Original Research

Randomized controlled trial combining constraint-induced movement therapy and action-observation training in unilateral cerebral palsy: clinical effects and influencing factors of treatment response

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Abstract

Introduction: Constraint-induced movement therapy (CIMT) improves upper limb (UL) motor execution in unilateral cerebral palsy (uCP). As these children also show motor planning deficits, action-observation training (AOT) might be of additional value. Here, we investigated the combined effect of AOT to CIMT and identified factors influencing treatment response.

Methods: A total of 44 children with uCP (mean 9 years 6 months, SD 1 year 10 months) participated in a 9-day camp wearing a splint for 6 h/day and were allocated to the CIMT + AOT (n = 22) and the CIMT + placebo group (n = 22). The CIMT + AOT group received 15 h of AOT (i.e. video-observation) and executed the observed tasks, whilst the CIMT + AOT group watched videos free of biological motion and executed the same tasks. The primary outcome measure was bimanual performance. Secondary outcomes included measures of body function and activity level assessed before (T1), after the intervention (T2), and at 6 months follow-up (T3). Influencing factors included behavioural and neurological characteristics.

Results: Although no between-groups differences were found ($p > 0.05$; $\eta^2 = 0–16$), the addition of AOT led to higher gains in children with initially poorer bimanual performance ($p = 0.02$; $\eta^2 = 0.14$). Both groups improved in all outcome measures after the intervention and retained the gains at follow up ($p < 0.01$; $\eta^2 = 0.02–0.71$). Poor sensory function resulted in larger improvements in the total group ($p = 0.03$; $\eta^2 = 0.25$) and high amounts of mirror movements tended to result in a better response to the additional AOT training ($p = 0.06$; $\eta^2 = 0.18$). Improvements were similar irrespective of the type of brain lesion or corticospinal tract wiring pattern.

Conclusions: Adding AOT to CIMT, resulted in a better outcome for children with poor motor function and high amounts of mirror movements. CIMT with or without AOT seems to be more beneficial for children with poor sensory function.

Trial registration: Registered at ClinicalTrials.gov on 22nd August 2017 (ClinicalTrials.gov identifier: NCT03256357).

Keywords: Upper limb, Unilateral cerebral palsy, Action Observation Training, Constraint Induced Movement Therapy, Intensive training, Predictors, Randomized Controlled Trials, Corticospinal Tract Wiring Pattern

Introduction

The quality of life of children with unilateral cerebral palsy (uCP) can be compromised by their upper limb (UL) sensorimotor problems.[1] In the last few decades, improving these deficits has been the focus of many studies. Constraint-induced movement therapy (CIMT) is one of the few treatments that has been thoroughly investigated

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and proven to be effective.[2] It consists of constraining the less impaired hand while intensively training the more impaired UL to promote increased use of the latter.[3] Whilst CIMT focuses on improving UL movement quality and efficiency, children with uCP also show deficits in motor representation and motor planning.[4,5] To overcome these deficits, action-observation training (AOT) has been suggested as a potential treatment modality. AOT is based on the well-established principle that observation of actions activates the same cortical structures that are active during the actual performance of the task.[6] Although preliminary evidence has shown positive effects of AOT on UL function in children with uCP,[7] it remains unknown whether the combination of CIMT and AOT would enhance the effect of CIMT on improving UL sensorimotor function in these children.

Despite increasing evidence proving the effectiveness of CIMT, the large variability in reported results leads to overall small to medium effect sizes (ESs).[2] Therefore, identifying factors influencing treatment response would contribute to the development of more efficient and more individualized treatment planning. Poor initial hand function has influenced a better response to CIMT in previous studies,[8] but there remains controversy regarding age.[8,9] In adult stroke survivors, there is preliminary evidence that sensory deficits may also influenced UL motor outcome.[10] We hypothesize that children with impaired sensory function might also benefit more from the intensive use of their more impaired hand. Similarly, mirror movements (MM) have a negative impact on UL function,[11] yet their value to influence treatment response remains unknown. Among potential neurological factors are the underlying lesion type (predominantly white matter *versus* grey matter damage) and the corticospinal tract (CST) wiring pattern, due to their value in explaining variability in UL function.[12] Thus far, only one small study showed improvements after CIMT regardless of the lesion type.[13] However, there is controversy regarding the influence of the CST wiring pattern on treatment response.[13–15] Some studies have reported a worse outcome after CIMT in children with an ipsilateral CST wiring[14,15] whilst others showed positive outcome irrespective of the CST wiring pattern.[13] Nevertheless, these studies had small sample sizes and did not include children with different lesion types.

The aim of this study was twofold: we first investigated the added value of AOT to CIMT in improving UL sensorimotor function in children with uCP; and secondly, we explored the influence of behavioural and neurological factors treatment response.

Materials and methods

Participants
This prospective randomized with blinded evaluation trial has been fully described elsewhere,[16] and will be briefly summarized here. The study was conducted at KU Leuven and was approved by the Ethics Committee of the University Hospitals Leuven (S56513) and registered at www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT03256357). All children agreed to participate, and their parents or caregivers signed the informed consent.

Study population and randomization
Children with uCP were recruited between June 2014 and June 2017 *via* the cerebral palsy (CP) reference centre of the University Hospitals Leuven. Inclusion criteria were (a) confirmed diagnosis of uCP, (b) aged 6–12 years, (c) sufficient cooperation to complete the activities and assessments, and (d) minimal ability to actively grasp and stabilize an object with the more impaired hand [House Functional Classification Score (HFC) $\geqslant$ 4].[17] Children were excluded in case of UL surgery in the last 2 years, or botulinum toxin A-injections 6 months prior to enrolment. The participants were stratified according to the HFC scale (4–5 *versus* 6–7), age (6–9 years *versus* 10–12 years), and the CST wiring pattern (contralateral, bilateral, ipsilateral) and assigned to the CIMT + AOT or CIMT + placebo AOT group by using a permuted block design of two. Randomization was performed by a researcher (HF) independent of the recruitment and evaluation sessions. Sample size estimation for the primary outcome measure was conducted prior to study initiation, resulting in a total of 21 children in each group (ES = 0.9, alpha-level = 0.05, statistical power = 0.80), as described in more detailed in.[16] The sample size was increased to a total of 44 to account for dropouts.

Intervention
The intervention was delivered in a day camp model during 9 out of 11 consecutive days (6 h/day,

HFC levels 4-5
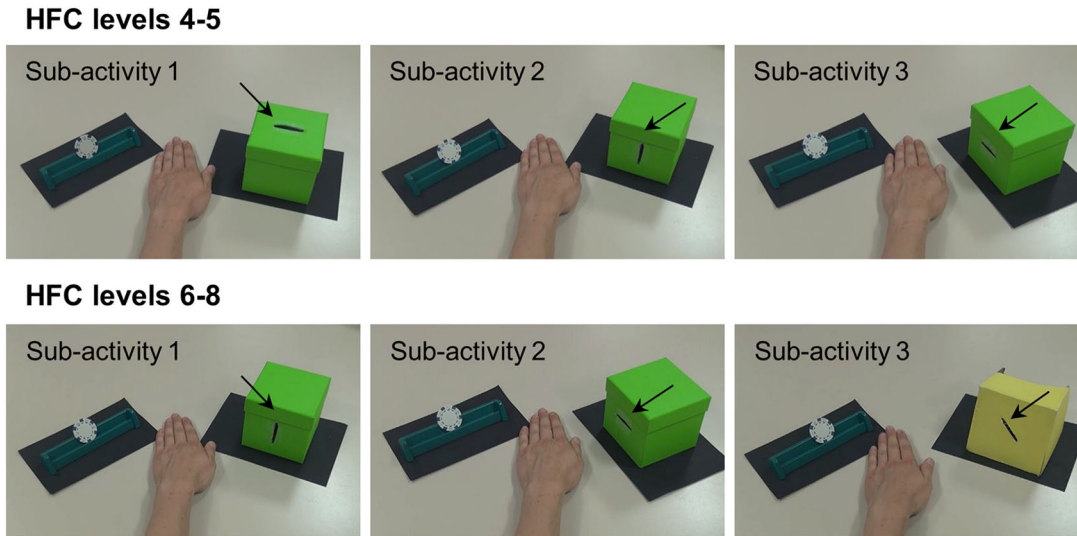
HFC levels 6-8

Figure 1. Illustration of a goal-directed activities used for the action-observation Training (AOT) for each different hand function level. On the top panel, the three sub-activities for children with House Functional Classification (HFC) levels 4–5. On the bottom panel, three sub-activities for children with HFC levels 6–8. For both levels, each consecutive sub-activity becomes one step more challenging by changing the direction of inserting the coin, as indicated by the arrows. Children were shown from the first-person perspective how to grasp the poker coin and insert it in the box through the slot. Note that the activities for levels 6–8 are more challenging, as they require a combination of increased wrist extension and supination.

total of 54h of therapy). During the camp, all children wore a tailor-made hand splint on the less impaired hand while performing unimanual exercises during individual therapy (9h), group activities (30h), and AOT/placebo condition (15h). A day (6h of therapy) was structured with 1h of individual therapy, 2h of AOT/placebo, and 3h of group activities. The children wore the hand splint during the whole time of the camp, as long as daily life activities (i.e. eating and toileting) were feasible.

