both AOT and MI have been found to enhance excitability in the corticospinal pathway, as indicated by increased motor evoked potentials amplitude (MEPs).[11, 12]

MT utilizes a mirror to provide visual feedback of the correct execution of the imagined action using the impaired limb.[13] The concept of MT was initially explored by Ramachandran and colleagues in the late 1990s[14, 15] as a method to alleviate phantom pain in amputees. MT involves the activation of mirror neurons when a patient observes their intact limb reflected in a mirror.[16] Through this mechanism, the brain prompts the patient to imagine both limbs as healthy, promoting cortical regeneration.

These cognitive-based strategies have shown great potential and promising results in the rehabilitation of stroke,[17-19] Parkinson's disease,[20, 21] and individuals recovering from orthopedic surgery.[22] Noteworthy for the aim of the present study, these approaches have shown interesting results in various studies involving children with cerebral palsy (CP).[23-25]

CP is a condition characterized by motor, sensory, and posture impairments resulting from a non-progressive disturbance in the developing brain.[26] It is the most prevalent cause of childhood disability: a recent systematic analysis of CP register data and published literature reported an overall CP birth prevalence of 1.6 per 1000 live births in regions of high-income countries, whereas this rises as high as 3.4 per 1000 live births for low- and middle-income countries.[27] In premature infants, the incidence increases significantly, ranging from 40 to 100 cases per 1000 live births. Among preterm infants weighing between 1500 and 2499 grams at birth, the median prevalence is 11.2 cases per 1000 live births.[28]

CP can be classified based on the pattern of affected body areas, including monoplegia (affecting a single limb), hemiplegia (affecting one side of the body), diplegia (primarily affecting the lower limbs), and tetraplegia (affecting all four limbs).[29] However, hemiplegia is the most common presentation, accounting for over 38% of cases. In premature infants, it is the second most prevalent form after diplegia, representing approximately 20% of cases.[30] Typically, the upper limb is more affected than the lower limb, leading to significant limitations in arm and hand usage during daily activities. Alternatively, CP can be categorized based on the type of motor impairment, such as spastic, dyskinetic, or ataxic presentations. The symptoms of CP vary widely and may include spasticity, difficulties with motor coordination and function, movement abnormalities, lack of postural control, altered gait patterns, balance problems, as well as associated challenges in sensation, cognition, communication, perception, behavior, and the occurrence of seizure disorders.[31]

CP significantly affects various aspects of a child's life, and its long-term prognosis is influenced by comorbidities, severity of the condition, and lifestyle choices in adulthood.[32] To enhance independence, a multidisciplinary treatment approach that focuses on managing symptoms and complications is essential.[33]

Currently, there are no standardized intervention protocols for CP, and rehabilitation programs vary in terms of duration, intensity of training, and frequency. Effective rehabilitation approaches include bimanual training, goal-directed training, and the combination of intramuscular botulinum toxin A (BoNT-A) injections with therapeutic training, as well as cognitive appr. However, there is no conclusive evidence to support one approach over the others (*i.e.*, "bottom-up" approach).[34]

Recent studies have demonstrated that, despite motor deficits in action execution, in children with CP the capacity to imagine actions may be preserved.[35, 36] As a result, interventions focusing on motor planning and imagery have emerged as potential treatment options for CP.[37]

One of the key advantages of employing these "top-down" approaches is the ability to leverage children's early capacity for observational imitation.[38] In this context, the incorporation of visual feedback enhances motor learning, improves skills, promotes gross motor function, and plays a pivotal role in a child's development, activities, participation, games, and social interactions.

In the present systematic review and metanalysis of current literature, we aim to assess the efficacy of cognitive strategies, including AOT, MI, and MT on the recovery of motor functions in children with CP.

Evidence acquisition

Search strategy

PubMed, Scopus, and Web of Science databases were systematically searched for English-language articles published to February 14th, 2023, according to each specific thesaurus, following the strategy depicted in Table I. This systematic review with network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Network Meta-analysis (PRISMA-NMA) guidelines.[39] The systematic review protocol is available on the International Prospective Register of Systematic Reviews (PROSPERO) (registration no.: CRD42023403794).

Table I.—*Search strategy.*

PubMed: (cerebral palsy) AND (action observation OR motor imagery OR mirror therapy OR cognitive therapy)
Scopus: TITLE-ABS-KEY ("cerebral palsy") AND ("action observation" OR "motor imagery" OR "mirror therapy" OR "cognitive therapy")
Web of Science: ("cerebral palsy") AND ("action observation" OR "motor imagery" OR "mirror therapy" OR "cognitive therapy")

Selection of articles

After removing duplicates, two reviewers independently screened all papers for eligibility. In case of disagreement, consultation with a third reviewer allowed for consensus. All randomized control trials were assessed for eligibility according to the following patient/population, intervention, comparison, and outcomes (PICO) model:

- P, participants: children with diagnosis of infantile cerebral palsy;
- I, intervention: cognitive rehabilitative techniques including action observation therapy, mirror therapy and motor imagery;
- C, comparator: conventional rehabilitation; sham therapy;
- O, outcome measure: functional outcomes for upper limb measured with validated scales.

