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ORIGINAL PAPER

Kinematic and Somatosensory Gains in Infants with Cerebral Palsy After a Multi-Component Upper-Extremity Intervention: A Randomized Controlled Trial

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Abstract

Upper extremity (UE) impairments in infants with cerebral palsy (CP) result from reduced quality of motor experiences and "noisy" sensory inputs. We hypothesized that a neuroscience-based multi-component intervention would improve somatosensory processing and motor measures of more-affected (UEs) in infants with CP and asymmetric UE neurologic impairments, while remaining safe for less-affected UEs. Our randomized controlled trial compared infants (6–24 months) with CP receiving intervention (N = 37) versus a waitlisted group (N = 36). Treatment effects tested a direct measurement of reach smoothness (3D-kinematics), a measure of unimanual fine motor function (Bayley unimanual fine motor raw scores), and EEG measures of cortical somatosensory processing. The four-week therapist-directed, parent-administered intervention included daily (1) bimanual play; (2) less-affected UE wearing soft-constraint (6 h/day, electronically-monitored); (3) reach training on more-affected UE; (4) graduated motor-sensory training; and (5) parent education. Waitlist infants received only bimanual play. Effectiveness and safety were tested; z-scores from 54 posttest-matched typically-developing infants provided benchmarks for treatment effects. Intervention and waitlist infants had no pretest differences. Median weekly constraint wear was 38 h; parent-treatment fidelity averaged > 92%. On the more affected side, the intervention significantly increased smoothness of reach (Cohen's $d = -0.90$; $p < .001$) and unimanual fine motor skill ($d = 0.35$; $p = .004$). Using unadjusted p values, intervention improved somatosensory processing ($d = 0.53$; $p = .04$). All intervention effects referenced well to typically developing children. Safety of the intervention was demonstrated through positive- or non-effects on measurements involving the constrained, less-affected UE and gross motor function; unexpected treatment effects on reach smoothness occurred in less-affected UEs ($d = -0.85$; $p = .01$). This large clinical trial demonstrated intervention effectiveness and safety for developing sensory and motor systems with improvements in reach smoothness, and developmental abilities.
Clinical Trail Registration: ClinicalTrials.gov NCT02567630, registered October 5, 2015.

Keywords Cerebral palsy · Somatosensory · Kinematics · EEG · Intervention · Motor

Introduction

Cerebral Palsy (CP) is characterized by sensorimotor impairments resulting from perinatal neural insults. CP incidence ranges from 2–3/1000, with potentially larger incidence in developing countries (Couper 2002; Cruz et al. 2006). Therefore, intervention strategies for children with CP adhering to neuroscientific and developmental principles should remain adaptable to limited-resource settings.

Asymmetric impairments of upper extremity (UE) neurological function in children result from a combination of motor and sensory dysfunctions (Hoon et al. 2009). Decreased UE functional ability can also derive from

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reduced quality of motor experiences (developmental disregard) (Aarts et al. 2011) and "noisy" sensory inputs (Körding and Wolpert 2006). Somatosensory function is abnormal in children with CP (Auld et al. 2012) with implications for perception and performance, especially when combined with other sensory co-morbidities (Hollung et al. 2020). Thus, it is more accurate to describe each UE as either "more-affected" or "less-affected" in children with CP with asymmetric neurological impairments. Measurement of somatosensory function is well-established in older children but requires behavioral responses and cognitive processing that are unfeasible in younger subjects. To address this gap, our team developed and validated novel EEG-based tools to specifically characterize somatosensory responses in young children with CP. Importantly, event-related potentials (ERPs) to calibrated light-touch in older children correlated with sensory function on behavioral measures, and were responsive to intervention (Maitre et al. 2012; Matusz et al. 2018). Similarly, for motor function, software-guided quantitative measurement of video-recorded reach (kinematics) allows objective measurements (e.g., smoothness of movement), even in infants. Children with CP have poor UE control with atypically numerous velocity peaks (movement units) and atypical speed during reaching (Schneiberg et al. 2010) and require intensive strategies to acquire improved function and underlying timing and coordination (Jackman et al. 2020). Approaches to improve UE function are postulated, but not conclusively proven, to work in infants with CP as they would in older children (Bleyenheuft et al. 2015; Burzi et al. 2016; Gordon et al. 2011). They range from cast to soft constraint (Eliasson et al. 2018) and while they show promise, are still considered "yellow light" interventions according to systematic reviews and the Evidence Alert Traffic Light System (Novak et al. 2020). These approaches can be combined with brief sessions of infant-initiated, goal-directed, success-motivated repetitive trials (Needham et al. 2017) to promote motor learning, while respecting fundamental principles of infant neurodevelopment (Damiano 2014). Such active learning is effective in all infants. Typically developing (TD) 4-month-olds learn to reach faster and more effectively by using "sticky mittens" for handling and exploring Velcro-enhanced toys (Needham et al. 2017). However, while intensive practice, active learning and high dosage of motor practice appear to be essential to successful therapeutic strategies, they have the potential to involve prolonged intrusions of health-care professionals into the home. In contrast, integration of evidence-based strategies into family routines and parent administration of interventions can preserve early parent–child relationships critical to later quality-of-life (Dusing et al. 2019).

