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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The efficacy of an integrated training approach on upper limb muscle strength and muscle fatigue in children with unilateral cerebral palsy

Kaat Dirkx
Jari Van Rompaey

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Katrijn KLINGELS

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This study would not have been possible without the guidance and advice of many people. We are grateful to all of those who helped us in the process of writing this master's thesis.

First and foremost, we would like to express our gratitude to Prof. dr. Klingels for the useful remarks and guidance in our master's thesis. She allowed this master's thesis to be our own work, but helped us whenever necessary in the process of researching and writing this master's thesis. She provided us the opportunity to participate in a day camp for children with unilateral cerebral palsy. It was a great experience and certainly an added value for our coming work as a physiotherapist.

Furthermore we thank copromotor drs. Lieke Brauers and Prof. dr. Rameckers, for their expertise, that greatly improved the master's thesis.

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Finally, we must express our gratitude to our parents for the continuous support and encouragement during the years of study and researching and writing this thesis.

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Neerpelt, 3/05 K.D.

Research context

This master's thesis is situated in the research domain of Paediatric rehabilitation and is closely related to the neurological rehabilitation. The thesis fits within the research field of promotor Prof. dr. Klingels focusing on upper limb function in paediatric populations, in collaboration with KU Leuven. The primary aim of the study was to investigate if modified Constraint-Induced Movement Therapy (mCIMT) in combination with Action Observation Therapy (AOT) is more effective in comparison to mCIMT alone to improve muscle strength and muscle fatigue in children with unilateral cerebral palsy (CP). Impaired upper limb function has been recognized as the most important clinical feature of unilateral CP and may be caused by muscle weakness and muscle fatigue. Muscle weakness and muscle fatigue are highly correlated with unimanual capacity and bimanual performance (Andersen, Majnemer, O'Grady, & Gordon, 2013; Brady & Garcia, 2009; van, van Rijn, Selles, Roebroeck, & Stam, 2007).

Previous studies have already demonstrated the efficacy of mCIMT on activity level, but the underlying mechanism of functional improvement still remain unknown (Sakzewski, Ziviani, & Boyd, 2014). The effect of AOT, a new therapy concept, has been investigated in three studies and demonstrated also a positive effect on activity level in children with unilateral CP, but the effect of AOT on muscle strength and muscle fatigue has not been investigated yet (Buccino et al., 2012; Kim, Kim, & Ko, 2014; Sgandurra et al., 2011).

A second research aim was to investigate the influencing factors on improvements in muscle strength and muscle fatigue such as age and baseline hand function. These insights can help in further optimizing mCIMT and AOT interventions in children with unilateral CP.

The scientific experiment has been determined by promotor Prof. dr. Klingels in consultation with two students Revalidatiewetenschappen en Kinesitherapie at the University of Hasselt. Both students contributed to the two-week day camp in July 2017. They were involved in the organisation and execution of the therapy program. There was a high degree of collaboration between the two students for all parts of this master's thesis. The statistics performed on the data, collected over all the day camps, were executed and interpreted by the students. The introduction, method, results and discussion were also written by them.

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The efficacy of an integrated training approach on upper limb muscle strength and muscle fatigue in children with unilateral cerebral palsy

Abstract

Background: An effective intervention to improve upper limb function in children with unilateral cerebral palsy (CP) is modified Constraint-Induced Movement Therapy (mCIMT). Recently, Action Observation Training (AOT), a new concept of neurophysiological therapy, has been developed to stimulate motor learning. However, many questions about the effects on body function level still remain unanswered.

Objectives: This randomized controlled trial aimed to determine whether mCIMT in combination with AOT is more effective in comparison to mCIMT alone on muscle strength and muscle fatigue in children with unilateral CP. Additionally, the influencing factors on changes in muscle strength and muscle fatigue, such as age and hand function at baseline were investigated.

Methods: Forty-four children diagnosed with spastic unilateral CP, aged between six and 12 years old, were randomized to the mCIMT+AOT or mCIMT group alone. The children had to wear a tailor-made hand splint on the non-affected hand for six hours on nine out of 11 consecutive days. Children in the mCIMT+AOT group received next to mCIMT also AOT for 1,5 hours a day. AOT consisted of watching videos showing goal-directed actions for three minutes. The children in the control group (mCIMT alone) played video games without biological movements for three minutes. The primary outcome measures were grip strength, muscle strength and muscle fatigue. Of the 44 children, 33 children had data on these outcome measures. Children were assessed before, directly after and six months after the day camp.

Results: No significant group-by-time interaction was found for grip strength ($p=.794$), grip strength ratio (affected/non-affected hand) ($p=.483$), SFI ($p=.414$) and MMT total ($p=.493$) after intervention. Both groups showed comparable significant improvements over time in grip strength, grip strength ratio (affected/non-affected) and MMT total ($p<.0001$). No significant improvements were found for SFI ($p=.520$). Correlation analyses showed a significant negative correlation after intervention between grip strength improvement and grip strength at baseline ($r=-.710$, $p<.0001$). A negative correlation was also found between MMT total improvement and MMT total at baseline ($r=-.542$, $p=.001$). Age and MACS level were no significant influencing factors on the outcome measures.

Conclusion: An integrated training approach combining mCIMT and AOT did not enhance the effects on muscle strength and muscle fatigue in comparison to mCIMT alone in children with unilateral CP. Both interventions demonstrated a significant improvement over time in grip strength and muscle strength, but not in muscle fatigue.

Introduction

Cerebral palsy (CP) is a term for a group of permanent disorders that affect the development of movement and posture, due to a defect or lesion of the brain, acquired in the prenatal period, perinatal period, or in the early years of life (Xu, He, Mai, Yan, & Chen, 2015). It is the most common paediatric neurodevelopmental disorder with an incidence of 2-2.5 per 1000 live births in Western industrialized nations (Oskoui, Coutinho, Dykeman, Jette, & Pringsheim, 2013). One third of children with CP have spastic unilateral CP, in which impaired upper limb function has been recognized as the most important clinical feature (Brady & Garcia, 2009). At body function level, according to the International Classification of Functioning Disability and Health (ICF) (ICF, 2001), impaired upper limb function may be caused by hypertonia, spasticity, dystonia, muscle fatigue, reduced range of motion, muscle strength and speed, as well as impaired selective motor control and sensation (Andersen et al., 2013; van et al., 2007). These sensorimotor impairments influence bimanual coordination, affecting daily life activities. To manage bimanual daily life activities, children with unilateral CP develop compensation strategies by using the non-affected hand (Arner, Eliasson, Nicklasson, Sommerstein, & Hagglund, 2008). This phenomenon is called developmental disregard (Hoare, Imms, Carey, & Wasiak, 2007).

To overcome developmental disregard, Constraint-Induced Movement Therapy (CIMT) can be applied. CIMT involves constraining movements of the non-affected upper limb, in combination with intensive task specific training of unimanual skills of the affected upper limb. The aim of CIMT is to stimulate the spontaneous use of the affected upper limb (Taub, Uswatte, & Pidikiti, 1999). The original concept of CIMT is first described in adults with stroke. It consists of using a sling for 90% of the waking hours, in combination with six hours of supervised training. In this population CIMT intervention has been proven to increase function and use of the upper limb (Taub et al., 1999). As the original protocol is very intensive and difficult to implement in a child population, modified CIMT (mCIMT), a less intensive intervention approach, has been developed (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010; Brady & Garcia, 2009; Taub et al., 1999). Modifications of the original protocol include intervention duration, type of constraint (e.g. glove, sling, splint, cast) and the hours a day the constraint is used (Sakzewski et al., 2014). The meta-analysis of Sakzewski, Ziviani and Boyd (2014) proved that mCIMT is more effective than usual care to improve upper limb function in children with CP.

Although positive effects on upper limb function after mCIMT have been shown, the underlying causes of these improvements still remain unknown. Muscle weakness and muscle fatigue are possible underlying factors that lead to upper limb dysfunction, but the influence of mCIMT on these factors have not yet clearly been discussed. Six studies mentioned no improvement after mCIMT intervention in muscle weakness of the affected upper limb (Bonnier, Eliasson, & Krumlinde-Sundholm, 2006; Charles & Gordon, 2006; Eliasson, Shaw, Ponten, Boyd, & Krumlinde-Sundholm, 2009; Gordon, Charles, & Wolf, 2006; Sakzewski et al., 2011; Thompson, Chow, Vey, & Lloyd, 2015), whereas four studies concluded a significant improvement after mCIMT intervention using Manual Muscle Testing (MMT), Jamar dynamometer or sphygmomanometer as measurement tool (Klingels et al., 2013; Sutcliffe, Logan, & Fehlings, 2009a; Xu, Wang, Mai, & He, 2012; Xu et al., 2015). The variability in results among these studies is due to different study designs and included age and therefore the effect of mCIMT still remains unclear. However, it seems that improvements in muscle strength depend on the duration of the intervention and not the intensity (Charles & Gordon, 2006; Klingels et al., 2013; Sakzewski et al., 2011; Sutcliffe et al., 2009a; Xu et al., 2012). It may also be assumed that more restrictive constraints such as a rigid hand orthosis, a cast from below the elbow to fingertips and a splint are superior to demonstrate significant improvements (Klingels et al., 2013; Sutcliffe et al., 2009a; Xu et al., 2012; Xu et al., 2015). The effect of mCIMT on muscle fatigue is still unknown. Muscle fatigue is defined as “the reduced capacity of muscles to produce force and power as a result of repeated contractions” (Dobkin, 2008). Only one study has investigated the effect of intensive training on muscle fatigue during a 30 seconds sustained grip strength contraction, based on the static fatigue index (SFI) (Brauers, Geijen, Speth, & Rameckers, 2017). The study showed a tendency towards an improvement in muscle fatigue after a two-week summer camp including six hours of mCIMT and two hours of Bimanual Intensive Movement Therapy (BIMT) each day.