We included only RCTs with two groups (study group and control group) that provided data at the end of the intervention. We excluded studies: 1) including adults; 2) focusing on treatment for other complications related to CP (*e.g.*, cognitive outcomes); 3) focusing on the non-affected limb; 4) including typically developed children as control group; 5) with a cross-over design; 6) written in a language other than English; 7) with no full text (*i.e.*, posters and conference abstracts); and 8) involving animals.

Data extraction

Two reviewers independently extracted data from included studies using a customized data extraction on a Microsoft

Excel sheet. In case of disagreement, a third reviewer was consulted to achieve consensus. We extracted the following data: 1) first author; 2) publication year; 3) nationality; 4) age of study participants; 5) rehabilitative approach performed; 6) comparator; 7) population and number of patients included; 8) functional outcome measures; and 9) main findings. Data extracted from included studies and data used for all analyses are available on request.

Quality assessment

The selected studies were synthesized describing extracted data. The study quality of the RCT reports was independently assessed by two reviewers according to the PEDro Scale.[40] In case of disagreement, a third reviewer was consulted to achieve consensus. According to the PEDro Scale,[40] studies were classified as excellent (9-10 points), good (6-8 points), fair (4-5 points), or poor (<4 points). Additionally, the risk of bias in RCT was assessed by two reviewers using version 2 of the Cochrane Risk of Bias tool for randomized trials (RoB 2).[41] Any disagreement was discussed with a third reviewer.

Statistical analysis

A network meta-analysis was performed to combine direct and indirect effects and compare cognitive and conventional techniques or sham therapies in the rehabilitation of CP. The treatment effect on functional outcome for each RCT was calculated as the mean difference (MD) and standard deviation. All statistical analyses were performed with RevMan (Cochrane).

Evidence synthesis

Descriptive analysis

A total of 328 articles were found in all searches of databases. After removing duplicates, 244 papers were reviewed by title and abstract, and 83 articles were excluded. Thus, 161 articles were evaluated with the PICO model. We identified 31 full-text articles and retrieved them for a detailed evaluation. Finally, 12 RCTs[42-53] were included in the systematic review (Figure 1).

The included studies were published from 2012[53] to 2022.[52] Seven were conducted in Europe (four in Italy,[43, 45, 52, 53] one in Belgium,[48] one in the UK, 1 in Türkiye);[42] one in Iran;[49] two in Egypt;[46, 51] one in South Korea[47] and one in India.[50] We analyzed data of 375 children (214 boys and 161 girls) diagnosed with cerebral palsy; 180 were included in the control group. Sample sizes ranged from 7[43, 53] to 35[44] in the experimental and control groups, with an age range from 3 to 16 years old. Study samples presented with different forms of cerebral palsy, namely: 1) unilateral cerebral palsy (N.=238; 63.5%); 2) unilateral spastic cerebral palsy (N.=76; 20%); 3) spastic diplegia (N.=18; 5%). In three studies[43, 52, 53] the type of cerebral palsy was not described (N.=43; 11,5%). Supplementary Digital Material 1 (Supplementary Table I)[42-53] summarizes the main characteristics of the RCTs included in our systematic review.

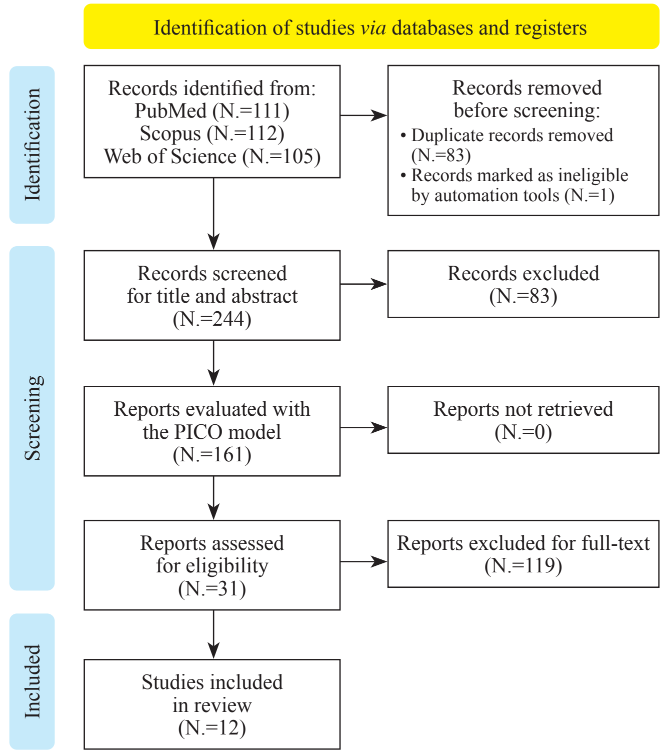

Figure 1.—PRISMA flow chart of the study selection.

