Intensive upper- and lower-extremity training for children with bilateral cerebral palsy: a quasi-randomized trial

YANNICK BLEYENHEUFT[1] | DANIELA EBNER-KARESTINOS[1] | BHAVINI SURANA[2] | JULIE PARADIS[1] | ALEXIS SIDIROPOULOS[2] | ANNE RENDERS[3] | KATHLEEN M FRIEL[2,4] | MARINA BRANDAO[5] | EUGENE RAMECKERS[6,7,8] | ANDREW M GORDON[2]

1 Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium. **2** Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, NY, USA. **3** Physical and Rehabilitation Medicine Department, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium. **4** Burke-Cornell Medical Research Institute, White Plains, NY, USA. **5** Departamento de Terapia Ocupacional, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. **6** Research in Function and Rehabilitation, Rehabilitation Medicine, CAPHRI, Maastricht University, Maastricht. **7** Center of Expertise, Adelante Rehabilitation, Hoensbroek; **8** Avans Plus, Breda, the Netherlands.

Correspondence to Yannick Bleyenheuft at Institute of Neuroscience, Université catholique de Louvain, avenue Mounier 53, Box B1.53.04, 1200 Brussels, Belgium.
E-mail: Yannick.bleyenheuft@uclouvain.be

PUBLICATION DATA
Accepted for publication 25th November 2016.
Published online

ABBREVIATIONS

BBT	Box and Blocks Test
HABIT	Hand–arm bimanual intensive therapy
HABIT-ILE	Hand–arm bimanual intensive therapy including lower extremity
JTTHF	Jebsen–Taylor Test of Hand Function

AIM An approach that simultaneously engages both the upper and lower extremities, hand–arm bimanual intensive therapy including lower extremity (HABIT-ILE), has recently demonstrated improvements in upper and lower extremities in children with unilateral cerebral palsy (CP). It is not known whether children with bilateral CP would benefit from this approach. The aim of this study was to examine the efficacy of HABIT-ILE in children with bilateral CP.
METHOD A quasi-randomized trial design was used, whereby 20 participants (age 6–15y, Gross Motor Function Classification System levels II–IV, Manual Ability Classification System levels I–III) were assigned to a treatment (HABIT-ILE) or a comparison group in the order in which they were enrolled. Children in the HABIT-ILE group were assessed before and after 84 hours of intervention over 13 days, as well as at 3 months' follow-up. Children in the comparison group were assessed at the same time points. Children in both groups were assessed using the Gross Motor Function Measure (GMFM-66) and ABILHAND-Kids (primary measures), and six secondary measures.
RESULTS A group×test session interaction indicated significant improvements in the HABIT-ILE group as assessed by the GMFM-66, lower-extremity performance (6-Minute Walk Test; Pediatric Balance Scale), functional upper-extremity abilities (ABILHAND-Kids/Pediatric Evaluation of Disability Inventory), and the dexterity of the less affected upper extremity.
CONCLUSION HABIT-ILE is efficacious for improving both upper- and lower-extremity function in children with bilateral CP.

Intensive rehabilitation approaches have been successfully developed for the upper extremities of children with unilateral cerebral palsy (CP) over the past 15 years. Two therapies have been particularly efficacious: constraint-induced movement therapy and bimanual training (e.g. hand–arm bimanual intensive therapy [HABIT]). Both approaches demonstrated improvements in upper-extremity function[1] and are among a handful of treatments determined to be sufficiently effective for recommendation for clinical implementation.[1] However, 60% to 70% of children with CP present bilateral impairments.[2] Owing to the specific focus on the affected upper extremity, neither approach is likely to be applied in children presenting bilateral CP with more symmetrical upper-extremity impairments; moreover, their lower extremities are also affected.

In children with bilateral CP, intensive interventions have been introduced with a focus on walking, including supported treadmill training and strength training.[3] In toddlers with CP, an intervention focused on gross motor function using dynamic weight assistance and applying motor skill learning has been developed,[4] with promising results. Goal-directed, task-specific training has also provided evidence of improvement in gross motor function[5,6] and upper-extremity abilities.[7] However, so far, no intervention has concomitantly targeted upper- and lower-extremity control in children with bilateral CP.[1] An intensive intervention for children with unilateral CP was recently introduced: hand–arm bimanual intensive therapy including lower extremity (HABIT-ILE). HABIT-ILE is a bimanual training approach that continuously incorporates

 DOI: 10.1111/dmcn.13379

lower-extremity function and postural control.[8] On the basis of HABIT,[9] HABIT-ILE was proposed as an intensive block of training using motor learning concepts (i.e. practice specificity, context of learning, feedback, speed–accuracy trade-off, transfer of learning),[10] aiming to elicit practice-induced brain changes arising from repetition, increasing movement complexity, motivation, and reward.[11] HABIT-ILE has been successfully tested in a randomized controlled trial in children with unilateral CP, showing improvements both in upper- and lower-extremity compared with conventional intervention.[12]

The aim of this study was to apply HABIT-ILE to children with bilateral CP (Gross Motor Function Classification System [GMFCS] levels II–IV) and to compare upper- and lower-extremity function with a non-treatment group. We hypothesized that HABIT-ILE would lead to improvements in upper and lower extremities in children with bilateral CP.