Recently, Action Observation Training (AOT), a new concept of therapy, has been developed. The aim of AOT is to improve motor execution and motor planning by using videos, showing activities of specific movements performed by another subject. After watching the video the same activities are performed by the subject. The treatment approach is based on the mirror neuron system, located in the ventral premotor cortex and in the inferior parietal lobule of the brain. This system activates during watching and performing goal-directed activities (Buccino et al., 2012; Sgandurra et al., 2011). The study of Ertelt et al. (2007) was one of the first studies and suggested a positive effect of AOT on motor recovery in adults with stroke. In children with unilateral CP three studies have investigated the effect of AOT and demonstrated a positive effect on activity level, but the effect of

AOT on muscle strength and muscle fatigue has not yet been investigated (Buccino et al., 2012; Kim et al., 2014; Sgandurra et al., 2011).

The innovation of the study was the combination of mCIMT and AOT. It can be hypothesized that an integrated training approach may lead to greater improvements in muscle strength and muscle fatigue, which leads to a better hand function. Therefore, the aim of the study was to investigate if mCIMT in combination with AOT is more effective in comparison to mCIMT alone to improve muscle strength and muscle fatigue in children with unilateral CP. A second aim is to investigate the influencing factors on changes in muscle strength and muscle fatigue, such as age and hand function at baseline.

Method

Participants

Forty-four children diagnosed with spastic unilateral CP, aged between six and 12 years old, were recruited from the CP-care program at the University Hospital Pellenberg. The participants were enrolled between 2014 and 2017. This study is part of a larger research project that investigates the effect of the day camp on different outcome measures of the ICF model and the neurologic predictors. The current study focused on muscle strength and muscle fatigue. Children were recruited according to the following selection criteria: (1) confirmed diagnosis of congenital or acquired unilateral CP according to the criteria of Surveillance of Cerebral Palsy in Europe (SCPE) (http://www.scpenetwork.eu/); (2) sufficient cooperation to comprehend and complete the test procedure; (3) minimal ability to actively grasp and stabilize an object (House Functional Classification Score ≥ 4). In case of previous upper limb surgery in the last two years, or botulinum toxin-A injections six months prior to testing children were excluded.

Study Design

A randomized controlled trial was performed to investigate the effects of mCIMT in combination with AOT in comparison to mCIMT alone on muscle strength and muscle fatigue. Additionally, influencing factors on muscle strength and muscle fatigue such as age and hand function at baseline were investigated. To categorize hand function at baseline, MACS (Manual Ability Classification System) was used. MACS level I means that the child handles objects easily and successfully. Level II means that the child handles most objects but with reduced quality and/or speed of achievement. Level III means that the child has difficulties with handling objects and thereby needs help to prepare and/or modify activities (Morris, Kurinczuk, Fitzpatrick, & Rosenbaum, 2006).

To obtain homogeneous groups at baseline, children were stratified according to (1) their age (6-9 years, 10-12 years), (2) the House Functional Classification Scale (HFCS) (level 4-5, level 6-7) (Geerdink et al., 2014; McConnell, Johnston, & Kerr, 2011) and (3) the types of corticospinal tract (CST) wiring pattern (contralateral, bilateral, ipsilateral), assessed by Transcranial Magnetic Stimulation (TMS). After stratification a permuted block design of two was used to randomize children to the mCIMT+AOT or mCIMT group within each stratum. The permuted block design was created by a computer random number generator.

The process of randomisation was executed by an independent individual, without involvement in the enrolment of the subjects and no access to clinical information of the subjects.

The study was approved by the Ethics committee of the University of Leuven and the Medical Ethical committee of Hasselt University (ML9913). Informed consent was obtained from the parents before participation in the study.

Intervention

The intervention consisted of a two-week day camp model in which children received intensive therapy for six hours a day. In total the children received 54 hours of therapy during nine out of 11 consecutive days. The total amount of hours was based on the study of Sakzewski et al. (2014) suggesting at least 40 hours of therapy to produce clinically relevant improvements in upper limb function.

In the mCIMT group all children had to wear a tailor-made hand splint at the less or non-affected upper limb for six hours a day. While wearing the splint unimanual exercises based on shaping and repetitive practice were performed individually or in group. Individual treatment was focused on treatment goals specified for each child based on the assessments (e.g. supination, grip force, wrist extension). Activities in group consisted of activities such as painting, crafts, cooking and water games. A one by one therapist-child ratio was applied to ensure individual guidance.

In the mCIMT+AOT group the children received next to mCIMT also AOT for 1,5 hours a day. AOT consisted of watching video sequences showing goal-directed actions for three minutes. These actions were chosen according to the level of upper limb function of the child. The children with HFCS 4-5 performed the same type of activities as those with HFCS 6-8, but the difficulty level was adapted to their capabilities. The videos were shown in the children's point of view to avoid potential mental rotation. The children were seated on a chair in front of a computer screen, positioned at 50 centimetres. To optimize attention during observation of the video, the therapist was seated next to the child's affected side. After watching the video for three minutes the child had to execute the observed actions with the more affected upper limb during three minutes. The therapist gave verbal encouragements without any demonstration. Each video was shown two times. The children observed 15 tasks, one each session. Each task consisted of three upper limb actions, for example (1) lift up a cover and place it over a candy, (2) take the candy and place it into a plastic cup and (3) take the bottle of water and fill the plastic cup containing a candy with water (Appendix II, III). One upper limb action was continuously repeated for a total duration of three minutes. The children in the control group (mCIMT alone) played video games without biological movements for three minutes. After playing video games, the children performed the same goal-directed actions as the AOT-group for three minutes after verbal instruction given by the therapist.

Assessment

Children were assessed before, directly after and six months after the day camp. The assessments were executed in the Clinical Motion Analysis Laboratory of the University Hospital Leuven, campus Pellenberg by one physiotherapist with the help of students.

Outcome measures

Muscle strength and muscle fatigue were analysed in both groups. The maximal grip test and the isometric endurance tests with a duration of 30 seconds were performed with the digital Jamar dynamometer (E-link, Biometrics Ltd, Newport, UK). The grip position of the Jamar dynamometer was adjusted to the hand size of the child. The standardized position was sitting on a chair with a straight back and feet flat on the ground. The Jamar dynamometer should be presented vertically and in line with the forearm. The forearm should be supported on the table and positioned between supination and pronation and the wrist should be positioned in a neutral position between flexion and extension. The forearm was fixated if the child could not support his or her hand in this position.

To measure maximal grip strength, the children were asked to squeeze as hard as possible for maximal three seconds. Three trials were performed with a rest of 30 seconds between the trials. If a difference of more than 20% occurred between the three measurements, one extra trial was added. The three maximal trials were used to define the mean maximal force of the child. The dominant hand was tested first, afterwards the same test was repeated with the non-dominant hand.

To measure muscle fatigue the isometric endurance task with a maximal contraction during 30 seconds was performed. The children were asked to squeeze the Jamar dynamometer as hard as possible during 30 seconds. The following instructions were given: “Ready to squeeze, three, two, one and squeeze”. Visual feedback about the elapsed time was offered to the children and verbal encouragement was given during the test. To determine muscle fatigue, the static fatigue index (SFI) was used (Surakka et al., 2004). This index is based on the assumption that the maximum force is reached in the first 10 seconds and after this point muscle fatigue can be measured. According to this assumption the absolute peak force (kgs) and the time to peak moment (TPM) should be determined at first. Secondly the hypothetical area under the curve (HAUC) was analysed. The HAUC

(Figure 1: area B and C) represents the curve that is obtained when the participant keeps its force constant for 30 seconds and is calculated by multiplying the maximal handgrip strength (in kg) with 30 minus time of maximal hand grip strength (TPM). Thereafter the actual area under the curve (AUC) was calculated. This calculation is based on the area under the force-time curve from Tmax to 30s (Figure 1: area C). The formula to determine the fatigue index is: 100%*[1– (AUC/HAUC)] (Severijns, Lamers, Kerkhofs, & Feys, 2015).

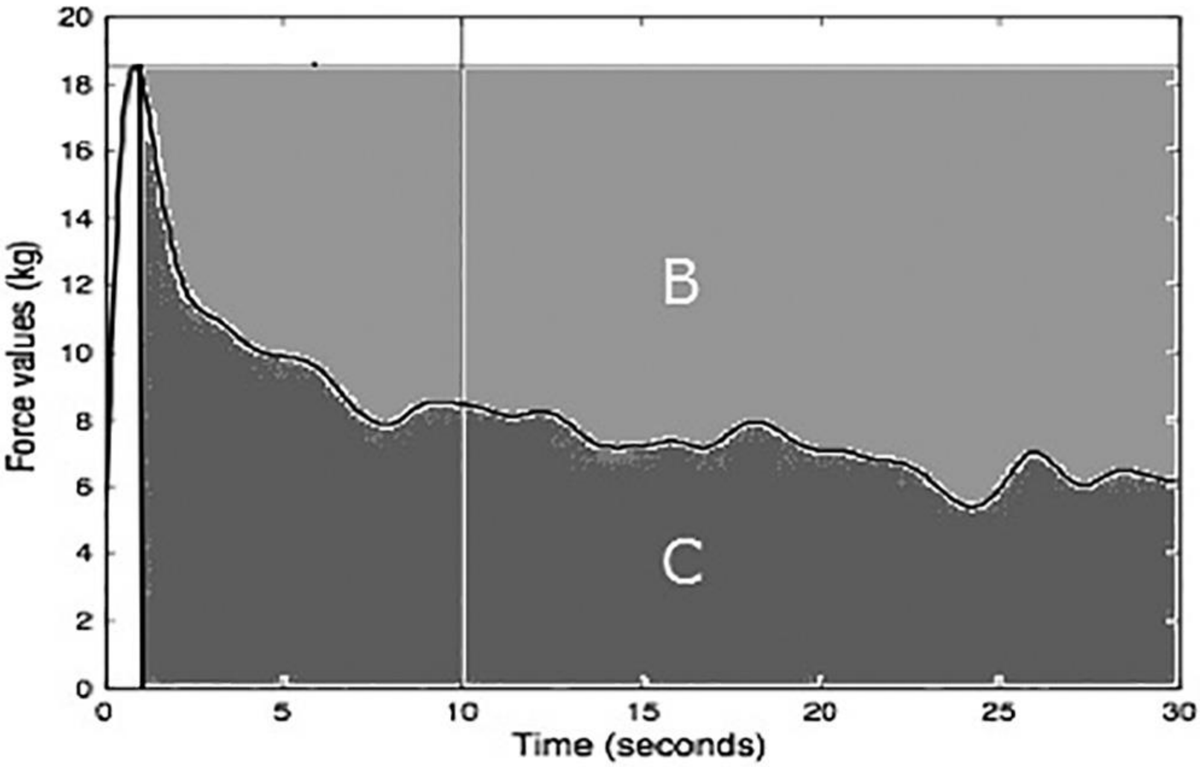

Figure 1. Strength-time curve during isometric contraction of 30s: the fatigue index is based on the AUC or area C and the HAUC or area B+C. The AUC and HAUC are calculated from the point where peak force has been reached (Brauers et al., 2017).

