Constraint-Induced Movement Therapy for Cerebral Palsy: A Randomized Trial

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abstract

OBJECTIVES: With the Children with Hemiparesis Arm and Hand Movement Project (CHAMP) multisite factorial randomized controlled trial, we compared 2 doses and 2 constraint types of constraint-induced movement therapy (CIMT) to usual customary treatment (UCT).

METHODS: CHAMP randomly assigned 118 2- to 8-year-olds with hemiparetic cerebral palsy to one of 5 treatments with assessments at baseline, end of treatment, and 6 months posttreatment. Primary blinded outcomes were the assisting hand assessment; Peabody Motor Development Scales, Second Edition, Visual Motor Integration; and Quality of Upper Extremity Skills Test Dissociated Movement. Parents rated functioning on the Pediatric Evaluation of Disabilities Inventory-Computer Adaptive Test Daily Activities and Child Motor Activity Log How Often scale. Analyses were focused on blinded and parent-report outcomes and rank-order gains across all measures.

RESULTS: Findings varied in statistical significance when analyzing individual blinded outcomes. parent reports, and rank-order gains. Consistently, high-dose CIMT, regardless of constraint type, produced a pattern of greatest short- and long-term gains (1.7% probability of occurring by chance alone) and significant gains on visual motor integration and dissociated movement at 6 months. O'Brien's rank-order analyses revealed high-dose CIMT produced significantly greater improvement than a moderate dose or UCT. All CIMT groups improved significantly more in parent-reported functioning, compared with that of UCT. Children with UCT also revealed objective gains (eg, 48% exceeded the smallest-detectable assisting hand assessment change, compared with 71% high-dose CIMT at the end of treatment).

CONCLUSIONS: CHAMP provides novel albeit complex findings: although most individual blinded outcomes fell below statistical significance for group differences, high-dose CIMT consistently produced the largest improvements at both time points. An unexpected finding concerns shifts in UCT toward higher dosages, with improved outcomes compared with previous reports.

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Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available one year after publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Sharon Ramey (slramey@vt.edu).

This trial has been registered at www.clinicaltrials.gov (identifier NCT01895660).

Dr Ramey conceptualized and designed the study, helped develop and refine data collection tools, provided guidance for data analysis and presentation strategies, wrote

WHAT'S KNOWN ON THIS SUBJECT: Constraint-induced movement therapy (CIMT) is widely endorsed scientifically, despite large variations in treatments, particularly in dosage and constraint type. It is critically important to assess whether lower CIMT doses and a splint rather than a cast can produce gains above usual customary treatment (UCT).

WHAT THIS STUDY ADDS: High-dose CIMT with a splint or cast produced a pattern of greater gains than that of UCT or a moderate dose at both posttreatment assessments (significant for rank-order multiple endpoints). Unexpectedly, UCT children displayed objective gains but not parent-reported improvement.

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The Centers for Disease Control and Prevention estimate that cerebral palsy affects 1.5% to 4.0% of US livebirths[1,2]; ~40% will develop hemiparesis.[3] For children with hemiparetic cerebral palsy (HCP), constraint-induced movement therapy (CIMT) is consistently designated highly efficacious to improve arm-and-hand use.[4,5] CIMT treatment protocols, however, vary widely in both dosage and constraint type, with uncertainty about the effects of these variations.[6]

CIMT involves a high therapy dosage (eg, ≥3-hour sessions, 5 days per week, and ≥2 weeks), constraint of the nonhemiparetic upper extremity (UE), and operant conditioning and motor learning techniques to elicit and shape new skills.[7,8] High CIMT doses are costly, however, and may be stressful. Theories of experience-driven neuroplasticity invoke a dose-response principle that higher doses induce larger brain and behavior changes.[9–11] Concerning constraint, a full-time cast (never applied without administering active treatment) encourages using the hemiparetic UE but limits practice of bimanual skills. Alternatively, part-time constraint only during therapy sessions promotes bilateral activities practice outside sessions but may insufficiently increase use of the hemiparetic side. In *Pediatrics*, results were published from the first randomized controlled trial (RCT) of CIMT[12] with 6-hour sessions for 20 days and novel use of a cast. Children showed large-effect size gains in acquiring new skills and using them in typical situations. Follow-up 6 months later revealed high maintenance of benefits.[13]

Subsequently, in many RCTs, researchers reported benefits using lower dosages and a splint or mitt or glove part-time.[4,5] Unfortunately, cross-study comparisons cannot identify which treatment components produce better outcomes because of varied patient populations and measured outcomes. Thus, we conducted a factorial RCT (the Children with Hemiparesis Arm and Hand Movement Project [CHAMP])14 to systematically compare specific combinations of dose and constraint. We did not know if the lower CIMT dose would produce improvements greater than usual care. Concerning constraint, we hypothesized both constraint types tested could be efficacious, each offering advantages and limitations.

METHODS

Recruitment and Patient Population

CHAMP's 3 sites (Charlottesville, VA; Columbus, OH; Roanoke, VA) recruited (January 2015 to December 2018; registration: NCT01895660) from clinics, programs, and Web sites, yielding 118 2-to-8 year olds with HCP, good health, and ability to follow directions. Exclusion criteria were uncontrolled seizures and/or receiving CIMT or botulinum toxin in the previous 6 months. CHAMP's protocol was institutional review board–approved and monitored by an external data safety and monitoring committee.

Study Design

CHAMP was a 2 × 2 factorial RCT with all groups assessed at baseline, end of treatment, and 6-months posttreatment. In the Consolidated Standards of Reporting Trials flow diagram (Fig 1), the 4 CIMT groups are identified: high dose with cast, high dose with splint, moderate dose with cast, and moderate dose with splint.

Description of CIMT Interventions

CHAMP implemented the CIMT published protocol named ACQUIRE,[15,16] on the basis of efficacy[12,13,17,18] and clinical-practice effectiveness.[16,19] A previous RCT revealed comparable benefits from 6-hour and 3-hour sessions, 5 days per week over 4 weeks.[17,18] Accordingly, we tested the 3-hour dose (60 total hours) and a lower dose of 2.5-hour sessions, 3 days per week over 4 weeks (30 hours). This lower dose is similar to forms of "modified CIMT."[14] CHAMP also compares 2 constraints: a lightweight full-arm cast worn continuously and a part-arm splint worn just during treatment sessions (see protocol article for details[14]). Even with the cast, children can use their nonhemiparetic UE in bilateral activities (eg, crawling, holding a large ball).