The individual therapy was based on motor learning principles of shaping and repetitive practice by focusing on four goals: (a) active wrist and elbow extension, (b) forearm supination, (c) grip strength, and (d) fine motor tasks. The group activities consisted of painting, crafting, cooking, and outdoor playing, selected to stimulate the intensive use of the more impaired hand. Children assigned to the CIMT + AOT group received 15h of AOT sessions. During these sessions, children watched video sequences showing unimanual goal-directed actions, adapted to the child's functional level: easier activities for children with a HFC level of 4–5 and more difficult activities for children with a HFC level of 6–7. The description of the activities can be found in more detail

elsewhere (Figure 1 and Additional files of Simon-Martinez and colleagues).[16] Each AOT session lasted about 1h and 15 AOT sessions were performed over 9 days (either 1 or 2 per day). Each AOT session contained 3 sub-activities, which were watched for 3 min. After watching the video, the children executed the observed task for 3 min. This process was repeated a second time for each sub-activity. The completion of the AOT session was achieved when the 3 sub-activities of the session were watched, and its tasks executed. In conclusion, per AOT session the videos were watched for 18 min (6 times, 3 min). The CIMT + placebo group watched video games free of human motion (e.g. Tetris, Word Soup, Hanged Game). The children interacted with the game whilst the therapists controlled the mouse and/or keyboard. After watching the video with the sub-activity being repeated for 3 min, they executed the same sub-activity for 3 min in the same order as the experimental group, for which only verbal, non-suggestive instructions (e.g. try to extend your wrist, open the hand) were provided. This ensured that the potential additional measured effect solely derived from the video-observation. To account for the compliance of the video observation in the experimental group, the therapists asked a yes/no question after the second execution of each sub-activity.

These questions were not related to how the movement was performed but rather to features related to the video (e.g. is the box taken from the top? Did you see the palm of the hand?). This procedure kept the motivation of the child in observing attentively. At the end of the intervention, the number of correct answers were summed, ranging from 0 (all answers incorrect) to 45 (all answers correct).

Evaluation

An experienced physiotherapist blinded to group allocation (JH) conducted the evaluations at T0 (baseline, 3–4 months before the intervention), T1 (within 4 days before the intervention), T2 (within 4 days after the intervention), and T3 (6 months after the intervention). At T0, we collected descriptive and clinical characteristics to individually set the child's therapy goals by experienced physiotherapists. Primary and secondary outcome measures were collected at T1, T2, and T3. At T1, we evaluated sensory function, MM, type of brain lesion, and CST wiring pattern, identified with magnetic resonance imaging (MRI) and Transcranial Magnetic Stimulation (TMS), respectively, as influencing factors.

Outcome measures. The primary outcome measure was the Assisting Hand Assessment (AHA), which evaluates the spontaneous use of the impaired hand during bimanual activities.[18,19] A certified rater scored the videos, blinded to group-allocation and time-point evaluation. The smallest detectable difference is 5 AHA units.[20]

Secondary outcome measures comprised body function (muscle tone, muscle strength and grip strength) and activity (unimanual movement speed and unimanual and bimanual dexterity) measures, following a valid and reliable protocol.[21] Muscle tone was assessed using the Modified Ashworth Scale,[22] We evaluated muscle strength using the 8-point ordinal scale of the Medical Research Council[23] and grip strength using the mean of three maximum contractions with the Jamar® dynamometer (Sammons Preston, Rolyan, Bolingbrook, IL, USA). Movement quality was evaluated with the Melbourne Assessment 2 (MA2).[24,25] The test was scored afterwards by a trained physiotherapist blinded to group-allocation and time-point evaluation. At activity level, we included unimanual movement speed and unimanual and bimanual dexterity. Movement speed (time) was evaluated

during six unimanual tasks with the modified version of the Jebsen-Taylor Hand Function test (JTHFT).[26,27] For this test, the minimal clinically important difference has been reported to be 54.7 s in a group of children with CP (80% of uCP).[28] Unimanual and bimanual dexterity were evaluated using the Tyneside Pegboard Test, an instrumented 9-hole pegboard test.[29] Lastly, parents were asked to complete the ABILHAND-Kids and the Children's Hand-use Experience Questionnaire (CHEQ). More detailed information on the evaluation of the secondary outcome measures can be found in Supplementary Materials.

Influencing factors of treatment response. Sensory assessments comprised measures of exteroception (tactile sense), proprioception (movement sense), two-point discrimination (2PD, Aesthesiometer®) and stereognosis (tactile object identification), which have been shown to be reliable in this population.[21] Tactile and movement sense were classified as normal (score 2), impaired (score 1) or absent (score 0). 2PD was classified according to the minimum width between the two points that the children could discriminate: normal (0–4 mm, score 2), or impaired (>4 mm, score 1).[30] Tactile object identification was quantified as the number of objects that the child could recognize (0–6). In addition, a kit of 20 nylon monofilaments (0.04–300 g) (Jamar® Monofilaments, Sammons Preston, Rolyan, Bolingbrook, IL, USA) was used to reliably determine threshold values for touch sensation.[31,32] Touch sensation was categorized as normal (0.008–0.07 g), diminished light touch (0.16–0.4 g), diminished protective sensation (0.6–2 g), loss of protective sensation (4.19–180 g) and untestable (300 g), according to the manual.

MM were quantitatively assessed with the grip force tracking device during a squeezing task, following the protocol defined by Jaspers and colleagues.[33] Before performing the task, we tested the maximum voluntary contraction of each hand, starting with the less affected hand. We instructed the children to play a game requiring rhythmic squeezing of one handle with one hand (active hand), while holding the second handle with the other hand (passive hand). The game consisted of controlling with the active hand the position of an astronaut (higher forces corresponding to a higher position on the screen), with the goal to jump over meteorites flying across the screen. MM characterization was

based on the comparison of grip force profiles of the active *versus* the passive hand and consisted of the calculation of MM amplitude. MM frequency represents the number of squeezes in the passive hand that exceeded a predefined threshold, expressed as a percentage of the total number of squeezes produced in the active hand. MM amplitude is the average amplitude ratio of the squeezes between both hands, based on only those squeezes in the passive hand that exceeded a predefined threshold. Lastly, MM amount was computed as the frequency by amplitude product, providing an overall indication of the MM occurrence. Full details on the calculation can be found in Rudisch and colleagues.[34] MM amount in each hand was used for further statistical analysis.

Brain imaging and neurophysiological evaluation were performed before the intervention. The MRI was acquired with a 3T system (Achieva, Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel coil. Structural images were acquired using three-dimensional fluid-attenuated inversion recovery and magnetization prepared rapid gradient echo. MRI results were used to characterize the lesion type according to the presumed timing (malformation, predominantly white matter, predominantly grey matter)[35] by a child neurologist (EO). To identify the underlying CST wiring pattern, a single-pulse TMS session was conducted. A MagStim 200 Stimulator (Magstim Ltd., Whitland, Wales, UK) equipped with a focal 70 mm figure-eight coil and a Bagnoli electromyography system (Delsys Inc., Natick, MA, USA) was used for data acquisition. After identifying the hotspot and the rest motor thresholds, motor evoked potentials were elicited and recorded on the thumb adductor and opponent muscles on both hands to identify the wiring pattern (contralateral, bilateral or ipsilateral). Children with contraindications to MRI or TMS did not undergo the respective measurement. There were no adverse events.

Statistical analyses

Effect of the intervention over time. Normality was checked using the Shapiro-Wilk test and inspection of the histograms for symmetry. To conduct parametric statistics, a logarithmic transformation was applied to the parameters of grip strength, the JTHFT, the instrumented pegboard test, the 'range of motion' subscale of the MA2, and the 'feeling bothered' subscale of the CHEQ questionnaire. A reflect and square root transformation was applied to the 'accuracy' subscale of the MA2. Descriptive statistics were reported according to the nature of the data (i.e. means and standard deviations for continuous data and median and interquartile ranges for ordinal data). Mixed models were used to study changes after the intervention over time. By using random effects, these models can correct for the dependency among repeated observations. Furthermore, these models deal with missing data offering valid inferences, assuming that missing observations are unrelated to unobserved outcomes.[36] Changes over time between groups were tested by including group×time interactions. In case of a significant interaction, group-dependent changes were investigated separately in each group. ESs for the full models were calculated from the *F*-values, according the Cohen's partial η^2 formula [partial $\eta^2 = (F \times df_{between})/((F \times df_{between}) + df_{within})$] and interpreted accordingly (small, 0.02–0.13; medium, 0.13–0.26; and large>0.26).[37] Significant time trends were further inspected using pairwise *post hoc* comparisons between T1–T2, T1–T3, and T2–T3 (Bonferroni corrected). The ESs of these comparisons were calculated and interpreted according to Cohen's *d* formula (ES-*d*) (small, 0.2–0.5; medium, 0.5–0.8, and large >0.8).[38]

Influencing factors of treatment response. Both behavioural (age, initial motor function based on AHA and JTHFT score at T1, sensory function, and MM amount) and neurological characteristics (type of brain lesion and CST wiring pattern) were evaluated as potential influencing factors of treatment response. All variables were included in their original scale except for a dichotomized score for initial motor function. Initial low motor function was defined as either <50 in the AHA units or >350 s in the JTHFT (defined as the 25th percentiles for the total group at T1). These variables were included as covariates in the models to influence outcomes in the AHA (bimanual) and JTHFT (unimanual), together with the time×group interaction. If the interaction with group was not significant, the interaction with time was examined. *Post hoc* analyses with Bonferroni correction were conducted in case of significant interactions and trends (<0.10), as this would allow us to capture tendencies immediately after the intervention.