Early interventions take advantage of neuroplasticity and maximize downstream effects of therapeutic strategies, possibly improving outcomes in children with CP (Ismail et al. 2017; Novak et al. 2017). Currently, there are no prospective randomized trials testing all the above-listed concepts in a rigorous scientific design. This knowledge gap occurred because (1) clinical practice made it challenging to intervene before 2 years (NINDS 2013) and (2) significant neuroscientific concerns exist regarding safety of continuous restrictive constraint-wear, as this may affect development of sensory afferent connections in the less-affected UE and have maladaptive effects on efferent pathways and projection topography of the spinal cord (Friel and Martin 2005; Hoare and Eliasson 2014; Ismail et al. 2017; Matusz et al. 2018). Recent implementation of international guidelines (Novak et al. 2017) for early CP detection changed clinical practice (Maitre et al. 2020), providing opportunities for interventions within the first year. Importantly, UE trials often focus on children with hemiplegic CP originating from well-circumscribed lesions (Taub et al. 2004) such as infarcts. However, a large proportion of infants with CP have neural insults in the spectrum of encephalopathy of prematurity (Eunson 2012), where white matter lesions to motor tracts frequently result in asymmetric neurological impairments (Ferre et al. 2020; Volpe 2009). To be generalizable and impact the majority of infants with UE dysfunction in CP, interventions should be effective and safe for all with asymmetric neurological impairments. While this precept may decrease measured effects due to more heterogeneous populations with CP, others have suggested that it may offer the most widespread approach to helping affected infants and their families (Eliasson et al. 2005).

Therefore, we hypothesized that a neuroscience-based, multi-component intervention could effectively improve somatosensory and motor measures of more-affected UEs in infants with CP and asymmetric neurological impairment, while remaining safe for less-affected hand sensory function. We tested our hypothesis in a randomized clinical trial of infants aged two and under, with CP affecting one UE more than the other. Treatment effects were measured on the more-affected UE and safety effects were measured on the less-affected UE. We measured treatment effects on a direct prespecified kinematic measurement of reach smoothness, a downstream measure of unimanual fine motor function, and ERP measures of somatosensory processing. Because our outcomes measures had not been previously studied in infants, we also obtained reference values from typically developing infants matched to the cohort with CP post-intervention.

Materials and Methods

Trial Design

For more details of study design and methodology, we refer to the protocol publication (Chorna et al. 2015). This was a

prospective randomized trial with parent–child dyads randomly assigned to intervention or waitlist control groups with a 1:1 allocation using permuted blocks of random sizes (Chorna et al. 2015). After trial registration (NCT02567630, clinicaltrials.org), a selection criterion was changed to 6 (from 9) to 24 months corrected age (CA) due to average age at CP diagnosis decreasing at our institution with implementation of early detection guidelines (Byrne et al. 2017).