Occupational or physical therapists received intensive instruction in ACQUIRE, particularly operant conditioning techniques to elicit and shape new UE skills. ACQUIRE sets individualized treatment goals with parents and emphasizes enjoyable play and self-help activities. Treatment occurs in home or homelike settings to promote generalization and maintenance of new skills. Parents participate in sessions weekly. Constraint is removed the last 3 days to promote bimanual skills. Finally, with a transfer package, posttreatment progress is encouraged.

We documented treatment fidelity via weekly video-recordings and daily treatment logs, applying standardized criteria.[14] Therapists received feedback and additional training if needed.

Outcome Measures

No single, widely used assessment tool adequately captures the breadth of the bilateral and unilateral skills and functional outcomes ACQUIRE targets. Accordingly, we selected 3 primary blinded outcomes based on their distinctive domain relevance, psychometric properties, and sensitivity to change: (1) the

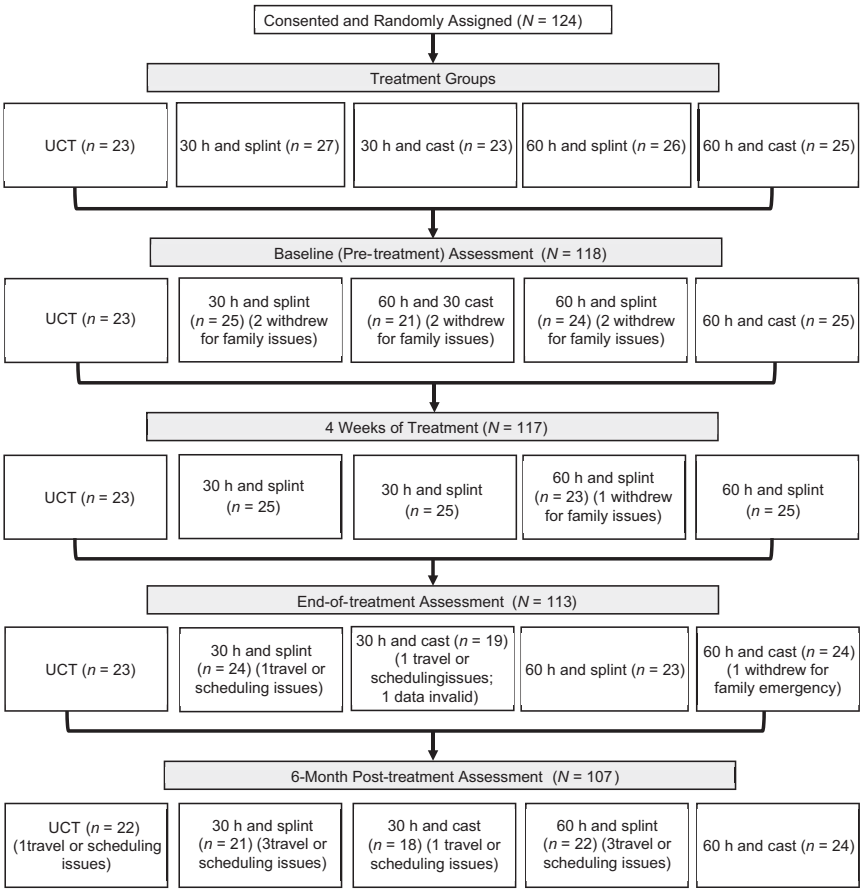

FIGURE 1
Consolidated Standards of Reporting Trials diagram for CHAMP 2 × 2 factorial RCT of variations in CIMT dose and constraint type.

Assisting Hand Assessment (AHA),[20–24] which rates use of the hemiparetic UE as a "helper" in bimanual play activities; (2) the modified Peabody Developmental Motor Scales, Second Edition, (PDMS-2)[25,26] Visual Motor Integration (VMI) subtest with 72 items about eye-hand coordination (eg, reaching and grasping objects, building blocks, and copying line). Modification involved administering items separately for each UE, yielding an affected side raw-score sum. This subtest avoids floor and ceiling problems; has excellent test-retest (0.90) and interrater (0.98) reliability and high Cronbach's coefficient α (0.95); and works well with motor-delayed children >6 years old[26,27]; and (3) the Quality of Upper Extremity Skills Test (QUEST)[28,29] Dissociated Movement (Affected Side) subtest that measures UE use dissociated from the body trunk. All have been used in CIMT research.

We further identified 2 primary parent-reported outcomes: following Enhancing the Quality and Transparency of Health Research guidelines for patient and proxy–reported outcomes[30,31]: (1) the How Often scale of the Child Motor Activity Log (CMAL), a 19-item tool adapted from the Pediatric Motor Activity Log,[12–15] which reveals 17 of 19 items are correctly ordered (see Supplemental Materials; parents rate the frequency of use of the hemiparetic UE in common play and self-help activities) and (2) the Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDI-CAT)[32,33] Daily Activities scale, a widely used, validated scale about eating and mealtime, getting dressed, hygiene, and home tasks. Parents are well-qualified to report these patient-valued functional outcomes.

Two secondary outcomes are the QUEST Grasp[28,29] and the CMAL How Well scale (highly correlated with the How Often scale). We excluded the PDMS-2 Object Manipulation subtest about using balls because many items are lower extremity only and unrelated to treatment goals. Finally, parents

completed the Perceived Stress Scale[34] and reported about their child's adjustment to treatment.

Randomization

Randomization involved site stratification. Group assignment had equal probability using a random permutated block design with randomly chosen block sizes of 5 and 10. The study statistician (M.C.) created a computer-generated randomization list, given only to the central study coordinator who revealed assignment to sites after consenting. Local site blinding involved no contact between staff who consented, scheduled, and treated and those who conducted blinded assessments.

Sample Size

Based on AHA logit scores from a previous RCT,[17] we sought 27 per group, projecting 10% attrition for a final group size of 24. This results in the F-test having 80% power, with a 5% significance level for a main effect size of 0.58 and interaction size effect of 1.18.