To assess the strength of individual muscle groups Manual Muscle Testing (MMT) according to the 8-point ordinal scale of Daniels and Worthingham was used. This scale ranges from 0 (no contraction) to 5 (full active ROM against maximal resistance). Scores for muscle strength of the shoulder (anteflexors, adductors and abductors), elbow (flexors and extensors) and wrist (supinators, pronators, flexors and extensors) were assessed. Sub-scores for the muscle groups of the shoulder (range 0-15), elbow (range 0-10) and wrist (range 0-20) were calculated as well as a total score ranging between 0 and 45.

Data analysis

Baseline characteristics were analysed to check for differences between groups using independent t tests. The normality of the data was analysed by the Shapiro–Wilk tests and graphically checked for symmetry. To meet the assumption of normality, a logarithmic transformation was used for grip strength.

To compare the differences between the intervention groups (mCIMT+AOT and mCIMT alone) and to study time effects of the intervention, repeated measures ANOVA was used. Time trends were further analysed with pairwise post hoc tests to compare different time points. Eta squared statistic was used to calculate the effect size. The interpretation of this value is proposed by Cohen (1992): 0.01=small effect, 0.06=moderate effect, 0.14=large effect.

For the composite scores and individual muscle scores of MMT, a Mann-Whitney U test was used to demonstrate differences between groups based on difference scores between T0 and T1, T1 and T2 and between T0 and T2. If significant differences were shown, a repeated measures Friedman test for both groups was executed, if not the Friedman test was executed on the whole group. Post hoc analysis with Wilcoxon signed rank test was used to assess within group differences between the three measurement points.

A Pearson correlation test was used to study the correlation between baseline measures of the outcome measures and the changes after intervention. Furthermore, the test was also used to investigate the influencing factor 'age' on the outcome measures. Correlation coefficients were interpreted according to Hinkle, Wiersma and Jurs (2003): $r>0.90$ very high correlation; $r=0.70-0.90$ high or strong correlation, $r=0.50-0.70$ moderate correlation, $r=0.30-0.50$ low or weak correlation and $r<0.30$ little or no correlation.

A one-way analysis of variance with post hoc tests was used to evaluate differences in changes in the outcome measures between the three MACS levels. The statistical analysis was performed using SPSS software (SPSS Inc, Chicago Il). A probability level (p-value) of 0.05 was used.

Results

Participants

Forty-four children were enrolled in the study between 2014 and 2017 and 33 of them have data on muscle strength and muscle fatigue. The statistical analysis for this study was executed on this subgroup, including 21 boys and 12 girls. The mean age was 9 years 4 months (SD = 1 year 10 months). Nineteen children had a left-sided hemiplegia and 14 children a right-sided hemiplegia. Nine children (27%) were classified with a MACS level I, nine (27%) with a MACS level II and 15 (46%) with a MACS level III (Eliasson et al., 2006). Sixteen children were randomly allocated to the mCIMT+AOT group and 17 to the mCIMT group. Two children, who were allocated to the mCIMT group, withdrew from the follow-up assessment. The details about the participants and missing data are described in Figure 2. Descriptive characteristics showed no significant differences at baseline between both groups (Table 1). Also, baseline measures (T0) showed no significant differences between both groups for grip strength (p=.524), grip strength ratio (affected/non-affected hand) (p=.106), SFI (p=.829) and MMT total (p=.263).

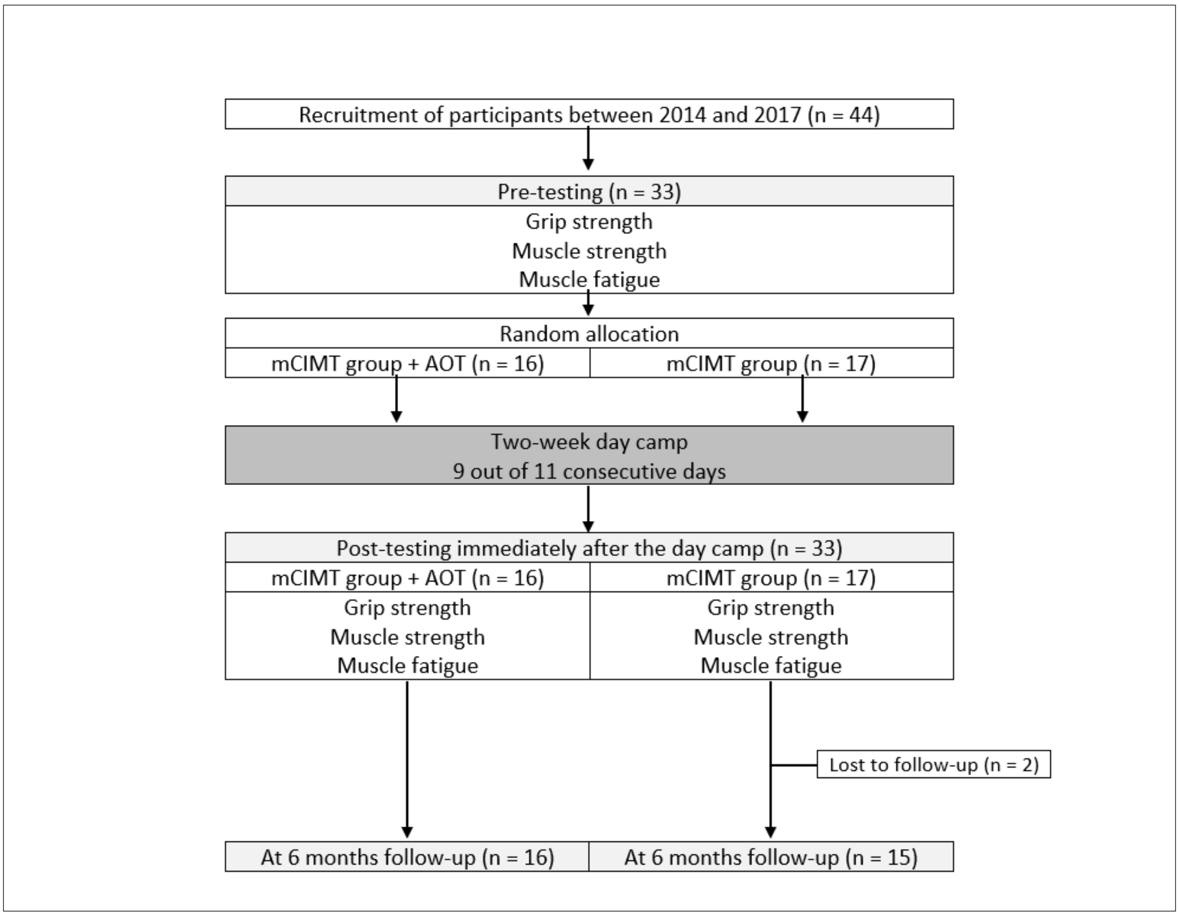

Figure 2. Experimental design with assessments before, directly after the day camp and six months after the day camp. Number of children participating and missing data at the three measurement points. Abbreviations: mCIMT; modified Constraint-Induced Movement Therapy; AOT, Action Observation Therapy

Table 1. *Baseline characteristics in both groups*

		mCIMT+AOT (n = 16)	mCIMT (n = 17)	p-value
Age	Mean (SD)	9 y 2 mo 1 d (2 y 12 d)	9 y 7 mo 13 d (1 y 9 mo 16 d)	.507
Sex				
Male	n (%)	12 (75,0)	9 (52,9)	
Female	n (%)	4 (25,0)	8 (47,1)	.340
Affected side				
Left	n (%)	6 (37,5)	13 (76,5)	
Right	n (%)	10 (62,5)	4 (23,5)	.056
HFCS				
4	n (%)	6 (37,5)	6 (35,3)	
5	n (%)	4 (25,0)	7 (41,2)	.863
6	n (%)	4 (25,0)	1 (5,9)	
7	n (%)	2 (12,5)	3 (17,6)	
MACS				
Level I	n (%)	6 (37,5)	3 (17,6)	
Level II	n (%)	4 (25,0)	5 (29,4)	.237
Level III	n (%)	6 (37,5)	9 (52,9)	

Abbreviations: n, number; SD, standard deviation; y, years; mo, months; d, days; mCIMT, modified Constraint-Induced Movement Therapy; AOT, Action Observation Therapy; HFCS, House Functional Classification Scale; MACS, Manual Ability Classification System

Treatment efficacy

The results for both groups are shown in Table 2. There were no significant differences between both groups for grip strength (p=.794), grip strength ratio (affected/non-affected hand) (p=.483), SFI (p=.414) and MMT total (p=.493). The total group showed significant improvements over time in grip strength, grip strength ratio (affected/non-affected) and MMT total (p<.0001). No significant improvements were found for SFI (p=.520) in the total group. Pre- and post-test values and values at six months follow-up of the outcome measures are shown in Figure 3 a, b, c, d.