All statistical analyses were performed using SPSS Statistics for Windows version 25.0 (IBM Corp. Armonk, NY: IBM Corp.). The two-sided

5% level of significance was used for interactions and main effects.

Results

Participants

A total of 44 children participated in the study [mean age (SD) 9 years 6 months (1 year 10 months); 27 boys; 23 left-sided uCP; 9 Manual Ability Classification System I (MACS),[39] 15 MACS II, and 20 MACS III], and were allocated to the CIMT + AOT group ($n = 22$) and CIMT + placebo group ($n = 22$) (Table 1; Supporting information Table S1). All children completed the intervention program (100% compliance), but two allocated to the CIMT + placebo group were lost to follow-up (Figure 2).

Treatment efficacy

Table 2 summarizes the outcome measures for each intervention group at every time point. All children who received AOT sessions showed a good compliance to the video observation, based on the number of correct answers to the video-related questions (median = 42, interquartile range = 5, range 30–45). No differences in hand function between groups were found at T1 (all $p > 0.05$, Table S2 Supporting information).

The added value of AOT to CIMT. We did not find between-groups differences in improvements over time on the primary outcome (AHA; $p > 0.05$) nor on the secondary outcomes (all $p > 0.05$, Table 2).

Improvements over time. The descriptive data is shown in Table S3 of Supporting information. The total group improved over time in the AHA ($p < 0.001$), with a significant mean improvement of 2.21 AHA units immediately after the intervention (T1–T2, $p < 0.001$) and maintained at follow-up (T2–T3, $p < 0.001$). ESs were low (ES = 0.14–0.18). Immediately after the intervention, most of the children ($n = 32$, 74%) improved their AHA score, of which 28% ($n = 9$) showed an improvement $\geqslant 5$ AHA units (Figure 3 a).

Each bar represents an individual child. The grey horizontal line represents the smallest detectable difference for the AHA test (5 AHA units) and the minimal clinically important difference for the JTHFT (54.7 s).

At body function level, we found an improvement in grip and muscle strength ($p < 0.001$), occurring immediately after the intervention ($p < 0.001$) and maintained at follow-up ($p < 0.001$). From the MA2 scale, only range of motion improved over time ($p = 0.04$), although the improvements were not immediately after the camp ($p > 0.05$), but at follow-up ($p = 0.04$). No significant changes were found for spasticity scores ($p > 0.05$).

At activity level, we found large improvements in movement speed (JTHFT, $p < 0.001$), performing on average 43 s faster after the intervention ($p < 0.001$) and retaining the gains at follow-up ($p < 0.001$). After the intervention, 89% of the children ($n = 39$) improved, and 39% ($n = 17$) improved more than the minimal clinically important difference (54.7 s) (Figure 3 b). At follow-up, 68% ($n = 30$) maintained the gains, and 32% ($n = 14$) maintained the gains beyond the minimal clinically important difference. The improvements were also large in unimanual and bimanual dexterity (pegboard test, all $p < 0.02$). Unimanual dexterity improved immediately after the intervention ($p < 0.01$) and improvements were retained at follow-up ($p < 0.05$). The 'small pegs' condition was incomplete for eight children before the camp, although six of these eight children could complete the task after the camp, and four of them still completed it at follow-up. Bimanual dexterity also improved immediately after the intervention ($p < 0.01$) and at follow-up ($p < 0.01$). Lastly, the CHEQ results showed a reduction in time consumption and feeling bothered while performing activities ($p = 0.009$ and $p = 0.04$, respectively), increasing by 4.47% (T1 *versus* T2, $p = 0.008$) and 5.96% (T1 *versus* T2, $p = 0.03$), respectively. ABILHAND-Kids did not change after the intervention ($p = 0.65$).

In summary, we found large ESs ($\eta^2 > 0.26$) on most outcomes over time. We found improvements immediately after the intervention on muscle strength (ES-*d* 0.93) and grip strength (ES-*d* 0.16), on unimanual dexterity measured with the JTHFT (ES 5.81) and in unimanual (ES-*d* 0.65–1.57) and bimanual dexterity (ES-*d* 0.85–1.44) measured with the instrumented pegboard test. Lastly, the subscales of the CHEQ 'feeling bothered' and 'time used' improved with large (ES-*d* 0.85) and small (ES-*d* 0.31) ESs, respectively. In addition, the retained gains were also captured by these assessments with similar ESs.

Table 1. Demographic characteristics of the participants per group.

		CIMT + placebo group (*n* = 22)	CIMT + AOT group (*n* = 22)	*p*-value
Age	mean (SD)	9 years 6 months (1 year 10 months)	9 years 6 months (1 year 11 months)	0.89[1]
Sex	*n* (%)			
Boys		12 (55)	15 (68)	0.35[2]
Girls		10 (45)	7 (32)	
More affected side	*n* (%)			
Left		14 (64)	9 (41)	0.13[2]
Right		8 (36)	13 (59)	
MACS	*n* (%)			
I		3 (14)	6 (27)	0.39[2]
II		7 (32)	8 (36.5)	
III		12 (55)	8 (36.5)	
HFC system	*n* (%)			
Levels 4–5		18 (82)	16 (73)	0.47[2]
Level 6–8		4 (18)	6 (27)	
Lesion type	*n* (%)			
Malformation		0 (0)	1 (4.5)	0.18[2]
PV lesion		5 (23)	12 (54.5)	
CSC lesion		13 (59)	7 (32)	
Acquired		1 (4.5)	0 (0)	
Other		3 (13.5)[§]	0 (0)	
Unknown		0 (0)	2 (9)[$]	
CST wiring	*n* (%)			0.42[2]
Contralateral		1 (5)	3 (14)	
Bilateral		8 (36)	5 (23)	
Ipsilateral		7 (32)	8 (36)	
Unknown[‡]		6 (27)	6 (27)	

AOT, action-observation training; CIMT, constraint-induced movement therapy; CSC, cortico-subcortical; CST, corticospinal tract; HFC, House Functional Classification; MACS, Manual Ability Classification System; MRI, Magnetic resonance imaging; PV: periventricular.
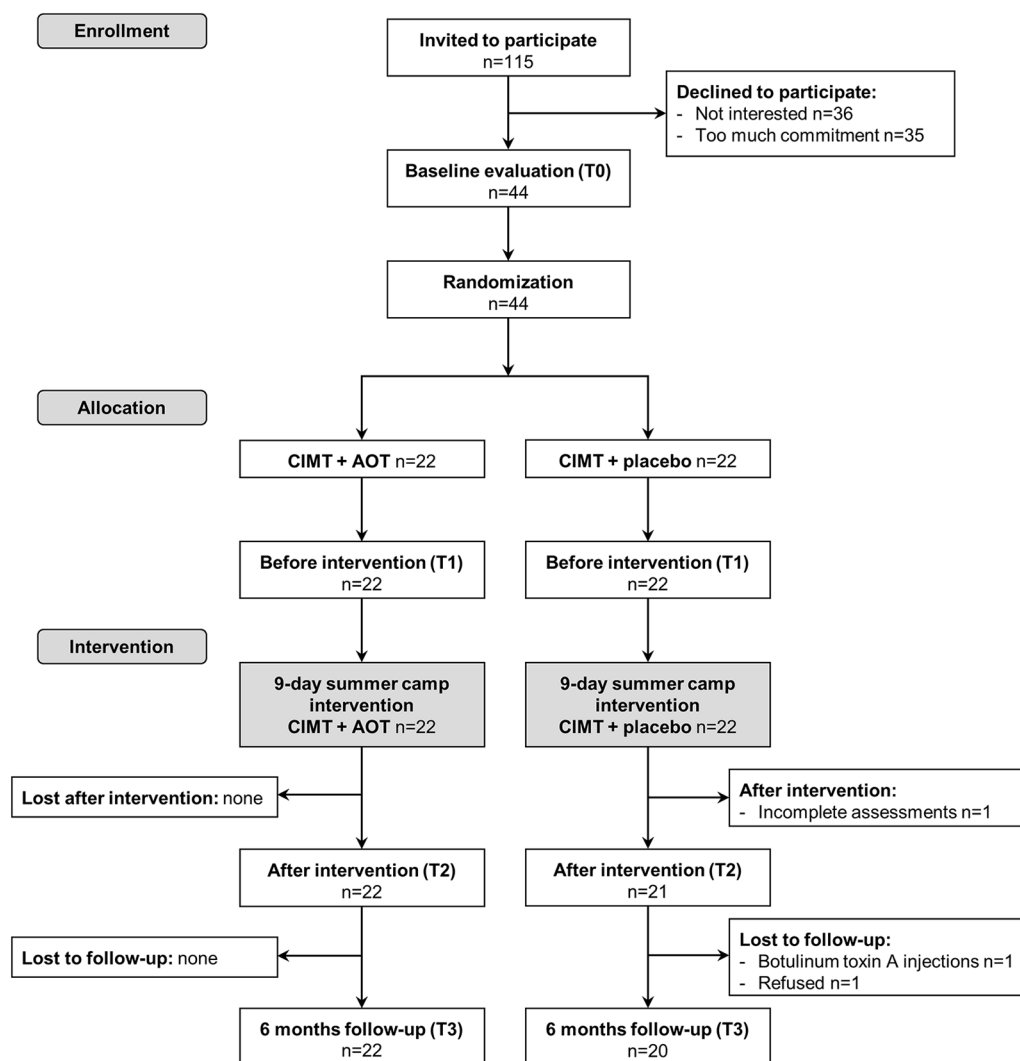[§]Other: brainstem tumour (*n* = 1), hemispherectomy (*n* = 2).
[$]No MRI performed (*n* = 1 panic attack, *n* = 1 refused to complete MRI).
[‡]TMS not performed or inconclusive.
[1]Independent samples *t*-test.
[2]Pearson chi-squared test.