Data Analysis Strategy

In analyzing continuous-variable outcomes for intention-to-treat participants, we controlled for each child's baseline and used repeated-measures analyses of covariance (ANCOVAs), with an unstructured covariance matrix applying Bonferroni corrections for multiple comparisons. For the binary AHA outcome of $\geq$5 logit points (a minimally detectable difference), we used logistic regression. After reviewing obtained results, we identified 2 exploratory statistical methods to estimate the significance of the pattern of greatest improvement occurring among children who received one of the high-dose CIMT treatments. First, we applied a permutation test to answer the following: what is the probability under the null hypothesis that the mean change among groups at each assessment is the same for all outcomes that any 2 groups would have the greatest change on 10 outcomes (5 primary outcomes at both posttreatment assessments)?[35] (see Supplemental Materials). Second, we used the O'Brien[36] method for exploring group gain differences on all 7 outcomes. With the O'Brien method, one quantifies an individual child's multidomain profile of gains on identified outcomes, equally weighted. This helps overcome the challenge of no adequate single outcome.[36–38] O'Brien creates a score using each child's rank-order in the study population from each outcome ranking. Because this requires data for all outcomes, we applied multiple imputation, creating 250 completed data sets in which participants had observed or imputed values for all outcomes (see Supplemental Materials).[39,40] Multiple imputation values made up the data set: individual gain scores on each outcome were assigned rank-orders from 1 (lowest change) to 118 (highest) and then averaged, yielding a mean rank-order score per child.

RESULTS

Table 1 reveals demographic and clinical characteristics. Some group variation in age, Manual Ability Classification System (MACS)[41–43] or Mini-MACS,[44] Gross Motor Functional Classification System (GMFCS),[45] and previous CIMT appeared; adjustments by any or all of these did not change any conclusions. At baseline, groups received highly comparable weekly means of 4.5 hours usual customary treatment (UCT) (SD = 4.0), the sum of occupational, physical, and speech and language therapy. UCT doses varied widely: 11% had no weekly treatment, whereas 25% had >7 hours per week. Parent-reported stress levels were below national norms. Table 1 also reveals group mean baseline scores for primary and secondary outcomes.

Treatment Compliance and Adverse Events:

CIMT groups had >95% compliance with the intended dose; 100% correctly used the constraint. One child stopped treatment because of a family emergency. Four adverse events occurred; none were treatment-related. At treatment end, only 2 groups met the originally intended cell size of 24; only 1 did 6 months later. Overall, the final sample was 94% (treatment end) and 89% (6 months posttreatment) of the planned 120.

In Tables 2 and 3, we present posttreatment values for all outcomes. We encountered higher-than-predicted variances within groups; specifically, we estimated a residual SD of 5.78 but encountered 8.10, ~30% greater. This resulted in repeated-measures ANCOVAs that likely were underpowered to detect true group differences. We nonetheless fully present analytic results and later discuss study limits. We also applied statistical approaches better-suited for smaller sample sizes and considering multiple outcomes, (eg, O'Brien,36 Ramchandani et al,[37] and Ristl et al38) as described above.

Across all primary outcomes and times (10 occasions), the largest gains occurred in one of the High-dose CIMT groups. The permutation test[35] revealed the likelihood of this occurring for any 2 groups by chance was $P = .017$; it was even less likely ($P = .006$) for 2 prespecified groups, such as high-dose CIMT. At the end of treatment, AHA improvement $\geq$5 logit points appeared in all groups, ranging from just <50% in UCT to 71% for high-dose CIMT. At 6 months posttreatment, both splint groups revealed declined percentages,

TABLE 1 Descriptive Characteristics and Baseline (Pretreatment) Scores for 5 Treatment Groups

	UCT (n = 23)	30 h and Splint (n = 25)	30 h and Cast (n = 21)	60 h and Splint (n = 24)	60 h and Cast (n = 25)	Total Sample (N = 118)
Demographic, clinical, and previous treatment variables[a]						
Sex, *n* (%)						
Male	8 (35)	12 (48)	8 (38)	10 (42)	6 (24)	44 (37)
Female	15 (65)	13 (52)	13 (62)	14 (58)	19 (76)	74 (63)
Race, *n* (%)						
White	20 (87)	19 (76)	14 (67)	21 (88)	18 (72)	92 (78)
Black or African-American	1 (4)	2 (8)	4 (19)	1 (4)	3 (12)	11 (9)
Asian American	1 (4)	0 (0)	2 (10)	0 (0)	1 (4)	4 (3)
Multiracial	1 (4)	2 (8)	1 (5)	1 (4)	2 (8)	7 (6)
Ethnicity, *n* (%)						
Hispanic	0 (0)	3 (14)	0 (0)	1 (4)	1 (5)	5 (4)
Age, mean (SD), y	4.5 (2.1)	4.4 (2.1)	5.3 (2.5)	4.6 (2.5)	3.4 (1.2)	4.4 (2.1)
MACS or Mini-MACS,[38–41] *n* (%)	13 (57)	9 (36)	15 (71)	13 (54)	15 (60)	65 (55)
MACS III	10 (43)	13 (52)	5 (24)	5 (21)	10 (40)	43 (36)
MACS IV	0 (0)	3 (12)	1 (5)	6 (25)	0 (0)	10 (85)
GMFCS,[42] *n* (%)						
GMFCS I	14 (61)	11 (44)	11 (52)	11 (46)	11 (44)	58 (49)
GMFCS II	9 (39)	11 (44)	8 (38)	13 (54)	13 (52)	54 (46)
GMFCS III	0 (0)	2 (8)	2 (10)	0 (0)	1 (4)	5 (4)
GMFCS IV	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	1(<1)
Previous CIMT, yes, *n* (%)	9 (39)	11 (44)	7 (33)	10 (42)	11 (44)	48 (40)
Affected UE side, *n* (%)						
Left	14 (61)	11 (44)	7 (33)	8 (33)	13 (52)	53 (45)
Right	9 (39)	14 (56)	14 (67)	16 (67)	12 (48)	65 (55)
Parent stress mean (SD)	30.1 (7.1)	31.9 (6.2)	33.3 (10.3)	34.1 (7.6)	32.0 (7.5)	32.3 (7.7)
Hours per wk of therapy, pretreatment, mean (SD)	4.2 (4.7)	4.4 (3.7)	4.9 (3.6)	4.4 (4.8)	4.7 (3.7)	4.5 (4.1)
Baseline means on primary outcomes						
Blinded objective outcomes						
AHA logit, mean (SD)	43.5 (20.0)	42.9 (22.3)	46.9 (22.3)	40.8 (21.9)	42.0 (26.9)	43.2 (22.7)
Peabody VMI (affected side), mean (SD)	33.1 (24.1)	39.6 (24.2)	44.8 (20.3)	33.0 (24.2)	31.7 (21.0)	36.4 (22.8)
QUEST DM (Affected side), mean (SD)	12.0 (6.7)	12.8 (7.3)	15.3 (7.0)	11.0 (6.7)	12.6 (7.0)	12.7 (6.9)
Parent-Reported Outcomes						
CMAL how often, mean (SD)	2.3 (1.4)	2.0 (1.2)	2.1 (1.1)	1.9 (0.9)	1.7 (1.0)	2 (1.12)
PEDI-CAT Daily Activities, Mean (SD)	50.2 (2.8)	50.1 (3.3)	51.2 (2.2)	50.3 (3.6)	49.3 (2.6)	50.2 (2.9)