What this paper adds

- Hand–arm bimanual intensive therapy including lower extremity can be adapted for children with bilateral cerebral palsy (CP).
- Children demonstrate improvements in upper extremities, gross motor function, walking, and balance.
- They also demonstrate improvements in goal performance.
- Therapies based on motor skill learning are adaptable and efficient for children with bilateral CP.

METHOD

Twenty children participated: 10 were included in a research program of the Université catholique de Louvain, Brussels, Belgium, and 10 were included in a research program of the Center for Cerebral Palsy Research at Teachers College, Columbia University, New York. In the New York program, participants were recruited from area clinics, the laboratory website (http://www.tc.edu/centers/cit/), and online parent forums. In the Brussels program, children were recruited from area clinics. Potential participants were contacted by e-mail or telephone. Those who were available and interested in participating were invited to receive a physical screening. Initially, 24 participants were screened for this study; three presented exclusion criteria (New York: one had uncontrolled seizure, two were unable to make a few steps with a walker) and one declined (Brussels: unavailable).

Inclusion criteria included: (1) children diagnosed with bilateral CP in GMFCS levels II to IV; (2) aged 6 to 16 years; (3) with an ability to grasp light objects and lift the more affected arm 15cm above a table surface; (4) school level equal to that of typically developing peers, ensuring an ability to understand games; and (5) ability to follow instructions and complete testing. Exclusion criteria were: (1) uncontrolled seizures; (2) botulinum neurotoxin injections or orthopedic surgery in the previous 6 months/during the study period; (3) visual problems likely to interfere with treatment/testing; and (4) a total inability to walk a few steps (with a walker). This study was approved by the institutional review boards of Teachers College, Columbia University (number 13-220) and Université catholique de Louvain (number 2013/069; Belgian register B403201316810).

Design

A quasi-randomized trial design was used, whereby participants were assigned to a treatment or comparison group in the order in which they enrolled in the study (the first 10 participants were assigned to the treatment arm, the last 10 participants to the comparison arm).

The treatment arm included a HABIT-ILE day camp in Brussels (six children, April 2013) and New York (four children, July 2013), both providing 6.5 hours per day of intensive intervention over 13 days (84.5h). Children in the treatment group were assessed before and after HABIT-ILE and at follow-up (3mo later). Children in the comparison group were assessed at the same corresponding time points. All children continued their usual and customary care.

HABIT-ILE procedures

HABIT-ILE[8] was provided by one or two interventionists for each child, depending on balance abilities (i.e. whether a child needed a spotter). Most interventionists were physical/occupational therapy students, two were occupational therapists, and one was a physical therapist. Family-centered approaches, taking into account parents' and supervisors' recommendations, were used to match participants and interventionists. Interventionists were asked to provide only HABIT-ILE procedures to which they were trained during a 2-day training session before the camp, on the basis of a manual of procedures. During the camps, supervision by experienced physical/occupational therapists and daily meetings dedicated to discussions of therapeutic goals and strategies allowed monitoring compliance with this instruction. Two supervisors involved in both camps ensured consistency in procedures/protocols for the interventionists. HABIT-ILE has been fully described previously[8] and is described in Appendix S1 (online supporting information). Briefly, HABIT-ILE is a motor-learning-based approach using problem-solving and highly structured practice in tasks requiring simultaneous control and coordination of upper and lower extremities. In the course of the intervention, activities and tasks are progressively graded towards increasing demands of the lower extremity/postural control and more complex bimanual coordination of the upper extremity. A few adaptations were made in this study to match the needs of children with bilateral CP. Essentially, a new possibility was added in the evolution of balance, consisting of stool sitting (proposed alternately with balls, especially at the start); in addition, most of the time, activities that involved running or jumping could not be proposed. Transition activities were introduced (including playing in a kneeling position, transferring from one position to the other, and fall school).

Usual care

Usual care was provided to the children in the non-treatment group during the 2 weeks they were used for comparison. In both groups, this usual treatment was provided during follow-up. In the comparison group, this care consisted of physical therapy based on neurodevelopmental treatments (four out of 10 children) or on a functional basis (six out of 10 children) and on weekly occupational therapy. Usual care in the treatment group also comprised weekly physical therapy sessions based on neurodevelopmental treatment (eight out of 10 children) or on functional training (two children, one following conductive education) and on weekly occupational therapy.

Assessments

Children's abilities were classified using the Manual Ability Classification System[13] and the GMFCS.[14] The less-affected hand of each child was determined by writing-hand preference.[15] The assessments covered the three domains of the International Classification of Functioning, Disability and Health. The primary outcome measures included the Gross Motor Function Measure (GMFM-66,[16] b710/b755/b760/d410/d415/d450/d455) and the ABILHAND-Kids (d510/d520/d540/d550/d560).[17]

Three secondary upper-extremity assessments were performed: the Pediatric Evaluation of Disability Inventory (self-care domain, functional skills[18]/d5–7), the Box and Blocks Test (BBT[19]/b760/d430–39) on both hands, and the Jebsen–Taylor Test of Hand Function (JTTHF[20]/b760/d430–39) on both hands.