Action observation therapy

The effectiveness of the action observation therapy was assessed in seven studies. Control groups received sham treatment consisting of video clips without motor content in three studies;[43, 45, 53] independent play with parental supervision in one study;[44] conventional physiotherapy in two studies;[47, 52] AOT combined with CIMT compared with CIMT and movies without biological motion in one study.[48] The video mode of Action Observation Therapy was used in all included studies except one study[44] that used live Action Observation Therapy. The duration of the Action Observation Therapy ranged from 9 days to three

Table II.—*Upper limb scores utilized in the articles included in the review.*[5, 54-62]

Scale	Acronym	Aim	Reliability
Quality of Upper Extremity Skill Test	QUEST	To measure quality of upper limb movement and function in a clinical trial of therapy and upper limb casting for children with CP	Inter-rater reliability: ICC=0.86 Intra-rater reliability, ICC=0.96[54]
Melbourne Assessment of Unilateral Upper Limb Function Scale	MUUL	Evaluation tool that objectively measures upper-extremity function in children with cerebral palsy	Interrater reliability ICC=0.97 SEM=2.6%[55]
Assisting Hand Assessment	AHA	A measure reflecting how well the hand is used as an assisting hand.	Interrater ICC=0.97; SEM=1.5. Intrarater ICC=0.99; SEM=1.2[56]
ABILHAND-KID		ABILHAND-Kids explores unimanual and bimanual activities completed without technical or human assistance	reliability (R=0.94), reproducibility over time (R=0.91)[5]
Pediatric Reaching Test	PRT	measures side reaching and forward reaching in both sitting and standing positions	Test-retest reliability ICC 0.54 to o.88 Inter tester reliability ICC 0.50 to 0.93[57]
Jebsen Taylor Hand Function Test	JTHFT	Measure of fine and gross motor hand function using simulated activities of daily living	Test-retest reliability ICC=0.88[58]
Tyneside Pegboard Test		Timed test of unimanual and bimanual dexterity	Test-retest ICC from 0.74 to 0.91[59]
Children Hand-use Experience Questionnaire	CHEQ	Evaluates the *experience* of *children* and adolescents in *using* the affected *hand* in activities where usually two *hands* are needed	Test–retest reliability for: grasp efficacy, ICC=0.91; time taken, ICC=0.88; and feeling bothered, ICC=0.91[60]
Fugl Meyer Assessment Upper limb	FMA-UE	Upper *extremity motor function in persons with moderate to severe deficits*	Test-retest reliability 0.96; Inter-rater reliability 0.99 in stroke patients[61]
Upper Extremity Functional Index		Measures upper extremity function in individuals with hand and upper extremity disorders	Test re-test reliability (ICC 0.85-0.95) in musculoskeletal conditions[62]

Table III.—*Quality assessment of the included studies according to the PEDro Scale.*[42-53]

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Pedro Score
Kara *et al*. 2019[42]	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Buccino *et al*. 2018[43]	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	4
Kirkpatrick *et al*. 2016[44]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Sgandurra *et al*. 2013[45]	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Elsepaee *et al*. 2016[46]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	6
Jeong *et al*. 2020[47]	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Simon-Martinez *et al*. 2020[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Narimani *et al*. 2019[49]	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Elanchezhian *et al*. 2019[50]	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Nour *et al*. 2016[51]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Molinaro *et al*. 2020[52]	No	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5
Buccino *et al*. 2012[53]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7

Item 1: eligibility criteria; Item 2: random allocation; Item 3: concealed allocation; Item 4: baseline comparability; Item 5: blind subjects; Item 6: blind therapists; Item 7: blind assessors; Item 8: adequate follow-up; Item 9: intention-to-treat analysis; Item 10: between-group comparisons; Item 11: point estimates and variability.

months, with a frequency ranging from three to five sessions per week, each session lasting between 15 to 120 minutes. The follow-up evaluation range was 1 week to 6 months.

According to the PEDro quality assessment scale, one study had excellent quality; three studies had a good quality, and the other three studies had fair quality (Table II, III);[5, 42-53, 62] the risk of bias in RCTs is reported in Figure 2 (traffic light plot).

Simon-Martinez *et al.*[48] used AOT combined with CIMT compared to CIMT plus placebo in children affected by UCP to find out if AOT might be of additional value on UL functioning. They used the AHA, MAS, MRC, dynamometer, MA2, JTHFT, Tyneside Pegboard Test, ABILHAND-kids and CHEQ as confronted parameters. CIMT was provided utilizing a splint during activities in both groups, whereas in the intervention group 15 hours of AOT watching videos of actions was also provided. Although no between-groups differences were found (P>0.05), the addition of AOT led to higher improvements in children with initially poorer bimanual performance (P=0.02). Moreover, both groups improved in all outcome