Allocation Concealment and Masking

Data were de-identified using study identification numbers. Parents could not be masked to waitlist allocation, but no measures were parent reports or derived from parent–child interaction sessions. We controlled for assessment bias by requiring all outcome examiners to be blind to group assignment. This was possible because examiners were not treating therapists.

Sample Size and Power

A priori study hypotheses and power calculations determined a sample size ($n = 72$) would allow a 90% power to detect a 0.54 SD difference between control and intervention primary outcomes measures.

Recruitment

Inclusion criteria were confirmed diagnosis of hemiplegic or quadriplegic CP determined by published algorithms (Kuban et al. 2008) and neurological examination, with CA 6 to 24 months. Asymmetry of neurologic impairments in CP was defined by a Hammersmith Infant Neurological Examination (HINE) Asymmetry Score (Hay et al. 2018) > 6 determined by one of two physicians (physicians had > 90% intra- and inter-rater reliability for HINE administration and scoring). The asymmetry score examined differences in tone, posture, movement and reflexes between UEs. Exclusion criteria were congenital brain malformations, receipt of botulinum toxin to the affected extremity ≤ 3 months before study entry, and any prior prolonged hard constraint programs. Infants were encouraged to continue all developmental therapies in both groups for the 4 week-period, with the exception of therapist-administered training of UE function. The rationale for this was that children already received daily training from their parents that was guided by an experienced therapist on a weekly basis.

Infants were screened for eligibility in the electronic medical record of outpatient clinical therapy, Neurology/Stroke and High-Risk Infant Follow-up clinics at Nationwide Children's Hospital. Informed consent was obtained for each subject per protocols approved by the hospital's Institutional Review Board (IRB). A group of 54 TD infants matched for gestational age and CA at post-intervention testing (±2 weeks) was recruited using IRB-approved flyers and hospital community emails, to provide normative information about measures used in infants with CP. TD infants had HINE scores in the optimality range for age, no history of birth events other than prematurity, no evidence of insults on neuroimaging, and no diagnoses of developmental impairments or delays for CA. Patients were enrolled 10/05/2016-02/20/2019; follow-up finished 3/20/2019 for this initial RCT phase. All data were collected at Nationwide Children's Hospital. Figure 1 shows the study design, including timing of the measurement periods.

Data Management

All data were recorded in REDCap (Research Electronic Data Capture) (Harris et al. 2019). A review of the Pediatric Neuroradiologist's clinical neuroimaging reports was conducted by two physicians independently to allow concordance on classification of the primary insult into three categories: encephalopathy of prematurity, neonatal encephalopathy, and perinatal infarct/thrombosis. REDCap enabled data entry error checks and correction when entry errors were discovered.

Intervention

For the intervention group, the loose soft-constraint harness (C-Mitt, USPTO 29/577,142) was designed for the less-affected UE to encourage use of the more-affected UE. The C-Mitt allowed sensory feedback, full arm range of motion and use of hand as an assist or for gross motor skills such as crawling. The main restriction the C-Mitt imposed was on fine manipulation and grasping in the less-affected hand. After therapist training in the laboratory for one hour/week, the 28-day intervention was provided by parents in the home. Intervention goals were set at the participant's initial skill level and advanced with achievement (Chorna et al. 2015). Parents were provided child-safe, sanitizable, and inexpensive toys, appropriate for the skill level of the child and guided by the child's interest; the bins with sensory environments; and the C-Mitt tailored to their child's arm length. The daily intervention included the following components:(1) bimanual play with suggested toys without the C-Mitt (20 min/day); (2) soft-constraint harness (C-Mitt) worn 6 h/day total; (3) reaching with and exploration by the non-constrained hand of age-appropriate small toys in provided bins with varying sensory environments (e.g., rough/smooth texture, small/large particle size), with graduated motor difficulty introduced by decreasing size and increasing depth into the sensory medium (10–20 min/day); (4) reaching with the more-affected and non-constrained hand in a mitten made "sticky" with Velcro (Needham et al. 2017) at