Post hoc tests revealed a significant improvement in grip strength, grip strength ratio (affected/non-affected) and MMT total between T0 and T1 (p<.0001). The improvements were retained at follow-up (T0-T2 p<.0001) (Table 3). Scores between T1 and T2 remained stable, except for MMT total. MMT total showed a significant decrease between T1 and T2 (p=.01). The mean difference between T0 and T1 was 0.20 (SD = 0.20) for grip strength with a large effect size of 0.50, 0.15 (SD = 0.19) for grip strength ratio (affected/non-affected) with a large effect size of 0.41, and 1.48 (SD = 1.43) for MMT total with a large effect size of 0.53.

Between T0 and T2 the mean difference was 0.25 (SD = 0.22) with a large effect size of 0.35 for grip strength, 0.17 (SD = 0.21) with a large effect size of 0.43 for grip strength ratio (affected/non-affected) and 1.10 (SD = 1.52) with a large effect size of 0.35 for MMT total.

Table 2. *Outcome measures before, after intervention and after six months follow-up and statistical comparison (p-values)*

		Baseline (T0)		Postintervention (T1)		Follow-up (T2)		Time*Group	Time
		X (SD)	Min-Max	X (SD)	Min-Max	X (SD)	Min-Max		
Grip strength (kg)	mCIMT+AOT	5.04 (3.70)	1.00 – 12.67	6.29 (3.60)	2.00 – 13.50	6.99 (3.87)	1.67 – 12.67	.794	<.0001
	mCIMT	4.50 (3.94)	0.67 – 13.00	6.52 (4.07)	1.00 – 15.33	7.76 (4.47)	2.67 – 16.43		
Grip strength ratio (kg) (affected/non-affected hand)	mCIMT+AOT	0.41 (0.25)	0.10 – 1.00	0.47 (0.20)	0.21 – 0.81	0.44 (0.16)	0.14 – 0.62	.483	<.0001
	mCIMT	0.29 (0.17)	0.07 – 0.65	0.42 (0.19)	0.10 – 0.90	0.48 (0.18)	0.16 – 0.77		
Static fatigue index (SFI) (kg)	mCIMT+AOT	53.01 (19.03)	22.45 – 84.86	55.40 (22.59)	1.91 – 85.10	54.88 (10.86)	35.81 – 72.18	.414	.520
	mCIMT	54.32 (15.54)	26.27 – 78.86	52.02 (13.97)	32.23 – 80.15	51.86 (12.19)	34.72 – 71.46		
Manual Muscle Testing (MMT) total	mCIMT+AOT	31.44 (2.42)	27.00 – 35.50	33.00 (2.11)	28.00 – 35.50	32.91 (2.10)	28.50 – 36.00	.493	<.0001
	mCIMT	32.27 (1.71)	30.00 – 35.50	33.68 (1.40)	31.00 – 36.00	32.90 (1.76)	30.50 – 36.00		

Abbreviations: X, mean; SD, standard deviation; kg, kilogram; min, minimum; max, maximum; mCIMT, modified Constraint-Induced Movement Therapy; AOT, Action Observation Therapy

Figure 3a

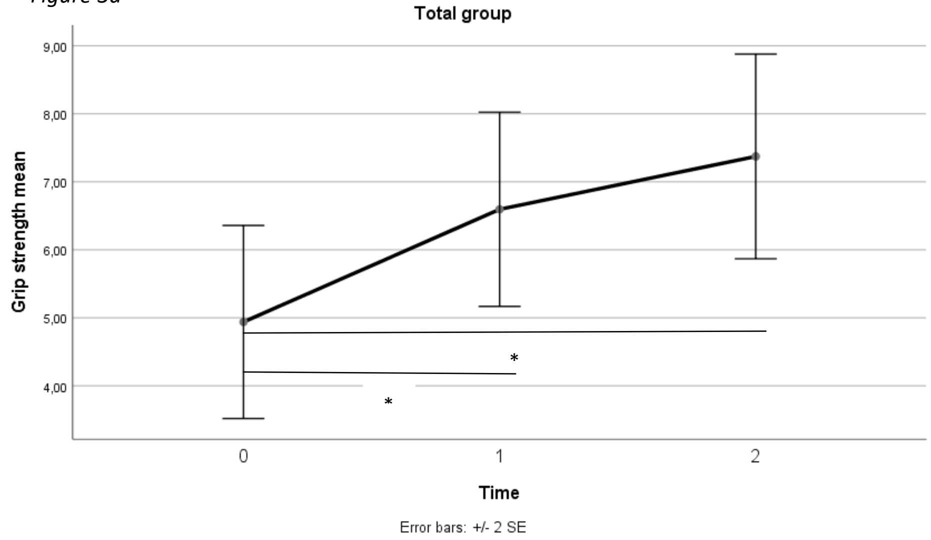

Figure 3b

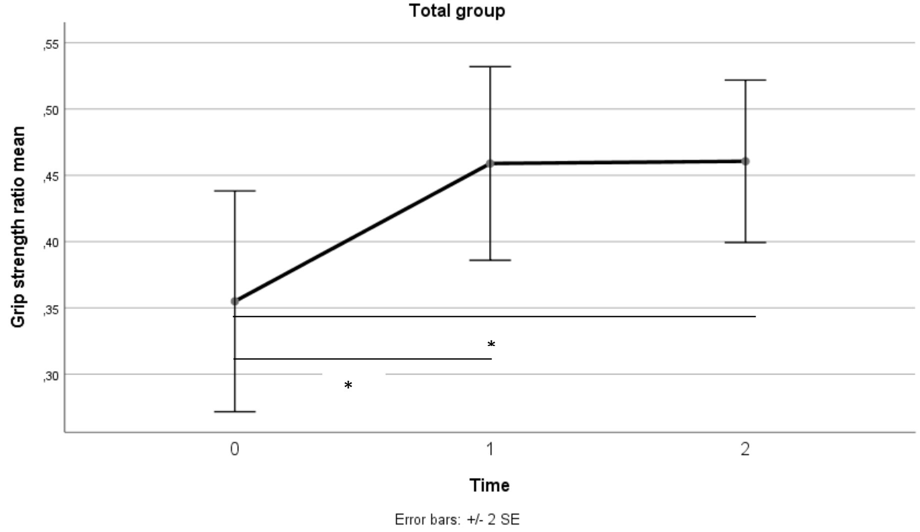

Figure 3c

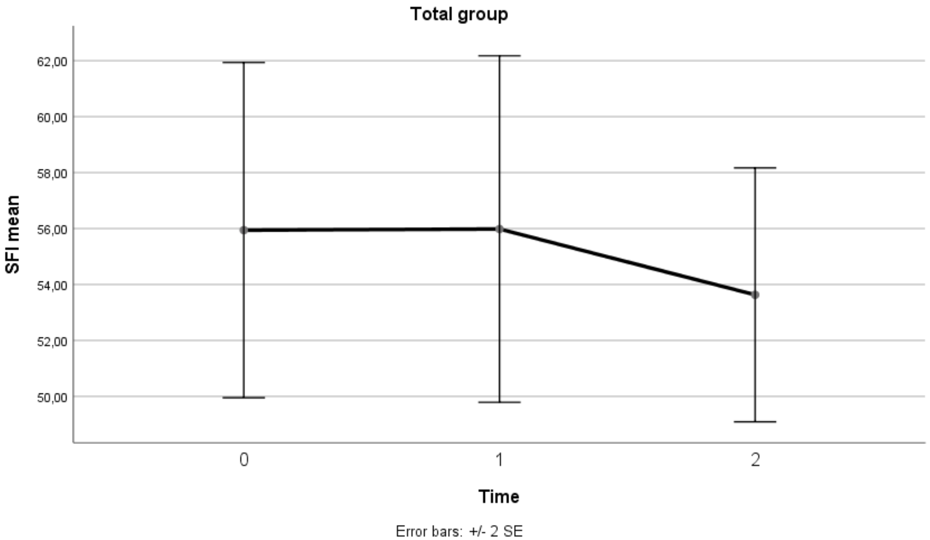

Figure 3d

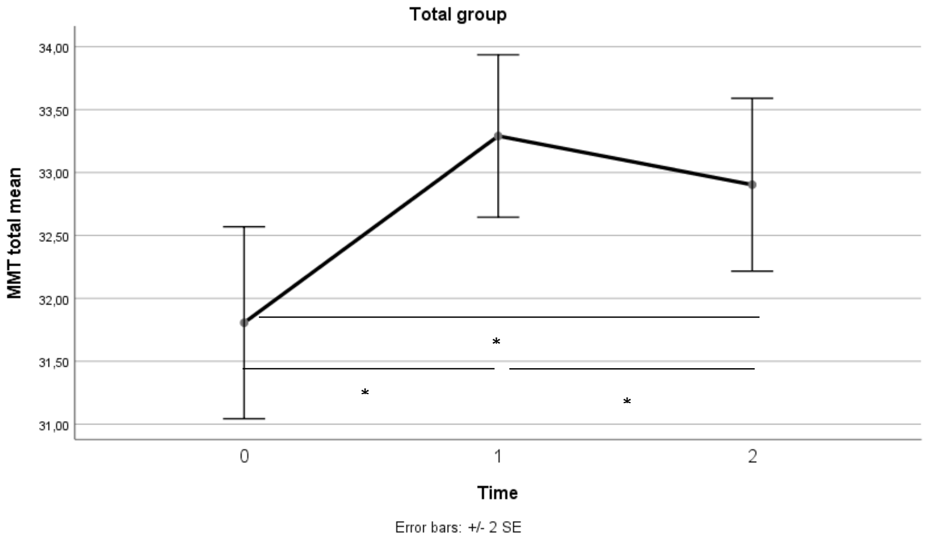

Figure 3 a, b, c, d. Pre- and post-test values and values at six months follow-up for grip strength, grip strength ratio (affected/non-affected), SFI and MMT total. 0 = baseline, 1 = postintervention and 2 = follow-up. Abbreviations: SFI, static fatigue index; MMT, Manual Muscle Testing; SE, standard error