Three secondary lower-extremity assessments were performed: the ABILOCO-Kids[21] (d450/455/460), the Pediatric Balance Scale[22] (b710/b755/b760/d410/d415/d420/d455), and the 6-Minute Walk Test (b147/d410–429/d450/d455).[23]

Finally, the Canadian Occupational Performance Measure[24] (d1–9) was administered with the parents of the treatment group to establish functional goals and to grade children's performance and satisfaction.

Both the GMFM-66 (primary outcome) and Pediatric Balance Scale were videotaped and blindly scored by a trained examiner.

Statistics

The HABIT-ILE and non-treatment groups were compared at baseline using t-tests. For each variable, a 2 (group)×3 (test session) analysis of variance (ANOVA) with repeated measures on test session was performed. The overall interaction (group×test session) allowed testing of whether the time course differed between groups. Newman–Keuls post-hoc analyses were subsequently performed. The effect size was estimated using the value of η^2. Under non-parametric conditions (normality/homoscedasticity violated), we used a repeated-measures ANOVA on ranks (Friedman). A one-way repeated-measures ANOVA was used to investigate changes in the Canadian Occupational Performance Measure in the treatment group.

Sample size

Sample size analysis was based on the ABILHAND-Kids derived from a study of children with unilateral CP.[12] A mean improvement of 1.81 (standard deviation [SD] 1.55) logits during the camp for the immediate HABIT-ILE group was reported. With α=0.05 and $1-\beta$=0.8, a minimum of eight participants total per group was required. Considering potential drop-outs, 10 participants were included in each group.

RESULTS

No significant differences were observed between groups at baseline for any measure (Table I). Intent-to-treat procedures were used in case of missing values (children not showing up at follow-up, n=2, comparison group). Because

Table I: Characteristics of each group at baseline

General characteristics	HABIT-ILE group (n=10)	Comparison group (n=10)	p, t-test
Sex	Six males; four females	Five males; five females	
Dominant (less affected) side	Four left; six right	Three left; seven right	
GMFCS level			
II	2	2	
III	7	7	
IV	1	1	
MACS level			
I	1	2	
II	4	4	
III	6	5	
MACS by GMFCS			
GMFCS II			
MACS I	0	1	
MACS II	1	0	
MACS III	1	1	
GMFCS III			
MACS I	1	1	
MACS II	3	3	
MACS III	3	3	
GMFCS IV			
MACS I	0	0	
MACS II	0	1	
MACS III	1	0	
Topography			
Diplegia	4	3	
Quadriplegia	6	7	
Mean age, y (SD)	10.5 (2.8)	11.4 (3.9)	p=0.566
More affected hand			
Box and Blocks Test, n (SD)	25 (13.0)	30 (16.4)	p=0.408
JTTHF, s (SD)	263 (248)	145 (94)	p=0.196
Less affected hand			
Box and Blocks Test, n (SD)	32 (11.8)	36 (20.6)	p=0.579
JTTHF, s (SD)	110 (85)	116 (84)	p=0.889
Abilities			
ABILHAND-Kids, logit (SD)	1.0 (1.4)	1.9 (2.2)	p=0.288
PEDI (/73) (SD)	52 (12.4)	51 (14.6)	p=0.987
Lower extremity and trunk			
GMFM-66, % (SD)	55 (5.9)	55 (8.7)	p=0.894
ABILOCO-Kids, logit (SD)	−2.5 (2.1)	−1.4 (2.2)	p=0.291
6MWT, m (SD)	190 (108.5)	194 (101.1)	p=0.940
PBS (SD)	33 (17.5)	30 (23.9)	p=0.749

HABIT-ILE, hand–arm bimanual intensive therapy including lower extremity; GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; SD, standard deviation; JTTHF, Jebsen–Taylor Test of Hand Function; PEDI, Pediatric Evaluation of Disability Inventory; GMFM, Gross Motor Function Measure; 6MWT, 6-Minute Walk Test; PBS, Pediatric Balance Scale.

of a lack of translation in the parents' native language, two questionnaires (ABILOCO-Kids/ABILHAND-Kids) could not be used for two children in the comparison group. Owing to a lack of cooperation at the second assessment, the data of one child (comparison group) are missing for the JTTHF.

Usual care characteristics

Children in the comparison group received a mean of 2.8 (SD 1.3) hours per week of usual care (a mean of 82.5min physical therapy, 72min occupational therapy). This amount did not differ from the treatment group (usual care 3h [SD 1.1h] per week, including a mean of 101min physical therapy and 72min occupational therapy; p=0.678).

HABIT-ILE characteristics

Children in the treatment group received all 13 days of HABIT-ILE, representing 84.5 hours of treatment. During this period, their daily treatment logs (completed by interventionists) allowed us to quantify the amount of time children were engaged in functional and play activities. Children were engaged on average for 82.7 hours (SD 2.2h), representing 97% (range 94–100%) of the total time. This very high percentage is explained by the fact that all activities (including walking to the bathrooms, toileting, eating time, etc.) are part of the training.