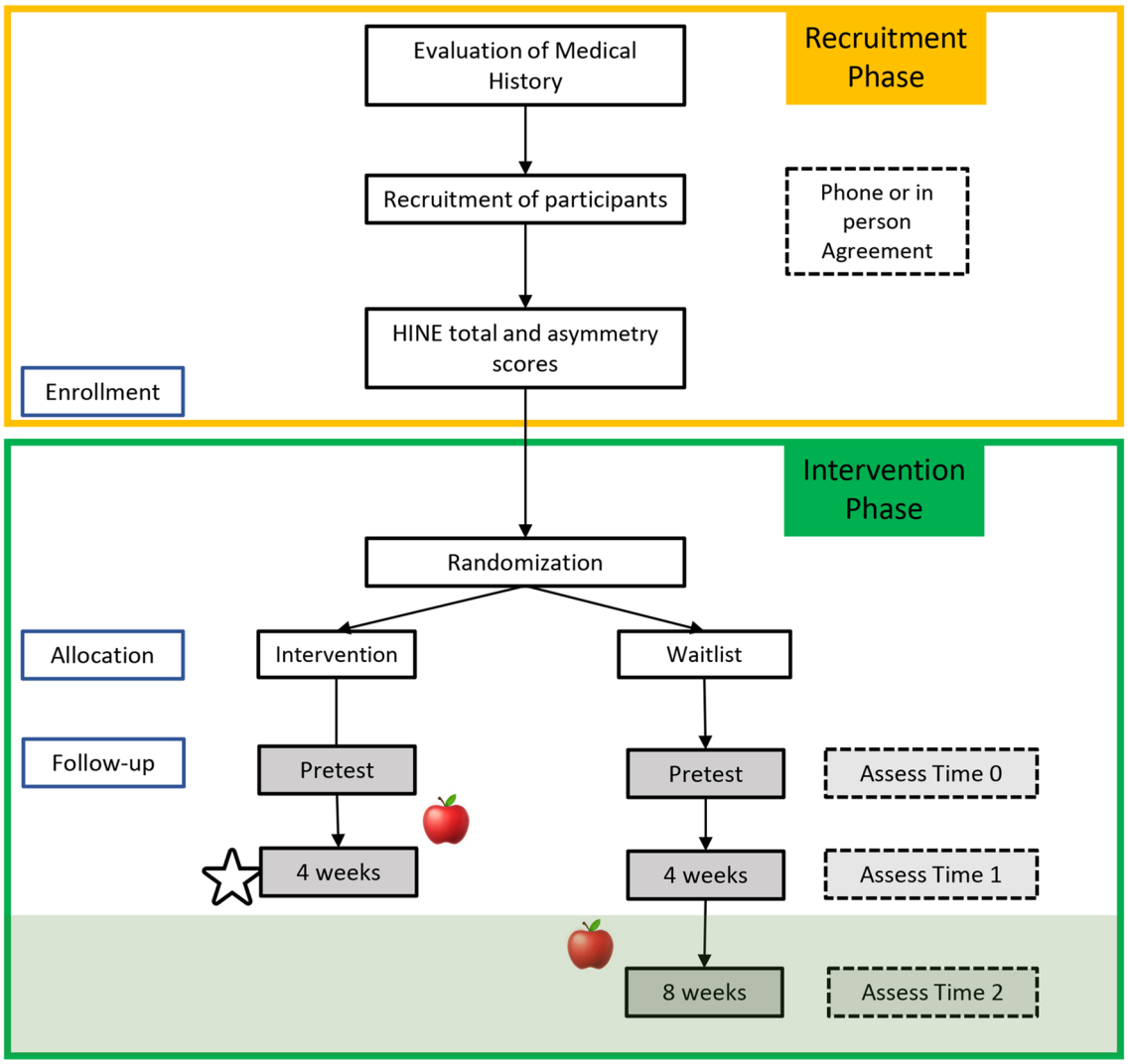

Fig. 1 Study flow process**.** Infants meeting eligibility were enrolled into either the intervention or the waitlist control group. After 4 weeks, both groups were assessed again. The RCT phase of the trial was over at this stage and these are the results reported in the current study. The longitudinal assessment of all infants who received the intervention until 3 years will continue and be compared to a matched group of typically developing children. The apple symbol represents the intervention. The star represents the posttest time at which intervention effects were assessed and typically developing children matched for gestational age at birth and corrected age at testing time