Table 3. *Change scores between baseline, immediately after intervention and after six months follow-up and statistical comparison (p-values)*

		T0 – T1	Effect size T0 – T1	p-value T0 – T1	T1 – T2	Effect size T1 – T2	p-value T1 – T2	T0 – T2	Effect size T0 – T2	p-value T0 – T2
Grip strength (kg)	X (SD)	0.20 (0.20)	0.50	<.0001	0.06 (0.17)	0.11	.06	0.25 (0.22)	0.35	<.0001
Grip strength ratio (kg) (affected/non-affected hand)	X (SD)	0.15 (0.19)	0.41	<.0001	0.01 (0.14)	0.01	.61	0.17 (0.21)	0.43	<.0001
Manual Muscle Testing (MMT) total	X (SD)	1.48 (1.43)	0.53	<.0001	-0.39 (0.81)	0.19	.01	1.10 (1.52)	0.35	<.0001

T0 = baseline, T1 = postintervention, T2 = follow-up. Abbreviations: X, mean; SD, standard deviation; kg, kilogram

A Wilcoxon signed rank test was used to investigate the effect of the intervention on the composite scores and individual scores of MMT (Table 4). The composite scores for elbow and wrist strength showed significant improvements immediately after intervention (p<.0001) and at follow-up (T0-T2 p=.001, p=.008). Between T1 and T2 a significant decrease for wrist strength was found (p=.006). Significant improvements immediately after intervention are also shown for the elbow extensors (p=.046), forearm supinators (p<.0001), forearm pronators (p=.002), wrist flexors (p=.002) and wrist extensors (p<.0001). Significant improvements were retained at follow-up. For the elbow flexors only a significant improvement was found after follow-up (p=.048) and a tendency towards an improvement after intervention (p=.083). No significant improvements were found at the level of the shoulder (p=.150).

Table 4. *Manual Muscle Testing before, after intervention and after six months follow-up and statistical comparison (p-values)*

		T0	T1	T2	p-value T0-T1	p-value T1-T2	p-value T0-T2
Composite scores							
Elbow	Me (IQR)	14.5 (13.75-15.25)	15 (14.5-15.5)	14.5 (14.5-15.5)	<.0001	.344	.001
Wrist	Me (IQR)	6.5 (6-7)	7 (6.5-7.5)	7 (6-7.5)	<.0001	.006	.008
Individual muscles							
Elbow							
Flexors	Me (IQR)	4 (3.75-4)	4 (4-4)	4 (3.54-4)	.083	.417	.048
Extensors	Me (IQR)	4 (4-4)	4 (4-4)	4 (4-4)	.046	.102	.025
Wrist							
Supinators	Me (IQR)	3 (3-3.5)	3.5 (3.5-3.5)	3.5 (3-3.5)	<.0001	.971	<.0001
Pronators	Me (IQR)	3.5 (3-4)	3.5 (3.5-4)	3.5 (3.5-4)	.002	.541	.005
Flexors	Me (IQR)	3.5 (3-3.5)	3.5 (3-4)	3.5 (3-4)	.002	.957	.022
Extensors	Me (IQR)	3.5 (3-3.5)	3.5 (3.5-4)	3.5 (3-3.5)	<.0001	.198	.010

T0 = baseline, T1 = postintervention, T2 = follow-up. Abbreviations: Me, median; IQR, interquartile range

Prognostic factors

Age, MACS level and baseline measures of grip strength, grip strength ratio (affected/non-affected) and MMT total were investigated as prognostic factors. Correlation analysis between age and improvements in grip strength confirmed a low negative correlation ($r=-.313$, $p=.052$) after intervention, which indicates that a higher age tends to lead to less improvements in grip strength (Figure 4a). At follow-up no correlation was found ($r=.188$, $p= .295$). A similar low negative correlation ($r=-.351$, $p =.045$) was found between age and improvements in grip strength ratio (affected/non-affected) after intervention, which indicates that higher age leads to less improvements in grip strength ratio (affected/non-affected) (Figure 4b). After follow-up, no correlation was found ($r=-.091$, $p=.631$). Furthermore, no significant association was found between age and improvements in MMT total after intervention ($r=.147$, $p=.414$) and at follow-up ($r=.204$, $p=.254$).

A high negative correlation was found between grip strength at baseline and grip strength improvement after intervention ($r=-.710$, $p<.0001$) and at follow-up ($r=-.778$, $p<.0001$) (Figure 5a, 5b). Between grip strength ratio (affected/non-affected) at baseline and grip strength ratio (affected/non-affected) improvement after intervention a moderate negative correlation was found ($r=-.693$, $p<.0001$). A high negative correlation was found after follow-up ($r=-.789$, $p<.0001$) (Figure 5c, 5d). A moderate negative correlation was found between MMT total at baseline and MMT total improvement after intervention ($r=-.542$, $p=.001$), and at follow-up ($r=-.491$, $p=.005$) (Figure 5e, 5f). (Hinkle, Wiersma, & Jurs, 2003). This indicates that the larger the score for grip strength, grip strength ratio (affected/non-affected) and MMT total at baseline, the less improvements after intervention and follow-up.

A one-way analysis of variance showed that there were no differences in improvements in grip strength ($p=.113$), grip strength ratio (affected/non-affected) ($p=.358$) and MMT total score ($p=.533$) for the different MACS levels.