For the upper extremity, this treatment consisted on average of 41% gross dexterity, 21% manipulative games, 5% card games, 2% arts and crafts, and 31% activities of daily living. For the lower extremity, 34% of the intervention was spent sitting on a ball, 21% sitting on a stool, 7% in transition situations, 1% on a balance board, 15% standing, and 18% walking/running.

Upper extremity

For the ABILHAND-Kids questionnaire (primary upper-extremity outcome), a main effect of test session and a group×test session interaction was found (Fig. 1b and Table II, p<0.001). Post-hoc tests indicated that for the HABIT-ILE group, ABILHAND-Kids values were significantly higher at the immediate posttest and follow-up than they were in the pretest. The values were also significantly higher at the follow-up than at the immediate posttest. In the comparison group, no significant difference was observed between the three assessments.

For the Pediatric Evaluation of Disability Inventory (self-care domain), a main effect of test session with a group×test session interaction was found (p=0.001). The post-hoc tests indicated that in the HABIT-ILE group, scores were significantly higher at the posttest and follow-up than they were at the pretest. In the comparison group, no significant difference was observed between the three assessments (see Fig. 1a and Table II).

The BBT and JTTHF showed a group×test session interaction, but only on the less affected hand (Fig. 1c,d, and Table II, p<0.027). The post-hoc tests indicated that in the HABIT-ILE group, more blocks were moved and faster times were observed for the BBT and JTTHF respectively at the posttest and follow-up than they were at the pretest. In the comparison group, no significant difference was observed between the three assessments for either measure. In the more affected hand, although a main effect of test session was observed for the BBT, no interaction was found in the BBT or the JTTHF (all p>0.121).

Lower extremity and postural control

For the GMFM-66 (primary lower-extremity outcome) a main effect of test session and group×test session interaction was observed (p<0.001). The post-hoc tests indicated that in the HABIT-ILE group, children's scores improved at posttest and follow-up compared with the pretest. The values were also significantly higher at the follow-up compared with the immediate posttest. In the comparison group, no significant difference was observed between the three assessments (Fig. 1e and Table III).

For the 6-Minute Walk Test, a group×test session interaction was observed (p=0.026). The post-hoc tests indicated that in the HABIT-ILE group, children walked farther at the posttest and follow-up than at the pretest (Fig. 1g and Table III). In the comparison group, no significant difference was observed between the three test sessions.

Similar effects were observed for the Pediatric Balance Scale, where a group×test session interaction was found (p=0.002). The post-hoc tests indicated that in the HABIT-ILE group, children had a better balance score at the posttest and follow-up than in the pretest. In the comparison group, no significant difference was observed between the three assessments (Fig. 1f and Table III).

The ABILOCO-Kids questionnaire showed a trend for a change in the treatment group (Friedman, p=0.072; Fig. 1h and Table III), while no significant difference was observed between the three test sessions for the comparison group (p=0.236).

Figure 1 (See next page): Improvements during the hand–arm bimanual intensive therapy including lower extremity training. Black circles, mean (whiskers, standard error) of the treatment group; grey squares, mean (whiskers, standard error) of the comparison group. TS1, testing session 1; TS2, testing session 2 after 2 weeks; TS3, testing session 3 after 3 months. (a) Pediatric Evaluation of Disability Inventory (PEDI), self-care subscale (*n*/73); (b) ABILHAND-Kids questionnaire (logits); (c) Jebsen–Taylor Test of Hand Function (JTTHF) of the less affected hand (s); (d): Box and Blocks Test of the less affected hand (*n*); (e) Gross Motor Function Measure (GMFM)-66 (with Rasch analysis) (%); (f) Pediatric Balance Scale (PBS) (%); (g) 6-Minute Walk Test (6MWT) (m); (h) ABILOCO-Kids questionnaire (logits).