[a] Frequencies may not add to group totals because of missing values.

whereas CIMT plus cast and UCT did not. AHA gain scores provided a similar result: High-dose CIMT with cast displayed the highest gains of 7.0 (SE: 2.0) and 8.3 (SE: 2.0) units at the end of treatment and 6-months posttreatment, respectively, whereas the lowest gains were for UCT (5.5 [SE: 1.9]) at the end of treatment and for high dose with splint (4.4 [SE: 2.0]) 6 months posttreatment. For PDMS-2 VMI, high-dose groups had a mean gain of 5.3 (SE: 2.4) and 13.4 (SE: 3.3) end of treatment and 6-months posttreatment respectively, more than that of UCT notably at 6-months. Moderate-dose groups and UCT had comparable and low gains. For QUEST DM, the largest mean group gain appeared 6-months posttreatment (3.1 points; SE: 0.8) for high-dose CIMT with cast, more than double the UCT gain of 1.4 (SE: 0.9).

In Tables 4 and 5, we present results of statistical analyses contrasting each dose and constraint component to UCT. For the planned AHA outcome, the largest difference was high-dose versus UCT (mean difference [MD] = 23.7%; 95% confidence interval [CI] −1.6% to 49.1%) at end of treatment. For VMI gains, the largest difference obtained was for high-dose 6-months posttreatment (MD = 6.7; 95% CI −0.8 to 14.2). For DM, the largest group contrast also was high-dose 6-months posttreatment (MD = 1.4; 95% CI −0.6 to 3.5). In Fig 2, we graph the primary blinded outcomes.

In Fig 3, we display primary parent-reported outcomes. For the CMAL How Often scale, all CIMT groups revealed significant and large gains at both times, whereas UCT revealed low or no gains. The highest gains occurred for high dose with cast at both times. For PEDI-CAT Daily Activities at the end of treatment, all

TABLE 2 Primary Outcomes for 5 CHAMP Groups at the End of Treatment and 6-Months Posttreatment: Changes From Baseline by Treatment Groups

	UCT	30 h and Splint	30 h and Cast	60 h and Splint	60 h and Cast
AHA					
Percentage with ≥5 logit units, % (SE)[a]					
End of treatment	48 (10.9)	57 (10.3)	60 (12.6)	73 (9.5)[b]	70 (10.2)
6-mo posttreatment	53 (11.5)	50 (11.2)	65 (11.6)	47 (12.1)	71 (11.1)[b]
Mean logit unit gains (SE)[c]					
End of treatment	5.5 (1.9)	6.8 (1.9)	6.5 (2.3)	5.7 (2.0)	7.0 (2.0)[b]
6-mo posttreatment	6.4 (1.9)	6.3 (1.8)	7.4 (2.0)	4.4 (2.0)	8.3 (2.0)[b]
PDMS-2 VMI, mean point gain (SE)					
End of treatment	3.5 (2.3)	1.2 (2.3)	2.4 (2.6)	6.2 (2.4)[b]	4.2 (2.4)
6-mo posttreatment	6.8 (3.0)	3.4 (3.5)	1.6 (3.4)	15.6 (3.2)[b]	11.3 (3.3)
QUEST Dissociated Movement, mean point gains (SE)					
End of treatment	1.4 (0.9)	1.5 (0.9)	−1.0 (1.0)	2.1 (0.9)[b]	1.4 (0.9)
6-mo posttreatment	1.4 (0.9)	1.6 (0.8)	0.7 (0.9)	2.5 (0.8)	3.1 (0.8)[b]
CMAL How Often (parent-reported)					
End of treatment	−0.1 (0.2)	0.7 (0.2)	0.9 (0.2)	0.9 (0.2)	1.3 (0.2)[b]
6-mo posttreatment	−0.1 (0.2)	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	0.7 (0.2)[b]
PEDI-CAT Daily Activities (parent-reported)					
End of treatment	0.0 (0.3)	1.2 (0.3)	1.7 (0.4)	2.0 (0.3)[b]	0.9 (0.3)
6-mo posttreatment	1.4 (0.5)	2.1 (0.5)	1.1 (0.5)	3.1 (0.4)[b]	2.1 (0.4)

[a] Permutation test[35] results (see Supplemental Materials for details about computation) indicate the probability of 2 groups having all top scores for 5 measures on 2 occasions is 0.017 and the probability for all 10 outcomes coming from a pair of predesignated groups is 0.006.
[b] Group with greatest change.
[c] The binary AHA outcome of ≥5 logit points was designated as a primary outcome in the original study design,[14] reflecting a change above the minimally detectable threshold as recommended by the test authors. The actual AHA logit unit gains are shown just below the percentages for the binary outcome. Note: for computing the permutation test, only the actual logit unit gains were considered.

CIMT groups improved, although high-dose with cast improved the least and UCT did not improve. By 6 months posttreatment, however, UCT did reveal some gains, and 3 of the 4 CIMT groups revealed additional improvement. As Table 2 reveals, tests contrasting each treatment component to UCT were statistically significant for the How Often scale at both times. For the Daily Activities scale, the high-dose and cast contrasts but not moderate dose or splint were significantly more than UCT at both times.

Parent stress (Table 3) declined modestly over time and comparably across groups. Parents were >95% favorable about their child's excellent adjustment to full-time cast within 2 days and reported both doses highly acceptable.