Figure 2. CONSORT flowchart with number of participants and reasons for missing data in each group, at each time point.

Influencing factors

We evaluated the influence of behavioural and neurological characteristics on treatment outcome for the primary outcome measure (AHA) and for movement speed (JTHFT), as it showed the largest ES (>5, Table 2). An overview of the statistical results is reported in Table 3. Table S4 in 'Supporting information' reports the number of children included in each category for the significant influencing factors.

Are there subgroups of children who respond better to AOT? We found a trend toward a significant influence of initial hand function (AHA

score) on treatment response at three time points ($F = 3.00$, $p = 0.06$; Figure 4 (a), which was significant between T1–T2 ($p = 0.02$). This interaction indicated that if the initial AHA score was low, the CIMT + AOT group benefitted more than the CIMT + placebo group. If the initial AHA score was high, both groups improved equally (Figure 4 b).

Similarly, we found a trend toward a significant influence of MM amount in the less affected hand (more affected hand actively moving) on treatment response of bimanual performance ($F = 3.21$, $p = 0.06$, Figure 5). This interaction indicated that

Table 2. Estimated marginal means (standard error) of outcome measures at each time point, and statistical comparison [F(p-values; partial η^2)].

		T1 (pre)	T2 (post)	T3 (6 months follow-up)	Time × Group	Total group (n=44)		
						Time	ES T1 versus T2	ES T1 versus T3
Primary outcome measure								
AHA (units 0–100)	CIMT + placebo	54.73 (2.64)	56.59 (2.60)	56.10 (2.75)	0.56 (0.58; 0.03)	**18.62 (<0.001; 0.45)**§*	0.18	0.14
	CIMT + AOT	58.68 (2.64)	61.23 (2.60)	60.73 (2.75)				
Secondary outcome measures								
Spasticity (MAS)	CIMT + placebo	4.60 (0.37)	4.41 (0.34)	4.89 (0.38)	1.56 (0.22; 0.07)	2.95 (0.06; 0.12)	0.14	0
	CIMT + AOT	5.05 (0.38)	4.77 (0.34)	4.77 (0.37)				
Muscle strength (MMT)	CIMT + placebo	10.21 (0.20)	11.11 (0.16)	10.82 (0.16)	3.01 (0.06; 0.13)	**52.07 (<0.001; 0.71)**§	0.93	0.79
	CIMT + AOT	10.23 (0.20)	10.86 (0.16)	10.89 (0.15)				
Grip strength (kg)	CIMT + placebo	4.06 (1.15)	5.24 (1.13)	6.10 (1.13)	0.49 (0.62; 0.02)	**16.44 (<0.001; 0.44)**§*	0.16	0.24
	CIMT + AOT	4.47 (1.16)	5.58 (1.13)	5.94 (1.13)				
MA2–Range of Motion (%)	CIMT + placebo	62.57 (1.05)	65.09 (1.05)	68.08 (1.06)	2.95 (0.06; 0.13)	**3.51 (0.04; 0.14)***	0.13	0.44
	CIMT + AOT	68.61 (1.05)	67.65 (1.05)	69.12 (1.06)				
MA2–Dexterity (%)	CIMT + placebo	59.07 (4.02)	62.96 (3.83)	62.56 (4.29)	1.18 (0.32; 0.05)	2.12 (0.13; 0.09)	0.10	0.12
	CIMT + AOT	68.80 (4.03)	68.73 (3.81)	70.06 (4.26)				
MA2–Accuracy (%)	CIMT + placebo	88.33 (0.81)	87.17 (0.86)	91.92 (0.85)	2.10 (0.14; 0.09)	0.51 (0.61; 0.02)	0	0
	CIMT + AOT	94.42 (0.81)	94.91 (0.86)	93.74 (0.86)				
MA2–Fluency (%)	CIMT + placebo	78.36 (2.80)	77.27 (2.61)	77.71 (2.71)	2.08 (0.14; 0.09)	2.92 (0.07; 0.12)	0.15	0.06
	CIMT + AOT	82.60 (2.82)	80.09 (2.60)	84.71 (2.68)				
JTHFT (s)	CIMT + placebo	211.94 (1.17)	155.83 (1.18)	176.94 (1.18)	3.21 (0.05; 0.14)	**26.40 (<0.001; 0.56)**§*	5.81	5.21
	CIMT + AOT	172.29 (1.17)	140.42 (1.18)	132.56 (1.18)				
IPT–Large pegs bimanual (more aff toward less-aff)	CIMT + placebo	39.65 (1.10)	30.45 (1.11)	32.65 (1.10)	1.90 (0.16; 0.09)	**20.98 (<0.001; 0.53)**§*	0.85	0.80
	CIMT + AOT	35.83 (1.10)	32.73 (1.10)	31.30 (1.10)				

(Continued)

Table 2. (Continued)

		T1 (pre)	T2 (post)	T3 (6 months follow-up)	Time × Group	Total group (n=44) Time	ES T1 versus T2	ES T1 versus T3
IPT – Large pegs bimanual (less-aff toward more-aff)	CIMT + placebo	61.58 (1.16)	48.76 (1.16)	51.73 (1.16)	0.15 (0.86; 0.01)	6.73 (0.004; 0.32)§*	1.44	1.20
	CIMT + AOT	53.17 (1.15)	44.64 (1.15)	45.51 (1.15)				
IPT–Large pegs unimanual (more-aff hand)	CIMT + placebo	44.90 (1.14)	37.17 (1.12)	37.87 (1.12)	0.13 (0.88; 0.01)	7.46 (0.002; 0.33)§*	0.93	0.93
	CIMT + AOT	38.13 (1.14)	32.30 (1.11)	31.96 (1.11)				
IPT–Medium pegs unimanual (more-aff hand)	CIMT + placebo	42.15 (1.13)	37.40 (1.12)	36.71 (1.14)	0.01 (0.99; 0)	7.40 (0.002; 0.28)§*	0.65	0.77
	CIMT + AOT	39.62 (1.12)	35.02 (1.11)	34.07 (1.13)				
IPT–Small pegs unimanual (more-aff hand)	CIMT + placebo	73.44 (1.17)	55.07 (1.16)	56.97 (1.17)	0.80 (0.46; 0.05)	13.13 (<0.001; 0.44)§*	1.57	1.63
	CIMT + AOT	50.33 (1.16)	43.76 (1.15)	41.39 (1.16)				
ABILHAND-Kids (logits)	CIMT + placebo	1.64 (0.25)	1.90 (0.66)	1.79 (0.28)	1.04 (0.37; 0.05)	0.44 (0.65; 0.02)	0.08	0.11
	CIMT + AOT	1.67 (0.25)	1.63 (0.26)	1.77 (0.28)				
CHEQ–Grip efficacy (%)	CIMT + placebo	45.78 (3.20)	48.15 (2.78)	49.30 (3.73)	0.40 (0.68; 0.02)	3.24 (0.05; 0.17)	0.30	0.30
	CIMT + AOT	42.08 (3.24)	47.86 (2.64)	47.75 (3.43)				
CHEQ–Time used (%)	CIMT + placebo	39.15 (3.18)	44.69 (2.99)	41.62 (3.21)	0.45 (0.64; 0.02)	5.38 (0.009; 0.23)§	0.31	0.22
	CIMT + AOT	38.17 (3.23)	41.86 (2.93)	41.82 (2.99)				
CHEQ–Feeling bothered (%)	CIMT + placebo	40.02 (1.10)	50.03 (1.06)	46.24 (1.06)	3.12 (0.06; 0.16)	3.66 (0.04; 0.18)§	0.85	0.78
	CIMT + AOT	45.03 (1.10)	47.74 (1.06)	49.20 (1.06)				