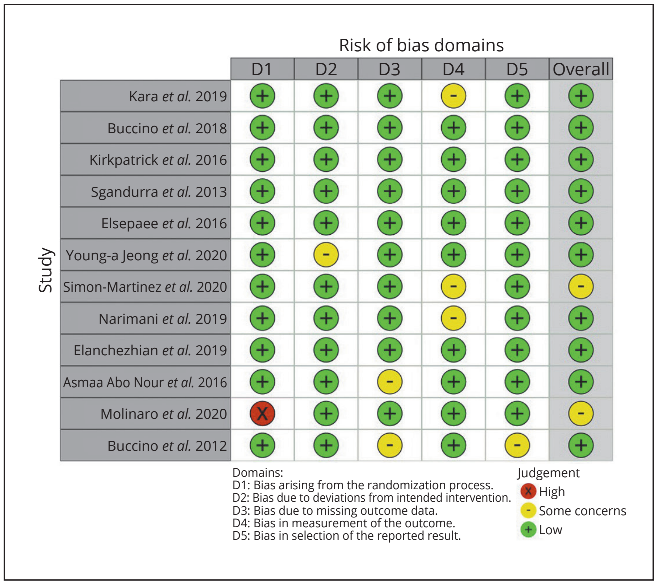

Figure 2.—Risk of bias domains of included RCTs (Traffic Light Plot).

measures after the intervention and retained the gains at follow-up (P<0.01).

In the study of Buccino *et al.*[43] tried AOT combined to a conventional rehabilitation program compared to the same conventional program associated to the vision of short video clips showing scenes with no motor content in children with CP. It emerged that children in the experimental group, improved significantly in both MUUL (P<0.001) and AHA (P<0.001) at the end of the treatment and this improvement persisted at 2-months of FU (P<0.001) whereas there was not significant difference in the control group.

Furthermore, Kirkpatrick *et al.*[44] are the only group who tried AOT delivered by parents at home combined with repeated practice alongside repeated practice alone (children played independently with parental supervision). They did not report between-group differences in AHA, MA2, or ABILHAND-Kids at 3 or 6 months *versus* baseline (all P>0.05), but they observed Combined-group improvements at 3 months and 6 months (P<0.001) concluding that Parent-delivered RP (with or without AOT) improves upper limb function in children with UCP.

In addition, Sgandurra *et al.*[45] tried a protocol of AOT directed to the upper arm in children with UCP (called UP-CAT: Upper Limb Children Action Observation Training) associated to routine therapy and compared it to doing the same actions after watching video-games with routine therapy. They found that the experimental group improved more and significantly at the primary endpoints T1 (P=0.008), T2 (P=0.019) of AHA, and these effects persisted at 6 months T3 (P=0.049).

Moreover, Young-a Jeong *et al.*[47] tried video AOT performed by a therapist confronted to conventional physical therapy in children with spastic diplegia CP and measured GMFM, PRT, MTS before and after training: the results were significantly increased between pre- and post-intervention within both groups (P<0.05); furthermore, there was an indicative difference (P<0.05) between the two groups suggesting that AOT is both feasible and beneficial for improving spasticity, gross motor function, and balance.

Molinaro *et al.*[52] investigated the effect of AOT associated to conventional treatment, in children with CP who followed the AOT program at home with remote supervision by a child neurologist located at the hospital. Outcome measures were the scores at the MUUL scale and the AHA. Scores obtained after treatment and at a two months' follow-up importantly differed from baseline (Ps<0.001); in contrast, the control group used, who did conventional treatment and sham, did not show a significant increment.

In the study of Buccino *et al.*[53] children were asked to observe video clips showing daily age-appropriate actions, and afterwards to imitate them in addition to routine therapy; conversely, the control group were asked to observe video clips with no motor content and afterwards to execute the same actions as cases, always in addition to routine therapy. The primary outcome measure was the Melbourne Assessment Scale. Children were scored twice at baseline (2 weeks apart), and at the end of treatment: after treatment, the functional score gain was remarkably different in the case and control groups in favor of cases (P=0.026).

Mirror therapy

The effectiveness of the mirror therapy approach was examined in five articles. In one study[51] it was associated with HABIT and confronted with a modified version of HABIT excluding the mirror apparatus; in the study of Narimani *et al.*[57] MT was associated to occupational therapy (OT) and compared with OT alone. In Kara *et al.*[42] MT was associated to strength and power training and confronted to OT; Elanchezhian *et al.*[50] compared MT with conventional treatment for the affected hand; finally, Elsepaee *et al.*[46] combined MT with physical therapy *versus* physical therapy. The mirror system used was always a mirror placed in front of the patient's midline to completely cover the impacted limb, and the reflection of the unaffected limb was fully obvious. The dimension of the mirror was big enough to cover the entire affected limb to allow patients see all major movements in the mirror. The duration of the MT ranged from one month to three months, from three to seven sessions per week, each session lasted between 30 to 90 minutes. None of the selected studies performed a follow-up evaluation.

Motor imagery

None of the 12 studies used MI as intervention therapy.

According to the PEDro quality assessment scale, four studies had a good quality, and one had fair quality (Table III); the risk of bias in RCT is reported in Figure 2 (Traffic Light Plot).