TABLE 3 Secondary Outcomes for 5 CHAMP Groups at the End of Treatment and 6-Months Posttreatment: Changes From Baseline by Treatment Groups

	UCT	30 h and Splint	30 h and Cast	60 h and Splint	60 h and Cast
QUEST Grasp, mean point gain (SE)					
End of treatment	0.1 (0.4)	0.5 (0.4)	0.0 (0.5)	0.3 (0.4)	0.6 (0.4)
6-mo posttreatment	0.9 (0.5)	1.0 (0.5)	0.3 (0.6)	0.0 (0.5)	0.8 (0.5)
CMAL How Well, mean point gain (SE)					
End of treatment	0.1 (0.2)	0.9 (0.2)	0.9 (0.2)	1.1 (0.2)	1.1 (0.2)
6-mo posttreatment	0.2 (0.2)	0.8 (0.2)	0.5 (0.2)	0.9 (0.2)	0.8 (0.2)
Parent Perceived Social Stress since the baseline, descriptive measure only, mean point change (SE)					
End of treatment	−0.5 (1.7)	−1.6 (1.5)	−3.4 (1.9)	−1.8 (1.6)	−1.7 (1.5)
6-mo posttreatment	−1.5 (1.5)	−1.9 (1.4)	0.6 (1.6)	−1.9 (1.4)	−1.5 (1.3)

TABLE 4 Primary and Secondary Outcomes for 5 CHAMP Groups at the End of Treatment and 6-Months Posttreatment: Primary Outcomes (Selected Contrasts Between Manipulated Treatment Components and UCT)

	High-Dose CIMT Minus UCT			Moderate-Dose CIMT Minus UCT			Cast CIMT Minus UCT			Splint CIMT Minus UCT		
	MD (SE) or %	Lower 95% CI	Upper 95% CI	MD (SE) or %	Lower 95% CI	Upper 95% CI	MD (SE) or %	Lower 95% CI	Upper 95% CI	MD (SE) or %	Lower 95% CI	Upper 95% CI
AHA ≥5 logit points, %												
End of treatment	23.7	−1.6	49.1	10.6	−16.1	33.3	17.4	−9.3	44.0	17.0	−8.4	42.4
6-mo posttreatment	6.2	−21.4	33.8	4.7	−22.7	32.2	15.0	−12.4	42.4	−4.1	−31.8	23.6
PDMS-2 VMI												
End of treatment	1.6 (2.8)	−4.0	7.3	−1.7 (2.9)	−7.5	4.0	0.2 (2.8)	−5.4	5.8	−0.2 (2.9)	−6.0	5.5
6-mo posttreatment	6.7 (3.8)	−0.8	14.2	−4.3 (3.9)	−12.0	3.4	2.7 (3.8)	−4.8	10.3	−0.3 (3.8)	−7.9	7.3
QUEST Dissociated Movement												
End of treatment	0.3 (1.1)	−1.8	2.5	−1.2 (1.1)	−3.4	1.0	0.4 (1.1)	−1.8	2.5	−1.2 (1.1)	−3.4	1.0
6-mo posttreatment	1.4 (1.0)	−0.6	3.5	−0.3 (1.1)	−2.4	1.8	0.7 (1.0)	−1.4	2.7	0.5 (1.0)	−1.6	2.6
CMAL How Often												
End of treatment	1.2 (0.2)	0.7	1.7	0.9 (0.2)	0.4	1.4	0.9 (0.2)	0.5	1.4	1.2 (0.2)	0.7	1.7
6-mo posttreatment	0.8 (0.3)	0.3	1.3	0.7 (0.3)	0.1	1.2	0.7 (0.3)	0.2	1.2	0.7 (0.3)	0.2	1.2
PEDI-CAT Ddily Activities												
End of treatment	1.5 (0.4)	0.7	2.3	1.5 (0.4)	0.6	2.3	1.6 (0.4)	0.8	2.5	1.3 (0.4)	0.5	2.2
6-mo posttreatment	1.3 (0.6)	0.1	2.4	0.2 (0.6)	−0.9	1.4	1.2 (0.6)	0.1	2.4	0.3 (0.6)	−0.9	1.4

—, not applicable.

Rank-Order Multiple End Point Results

Figure 4 reveals boxplots for the 5 groups in terms of their rank-ordered gains. At both assessment times, a similar pattern appeared with the smallest mean rank-order gains for UCT, intermediate for moderate-dose CIMT groups, and largest for high-dose CIMT groups. Figure 4 also reveals the CIs for planned contrasts, indicating the high-dose groups and splint groups had children who ranked statistically significantly more than UCT at both times, whereas moderate dose and cast were significantly more than UCT only at the end of treatment.

DISCUSSION

Results of CHAMP data analyses are complex, supporting some predicted and some unexpected findings. CHAMP also reveals challenges likely to be encountered with highly heterogeneous pediatric patient populations.

First, the important finding that UCT produced objective benefits at end of treatment and 6-months later on blinded outcomes was unanticipated. This differs from previous RCT findings of either no or small gains for UCT children.[4,46] UCT doses in CHAMP, however, were relatively high with a mean of 4 to 5 hours per week, more than double the 2.1 hours per week reported in the first pediatric CIMT trial[12] and later studies.[2,17] In fact, some children received UCT dosages similar to the tested moderate-dose CIMT. This suggests that pediatric rehabilitation dosage (at least in these CHAMP sites) has increased, likely because of the ascribed dosage importance in CIMT and other efficacious interventions.[47–49] We do not know, however, if CHAMP sites reflect nationwide practices. In addition, 40% of CHAMP participants previously

TABLE 5 Primary and Secondary Outcomes for 5 CHAMP Groups at End of Treatment and 6-Months Posttreatment: Secondary Outcomes

	High-Dose CIMT Minus UCT			Moderate-Dose CIMT Minus UCT			Cast CIMT Minus UCT			Splint CIMT Minus UCT		
	MD (SE)	Lower 95% CI	Upper 95% CI	MD (SE)	Lower 95% CI	Upper 95% CI	MD (SE)	Lower 95% CI	Upper 95% CI	MD (SE)	Lower 95% CI	Upper 95% CI
QUEST Grasp												
End of treatment	0.4 (0.5)	−0.7	1.4	0.1 (0.5)	−1.0	1.2	0.3 (0.5)	−0.8	1.3	0.2 (0.5)	−0.9	1.3
6-mo posttreatment	−0.5 (0.6)	−1.8	0.7	−0.2 (0.7)	−1.5	1.1	−0.4 (0.6)	−1.7	0.9	−0.4 (0.7)	−1.7	0.9
CMAL How Well												
End of treatment	1.0 (0.2)	0.5	1.4	0.8 (0.2)	0.3	1.3	0.8 (0.2)	0.4	1.3	0.9 (0.2)	0.4	1.4
6-mo posttreatment	0.7 (0.2)	0.2	1.2	0.5 (0.3)	0.0	1.0	0.5 (0.3)	0.0	1.0	0.7 (0.3)	0.2	1.2

received CIMT, which other CIMT trials considered an exclusionary criterion. Future CHAMP analyses need to explore whether previous CIMT, perhaps combined with other child and family variables, moderates subsequent CIMT effects. For example, parents whose children received previous CIMT may subsequently have sought higher-than-usual doses of therapy and increased their expectations for their children's improvement. This unanticipated UCT finding highlights the importance of including a UCT group, in contradiction to the trend since 2010 revealing a UCT control was excluded in more than one-third of CIMT clinical trials.[47]