AHA, Assisting Hand Assessment; AOT, action-observation training; CHEQ, Child's Hand Experience Questionnaire; CIMT, modified constraint-induced movement therapy; ES, effect size; IPT, instrumented pegboard test; JTHFT, Jebsen–Taylor Hand Function test; kg, kilograms; MA2, Melbourne Assessment 2; MAS, Modified Ashworth Scale; MMT, manual muscle testing; T1, pre-intervention evaluation; T2, post-intervention evaluation; T3, 6 months follow-up evaluation.
§Significant at the T1 *versus* T2 comparison.
*Significant at the T1 *versus* T3 comparison.
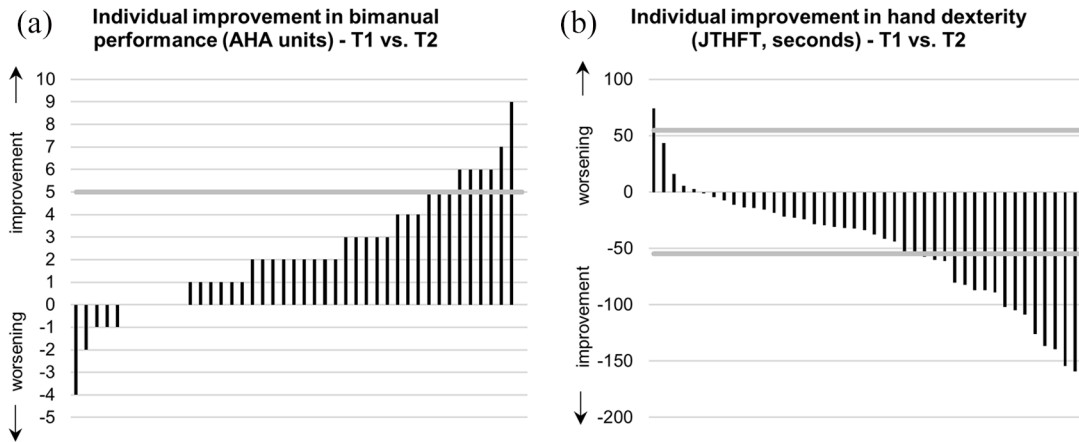
Figure 3. Individual change in Assisting Hand Assessment (AHA) (a) and Jebsen-Taylor Hand Function test (JTHFT) (b) scores immediately after the intervention (T1 *versus* T2).

if the initial amount of MM was high, the CIMT + AOT group benefitted more than the CIMT + placebo group. If the initial MM amount was low, both groups improved similarly.

Responsiveness to AOT did not depend on age nor sensory function for either AHA or JTHFT ($p > 0.05$). Regarding neurological characteristics, neither type of brain lesion nor CST wiring pattern had an influence on responsiveness to AOT ($p > 0.05$).

Are there subgroups of children who respond better to CIMT with or without AOT? We found that sensory function was able to influence treatment response for the total group for unimanual dexterity. More specifically, exteroception, 2PD, and touch sensation influenced the outcome of the JTHFT ($p = 0.03–0.08$; Table 3), indicating that children with more impaired sensory function benefitted more from the CIMT intervention, compared with those with normal sensory function (Figure 6). Note that initial motor function did not interfere with these interactions (interaction term $p < 0.05$).

The responsiveness to CIMT with or without AOT did not depend on age, initial motor function, stereognosis, nor amount of MM ($p > 0.05$, Table 3). Similarly, neither type of brain lesion nor CST wiring pattern had an influence on responsiveness to CIMT with or without AOT when tested individually ($p > 0.05$, Figure 7) or combined (interaction between CST wiring pattern and type of the brain lesion, $p > 0.05$).

Discussion

This randomized controlled trial was the first to investigate the effects of an intensive camp-based treatment model combining CIMT and AOT to improve UL function at body function and activity level, by including clinical and instrumented outcome measures, as well as both behavioural and neurological factors to determine their influence on treatment outcome. The effects showed that, with or without AOT, an intensive CIMT training approach delivered in a summer camp setting leads to improvements in UL function. Although we could not demonstrate an overall added effect of AOT, our results suggest that the addition of AOT to CIMT may be beneficial for children with initial poor hand function and high amount of MM. In addition, we found that sensory function influenced treatment response following CIMT (with or without AOT).

What is the added value of AOT to CIMT on UL function?

The novelty of this RCT lies in the investigation of the added value of AOT to a well-established therapy approach, such as CIMT. Overall, our results show similar improvements in the CIMT + AOT and CIMT + placebo group. To date, the first studies exploring AOT in children with uCP have proven its effectiveness in improving UL motor function.[7,40–42] However, these studies investigated the effect of AOT alone compared with a placebo or no observation, and not the added effect of AOT to a well-established UL therapy, such as CIMT. Our results are in

Table 3. Statistical inference overview of the influencing value of behavioural, and neurological characteristics on treatment response [F (p-values; partial η^2)].

		Bimanual performance (AHA)	Unimanual dexterity (JTHFT)
Age (years, continuous)	Interaction with group	0.74 (0.49; 0.04)	1.87 (0.17; 0.09)
	Total group	0.24 (0.79; 0.01)	0.18 (0.84; 0.01)
Initial motor function			
AHA score (low (<50 units) *versus* high (>50 units); class)	Interaction with group	**3.00 (0.06; 0.14)**$^{\$*}$	
	Total group	0.45 (0.64; 0.02)	
JTHFT score (low (>355 s) *versus* high (<355 s); class)	Interaction with group		0.33 (0.72; 0.02)
	Total group		0.43 (0.66; 0.02)
Sensory function			
Exteroception (0–2; class)	Interaction with group	1.36 (0.87; 0.01)	0.54 (0.59; 0.03)
	Total group	0.90 (0.48; 0.09)	**3.13 (0.03; 0.25)***
Proprioception (0–2; class)	Interaction with group	0.41 (0.67; 0.02)	0.05 (0.95; 0)
	Total group	1.14 (0.33; 0.06)	0.92 (0.41; 0.05)
2PD score (impaired and normal; class)	Interaction with group	0.05 (0.95; 0)	0.65 (0.53; 0.04)
	Total group	0.59 (0.56; 0.03)	**2.66 (0.08; 0.10)***
Stereognosis (0–6; categorical)	Interaction with group	1.87 (0.17; 0.09)	1.38 (0.27; 0.07)
	Total group	1.59 (0.22; 0.08)	2.28 (0.12; 0.11)
Touch sensation (monofilaments (0–4; categorical)	Interaction with group	1.67 (0.20; 0.08)	1.90 (0.16; 0.09)
	Total group	1.62 (0.21; 0.08)	**3.27 (0.05; 0.14)***
MM amount			
In the more affected hand (continuous)	Interaction with group	1.73 (0.19; 0.10)	0.67 (0.52; 0.04)
	Total group	0.14 (0.87; 0.01)	0.26 (0.78; 0.02)
In the less affected hand (continuous)	Interaction with group	**3.21 (0.06; 0.18)**$^{\$*}$	0.06 (0.95; 0)
	Total group	2.68 (0.08; 0.14)	0.63 (0.54; 0.04)
Neurological characteristics			
Lesion type (PV and CSC; class)	Interaction with group	0.11 (0.90; 0)	0.63 (0.54; 0.04)
	Total group	0 (1; 0)	1.89 (0.17; 0.10)
CST wiring (contralateral, bilateral, and ipsilateral; categorical)	Interaction with group	0.54 (0.71; 0.08)	1.34 (0.28; 0.18)
	Total group	0.28 (0.89; 0.04)	0.52 (0.72; 0.07)
Lesion type & CST wiring	Total group	1.98 (0.13; 0.33)	0.33 (0.85; 0.07)