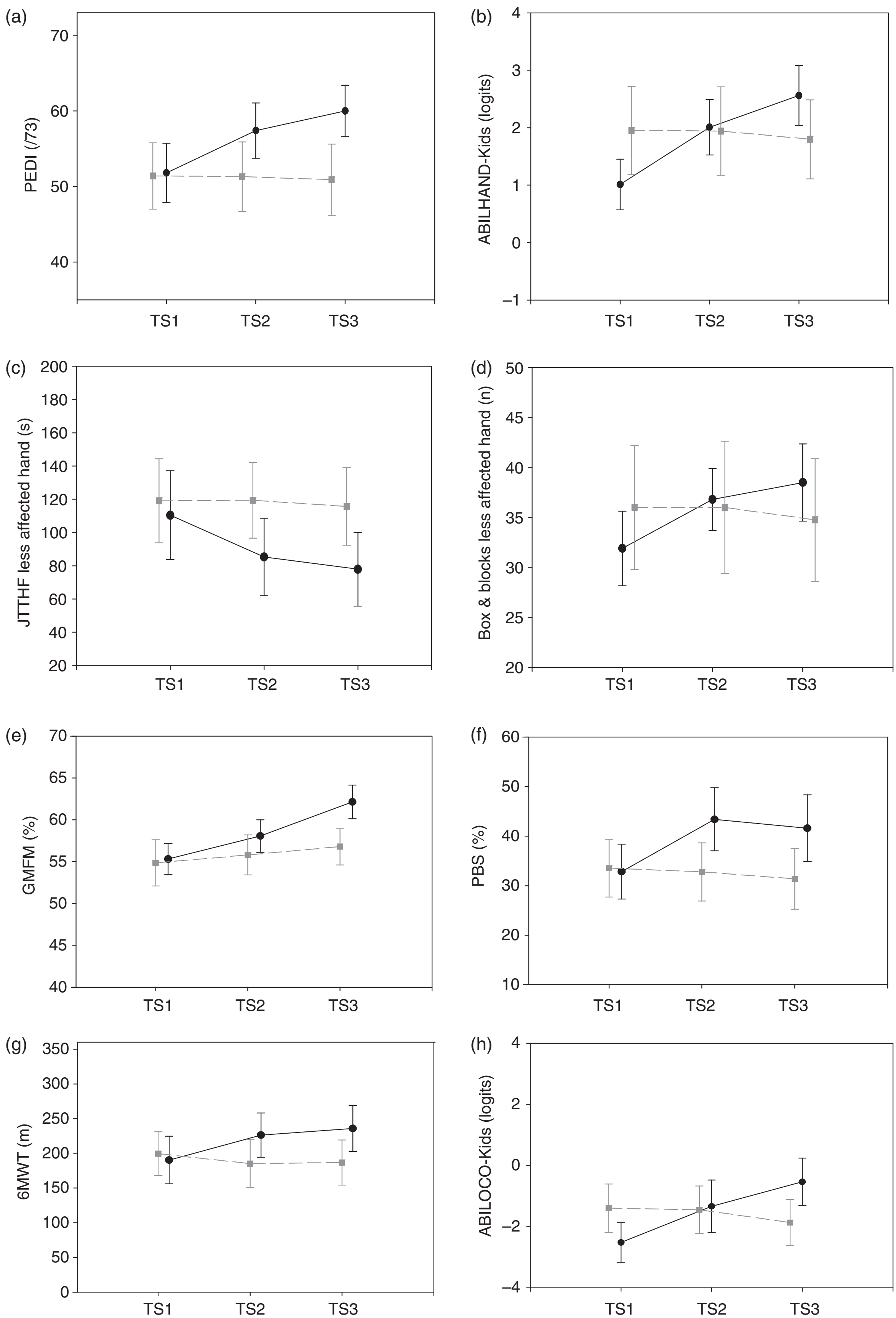
(a)
PEDI (/73)
70
60
50
40
TS1
TS2
TS3
(b)
ABILHAND-Kids (logits)
4
3
2
1
0
−1
TS1
TS2
TS3
(c)
JTTHF less affected hand (s)
200
180
160
140
120
100
80
60
40
20
TS1
TS2
TS3
(d)
Box & blocks less affected hand (n)
50
45
40
35
30
25
20
TS1
TS2
TS3
(e)
GMFM (%)
70
65
60
55
50
45
40
TS1
TS2
TS3
(f)
PBS (%)
60
50
40
30
20
10
TS1
TS2
TS3
(g)
6MWT (m)
350
300
250
200
150
100
50
0
TS1
TS2
TS3
(h)
ABILOCO-Kids (logits)
4
2
0
−2
−4
TS1
TS2
TS3

Table II: Upper-extremity changes

	TS 1, mean (SD)	TS 2, mean (SD)	TS 3, mean (SD)	Two-way RM analysis of variance, two groups×three TS: Time effect		Time×group interaction	
					p (η^2)	df; F	p (η^2)
Activity limitations							
ABILHAND-Kids, logits				df=2.15; F=7.754	p=0.002[a] (0.223)	df=2.15; F=11.053	p<0.001[a] (0.318)
HABIT-ILE group	1.0 (1.4)	2.0 (1.5)	2.6 (1.7)		TS 1≠2.3; TS 2≠3		
Comparison group	1.9 (2.2)	1.9 (2.2)	1.8 (1.9)		NS		
PEDI, n				df=2.17; F=7.173	p=0.002[a] (0.210)	df=2.17; F=8.906	p=0.001[a] (0.263)
HABIT-ILE group	52 (12.4)	57 (11.5)	60 (10.7)		TS 1≠2.3		
Comparison group	51 (14.6)	51 (15.3)	51 (15.8)		NS		
More affected hand							
Box and Blocks Test, n				df=2.17; F=6.805	p=0.003[a] (0.268)	df=2.16; F=0.546	p=0.584 (0.021)
HABIT-ILE group	25 (13.0)	28 (13.3)	28 (13.2)		TS 1≠2.3		
Comparison group	30 (16.4)	33 (16.5)	32 (16.5)		NS		
JTTHF, s				df=2.16; F=2.082	p=0.140 (0.098)	df=2.16; F=2.251	p=0.121 (0.105)
HABIT-ILE group	263 (248)	207 (201)	196 (190)				
Comparison group	145 (94)	143 (101)	144 (104)				
Less affected hand							
Box and Blocks Test, n				df=2.17; F=2.278	p=0.117 (0.094)	df=2.17; F=4.050	p=0.026[a] (0.165)
HABIT-ILE group	32 (11.8)	37 (9.8)	39 (12.2)				TS 1≠2,3
Comparison group	36 (20.6)	36 (21.7)	35 (20.4)				NS
JTTHF, s				df=2.16; F=3.410	p=0.045[a] (0.139)	df=2.18; F=4.035	p=0.027[a] (0.165)
HABIT-ILE group	110 (85)	85 (74)	78 (70)		TS 1≠2.3		
Comparison group	116 (84)	116 (84)	112 (86)		NS		