Kara *et al.*[42] combined MT with strength and power exercises in the study group, while the control group did OT, in a population of children with unilateral spastic CP. They used as outcome scales the COPM and the QUEST and measured muscle strength with a dynamometer at the beginning and at the end of the protocol. The results indicated that, compared to the control group, a largest improvement was found in dissociated movements ($P<0.001$), grasp ($P<0.001$), weight bearing ($P=0.006$), and total scores ($P=0.001$) of QUEST; performance ($P<0.001$), satisfaction ($P<0.001$), and total scores ($P<0.001$) of COPM; and isometric muscle strength of the biceps brachii ($P<0.001$) and triceps brachii ($P=0.002$) of the affected upper limbs in the experimental group. They concluded that MT combined with power and strength exercises is a promising intervention approach to improve activity performance and upper-limb function in children with USCP.

Elsepaee *et al.*[46] included children with UCP: the control group received a specially designed physical therapy exercise program and the study group received a mirror exercise program in addition to the same physical program. Hand functions assessments using Peabody developmental motor scale (PDMS-2) and Hand grip strength using handheld dynamometer were evaluated pre and post treatment program revealing a significant improvement in the scores of the two groups ($P<0.005$). Post treatment results were higher in the study group as compared with the control group ($P<0.005$).

Narimani *et al.*[49] studied the effect of mirror therapy upon dexterity and hand grasp in children with hemiplegic cerebral palsy. OT exercise was done routinely in both groups. The grasp was evaluated with dynamometer and the dexterity with box and block test. The mean scores of the two groups in dexterity were notably different after the intervention ($P=0.008$) with higher scores in the experimental group, however, there was no significant difference between the two groups in grasp after the intervention ($P=0.32$).

Elanchezian *et al.*[50] focused their research on hand function in spastic hemiplegic cerebral palsy: they administered MT in the study group and conventional therapy in the control group. The mean post-test values of the MAS, 9HPB and FMA-UE scales were significantly better in the mirror group compared to the conventional group ($P<0.005$) showing spasticity reduction and improvement in the function of the hand using MT.

Finally, Abo Nour *et al.*[51] compared Mirror therapy combined with HABIT to HABIT alone in two groups of children affected by hemiparetic cerebral palsy to check pinch and palmar grasp pre and post treatment. Comparing the post treatment results of both groups was statistically non-significant ($P>0.1$ for palmar grasp and for pinch grasp) even if the mirror therapy group showed greater improvement; this indicates that MT combined with HABIT has positive effects on the improvement of hand function in children with hemiparesis.

Assessment

The variables evaluated and the outcome measures correspondents were classified according to the model of the ICF (International Classification of Functioning) and they fell under two domains: the Body Structure and Function and the Activity domains. Three ICF sub-domains of the Activity domain were pooled meta-analytically: 1) the Capacity (MUUL); 2) the Perceived manual Performance (ABLIHAND-KID Questionnaire); 3) the actual bimanual Performance (AHA). The AHA and the MUUL scales assess fine motor skills of the upper limb; the ABILHAND-Kids assesses manual function in bimanual activities at home and in daily living.

All studies except one[45] performed measurement of variables pre-treatment (T0), even with two measurements in one study (T0A, T0B);[48] three performed measurement during treatment (T1)[43, 51, 52] and all of them at the end (T2). In addition, measurements were made post-treatment at follow-up (T3) in five studies[43-45, 48, 52] even with two measures in one[45] of them (T3A, T3B).

In our Meta-Analysis, three-time intervals were specified ‘according to homogeneity’: they were specified to baseline; immediate post-intervention and short intermediate follow-up for up to three months. We compared the gain between two end-points of the outcome considered to highlight the effect of the therapy. In particular, we considered the difference in the score of outcome among the baseline (T0), the treatment (T1), and the first follow-up

(T2). In detail, we analyzed the change between post-intervention and baseline, and follow-up and post-intervention.

Five studies[43-45, 52, 53] were pooled on the Meta-Analysis to assess the effect of AOT. In the included articles, the intervention group underwent AOT in addition to conventional rehabilitation treatment. Four studies included sham therapy in the control group (the participants watched images of no motor content) and all studies used conventional physiotherapy for comparison purposes. Results of studies reporting individualized outcomes are summarized in Figure 3, 4, 5, 6, 7, 8. There was not a significant effect (P<0.05) in any of the evaluations.

MUUL score gains were computed from the end of treatment to baseline including 4 studies in meta-analysis, comparing AOT (N.=41) with control (N.=33), with a mean difference (MD) of 2.33 (95% CI: -7.34 to 12; P=0.64)[43, 45, 52, 53] (Figure 3).

The effect of AOT in MUUL compared with the control groups at the follow-up, was assessed in three studies[43, 45, 52] with 33 patients receiving AOT and 26 controls (Figure 4): a MD of 0.27 (95% CI: -10.94 to 11.47; P=0.96).

Four studies[43-45, 52] assessed AHA after intervention and at FU, but Sgandurra *et al.* presented the data in logits, making it difficult to convert them. Even after contacting the author, we could not obtain the data related to this outcome. We pooled the data presented with the three remaining studies using logit-based 0-100 units AHA. AOT (N.=49) in the intervention group had a positive but not significant effect on hand function compared with control group (N.=44): MD 2.95 (95% CI: -4.84 to 10.74; P=0.46) (Figure 5). Moreover, the improvement achieved were maintained at the follow-up (Figure 6) excepting in one study (MD: 0.46; 95% CI: -7.21 to 8.13; P=0.91).