2PD, two-point discrimination; AHA, Assisting Hand Assessment; CSC, cortico-subcortical; CST, corticospinal tract; JTHFT, Jebsen-Taylor Hand Function test; MM, mirror movements; PV, periventricular.
The significant comparisons are highlighted in grey, indicating factors influencing different outcome for the total group or also depending on the intervention group.
*Significant between T1–T2.
$^{\$}$In favour of CIMT + AOT group.
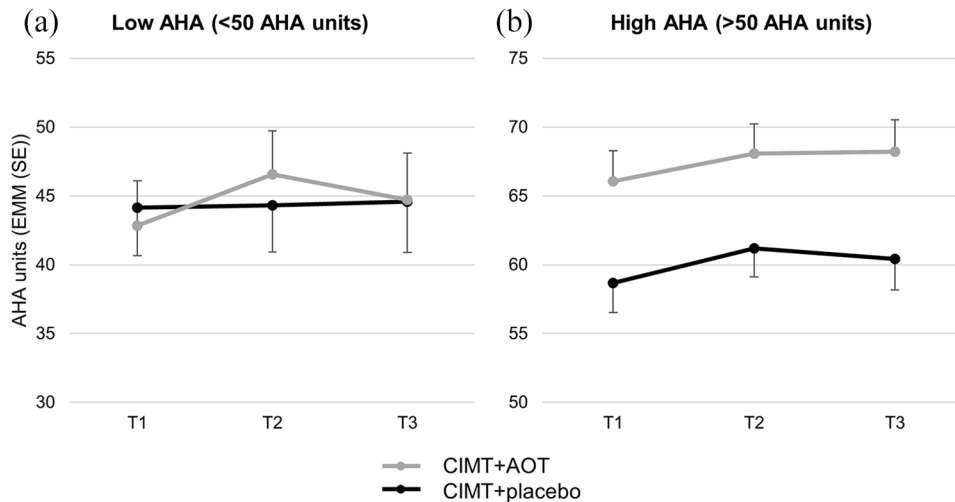
Figure 4. Interaction over time between intervention group and initial bimanual performance score (a, low initial score, *n* = 6 in CIMT + placebo group, *n* = 7 in CIMT + AOT group; b, high initial score, *n* = 16 in CIMT + placebo group, *n* = 15 in CIMT + AOT group). With low initial bimanual performance, the action-observation training showed an added value to modified constraint-induced movement therapy immediately after the intervention.
EMM, estimated marginal means; SE, standard error.
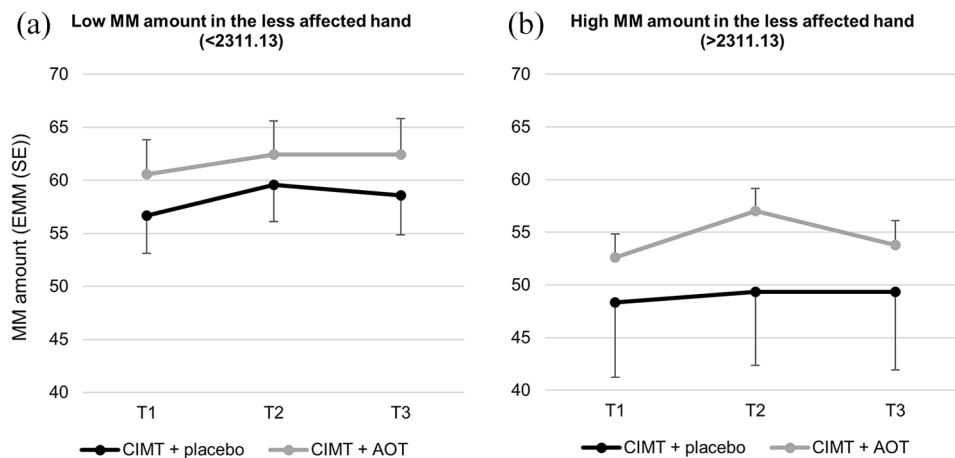
Figure 5. Impact of amount of mirror movements (MM) in the less affected hand on bimanual performance over time. Whilst children with low amount of MM responded similarly to either training, children with high amount of MM seemed to improve more after the CIMT + AOT training compared with the CIMT + placebo group. Children are divided according to their MM amount (cut-off = 2311.13, derived from the linear mixed model) for visualization purposes.

agreement with Kirkpatrick and colleagues who found no effect of AOT compared with repetitive practice in a home setting.[43] In our study, the lack of additional value of AOT for the total group could be explained by a ceiling effect driven by the large gains after CIMT, reported in current and previous studies.[44–46]

Interestingly, we identified that children with initially poorer hand function (lower than 50 AHA units) benefitted more from the combined approach CIMT + AOT compared with CIMT alone. On average, the group receiving CIMT + AOT with initially poorer AHA scores improved 4 AHA units, while the CIMT + placebo
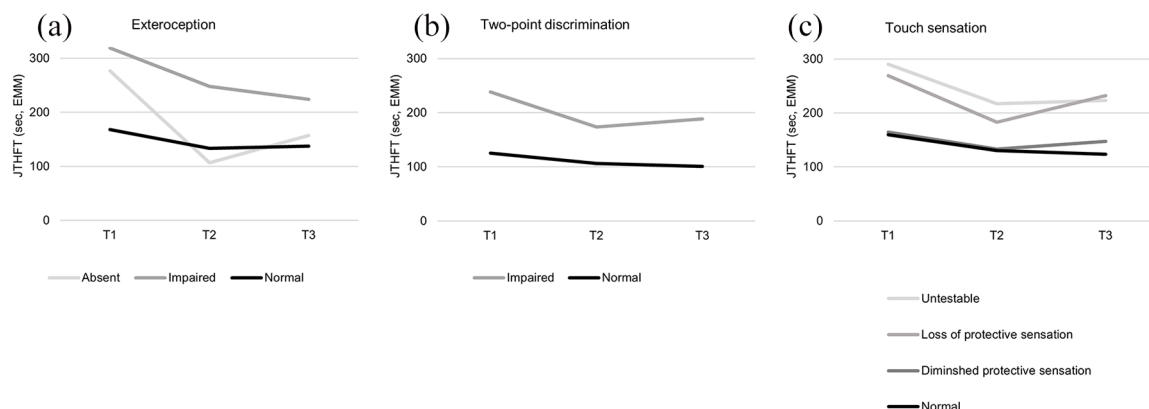
Figure 6. Interaction between sensory function modalities and improvement in hand dexterity, as measured with the Jebsen-Taylor Hand Function test (JTHFT) for the total group. (a) Exteroception ($n = 1$ absent; $n = 5$ impaired; $n = 35$ normal); (b) Two-point discrimination ($n = 22$ impaired, $n = 18$ normal); (c) Touch sensation ($n = 3$ untestable; $n = 8$ loss of protective sensation; $n = 5$ diminished protective sensation; $n = 0$ diminished light touch; $n = 26$ normal). Children with impaired sensory function benefitted more from the training immediately after the intervention, although had difficulties in retaining the gains. Data at each time point represents the estimated marginal means. Standard errors are not plotted as they are not visible at the current scale [exteroception (1.13–2.14 s), two-point discrimination (1.15–1.80 s), touch sensation (1.15–1.56 s)].
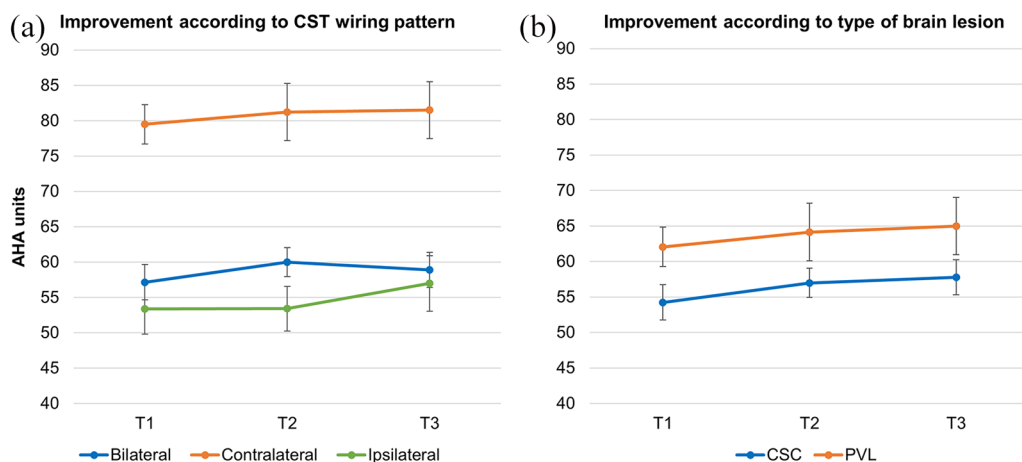
Figure 7. Improvement over time according to the neurological characteristics. (a) Type of corticospinal tract (CST) wiring pattern and (b) type of the lesion (predominantly grey matter, cortico-subcortical; predominantly white matter, periventricular).

group did not improve. Sgandurra and colleagues recently reported that poorer bimanual performance, measured with the AHA, was indicative of a more lateralized mirror neuron system in children with uCP (toward the non-lesioned hemisphere).[47] Given these results, it makes sense that the additional AOT intervention for children who had poorer bimanual performance was more effective, as AOT may have facilitated the activation of their mirror neuron system through the video-observation. For those children who showed high

bimanual performance, it seems plausible that the mirror neuron system cannot be further facilitated, as this may be intact, and other sensorimotor brain regions would need to be stimulated to further increase their motor function, for example to facilitate inter-hemisphere connectivity. Also, in contrast to other studies, the current study only included unimanual tasks to fit the unimanual concept of CIMT, although more challenging bimanual AOT tasks may be needed to further improve UL function in children with initially better

hand function. While this finding is clinically relevant, further studies are clearly needed to confirm our results, as well as to define the best delivery of AOT.

A second significant influencing factor of treatment outcome between groups following the intervention was the amount of MM in the less affected hand. Whilst children with few MM responded similarly to either training, children with a high amount of MM in the less affected hand seemed to improve more after the CIMT + AOT training. There is evidence for a relation between poor bimanual function and a high amount of MM.[11] Thus, this result is in line with the previous result where poor hand function influenced treatment outcome. Unfortunately, we cannot be certain that these changes are not led by concomitant reduction in the amount of MM. Additional studies including an evaluation of MM before and after intervention are needed to further clarify these relationships. Nevertheless, this novel finding points toward the importance of measuring MM and it is a first step toward the delineation of training strategies based on clinical characteristics.