Figure 4a

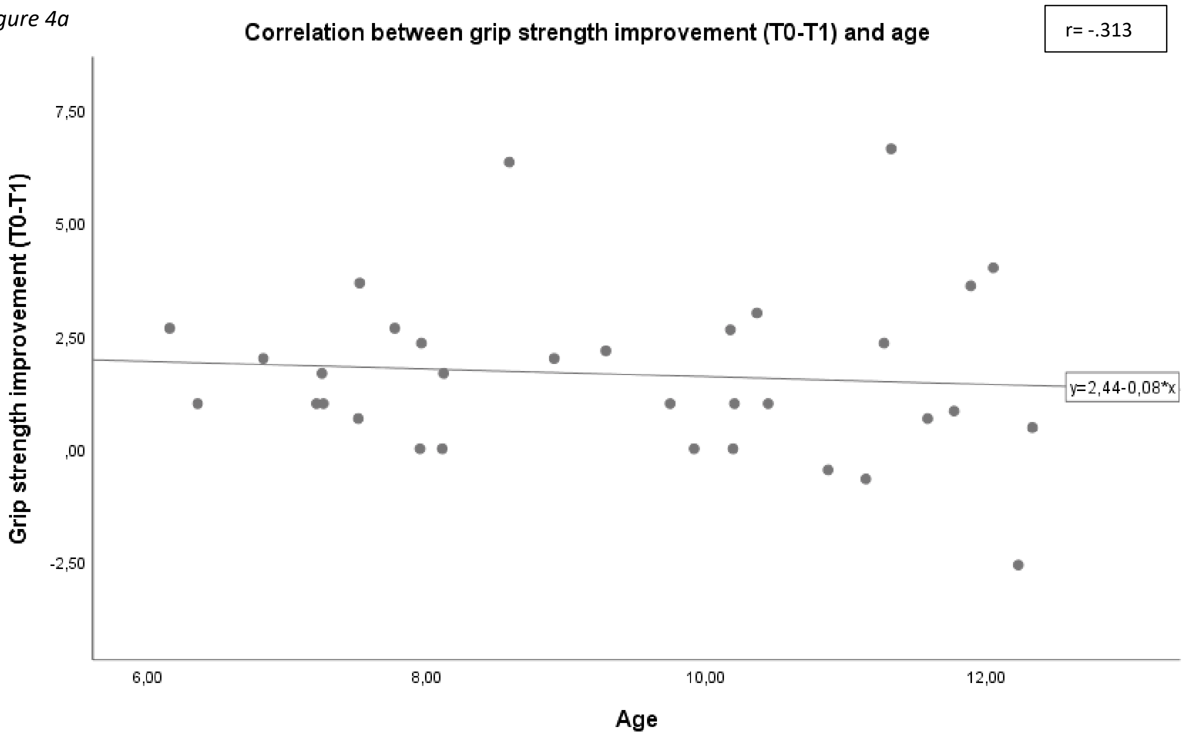

Figure 4b

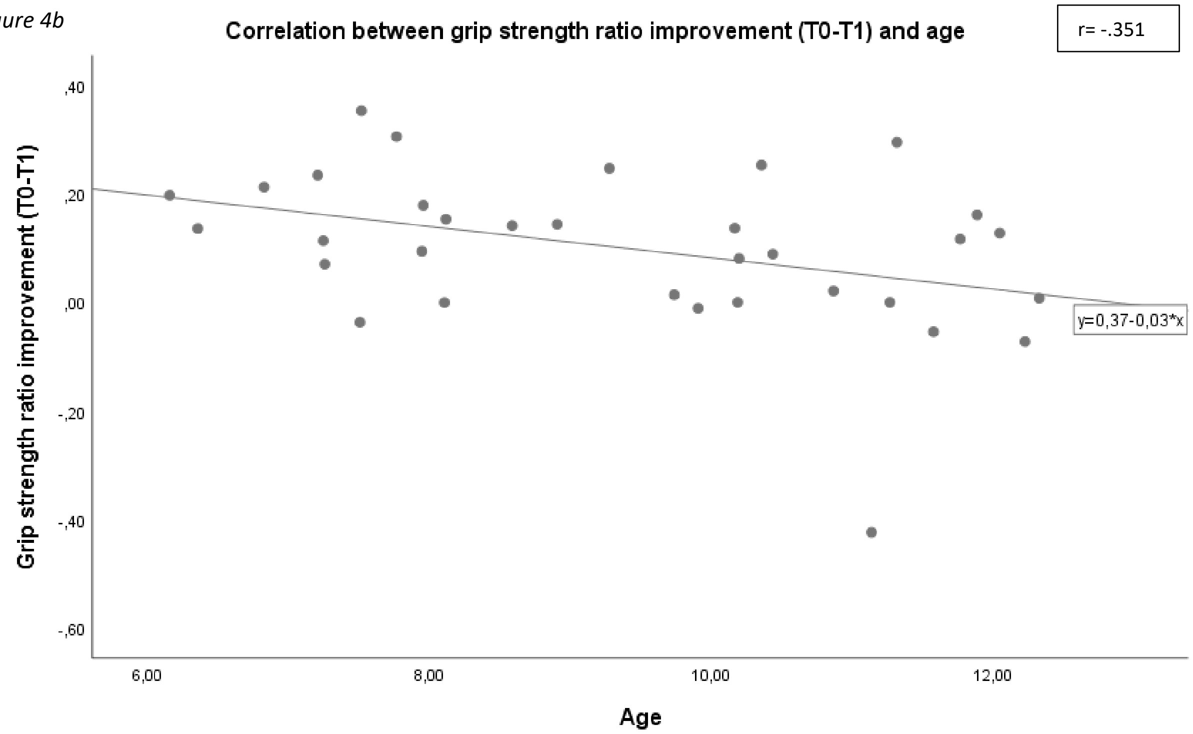

Figure 4 a, b. Correlation between age and improvements in grip strength (T0-T1) and between age and improvements in grip strength ratio (affected/non-affected) (T0-T1). The dots represent the individual values of the participants. The lines reflect the median values. T0 = baseline, T1 = postintervention