Pooling data from two studies[44, 45] of the ABILHAND-kids questionnaire with AOT group (N.=38) and control group (N.=39), the effect was not significant: we found a MD of 0.16 (95% CI: -1.12 to 1.45; P=0.80) immediate after the intervention (Figure 7) and 0.32 (95% CI: -0.77 to 1.41; P=0.57) at follow-up (Figure 8).

Discussion

This systematic review with meta-analysis investigated the efficacy of cognitive strategies including MI, AOT and MT in improving functional outcomes in children with CP, a disease that includes deficit in motor controls in addition

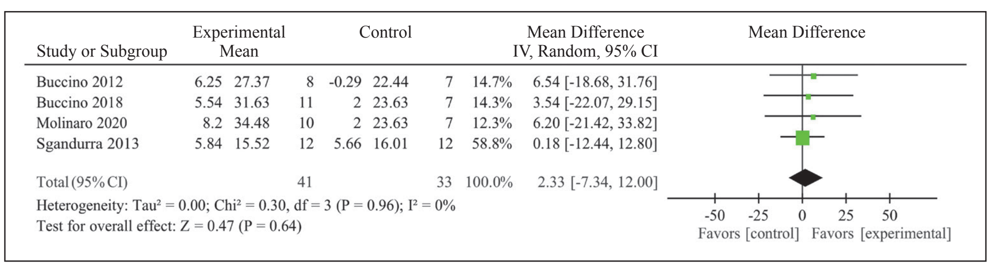

Figure 3.—Forest plot of meta-analysis of the mean difference of the gain from T1 to T0 of MUUL comparing AOT *versus* conventional therapy.

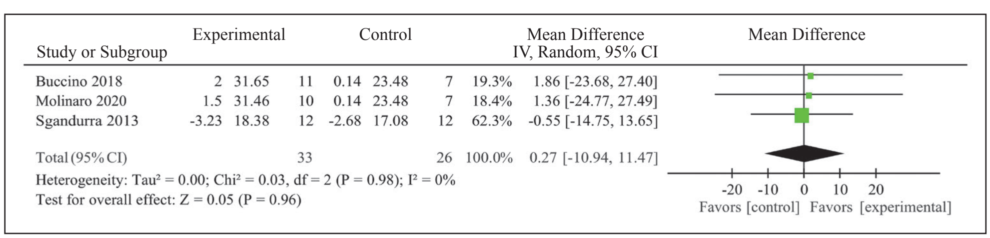

Figure 4.—Forest plot of meta-analysis of the mean difference of the gain from T2 to T1 of MUUL comparing AOT *versus* conventional therapy.

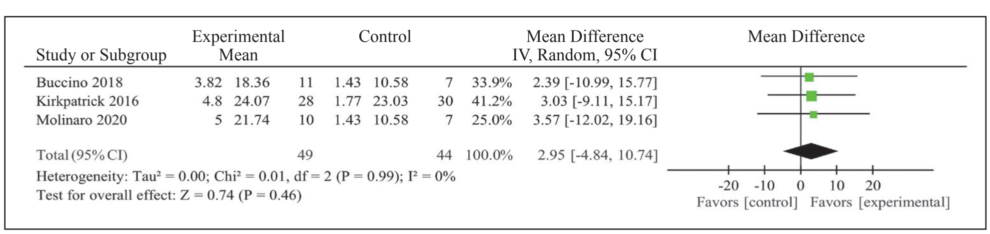

Figure 5.—Forest plot of meta-analysis of the mean difference of the gain from T1 to T0 of AHA comparing AOT *versus* conventional therapy.

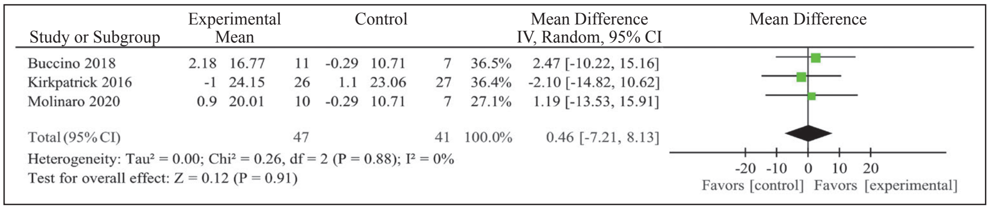

Figure 6.—Forest plot of meta-analysis of the mean difference of the gain from T2 to T1 of AHA comparing AOT *versus* conventional therapy.