What are the effects of CIMT (with or without AOT) on UL function?

Our results for the total group showed improvements in grip and muscle strength (ES 0.16–0.93), JTHFT (ES 5.81) and the instrumented pegboard test (ES 0.65–1.57), indicated by their large ESs. Moreover, the gains in muscle strength and unimanual dexterity were translated to bimanual dexterity, measured with the bimanual conditions of the instrumented pegboard test (ES 0.65–1.44). Interestingly, these gains also resulted in an increased comfort in using the hand in daily activities as confirmed by the improvement in the CHEQ-subscale 'feeling bothered' with a large ES (0.85). Still, this contrasts with the small ES found for the AHA (0.18). The ES of the AHA reported in previous CIMT studies in a camp model varies across studies: larger ESs (around 1.12) in younger children (18 months–8 years)[48,49] and smaller ESs (0.16–0.28) in children aged similar to our study.[13,50,51] According to Hung and colleagues, the AHA measures the quality of the assisting hand while performing bimanual movements and misses the spatiotemporal control of bimanual functioning.[52] A measure of spatiotemporal control of bimanual function would show the coupling between both hands while performing a bimanual activity. This coupling should be effective (accurate in space by having a good movement trajectory) and synchronized (accurate in time by reaching the target timely with both hands). A three-dimensional movement analysis[34,52] or placing accelerometers on each hand[35] during the execution of a bimanual task will capture how coupled the hands are and how effective and accurate the executed movements are. Integrating other measures of spatiotemporal control may help to capture these aspects.

In most measures, we found that the improvements were not only seen immediately after the therapy, but also after 6 months, which is in agreement with previous studies.[9,13,27,50,51] This maintenance is of clinical relevance, as intensive therapies are given in shorter periods. Charles and colleagues showed, however, that between 6 months and 1 year after the first camp, children typically showed a slight functional decline, and a second CIMT dose 1 year after resulted in continued improvements.[53] Boosts of intensive interventions with 6-months or 1-year intervals may result in long-lasting and clinically relevant effects.

Interestingly, we also found that children with impaired sensory function benefitted more from the intervention compared with children with normal sensory function. To the best of our knowledge, this is the first time that sensory function is investigated as an influencing factor of response to CIMT in children with uCP. The sensory deficits may lead to a failure to use the motor functions and capacities of the more affected UL for spontaneous use in daily life. This phenomenon is known as developmental disregard.[54,55] It is hypothesized that children with developmental disregard may respond better to CIMT due to the forced use of the more affected limb. The positive effects are however partially lost at follow-up, potentially due to the lack of ongoing stimulation of the more affected limb.

Does the response to CIMT depend on the underlying neurological characteristics?

In our study, we found that all children improved after a CIMT program, irrespective of their lesion type or CST wiring pattern. Interestingly, and adding to the controversy in the literature,[13–15,56] having an ipsilateral CST wiring pattern did not impede improvement after treatment as these

children improved almost 5 AHA units after CIMT (with or without AOT) (see Figure 7). Staudt and colleagues proposed that one neurological factor is insufficient to impact treatment response after CIMT,[57] and a multifactorial model including several neurological characteristics may have larger influence than any factor alone. Nevertheless, our study did not find that the interaction between the lesion type and the CST wiring pattern had a larger influence on treatment outcome. Our study results highlight the variability within each group, suggesting the influence of other factors. We hypothesize that functional measures of both sensory and motor function, and how these functions are integrated in the brain (sensorimotor integration), may be an important influencing factor of treatment outcome. Further investigations including both clinical and neurophysiological measures of the motor and sensory system (motor and sensory evoked potentials), as well as of sensorimotor integration (e.g. with the short latency afferent inhibition protocol)[58] are warranted.

Whilst this study was the first to investigate the merit of AOT in combination with CIMT in a camp model, its limitations should also be addressed. Firstly, we included 44 children according to the power calculation for the primary outcome measure.[16] This sample size could be too low when investigating influencing factors of treatment response, particularly for the neurological characteristics. A larger sample size may have also resulted in groups with more homogeneous characteristics at baseline. Although baseline characteristics were not significantly different between groups, the groups were not completely similar with regard to the type if the lesion (e.g. 5 children with a periventricular (PV) lesion in the CIMT + placebo group *versus* 12 children with a PV lesion in the CIMT + AOT group). A second limitation is the lack of a specific outcome measure that evaluates motor planning as targeted with the AOT.[7] Future studies investigating the added effect of AOT should also include such outcome measures, for example the end-posture comfort.[59,60] Lastly, it remains debatable whether a two-week camp can be translated to routine clinical practice, as it demands high commitment from both the parents and the children during the holiday period. In our study, despite a good cooperation during the AOT intervention, the children generally reported that the AOT sessions were monotonous. Hence, we advocate for trainings that are engaging and motivating for the children.

For example, a virtual reality environment[61,62] where the child sees himself as an avatar, could serve as a more motivating, engaging, and potentially more effective AOT approach.

In the future, it is crucial that forces between centres and institutions are joined to coordinate multicentre RCTs, which will contribute to fine-tune the identification of responders *versus* non-responders through clinical and neurological predictors in a statistically powerful study. Furthermore, future studies should investigate the neuroplastic changes derived from an intensive intervention.

Conclusion
AOT did not show an overall added effect on improving UL function in children with uCP when combined with CIMT in an intensive training approach. Still, AOT seemed to have an additional positive value in children with poor motor function and high amount of MM, suggesting that the responsiveness to AOT is patient specific. Such insights provide a further step toward patient-tailored intervention approaches. The findings of this study also confirm the efficacy of intensive models of CIMT interventions (with or without AOT), with large ESs found in unimanual and bimanual dexterity, which seems to be more beneficial for children with impaired sensory function. The novelty of this study lies within the exploration of behavioural and neurological influencing factors on treatment response, which paves the way toward an effective and individualized treatment planning for children with uCP.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Shikako-Thomas K, Majnemer A, Law M, *et al.* Determinants of participation in leisure activities in children and youth with cerebral palsy: systematic review. *Phys Occup Ther Pediatr* 2008; 28: 155–169.

2. Hoare BJ, Wallen MA, Thorley MN, *et al.* Constraint-induced movement therapy in children with unilateral cerebral palsy. *Cochrane Database Syst Rev* 2019; 4: CD004149.

3. Taub E, Uswatte G and Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation–a clinical review. *J Rehabil Res Dev* 1999; 36: 237–251.

4. Steenbergen B, Jongbloed-Pereboom M, Spruijt S, *et al.* Impaired motor planning and motor imagery in children with unilateral spastic cerebral palsy: challenges for the future of pediatric rehabilitation. *Dev Med Child Neurol* 2013; 55: 43–46.

5. Mutsaarts M, Steenbergen B and Bekkering H. Anticipatory planning deficits and task context effects in hemiparetic cerebral palsy. *Exp Brain Res* 2006; 172: 151–162.

6. Rizzolatti G and Craighero L. The mirror-neuron system. *Annu Rev Neurosci* 2004; 27: 169–192.

7. Sgandurra G, Ferrari A, Cossu G, *et al.* Randomized trial of observation and execution of upper extremity actions versus action alone in children with unilateral cerebral palsy. *Neurorehabil Neural Repair* 2013; 27: 808–815.

8. Sakzewski L, Ziviani J and Boyd RN. Best responders after intensive upper-limb training for children with unilateral cerebral palsy. *Arch Phys Med Rehabil* 2011; 92: 578–584.

9. Gordon AM, Charles J and Wolf SL. Efficacy of constraint-induced movement therapy on involved upper-extremity use in children with hemiplegic cerebral palsy is not age-dependent. *Pediatrics* 2006; 117: e363–e373.

10. Rowe JB, Chan V, Ingemanson ML, *et al.* Robotic assistance for training finger movement using a hebbian model: a randomized controlled trial. *Neurorehabil Neural Repair* 2017; 31: 769–780.

11. Klingels K, Jaspers E, Staudt M, *et al.* Do mirror movements relate to hand function and timing of the brain lesion in children with unilateral cerebral palsy? *Dev Med Child Neurol* 2016; 58: 735–742.

12. Simon-Martinez C, Jaspers E, Mailleux L, *et al.* Corticospinal tract wiring and brain lesion characteristics in unilateral cerebral palsy: determinants of upper limb motor and sensory function. *Neural Plast* 2018; 2018: 1–13.

13. Islam M, Nordstrand L, Holmström L, *et al.* Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? *Dev Med Child Neurol* 2014; 56: 252–258.

14. Kuhnke N, Juenger H, Walther M, *et al.* Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? *Dev Med Child Neurol* 2008; 50: 898–903.

15. Gillick B, Rich T, Nemanich S, *et al.* Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: a randomized, blinded, sham-controlled clinical trial. *Eur J Paediatr Neurol*. Epub ahead of print 11 February 2018. DOI: 10.1016/j.ejpn.2018.02.001.