75% full-reach distance (shoulder level) on an adjustable tray and with objects (also with Velcro) of increasing weight and size challenge for sensory reinforcement (10–20 min/day). For components 3 and 4, parents were trained on performing a demonstration sequence using progressive visual support from mirroring activities (Catmur 2013) across from their child to modeling the activity behind and in parallel with their child; and (5) education of parents on principles of positive parenting psychology, "just-right challenge", positive reinforcement, transactional interactions and emotional availability (Whittingham et al. 2016). A video version of the intervention manual demonstrating all components with explanations of the training steps and principles was available to parents and therapists online throughout the intervention. Infants in the waitlist group were provided only the first intervention component (i.e., bimanual play with suggested toys for 20 min/day). This bimanual play education encourages activity between parents and children and did not follow protocols published in older children (Gordon et al. 2011). Thus, the waitlist group was not an active treatment control.

Monitoring of compliance with the intervention was accomplished using two procedures. First, we inserted a movement sensor (Fitbit One, Fitbit, San Francisco, CA, USA) in the C-Mitt to measure wear time. Second, two independent raters scored parents' fidelity of the intervention each week in the laboratory (four-times during the intervention) using a checklist that addressed all six intervention

components while parents demonstrated how they administered the intervention. The average of their ratings was used for the final parent fidelity score.

Overview of Dependent Variables

Two a priori primary motor outcome measures were selected. First, smoothness of reach of the more-affected UE was measured using number of movement units derived from a kinematic analysis during a standardized paradigm. This was considered a direct motor outcome. Second, fine motor skill in the more-affected hand was measured using the unimanual raw score from the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley) (Bayley 2006). This was considered a downstream motor outcome.

Somatosensory processing was measured using ERP amplitude of N140 and P200 components to tactile stimulation of the more-affected hand at the contralateral and ipsilateral frontal scalp regions (Maitre et al. 2012). Because there were eight measures of somatosensory processing, alpha was adjusted for multiple significance testing for this class of outcomes (Benjamini and Hochberg 1995).

Additionally, we examined secondary outcomes deemed less-likely, but possible, to change due to the intervention: efficiency of reach as measured by kinematics measure of reach arc length of the more-affected UE and bimanual Bayley raw scores.

Safety outcomes were selected given the concern that restraint of an arm for the prescribed period may decrease somatosensory processing or motor functioning in the less-affected UE (Friel and Martin 2005; Hoare and Eliasson 2014; Matusz et al. 2018) kinematic measures of reach smoothness for the less-affected UE, ERP measures for the less-affected hand, and Bayley gross motor raw scores.

For outcomes on which there were treatment effects (i.e., significant differences between intervention and waitlist groups), we provided the mean (SD) values for infants with CP using a type of z-score that is computed in reference to the average performance on these measures by a cohort of matched TD infants ([observation in subject—TD mean]/TD SD) at the posttest period. Doing so aids interpretation of kinematic, ERP, and Bayley raw scores, which lack published norms and vary by age.

Assessment Procedures

Kinematic Measures of Reach

Infants were seated in a fixed highchair with a model tray ensuring objects would be placed at 75% full-reach, shoulder level, and midline. Blind examiners followed a scripted algorithm of toy presentation to elicit reach. Trials were video-recorded, and written data regarding details of the trials were kept separately. Vicon X system (Vicon Motion Systems Ltd., UK) software analyzed the videotaped movements; data were extracted using previously published MATLAB algorithms (Bhat et al. 2005). Two variables were derived using kinematic analysis of video-recorded reaching. The first variable, smoothness of reach, is quantified as the number of movement units, and is an outcome measure for UE intervention trials with high validity and reliability in children with CP (Schneiberg et al. 2010). In the current study, the average number of movement units was calculated from the velocity peaks. The second variable, arc length of the reach, is quantified as the length of the movement path taken divided by the shortest distance from hand to object; it is a measure of reaching coordination and efficiency (Gulde and Hermsdörfer 2018). Both variables were extracted during the first three trials in which infants had hand-toy contact with a small ball. Any trials without hand-toy contact were eliminated as un-codable. Off-site analysis staff who were blind to intervention group extracted positional data and calculated kinematic parameters in MATLAB software. The average number of trials performed during the standard algorithm for reach in children with CP at pre-test was 8.1 (SD 4.4).