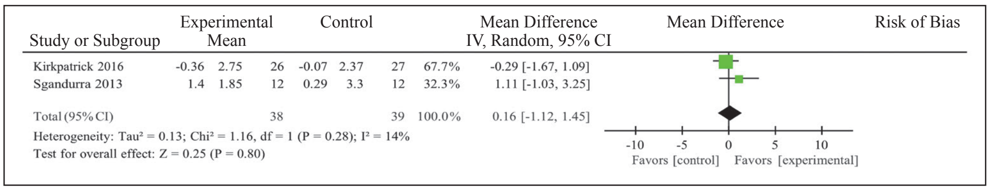

Figure 7.—Forest plot of meta-analysis of the mean difference of the gain from T1 to T0 of Abil-Hand-Kids comparing AOT *versus* conventional therapy.

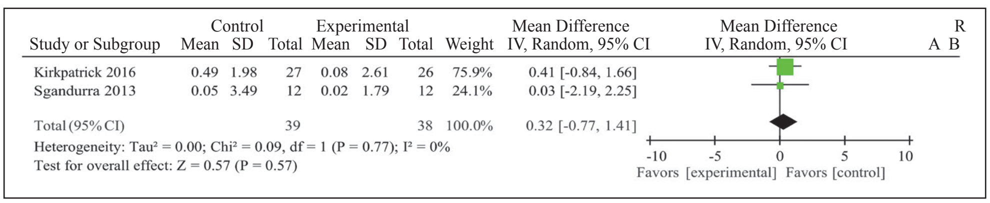

Figure 8.—Forest plot of meta-analysis of the mean difference of the gain from T2 to T1 of Abil-Hand-Kids comparing AOT *versus* conventional therapy.

to motor executions, that might benefit of rehabilitative strategies targeting the cerebral representations of motor actions planning and execution. We focused on the upper limb because for children with cerebral palsy, the effect on upper limb function is often more pronounced than that on lower limb function, with resultant limitations in daily independence, participation, and quality of life.[63]

Eight of the included studies considered children with Unilateral CP, two of them with spastic pattern. Most of the selected studies used AOT alone or combined with other interventions; five studies used MT and none used MI as intervention therapy. As a rehabilitative approach, MI has some intrinsic limits because therapists are unable to verify how correct 'the mental training' is or how to influence it. Moreover, it may be more demanding than other cognitive strategies because it is related to the capacity of individuals to imagine themselves performing specific actions as well as to the 'imageability' of certain actions.

Concerning AOT, the articles included in our review show that it has encouraging results in the recovery of upper limbs motor functions: in four studies[43, 45, 52, 53] AOT associated with conventional therapy, was compared with the conventional therapy alone. The results showed that the combination of AOT and conventional therapy was more effective than conventional therapy alone in improving fine motor skills; moreover, in three of them[43, 45, 52] the improvements persisted at follow-up. However, it is relevant to highlight that in the intervention protocol of Sgandurra *et al.*,[45] the AOT exercises were composed according to children ADL capabilities, in relation to the HFCS level, in contrast with the other authors that administered standard AOT video.

A key element that seems to affect functional outcomes when using AOT is the presence of a staff member that may prompt children's attention during the task. Confirming this, in the study of Kirkpatrick, the addition of live-AOT delivered by parents at home to the conventional therapy, did not lead to differences compared with conventional therapy in improving fine motor skills and upper limbs movement quality, possibly because of a less effective delivery of the treatment and/or monitoring of children's compliance to treatment by parents as compared to an expert therapist.[44] Moreover, as compared to other studies, they included younger children (from three years old) compared with other authors, that could represent a limitation, since it is still unclear when the capacity to use motor representations for cognitive strategies develops and at what age is fully operating.[64] It may be assumed that in primary school age-children is fully operating and only at this stage it may become a target of cognitive techniques.[44]

Summing up, five RCTs have been pooled in the present meta-analysis to state the evidence of the effectiveness of AOT in children with CP. Several studies showed heterogeneity in the characteristics of the population and the treatment program as different modes of application, doses, and population. The main findings suggest that AOT, in addition to the standard therapy of patients, provides an improvement, although not significant, in the functional outcome of the UL compared to standard care. Moreover, our meta-analysis showed conflicting evidence concerning the efficacy of AOT in Uni-manual capacity. The subdomains of performance with both hands showed no significant difference between treatment and control groups; this could be probably influenced by the larger sample size of Kirkpatrick *et al*.[44]

In the study by Simon-Martinez *et al*.,[48] AOT was associated to CIMT to assess the synergy of the two therapies. Interestingly, the main improvements in terms of upper limb function were achieved in patients with a poorer bimanual performance at T0. This could be explained through a double mechanism of action; namely, the CIMT which treats the *learned non-use*, while the AOT is based on the re-enactment of the action. Thus, integrating AOT to CIMT could be a good solution to overcome the limits of the CIMT in treating patients with severe movement impairment.[65] This is coherent with the results of Abdelhaleem *et al.* reporting in their meta-analysis[66] that children with poorer hand function showed more improvement with the AOT compared with children with higher bimanual performance. It is plausible that, in the latter case, the neural substrates involved in action re-enactment cannot benefit from the facilitating effect of the AOT. In this regard, Sgandurra *et al*.,[67] in a study using fMRI in children with CP, found an early lateralization of action observation network in children with lower performance of hand function. This represents a maladaptive plasticity in the context of the reorganization of the neural substrates, that could be targeted by AOT.