End-of-treatment blinded outcomes indicate all groups displayed gains, although the pattern of the largest gains occurred among children in 1 of the 2 high-dose groups, extremely unlikely because of chance. Because children's gain in moderate-dose groups were similar to that of UCT, we did not formally compare moderate- to high-dose CIMT in this article. In contrast, for parent-reported outcomes, children in all CIMT groups revealed significantly greater improvement in how often as well as how well they used their hemiparetic UE in typical activities. Notably, parents whose children received UCT reported almost no functional or real-world improvements in their children's UE use.

These somewhat complex results reflect mostly differences in statistical significance achieved with different statistical tests. Both the permutation test and the O'Brien[36] analysis of rank-order scores on all 7 outcomes affirm statistically significant benefits of high-dose CIMT. For the O'Brien[36] analysis, we weighted the 7 outcomes equally because we had no empirical basis for assigning different values. Perhaps a weighted-rank order method that adjusts for treatment goals and baseline performance would be even better. Nonetheless, this equal-weight approach supports the conclusion that high-dose CIMT, regardless of constraint type, produces many more improvements than the lower CIMT dose or UCT. In addition, these significant benefits appear at the end of treatment and endure at least 6 months. (Future reports will explore longer-term outcomes at 12 months posttreatment.) Increasingly, clinical trials methodologists advocate including statistical strategies that recognize the importance of multiple outcomes to accurately capture treatment impact on patients whose clinical conditions affect multiple domains, as HCP does.[38]

CHAMP has limits. Key is that the final study was modestly underpowered, largely because of lack of data from recent UCT groups and slightly lower recruitment and cohort maintenance. Nonetheless, CHAMP is the first to directly compare experimentally manipulated dosage and constraint type by using a standardized CIMT intervention protocol and constant outcome measures, thus providing unique findings. A fairly consistent pattern of results, despite differences in reaching statistical significance from alternative approaches, supports the acceptability and multiple benefits of the high-dose CIMT, thus providing relevant evidence for clinical decision-making.

Finally, we acknowledge the debate about including parent-reported outcomes. We justify including these because parents uniquely are able to observe daily behavior and functional outcomes. Blinded assessors seek to elicit a child's

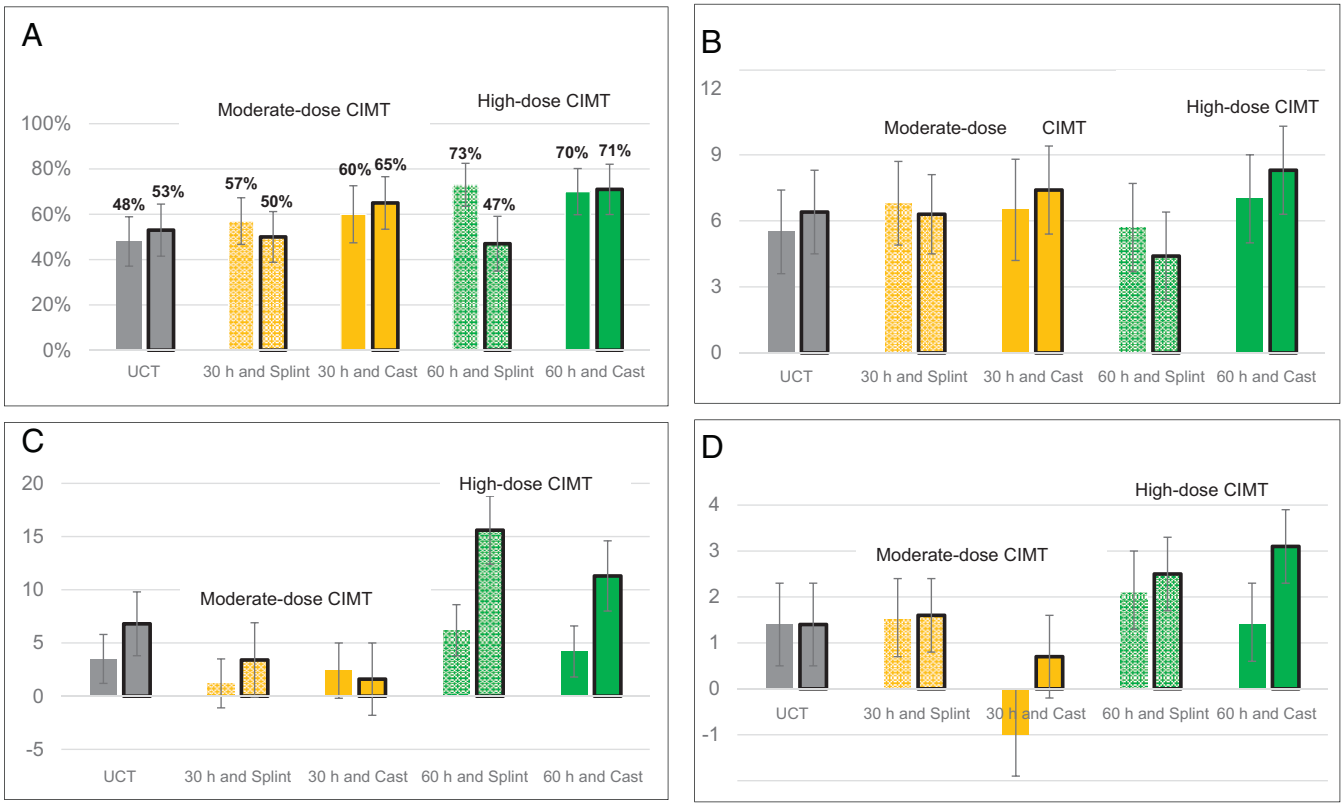

FIGURE 2

Primary blinded outcomes for CHAMP treatment groups at end of treatment (left bar) and 6 months posttreatment (right bar with outline). Means and SEs for groups for PMDS-2 VM and QUEST DM reflect gains since the baseline. In Table 1, we provide baseline scores so that final scores can be calculated by adding gain scores. In Table 2, we provide results of statistical analyses contrasting manipulated factors of Dose and Constraint to UCT. Grey indicates UCT; yellow indicates 30-hour moderate-dose CIMT; green indicates 60-hour high-dose CIMT; solid nongrey colors indicate full-time cast; dots indicate part-time splint; no outline indicates end of treatment; black outline indicates 6 months posttreatment. A, AHA: percentage with gain of ≥5 logit points. B, AHA: mean changes (SE) from the baseline. C, VMI (affected side): mean changes (SE) from baseline. D, QUEST Disassociated Movement (affected side): mean changes from baseline.