ERP Measures of Somatosensory Processing in Response to Light Touch

Prior work in older children (Chorna et al. 2019; Matusz et al. 2018) using the same paradigm as in the current study established that amplitude of the P200 ERP response to light touch had greater magnitude in less-affected compared to more-affected hand, correlated with functional somatosensory processing measures, and responded to constraint therapy. In the current study, as in validation studies, ERP data were acquired in response to calibrated tactile stimuli and a sham condition (Maitre et al. 2012, 2017). Infants were kept in calm and engaged behavioral states by music therapists using established protocols (Chorna et al. 2019). Attention to tactile stimuli was unnecessary as previously demonstrated (Chorna et al. 2015; Maitre et al. 2017), and any other stimulation was not time-locked, and therefore averaged into the background EEG. Data were acquired using 129-electrode EGI Hydrocel nets (EGI, Inc., Eugene, OR, USA), while E-Prime (Psychology Software Tools, Sharpsburg, PA, USA) controlled stimulus delivery, and Net Station Research software (EGI) allowed acquisition, preprocessing, and data extraction (Maitre et al. 2012). Preprocessing included filtering (0.3 Hz high-pass, 40 Hz low-pass), segmentation on stimulus onset (– 100 to 500 ms, sampling rate 1000 Hz), automatic artifact detection and manual review. An average of 34.1(± SD 3.2) trials per condition per infant were retained for analysis with a threshold of 15. Artifact-free trials were referenced to the common average reference and

baseline-corrected using the pre-stimulus period. To ascertain reliability of post-stimulus signal in data that remained after artifact removal, we performed a test of consistency using the global field power (Koenig and Melie-García 2010; Tzovara et al. 2012), assessed first across conditions for each subject and secondly across subjects. Analysis demonstrated that subjects across conditions and trials had > 95% consistency. Finally, we averaged the amplitude of the signal at electrodes that include and surround the pre-specified electrode locations of F3 and F4 (left and right frontal, respectively) with all data normalized by the mean of the global field power to control for general conductivity differences among participants. After preprocessing, 69 (94.5%) patients had high-quality data at both pre- and post-intervention timepoints (four excluded due to technical errors preventing accurate trial counts). Because the side of the more-affected UE varied, ERP variables were labeled as ipsilateral and contralateral relative to the stimulated hand.

Bayley Measures of Motor Skill Level

The Bayley Fine Motor and Gross Motor subscales were administered using standard and published protocols (Bayley 2006; Lowes et al. 2014). Reliability of assessments amongst testers was established to achieve > 90% by a central examiner (the site gold-standard for Neonatal Research Network (NICHD 2019) Bayley testing) and recertified annually. In addition to gross motor subscale raw scores, raw scores were determined for unimanual fine motor items for less-affected and more-affected UE (and bimanual fine motor items). When testing the more-affected UE, mild restraint of the less-affected extremity was administered as necessary (Lowes et al. 2014).

Statistical Analysis

The analysis followed intent-to-treat principles, regardless of C-Mitt wear time or fidelity of parent-implemented intervention. Unless the pretest × group interaction was significant, the treatment effects were tested using ANCOVA to test for between-group differences on immediate posttest scores controlling for the pretest of the dependent variable. To most accurately estimate treatment effect size, we calculated the pretest adjusted immediate posttest standardized mean difference between the intervention and waitlisted groups (i.e., pretest-adjusted Cohen's *d*). For the dependent variables on which there were treatment effects, we computed the means and SDs in the TD sample, which were used to compute TD-referenced z-scores at immediate posttest for the infants with CP to provide benchmarks for interpreting the kinematics, ERPs, and Bayley raw scores. Pearson's correlations examined associations between outcomes on which there were treatment effects to determine the extent to which the outcomes provide overlapping information. Finally, in the waitlist group, we examined whether there was an increase in the raw change scores during the waitlist group's intervention phase relative to the same duration prior to being treated using paired *t*-tests.