Figure 5a

r= -.710

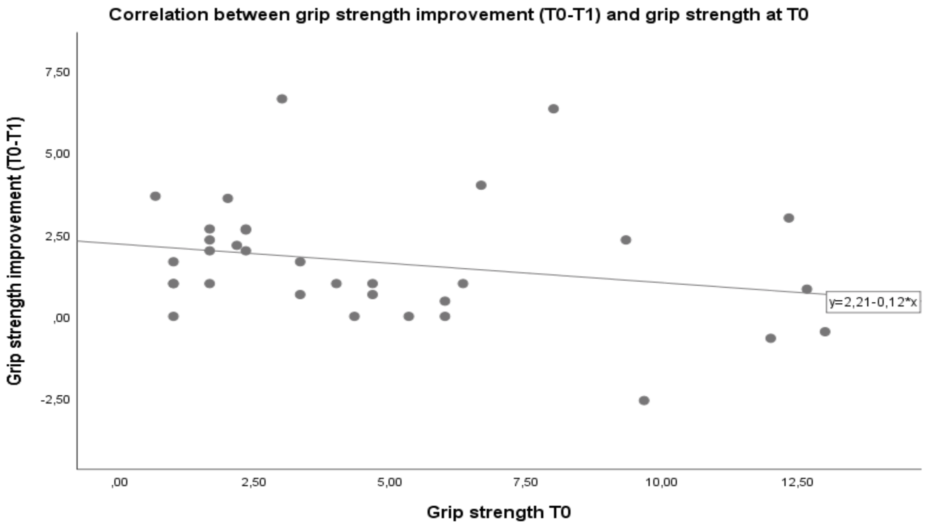

Figure 5b

r= -.778

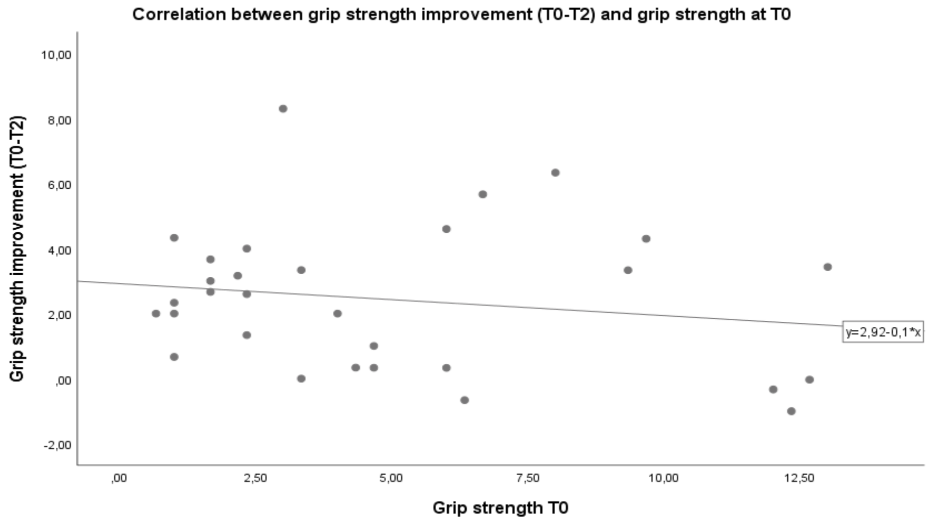

Figure 5c

r= -.693

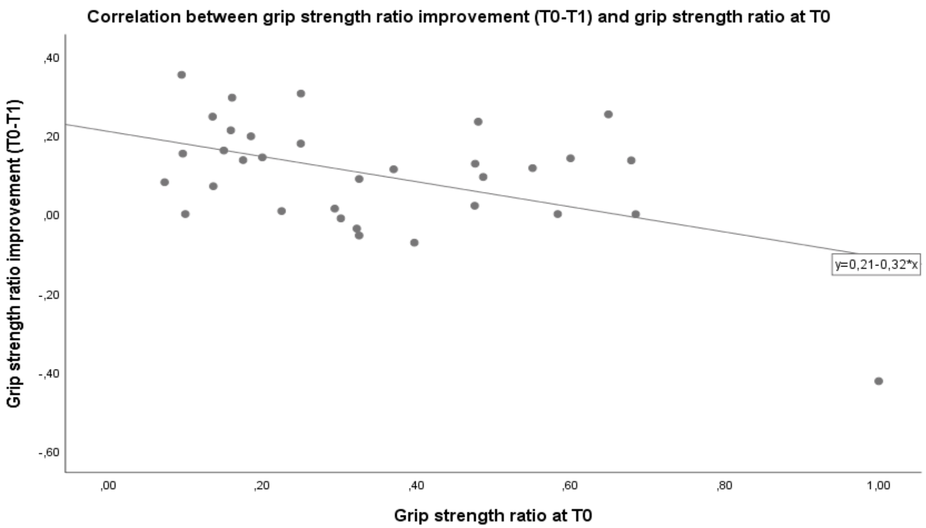

Figure 5d

r= -.789

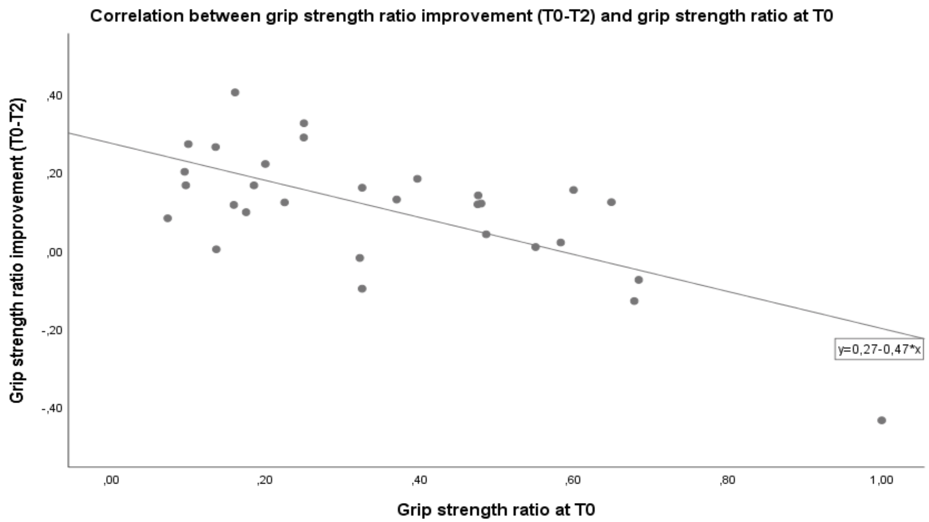

Figure 5e

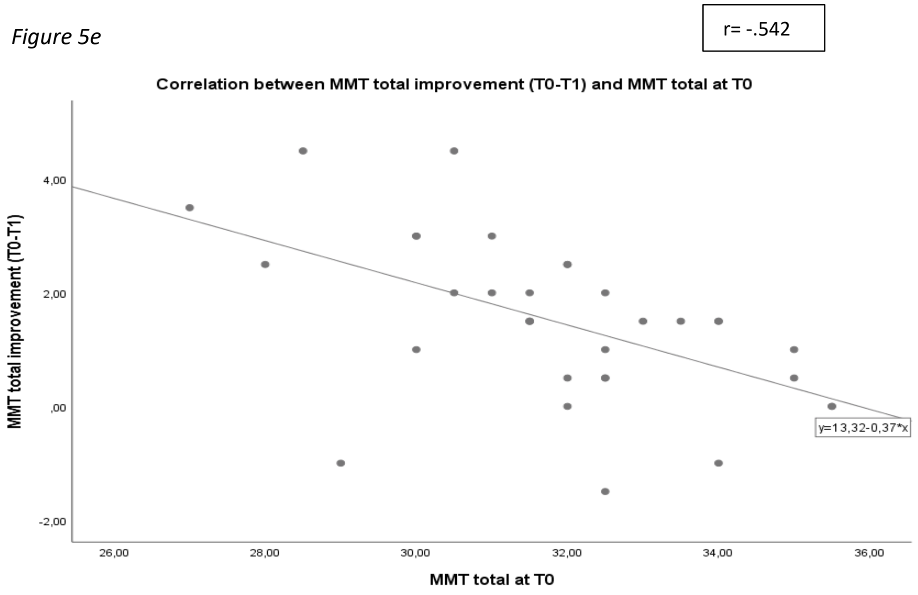

Figure 5f

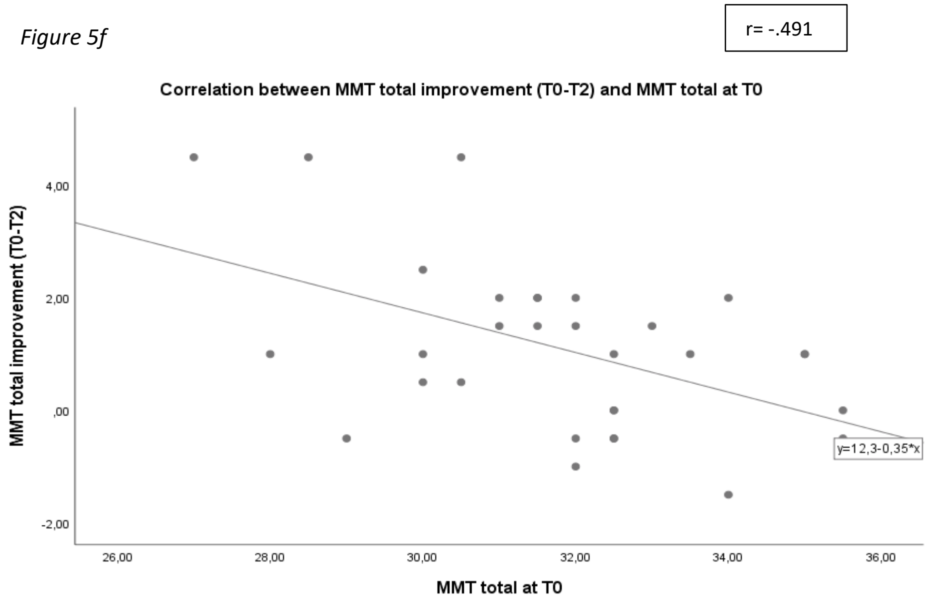

Figure 5 a, b, c, d, e, f. Correlation between grip strength, grip strength ratio (affected/non-affected) and MMT total at baseline and improvements in grip strength, grip strength ratio (affected/non-affected) and MMT total (T0-T1 and T0-T2). The dots represent the individual values of the participants. The lines reflect the median values. T0 = baseline, T1 = postintervention, T2 = Follow-up. Abbreviations: MMT, Manual Muscle Testing

Discussion

This randomized controlled trial, including 33 children with unilateral CP, investigated the efficacy of an integrated training approach (mCIMT+AOT) on upper limb muscle strength and muscle fatigue. The study concluded that there was no significant difference between mCIMT+AOT and mCIMT alone. However, when looking at the within-group results, there were statistically significant improvements in muscle strength. This indicated that both therapy forms had good effects for treating muscle weakness of the affected upper limb. The improvements were also sustained up to six months after intervention. For muscle fatigue, no significant improvements were found.

To our knowledge this was the first study showing that AOT had no additional benefits in combination with mCIMT on improving muscle strength. Previous studies investigating the efficacy of AOT in isolation showed benefits on activity level, but no studies reported the effect of AOT on muscle strength (Buccino et al., 2012; Kim et al., 2014; Sgandurra et al., 2011). Therefore, the results of the current study could not be compared with previous research.

Several possible reasons could be emphasized for not finding an augmented effect of AOT. First, there could be a large effect of mCIMT on muscle strength, whereby the effect of AOT could be suppressed. Second, AOT was mainly focused on performing functional activities. No analytical exercises to improve muscle strength were included in the intervention program, while it was demonstrated that targeted strength exercises were required to obtain an improvement in muscle strength (Elvrum et al., 2012). Third, previous studies used a longer intervention duration of three or four weeks, while the current study lasted only two weeks. Therefore, it could be possible that the intervention time in this study was insufficient to detect a difference. Nevertheless, the number and duration of AOT sessions was comparable to previous research (Buccino et al., 2012; Sgandurra et al., 2011). At last, AOT is time consuming and requires a lot of concentration of the child. Therefore, the difficulty of applying AOT could also cause the non-significant effect.

This study, using mCIMT with or without AOT, found overall improvements in grip strength and muscle strength, while in previous studies about mCIMT contradictory results have been reported (Bonnier et al., 2006; Charles & Gordon, 2006; Eliasson et al., 2009; Gordon et al., 2006; Klingels et al., 2013; Nordstrand & Eliasson, 2013; Sakzewski et al., 2011; Sutcliffe, Logan, & Fehlings, 2009b; Xu et al., 2012; Xu et al., 2015). Several explanations could be formed for the lack of significant results in previous studies. In the current study, grip strength was measured with the Jamar dynamometer. This is the gold-standard and the most accurate and reliable device to evaluate grip strength in children with CP (Klingels et al., 2010). Instead of the Jamar dynamometer, other studies used the hand-held dynamometer (HDD), sphygmomanometer or Grippit dynamometer (Bonnier et al., 2006; Charles & Gordon, 2006; Eliasson et al., 2009; Gordon et al., 2006; Klingels et al., 2013; Nordstrand & Eliasson, 2013; Sakzewski et al., 2011; Sutcliffe et al., 2009b; Xu et al., 2012; Xu et al., 2015). The psychometric properties of these measurement tools should be specified in children with unilateral CP (Dekkers, Rameckers, Smeets, & Janssen-Potten, 2014). The study of Xu et al. (2015) used surface electromyography (EMG) to assess muscle strength and found a significant improvement after applying mCIMT. This differs from other studies involving individuals with CP, which used MMT. MMT can be used to evaluate muscle strength from both upper and lower limb and showed a good interrater reliability for wrist strength and total upper limb muscle strength in children with CP (Dekkers et al., 2014).The interrater reliability for the assessment of the shoulder and elbow was low (Klingels et al., 2010). This could be the reason why no significant improvements for the shoulder were found after the two-week day camp. An additional finding that was revealed to be different from earlier research about mCIMT was the important focus on distal muscle strength during the individual and group activities. This could also explain the main improvement of muscle strength in the distal muscle groups. This result is in line with the study of Klingels et al. (2013). The improvements in the distal muscle groups were retained at six months follow-up and therefore it could be concluded that the therapy has a lasting effect for at least six months. Further research is needed to specify the long term effects after a period of more than six months.

So far there have been a few studies investigating the effect of a day camp on muscle strength and reported contradictory results (Bonnier et al., 2006; Charles & Gordon, 2006; Eliasson et al., 2009; Gordon et al., 2006; Nordstrand & Eliasson, 2013; Sakzewski et al., 2011; Thompson et al., 2015). Children in this study received six hours of therapy a day, for nine out of 11 consecutive days and demonstrated large gains in muscle strength. Contrary, the review of Rameckers, Janssen-Potten, Essers and Smeets (2014) suggested that a frequency of minimal three times a week and an intervention duration of minimal eight weeks might be necessary to improve muscle strength. The present findings indicated the effectiveness of this intensive therapy program, because gains in muscle strength were already found after two weeks (Elvrum et al., 2012; Rameckers, Speth, Duysens, Vles, & Smits-Engelsman, 2009).

Although the therapy program was effective for muscle strength, no significant improvements for muscle fatigue were found. This is in accordance with the results of the study of Brauers et al. (2017). A possible explanation could be the use of goal-directed actions during the intervention, which especially contain short and submaximal contractions (Moreau, Li, & Damiano, 2008). This is in contrast with the measurement of muscle fatigue, which contains an isometric maximal contraction during 30 seconds. In line with this, the study of Hawley, Myburgh, Noakes and Dennis (1997) suggested that long maximal contractions are needed to improve muscle fatigue. Therefore, it could be possible that the type of exercises used in this study were inadequate to improve muscle fatigue. A second cause could be the longer time needed to improve muscle fatigue. For muscle strength the NSCA guidelines advised a resistance program of 8 to 20 weeks. It could be possible that a longer intervention duration is also required to obtain significant improvements in muscle fatigue (Faigenbaum et al., 2009).

Furthermore the implemented protocol of SFI should be critically analysed. The motivation of the child, as well as the verbal encouragement of the researcher, could have had an influence on the measurement. Younger children could also have had more problems to understand how to perform the measurement. Moreover, the calculation of SFI also should be critically evaluated, because individuals with CP showed increased variability in force production and the measurement of SFI does not take this into account (Gordon, Charles, & Duff, 1999). Due to the force variability similar SFI values could be obtained, while the areas under the curve had different shapes. This should be considered when calculating SFI. The dynamic fatigue index as described by Schwid et al (1999) could also be used to measure muscle fatigue. For the dynamic fatigue index, the ratio between the maximal strength of the first three and last three hand grip trials was calculated with the use of the following formula: 100*[1–(MVC2 / MVC1)] (MVC: maximal voluntary isometric contraction) (Severijns et al., 2015). This muscle fatigue measurement using repeated contractions could be more motivating for children than a sustained contraction. Dynamic testing is also more natural and related to daily life activities. In general, there are different methods to measure muscle fatigue, but there is no gold-standard yet. Likewise, the psychometric characteristics of the different measurement methods have not been thoroughly investigated. Therefore, the use of SFI to measure muscle fatigue can be questioned. Further research concerning the phenomenon of muscle fatigue in children with unilateral CP and the responsiveness of muscle fatigue measurements is needed.