"best performance" on standardized tools to determine if a child can do something, whereas parents can report on real-world "typical" behavior concerning the extent to which their child actually uses skills. In theory, technology advances could be applied to generate blinded real-world functional outcomes (eg, time-sampled video-recordings and body sensors used on multiple days in multiple settings): a methodology achievement we eagerly await. Nonetheless, for CHAMP, we report both blinded assessor and parent outcomes, reasoning that each affords a relevant perspective.

The 60-hour high-dose CIMT, regardless of constraint type (ie, both cast and splint), yielded a predominant pattern of more positive outcomes, with some differences depending on the outcome or time, thus earning the greatest clinical potential for children with HCP. This finding of benefits from the 60-hour dosage level matches that of Sakzewski et al[48] on the basis of secondary analyses of 2 independent RCTs. These investigators also had a similar caregiver (nonblinded) finding about children's typical functioning with benefits appearing for both CIMT doses, whereas only the blinded outcomes supported the higher (but not lower) dose conclusion. In CHAMP, parental stress was not elevated in any treatment group and parents indicated no preference for cast or splint. Given a choice among the 5 treatment groups, with data available on all outcomes, we think most parents and clinicians would select high-dose CIMT. At the same time, we caution that some children in all groups revealed good progress, whereas some did not. In future analyses, researchers need to explore whether differential treatment benefits can be predicted more precisely by clinical and/or environmental variables.

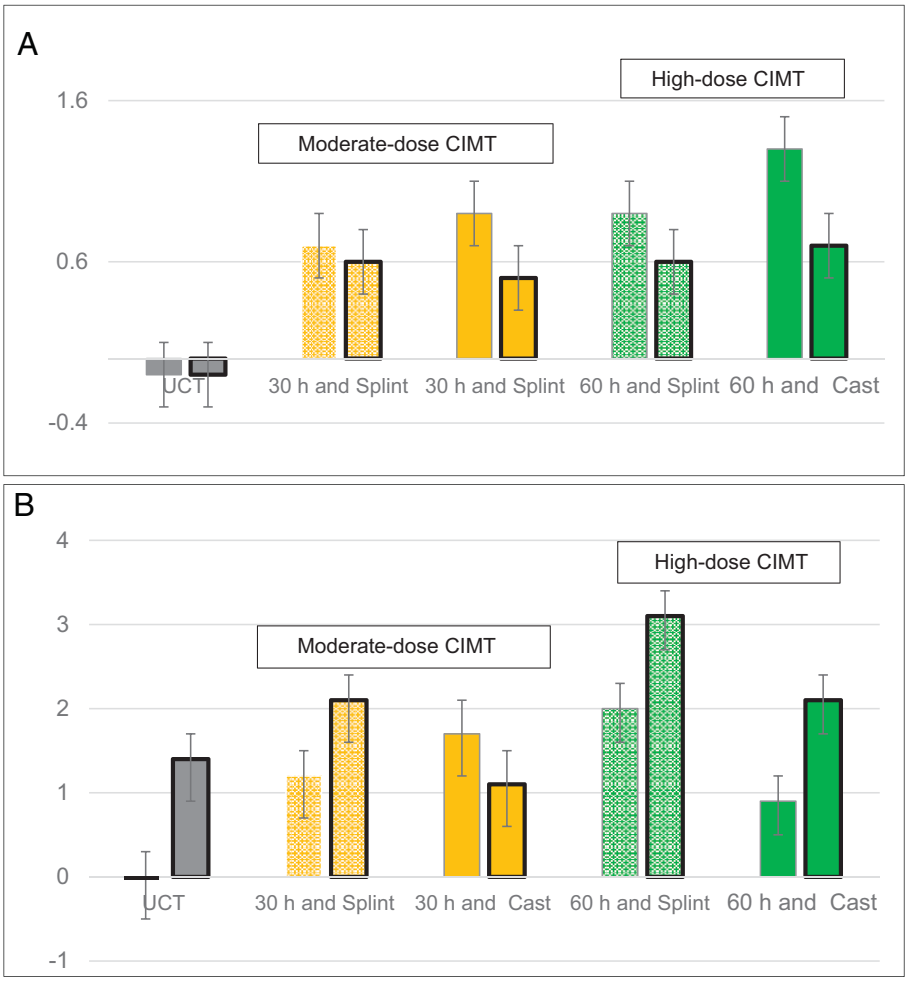

FIGURE 3
Primary parent-reported functional outcomes for CHAMP treatment groups at end of treatment (left bar) and 6 months posttreatment (right bar with black outline). Means and SEs for Groups for CMAL how often and PEDI-CAT Daily Activities reflect gains since the baseline. In Table 1, we provide baseline scores so that final scores can be calculated by adding gain scores. In Table 2, we provides results of statistical analyses contrasting manipulated factors of dose and constraint to UCT. Grey indicates UCT; yellow indicates 30-hour moderate-dose CIMT; green indicates 60-hour high-dose CIMT; solid nongrey colors indicate full-time cast; dots indicate part-time splint; no outline indicates end of treatment; black outline indicates 6-mo posttreatment. A, AHA: percentage with gain of ≥5 logit points. B, AHA: mean changes (SE) from the baseline. A, CMAL How Often. B, PEDI-CAT Daily Activities.

CONCLUSION

High-doses of CIMT delivered in 3-hour sessions 5 days per week for 4 weeks produced a consistent pattern of gains more than that of UCT on almost all blinded and parent-reported functional outcomes, although the findings are complex. Analysis of multiple end points and the pattern of gains, rather than individual ANCOVAs, provides the strongest support for the overall superiority of high-dose CIMT. A new finding about objective benefits from UCT also is encouraging.