[a]Significant value. RM, repeated measure, TS, testing session; df, degree of freedom; HABIT-ILE, hand–arm bimanual intensive therapy including lower extremity; NS, not significant; PEDI, Pediatric Evaluation of Disability Inventory; JTTHF; Jebsen–Taylor Test of Hand Function.

Goal performance

For the Canadian Occupational Performance Measure (treatment group only), significantly higher values were observed at the posttest and follow-up than at the pretest, both in the performance of children and in the satisfaction of the caregivers (p<0.001, Table III).

DISCUSSION

The aim of this study was to test the efficacy of HABIT-ILE in children with bilateral CP. Children in the HABIT-ILE group demonstrated improved performance in the lower extremity compared with the non-treatment group (GMFM-66, Pediatric Balance Scale, 6-Minute Walk Test). For the upper extremity, significant improvements were observed for the HABIT-ILE group in the ABILHAND-Kids, the Pediatric Evaluation of Disability Inventory (self-care domain), the BBT, and JTTHF (less affected hand for the JTTHF). Finally, children in the HABIT-ILE group exhibited significant changes in their Canadian Occupational Performance Measure.

Amount of practice and improvements in the upper and lower extremities

Gross motor abilities, walking endurance, and upper-extremity abilities improved after HABIT-ILE in children with unilateral CP. Although the total amount of time dedicated to practice in this study was similar to that observed in children with unilateral CP (97% here vs 96% in children with unilateral CP), some modifications in the time dedicated to the different tasks/activities were observed. For the upper extremity, compared with children with unilateral CP, children with bilateral CP had more activities of gross dexterity (41% vs 27% in unilateral CP) and fewer manipulative games (21% vs 27%). For the lower extremity, less time was spent sitting on a ball (34% vs 54% in unilateral CP) and less time standing (15% vs 24%). Similar amounts of time were dedicated to walking (18% vs 20% in unilateral CP) and activities of daily living (31% vs 36%). Two adaptations were proposed for children with bilateral CP: sitting on a stool and in transition situations. Although these modifications were required, the results in children with bilateral CP were in line with those of children with unilateral CP. Improvements in the activity levels of the International Classification of Functioning, Disability and Health in both the upper and lower extremities were observed. Although previous studies have demonstrated improvements in these children, notably during goal-directed training, either in gross motor abilities (postural/locomotor[5,6]) or in the upper limb,[7] we are not aware of other treatments demonstrating concomitant changes in both upper and lower extremities in this population. All variables measured improved after intervention, except the dexterity of the more affected hand.

Table III: Lower extremity, balance, and Canadian Occupational Performance Measure (COPM)

	TS 1, mean (SD)	TS 2, mean (SD)	TS 3, mean (SD)	Two-way RM analysis of variance, two groups×three TS: Test session		Time×group interaction	
				df; *F*	Effect *p*	df; *F*	*p*
Lower extremity							
GMFM, % of logits				df=2.17; *F*=21.944	p<0.001[a] (0.368)	df=2, 17; *F*=19.609	p<0.001[a] (0.329)
HABIT-ILE group	55 (5.9)	58 (6.2)	62 (6.4)		TS1≠2, 3; TS2≠3		
Comparison group	55 (8.7)	56 (7.6)	57 (6.6)		NS		
6MWT, m				df=2.17; *F*=1.170	p=0.322 (0.050)	df=2, 17; *F*=4.043	p=0.026[a] (0.174)
HABIT-ILE group	190 (108.5)	226 (100.8)	236 (105.1)				TS1≠2, 3
Comparison group	194 (101.1)	180 (111.1)	182 (101.1)				NS
Pediatric Balance Scale				df=2.17; *F*=2.246	p=0.120 (0.080)	df=2, 17; *F*=7.781	p=0.002[a] (0.278)
HABIT-ILE group	33 (17.5)	43 (20.1)	42 (21.3)				TS1≠2, 3
Comparison group	30 (23.9)	27 (22.2)	26 (23.2)				NS
ABILOCO-Kids, logits							
HABIT-ILE group[b]	−3.2 (−3.9; −1.2)	−1 (−2.8; −0.7)	0.4 (−1.7; −0.1)	df=2; χ^2=5.263	p=0.072		
Comparison group[b]	−1.2 (−1.7; 0.3)	−1.2 (−1.7; 0.3)	−1.4 (−2.6; −0.4)	df=2; χ^2=5.158	p=0.236		
COPM							
COPM performance (%)				df=2, 13; *F*=21.293	p<0.001[a] (0.348)		
HABIT-ILE group	3.2 (0.8	7.3 (1.7	7.1 (1.6		1≠2, 3		
COPM satisfaction (%)				df=2, 13; *F*=39.132	p<0.001[a] (0.425)		
HABIT-ILE group	2.8 (0.7)	7.6 (1.7)	7.4 (1.8)		1≠2, 3		