The second aim of this study was to investigate the influencing factors on changes in muscle strength and muscle fatigue, such as age and hand function at baseline. Although other studies showed controversy about the correlation between age and changes in muscle strength, a low negative correlation between age and improvements in grip strength was found (Bonnier et al., 2006; Charles & Gordon, 2006; Gordon et al., 2006; Klingels et al., 2013; Thompson et al., 2015; Xu et al., 2012; Xu et al., 2015). This means that younger children tend to show higher gains in grip strength. Therefore, it is important to start with the intervention as soon as possible to receive the highest possible gains. This is in line with the study of Martin, Choy, Pullman and Meng (2008), which mentioned that the body frame in younger children adapts faster than in older children and therefore the use of the affected limb in the early years of life seems important to improve motor skills. The low correlation between age and changes in muscle strength could be explained by high variability in muscle strength improvement. This variability was probably due to large interindividual differences in baseline muscle strength in children with the same age.

Improvements in muscle strength were also related to baseline muscle strength. This relation suggested that the lower the baseline score, the larger improvements in muscle strength were found. This could be due to the fact that a lower baseline scores might provide a larger window for improvement. This finding was confirmed in literature (Eliasson, Krumlinde-Sundholm, Shaw, & Wang, 2005; Klingels et al., 2013; Sakzewski et al., 2011).

Another possible influencing factor on the outcome measures is MACS level. However no significant interaction in the current study was found. In previous studies about mCIMT the majority of the children had a MACS level II (Bonnier et al., 2006; Charles & Gordon, 2006; Gordon et al., 2006; Klingels et al., 2013; Thompson et al., 2015; Xu et al., 2012; Xu et al., 2015). Therefore, no strong conclusions could be made about the effect of MACS level on the outcome measures after mCIMT intervention. It might be possible that children with poorer manual ability acquire greater improvements after intensive training. On the other side it could be more frustrating for children with a more disabled upper limb to execute task specific training. This frustration could lead to less attention and less motivation (Klingels et al., 2013).

The aim of the two-week day camp was to provide goal-directed activities in a playful and attractive setting. In addition the children had to learn to use their affected hand in a flexible manner. It can be concluded that the tailor-made hand splint was tolerated by the children and that this form of intensive therapy was easy to apply on a child population. In general, this therapy program is accessible and the findings are generalizable for children with unilateral CP within the age group from six to 12 years old.

Despite the promising results, this study has a few limitations. At first, the sample size of each group was rather small and this could reduce the power to detect between and within group interactions. Secondly, there was no control group included in the study because of the nature of this setting and the difficulty to recruit these children. Thirdly, the assessment of the outcome measures was not blindly executed. However, the measurements were performed in a standardized manner. Finally, detailed information about comorbidities and mental status was not taken into account and this could possibly influence the primary outcomes.

Future research

This RCT investigated the effects of mCIMT in combination with AOT on muscle strength and muscle fatigue in children with CP and compared it with mCIMT alone. Further research with larger sample sizes is needed to confirm the results. As mentioned above, the Jamar dynamometer has shown to be reliable in children with unilateral CP, but it is known that MMT is not reliable for all muscle groups. Further research should quantify muscle strength in an objective manner in children with unilateral CP. Furthermore, the psychometric properties of measurement methods for muscle fatigue have not been clearly discussed yet. Therefore, it is recommended to further investigate and develop a standardized method for measuring muscle fatigue. Future research should also focus on the specific amount and dosage of intervention to improve muscle strength and muscle fatigue. The development of a standardized protocol is necessary and this will lead to a more efficient rehabilitation.

Conclusion

There are four important findings in the current study. First, an integrated approach combining mCIMT and AOT demonstrated no significant difference in muscle strength and muscle fatigue compared with mCIMT alone in children with unilateral CP. Secondly, both interventions demonstrated significant improvements in grip strength and muscle strength over time. For muscle fatigue, no significant improvements were found. Third, children with lower strength at baseline seemed to have higher gains in strength after training. Finally, age and MACS level were no significant influencing factors on the outcome measures. Further research with larger sample sizes and optimization of the measurement of muscle strength and muscle fatigue is needed to confirm these results.

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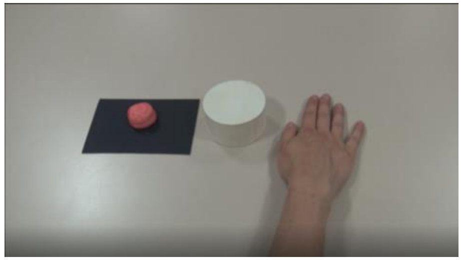
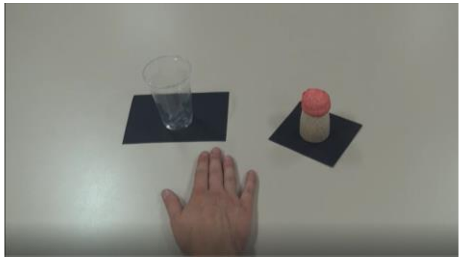
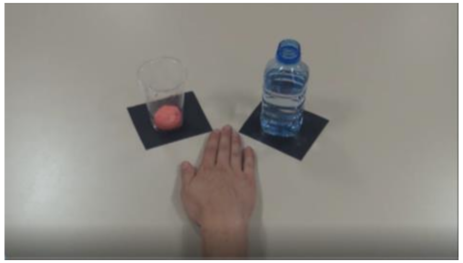
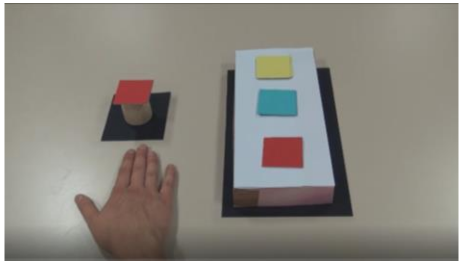
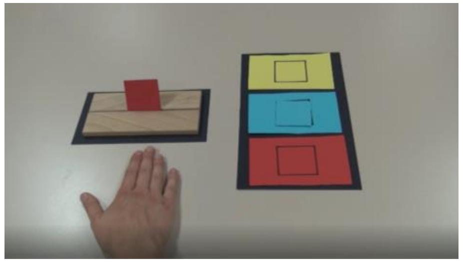
Appendix

Appendix I. *Schedule of one camp day*

Activities	Beginning	End
Welcome with robot Zora	09h00	09h10
AOT or placebo AOT	09h10	10h00
Group session or individual therapy	10h05	10h55
Pause	10h55	11h10
Group session or individual therapy	11h10	12h00
Lunch	12h00	13h00
AOT or placebo AOT or group session or individual therapy	13h05	14h00
AOT or placebo AOT or group session	14h05	14h55
Pause	14h55	15h10
Group session	15h10	15h55
End of the day with robot Zora	15h55	16h00

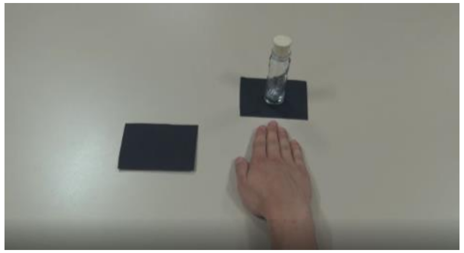
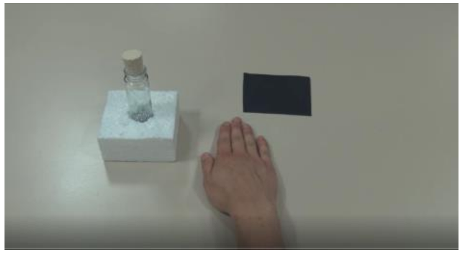
Abbreviations: AOT, Action Observation Therapy

Appendix II. *Some examples of the goal-directed actions of AOT (HFCS 4-5)*

Goal-directed action	Sub-activity 1	Sub-activity 2	Sub-activity 3
1	Lift up a cover and place it over a candy. Afterwards place it next to the candy	Take the candy and place it into a plastic cup	Take the bottle of water and fill the plastic cup containing a candy with water
			
2	Pick up a coloured card and place it on the same colour card out of three	Pick up a coloured card between thumb and index finger from a card holder and place it on the same colour	Pick up a card with an animal on between thumb and index finger from a card holder and place it on the same animal
			

Abbreviations: AOT, Action Observation Therapy; HFCS, House Functional Classification Scale

Appendix III. *Some examples of the goal-directed actions of AOT (HFCS 6-8)*

Goal-directed action	Sub-activity 1	Sub-activity 2	Sub-activity 3
1	Pick up a spray can and place it on the black surface	Pick up a spray can and place it in the v-shaped foam	Spray with the spray can into the plastic cup that lies in the v-shaped foam
			
2	Pick up a tube containing glittering powder and place it on the black surface	Take the cork lid off the tube and place it on the black surface	Pick up the tube and sprinkle some glittering powder on the drawing
			

Abbreviations: AOT, Action Observation Therapy; HFCS, House Functional Classification Scale

Appendix IV. *Progress form*

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
10/10/2017	Verder verloop masterproef 2.	Promotor: Copromotor: Student(e): Student(e):
25/01/2018	Afspraak met Dr. L. Bruckers. Voorbereidend werk op statistiek	Promotor: Copromotor: Student(e): Student(e):
05/04/2018	Bespreken statistiek	Promotor: Copromotor: Student(e): Student(e):
23/04/2018	Bespreken resultaten	Promotor: Copromotor: Student(e): Student(e):
25/05/2018	Bespreken discussie	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2018**

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