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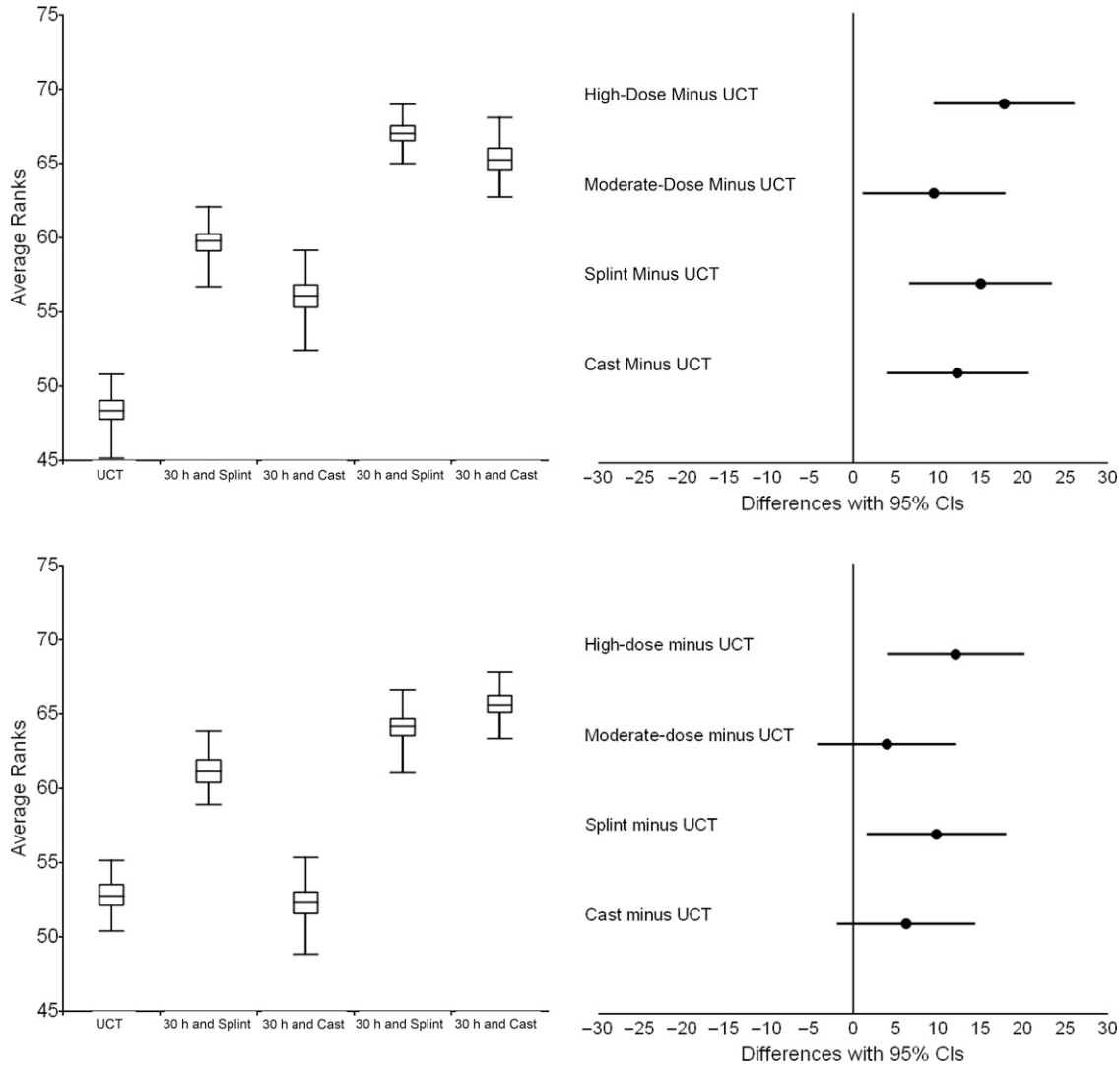

FIGURE 4

O'Brien's composite rank-order outcomes for CHAMP treatment groups at end of treatment and 6-months posttreatment. Panels A and C demarcate the lowest rank of a child in the group, the first quartile, the median group rank-order value, the third quartile, and the highest rank of a child in the group. Sections B and D reveal 95% CIs for contrasts of factors compared with UCT. A, end of treatment. B, end of treatment. C, 6 months posttreatment. D, 6 months posttreatment.

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ABBREVIATIONS

AHA: assisting hand assessment
ANCOVA: analysis of covariance
CHAMP: Children with Hemiparesis Arm and Hand Movement Project
CI: confidence interval
CIMT: constraint-induced movement therapy
CMAL: Child Motor Activity Log
GMFCS: Gross Motor Functional Classification System
HCP: hemiparetic cerebral palsy
MACS: Manual Ability Classification System
MD: mean difference
PEDI-CAT: Pediatric Evaluation of Disabilities Inventory-Computer Adaptive Test
PDMS-2: Peabody Motor Development Scales, Second Edition
QUEST: Quality of Upper Extremity Skills Test
RCT: randomized controlled trial
UCT: usual customary treatment
UE: upper extremity
VMI: visual motor integration

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the initial and revised articles, reviewed and edited the manuscript with coauthors, and was the lead multiple principal investigator for CHAMP; Dr DeLuca, multiple principal investigator, helped conceptualize and design the study, led the training of therapists and documentation of fidelity of treatment, oversaw training for data collection, developed data entry and verification systems, worked closely with the statistician (Dr Conaway) and lead multiple principal investigator (Dr Ramey) in delineating data analyses, contributed to preparing and finalizing the manuscript, and directed the clinical site in Roanoke, Virginia; Dr Stevenson, multiple principal investigator, helped conceptualize and design the study, served as the lead developmental pediatrics medical expert, contributed to interpretation of study findings, assisted in review and revision of the manuscript, and directed the clinical site in Charlottesville, Virginia; Dr Conaway, study statistician, established initial study power, created the randomization lists, conceptualized and conducted the data analyses, contributed to understanding the study's multivariate longitudinal findings, and helped review and revise the manuscript; Dr Darragh directed the clinical site in Columbus, Ohio, contributed to review of the data and the final manuscript, and joined CHAMP after Dr Case-Smith of The Ohio State University, one of the original multiple principal investigators, passed away in 2016; Dr Lo was a coinvestigator, contributed to the clinical oversight regarding pediatric neurology, referred patients for the Columbus, Ohio, clinical site, and assisted in review of findings and the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Constraint-Induced Movement Therapy for Cerebral Palsy: A Randomized Trial

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