[a]Significant value. [b]Non-parametric statistics (Friedman RM analysis of variance on ranks), with median and interquartile range.
RM, repeated measure; TS, testing session; df, degree of freedom; GMFM, Gross Motor Function Measure; HABIT-ILE, hand–arm bimanual intensive therapy including lower extremity; NS, not significant; 6MWT, 6-Minute Walk Test.

Asymmetric improvements in the upper extremities

The absence of improvement on the more affected hand was surprising. This is not in line with results observed both in HABIT[25] and HABIT-ILE[12] for children with unilateral CP, who exhibit greater dexterity improvements in the more affected hand. However, the fundamental difference is that, unlike unilateral CP, here both hands are affected to varying extents. In unilateral CP, the improvement of upper-extremity activities, notably bimanual activities, is dependent on the improvement of the more affected hand, as illustrated by the similar improvements in upper-extremity function in constraint-induced movement therapy and HABIT.[26] It might be that when both hands are affected, the crucial factor to improving activity level is not an improvement in the more affected hand (as in unilateral CP) but in the less affected one. Alternatively, it might be that the more affected hand, being frequently used to stabilize the body by resting on the table when sitting on ball or standing, does not have the same role when progressively shaping the skill progression (i.e. it is more involved in stabilization than manipulation).

Mechanisms underlying improvements

A first mechanism potentially underlying the improvements is the neuroplastic changes induced by motor learning interventions. Such changes have been demonstrated in children with unilateral CP after a 2- to 3-week period of intensive intervention, notably in constraint-induced movement therapy and bimanual training.[25,26] Interestingly, in both primary outcomes we observed an increase at follow-up regarding post-camp assessment, which was nearly as large as the immediate intervention effect. This improvement, continuing after intervention, is not in agreement with previous studies in children with unilateral CP – generally showing stable values at follow-up[12,27,28] – and might be related to the effect of the training at a muscular level. Changes in strength, induced by physical training, have previously been shown to be beneficial in improving functional abilities of children with bilateral CP.[29] Although it is known from resistance training studies that after only a few sessions some changes in muscle power may appear, caused notably by neuromuscular adaptations,[30] recent publications on strength/power training recommend 8 weeks, with three sessions per week, to maximize changes.[31] It is thus unlikely that a change in strength could solely explain the changes observed during the 13 days of camp. Thus we suggest that both strength and neuroplasticity may contribute to the changes observed.

Limitations

This first study included only 10 children in each group, most of them being in GMFCS level III. Larger samples are needed to determine more precisely the improvements in the different levels of GMFCS that can be achieved by children with bilateral CP.

Children in this study had no cognitive deficits. It is unknown whether the effects could also be observed in children with more significant cognitive deficits, leading to caution about the generalization of the results observed.

Excellent progression was shown at the follow-up at 3 months; however, because other treatments might have biased the study (e.g. botulinum neurotoxin injections or orthopedic interventions), a longer-term follow-up could not be performed. This would be required to show continued improvements and maintenance over longer periods, as well as the optimal frequency for delivering intensive interventions to these children.

In addition, we did not test trunk control, measurements of which – using tests such as the Segmental Assessment of Trunk Control[32] – would be useful for capturing potential changes in trunk control induced by the simultaneous training of the upper and lower extremities.

CONCLUSION

The findings of this study suggest that HABIT-ILE is efficacious for improving both upper- and lower-extremity function in children with bilateral CP in GMFCS levels II, III, and potentially IV, without cognitive deficits. The extent to which this intervention could be applied to children in GMFCS levels IV and V is unknown. There is also a need to investigate whether children with cognitive deficits might benefit from this approach.

ACKNOWLEDGEMENTS

This study was a pilot for a larger trial (NCT02667613). The work was supported in part by Goldman Sachs Gives and by Mindy and Mark Dehnert. YB had a research grant from the 'Fonds de la recherche clinique', cliniques universitaires Saint-Luc, Brussels, Belgium. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Description of HABIT-ILE.