The effect of AOT on the neural substrates involved in action re-enactment plasticity is confirmed by a recent Cochrane review with meta-analysis, of Borges *et al*.[68] In details, stroke survivors treated with AOT leads to improved UL motor function due to the direct effect of AOT on cortical activation and motor system reorganization in the supplementary motor area, bilateral ventral premotor cortex, insula, and superior temporal gyrus.

Moreover, in patients with Parkinson Disease, it has been demonstrated that AOT produces a brain reorganization of areas involved in sensorimotor integration and executive-attentive abilities.[69] This can be confirmed by the results achieved in children with CP, facilitating motor learning, by enhancing the activation of circuits involved in action motor representation, as observed in fMRI in the study of Buccino and colleagues.[43]

As for MT, three studies[46, 49, 50] compared it to conventional practice showing significant improvements respect the control group in UL movement, grip and dexterity, with significant results in terms of performance during ADLs and patient's compliance. Only for grasp there are conflicting results. In particular, only in the study of Nour *et al.*,[51] there was a significant improvement of grasp, probably due to the combined effect of MT and HABIT. In details, HABIT seems to be more effective that conventional therapy in CP because of higher intensity, that represents a key element of rehabilitation of CP,[70] and is hypothesized to be more useful than unilateral training, because enables the facilitation of the damaged hemisphere *via* interhemispheric connections.

In CP treatment, AOT has a key role in the rehabilitation program, because stimulates the interaction with external environment and ADL. However, in the study of Kara *et al.*,[42] they found that MT integrating high velocity and strength exercises improved UL performances and ADLs more than AOT in children with spastic hemiplegic CP. Strength and power exercises, stabilizing the proximal arm segment, determines an improvement of the entire kinetic chain of the UL and, consequently, improves fine motor function of the impaired hand, addressing both motor planning deficit (MT) and peripheric function (strength exercises).

The improvement of UL function is linked with an improvement of ADLs with a positive effect on independence, participation and inclusion in the society, as confirmed in stroke survivors by Nogueira *et al.*,[71] asserting that MT has some benefits in motor and functional recovery of the UL and ADLs.[72]

It was not possible to conduct a meta-analysis about MT in CP because, even though these RCTs are of good quality, they use different scales that are not comparable or they combine MT with other treatments like strength and power exercises[42] or HABIT.[51] However, the articles included suggest the effectiveness of MT on motor functions, participation, and activity of children with CP.

As a whole, cognitive strategies in the rehabilitation of children with CP appear to be ecological and not expensive treatments, easy to administer and with a relevant clinical impact. They provide the possibility to personalize the treatment, motivating patients, increasing their compliance, and can be integrated into the rehabilitation program. Video AOT is based on the use of videos that can also be shown in a tele-rehabilitation setting. The role of tele-medicine appears particularly relevant when patients have mobility or independence limitations; when caregivers are unable to take patients to rehabilitation centers or live in rural areas from where it may be difficult to join clinical centers and during health emergencies. However, as emerges from the comparison between the studies of Molinaro *et al.*[52] and Kirkpatrick *et al.*,[44] the figure of an expert therapist following the patient in video conference is fundamental to achieve significant results. Moreover, AOT could be administered with virtual reality devices to have better patient immersion and perception. Virtual reality, as shown in several studies, has the great advantage to improve the attention of the patient, and the compliance, with a positive effect on the rehabilitation outcome.[73]

Limitations of the study

This systematic review presents some limitations:

- most of the studies found included children with mild-moderate limitations of the manipulative capacity (excluding patients with MACS 4 and 5; HFCS <4 and MAS>2). These characteristics limit the generalizability of results of other types of CP and of those children with severe manual impairment;
- we included only English language studied, selected through three databases;
- the included studies have a small sample size and the included population have different types of CP.

Conclusions

Video AOT integrated in the conventional rehabilitation provides better results in the treatment of upper limb of children with CP compared to conventional practice, mainly in patients with higher impairments in motor functions. The synergic effect of the MSP in addition to conventional treatment led to a double effect: a reorganization of neural structures in the brain exploiting the cognitive approach directly targeting the motor representation of the UL action ensuring the top-down effect, and the bottom-up effect of the conventional motor rehabilitation.

Moreover, when children engage in successful and task-specific practice, they find it rewarding and enjoyable, leading to spontaneous and consistent practice, increasing motivation and attention, that represent a key element for neuroplasticity.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Andrea Demeco, Antonio Frizziero, Anna Molinaro, Elisa Fazzi, Cosimo Costantino, Giovanni Buccino have given substantial contributions to the conception or the design of the manuscript. Andrea Demeco, Anna Molinaro, Martina Ambroggi, and Giovanni Buccino to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript. Andrea Demeco, Anna Molinaro, Elisa Fazzi, Cosimo Costantino, Giovanni Buccino revised it critically. All authors read and approved the final version of the manuscript.

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