16. Simon-Martinez C, Mailleux L, Ortibus E, *et al.* Combining constraint-induced movement therapy and action-observation training in children with unilateral cerebral palsy: a randomized controlled trial. *BMC Pediatr* 2018; 18: 250.

17. Koman LA, Williams RMM, Evans PJ, *et al.* Quantification of upper extremity function and

range of motion in children with cerebral palsy. *Dev Med Child Neurol* 2008; 50: 910–917.

18. Krumlinde-Sundholm L, Holmefur M, Kottorp A, *et al.* The assisting hand assessment: current evidence of validity, reliability, and responsiveness to change. *Dev Med Child Neurol* 2007; 49: 259–264.

19. Krumlinde-Sundholm L and Eliasson A-C. Development of the assisting hand assessment: a rasch-built measure intended for children with unilateral upper limb impairments. *Scand J Occup Ther* 2003; 10: 16–26.

20. Krumlinde-Sundholm L. Reporting outcomes of the assisting hand assessment: what scale should be used? *Dev Med Child Neurol* 2012; 54: 807–808.

21. Klingels K, Cock PDE, Molenaers G, *et al.* Upper limb motor and sensory impairments in children with hemiplegic cerebral palsy. Can they be measured reliably? *Disabil Rehabil* 2010; 32: 409–416.

22. Bohannon RW and Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987; 67: 206–207.

23. Hislop HJ, Avers D and Brown M. *Daniels and Worthingham's muscle testing: techniques of manual examination and performance testing.* Missouri: Elsevier Saunders, 2013.

24. Wang TN, Liang KJ, Liu YC, *et al.* Psychometric and clinimetric properties of the melbourne assessment 2 in children with cerebral palsy. *Arch Phys Med Rehabil* 2017; 98: 1836–1841.

25. Randall M, Imms C, Carey LM, *et al.* Rasch analysis of the Melbourne assessment of unilateral upper limb function. *Dev Med Child Neurol* 2014; 56: 665–672.

26. Taylor N, Sand PL and Jebsen RH. Evaluation of hand function in children. *Arch Phys Med Rehabil* 1973; 54: 129–135.

27. Charles JR, Wolf SL, Schneider JA, *et al.* Efficacy of a child-friendly form of constraint-induced movement therapy in hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2006; 48: 635.

28. Araneda R, Ebner-Karestinos D, Paradis J, *et al.* Reliability and responsiveness of the Jebsen-Taylor test of hand function and the box and Block test for children with cerebral palsy. *Dev Med Child Neurol* 2019; 61: 1182–1188.

29. Basu AP, Kirkpatrick EV, Wright B, *et al.* The Tyneside Pegboard test: development, validation,

and observations in unilateral cerebral palsy. *Dev Med Child Neurol* 2018; 60: 314–321.

30. Cope EB and Antony JH. Normal values for the two-point discrimination test. *Pediatr Neurol* 1992; 8: 251–254.

31. Bell-Krotoski J and Tomancik E. The repeatability of testing with Semmes-Weinstein monofilaments. *J Hand Surg Am* 1987; 12: 155–161.

32. Auld ML, Ware RS, Boyd RN, *et al.* Reproducibility of tactile assessments for children with unilateral cerebral palsy. *Phys Occup Ther Pediatr* 2012; 32: 151–166.

33. Jaspers E, Klingels K, Simon-Martinez C, *et al.* GriFT: a device for quantifying physiological and pathological mirror movements in children. *IEEE Trans Biomed Eng* 2018; 65: 857–865.

34. Rudisch J, Butler J, Izadi H, *et al.* Kinematic parameters of hand movement during a disparate bimanual movement task in children with unilateral cerebral palsy. *Hum Mov Sci* 2016; 46: 239–250.

35. Braito I, Maselli M, Sgandurra G, *et al.* Assessment of upper limb use in children with typical development and neurodevelopmental disorders by inertial sensors: a systematic review. *J Neuroeng Rehabil* 2018; 15: 94.

36. Verbeke G. *Linear mixed models for longitudinal data.* New York, NY: Springer New York, 1997.

37. Cohen J. Eta-Squared and partial Eta-Squared in fixed factor anova designs. *Educ Psychol Meas* 1973; 33: 107–112.

38. Hinkle DE and Wiersma W. *Applied statistics for the behavioral sciences.* Boston, MA: Houghton Mifflin, 1998.

39. Eliasson AC, Krumlinde-Sundholm L, Rösblad B, *et al.* The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol* 2006; 48: 549–554.

40. Kim J, Kim J and Ko E. The effect of the action observation physical training on the upper extremity function in children with cerebral palsy. *J Exerc Rehabil* 2014; 10: 176–183.

41. Buccino G, Arisi D, Gough P, *et al.* Improving upper limb motor functions through action observation treatment: a pilot study in children with cerebral palsy. *Dev Med Child Neurol* 2012; 54: 822–828.

42. Buccino G, Molinaro A, Ambrosi C, *et al.* Action observation treatment improves upper limb

motor functions in children with cerebral palsy: a combined clinical and brain imaging study. *Neural Plast* 2018; 2018: 1–11.

43. Kirkpatrick E, Pearse J, James P, *et al.* Effect of parent-delivered action observation therapy on upper limb function in unilateral cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol* 2016; 58: 1049–1056.

44. Sakzewski L, Ziviani J and Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. *Pediatrics* 2014; 133: e175–e204.

45. Chen YP, Pope S, Tyler D, *et al.* Effectiveness of constraint-induced movement therapy on upper-extremity function in children with cerebral palsy: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil* 2014; 28: 939–953.

46. Chiu HC and Ada L. Constraint-induced movement therapy improves upper limb activity and participation in hemiplegic cerebral palsy: a systematic review. *J Physiother* 2016; 62: 130–137.

47. Sgandurra G, Biagi L, Fogassi L, *et al.* Reorganization of the action observation network and sensory-motor system in children with unilateral cerebral palsy: an fMRI study. *Neural Plast* 2018; 2018: 1–15.

48. Aarts PB, Jongerius PH, Geerdink YA, *et al.* Effectiveness of modified constraint-induced movement therapy in children with unilateral spastic cerebral palsy: a randomized controlled trial. *Neurorehabil Neural Repair* 2010; 24: 509–518.

49. Eliasson AC, Krumlinde-Sundholm L, Shaw K, *et al.* Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model. *Dev Med Child Neurol* 2005; 47: 266–275.

50. Sakzewski L, Ziviani J, Abbott DF, *et al.* Randomized trial of constraint-induced movement therapy and bimanual training on activity outcomes for children with congenital hemiplegia. *Dev Med Child Neurol* 2011; 53: 313–320.

51. Gordon AM, Hung YC, Brandao M, *et al.* Bimanual training and constraint-induced movement therapy in children with hemiplegic cerebral palsy. *Neurorehabil Neural Repair* 2011; 25: 692–702.

52. Hung YC, Casertano L, Hillman A, *et al.* The effect of intensive bimanual training on coordination of the hands in children with congenital hemiplegia. *Res Dev Disabil* 2011; 32: 2724–2731.

53. Charles JR and Gordon AM. A repeated course of constraint-induced movement therapy results in further improvement. *Dev Med Child Neurol* 2007; 49: 770–773.

54. Houwink A, Aarts PB, Geurts AC, *et al.* A neurocognitive perspective on developmental disregard in children with hemiplegic cerebral palsy. *Res Dev Disabil* 2011; 32: 2157–2163.

55. Deluca SC, Echols K, Law CR, *et al.* Intensive pediatric constraint-induced therapy for children with cerebral palsy: randomized, controlled, crossover trial. *J Child Neurol* 2006; 21: 931–938.

56. Juenger H, Kuhnke N, Braun C, *et al.* Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study. *Dev Med Child Neurol* 2013; 55: 941–951.

57. Staudt M and Berweck S. Is constraint-induced movement therapy harmful in unilateral spastic cerebral palsy with ipsilateral cortico-spinal projections? *Dev Med Child Neurol* 2014; 56: 202–203.

58. Voller B, St Clair Gibson A, Dambrosia J, *et al.* Short-latency afferent inhibition during selective finger movement. *Exp Brain Res* 2006; 169: 226–231.

59. Rosenbaum DA, Vaughan J, Barnes HJ, *et al.* Time course of movement planning: selection of handgrips for object manipulation. *J Exp Psychol Learn Mem Cogn* 1992; 18: 1058–1073.

60. Steenbergen B, Verrel J and Gordon AM. Motor planning in congenital hemiplegia. *Disabil Rehabil* 2007; 29: 13–23.

61. Massetti T, da Silva TD, Crocetta TB, *et al.* The clinical utility of virtual reality in neurorehabilitation: a systematic review. *J Cent Nerv Syst Dis* 2018; 10: 1–18.

62. McGrane N, Galvin R, Cusack T, *et al.* Addition of motivational interventions to exercise and traditional physiotherapy: a review and meta-analysis. *Physiotherapy* 2015; 101: 1–12.

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