REFERENCES

1. Novak I, Mcintyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013; **55**: 885–910.
2. Stanley F, Blair E, Alberman E. Cerebral Palsies: Epidemiology and Causal Pathways. Clinics in Developmental Medicine No. 151. London: Mac Keith Press, 2000.
3. Johnston TE, Watson KE, Ross SA, et al. Effects of a supported speed treadmill training exercise program on impairment and function for children with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 742–50.
4. Prosser LA, Ohlrich LB, Curatalo LA, Alter KE, Damiano DL. Feasibility and preliminary effectiveness of a novel mobility training intervention in infants and toddlers with cerebral palsy. *Dev Neurorehabil* 2012; **15**: 259–66.
5. Ketelaar M, Vermeer A, Hart H, van Petegem-van Beek E, Helders PJ. Effects of a functional therapy program on motor abilities of children with cerebral palsy. *Phys Ther* 2001; **81**: 1534–45.
6. Löwing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy – do goals make a difference? *Disabil Rehabil* 2009; **31**: 1808–16.
7. Novak I, Cusick A, Lannin N. Occupational therapy-home programmes for cerebral palsy: double-blind, randomized, controlled trial. *Pediatrics* 2009; **124**: e606–14.
8. Bleyenheuft Y, Gordon AM. Hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) for children with cerebral palsy. *Phys Occup Ther Pediatr* 2014; **34**: 390–403.
9. Charles J, Gordon AM. Development of hand–arm bimanual intensive therapy (HABIT) for improving bimanual coordination in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2006; **48**: 931–36.
10. Schmidt RA, Lee TD. Motor Control and Learning: A Behavioral Emphasis. 4th edn. Champaign, IL: Human Kinetics, 2005.
11. Nudo RJ. Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. *J Rehabil Med* 2003; **41**: 7–10.
12. Bleyenheuft Y, Arnould C, Brandao MB, Bleyenheuft C, Gordon AM. Hand and arm bimanual intensive therapy including lower extremity (HABIT-ILE) in children with unilateral spastic cerebral palsy: a randomized trial. *Neurorehabil Neural Repair* 2015; **29**: 645–57.
13. 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**: 549–54.
14. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
15. Waldron AM, Anton BS. Effects of exercise on dexterity. *Percept Mot Skills* 1995; **80**: 883–89.
16. Avery LM, Russell DJ, Raina PS, Walter SD, Rosenbaum PL. Rasch analysis of the Gross Motor Function Measure: validating the assumptions of the Rasch model to create an interval-level measure. *Arch Phys Med Rehabil* 2003; **84**: 697–705.
17. Arnould C, Penta M, Renders A, Thonnard JL. ABILHAND-Kids: a measure of manual ability in children with cerebral palsy. *Neurology* 2004; **63**: 1045–52.
18. Haley SM, Coster WJ, Dumas HM, et al. Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer-adaptive tests (PEDI-CAT). *Dev Med Child Neurol* 2011; **53**: 1100–06.
19. Mathiowetz V, Vollaand G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. *Am J Occup Ther* 1985; **39**: 386–91.
20. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch Phys Med Rehabil* 1969; **50**: 311–19.
21. Caty GD, Arnould C, Thonnard JL, Lejeune TM. ABILOCO-Kids: a Rasch-built 10-item questionnaire for assessing loco-motion ability in children with cerebral palsy. *J Rehabil Med* 2008; **40**: 823–30.
22. Chen CL, Shen IH, Chen CY, Wu CY, Liu WY, Chung CY. Validity, responsiveness, minimal detectable change, and minimal clinically important change of Pediatric Balance Scale in children with cerebral palsy. *Res Dev Disabil* 2013; **34**: 916–22.
23. Maher CA, Williams MT, Olds TS. The Six-Minute Walk Test for children with cerebral palsy. *Int J Rehabil Res* 2008; **31**: 185–88.
24. Verkerk GJ, Wolf MJ, Louwers AM, Meester-Delver A, Nollet F. The reproducibility and validity of the Canadian Occupational Performance Measure in parents of children with disabilities. *Clin Rehabil* 2006; **20**: 980–88.
25. Juenger H, Linder-Lucht M, Walther M, Berweck S, Mall V, Staudt M. Cortical neuromodulation by constraint-induced movement therapy in congenital hemiparesis: an FMRI study. *Neuropediatrics* 2007; **38**: 130–36.
26. Bleyenheuft Y, Dricot L, Gilis N, et al. Capturing neuroplastic changes after bimanual intensive rehabilitation

in children with unilateral spastic cerebral palsy: a combined DTI, TMS and fMRI pilot study. *Res Dev Disabil* 2015; **43–44**: 136–49.

27. Gordon AM, Charles J, Schneider JA, Chinnan A. Efficacy of a hand-arm bimanual intensive therapy (HABIT) for children with hemiplegic cerebral palsy: a randomized control trial. *Dev Med Child Neurol* 2007; **49**: 830–38.

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

29. Dodd KJ, Taylor NF, Damiano DL. A systematic review of the effectiveness of strength-training programs for people with cerebral palsy. *Arch Phys Med Rehabil* 2002; **83**: 1157–64.

30. Behringer M, Vom Heede A, Yue Z, Mester J. Effects of resistance training in children and adolescents: a meta-analysis. *Pediatrics* 2010; **126**: e1199–210.

31. Moreau NG, Holthaus K, Marlow N. Differential adaptations of muscle architecture to high-velocity versus traditional strength training in cerebral palsy. *Neurorehabil Neural Repair* 2013; **27**: 325–34.

32. Butler PB, Saavedra S, Sofranac M, Jarvis SE, Woollacott MH. Refinement, reliability, and validity of the segmental assessment of trunk control. *Pediatr Phys Ther* 2010; **22**: 246–57.