Results

At pretest, infants had a median age of 12 months CA (IQR 9–17 months). Average parent socioeconomic status was a median of 24 (range 4–41) on the Barratt Simplified Measure of Social Status (Barratt 2006), and 40% of mothers had a high school education or less. The two randomized groups did not differ on any demographic or CP characteristics (Table 1). In addition, there were no pretest differences between intervention and waitlist groups on any dependent variables (Table 2; unadjusted *p*-values 0.10 to 0.92). Information on screening, enrollment, and randomization for the 73 analyzed participants can be found in the CONSORT diagram (Fig. 2). While 5 subjects withdrew before intervention, no attrition occurred after intervention began.

Infants in the intervention group had median C-Mitt wear time of 38 h/week (range 3.9–65), equivalent to 5.3 h/day for the 28 days of the intervention. Average parent-intervention fidelity was as follows: week 1 = 93.4% SD = 8.9, week 2 = 93.6% SD = 4.8, week 3 = 92.8% SD = 7.7, week 4 = 99.3% SD = 1.5.

For all variables, except for Bayley bimanual raw score, the assumption of homogeneity of slopes was met, allowing ANCOVA to be used to statistically control the pretest when testing for treatment effects on the dependent variables. The statistical interaction between pretest Bayley bimanual raw score × treatment group predicting posttest Bayley bimanual raw score was statistically significant, $t(69) = -2.11$, $p < 0.04$, but the R^2 change for the product term was 0.02; a clinically trivial effect size. Thus, the Bayley bimanual raw score will not be discussed further.

Treatment Effects

Table 3 provides the pretest-adjusted immediate posttest means and SDs for the dependent variables by group. The significance adjusted for number of significance tests per class of dependent variable is the most conservative test of intervention efficacy. Three dependent variables were significantly different, favoring the intervention group: smoothness of reach of the more-affected UE, Cohen's $d = -0.90$; unimanual fine motor on the more-affected side, Cohen's $d = 0.35$; and smoothness of reach on the less-affected UE, Cohen's $d = -0.85$. Before multiple significance test correction using the Benjamini–Hochberg method, there was a significant difference in P200 measure of somatosensory

Table 1 Participant characteristics

	N	Intervention (n = 37)	Waitlist (n = 36)	*P*
Sex[a]	73			.29[d]
Female, *n* (%)		21 (57)	16 (44)	
Male, *n* (%)		16 (43)	22 (56)	
Race[a]	66			.84[d]
White, *n* (%)		20 (65)	21 (60)	
Black/African American, *n* (%)		8 (26)	9 (26)	
Multiracial/other, *n* (%)		3 (10)	5 (14)	
Ethnicity	73			.38[d]
Non-Hispanic, *n* (%)		35 (95)	32 (89)	
Hispanic, *n* (%)		2 (5)	4 (11)	
Birth GA, median [IQR], completed weeks	73	28 [23–38]	32 [25–38]	.75[e]
Corrected age at pretest, median [IQR], completed months	73	13 [9–18]	11 [9–15]	.28[e]
Right-side more-affected, *n* (%)	73	16 (43)	14 (39)	.70[d]
Neuroimaging[a]	73			.52[d]
Encephalopathy of prematurity, *n* (%)		26 (70)	26 (72)	
Hypoxic ischemic encephalopathy, *n* (%)		6 (16)	33 (8)	
Infarct/thrombosis, *n* (%)		5 (14)	7 (19)	
GMFCS at pretest, median [IQR]	73	3 [1–4]	3 [2–4]	.74[d]
BFMF[b] at pretest, median [IQR]	73	2 [1–3]	2 [2–3]	.6[d]
(C-Mitt) Fitbit wear, median [IQR], h/week	68	38 [27–48]	N/A	
Fidelity of parent training, mean (range), %	37	95.3 (76–100)	N/A	
Mother's Highest education	65			
Below High school, *n* (%)		4 (11)	2 (7)	.56[d]
High school diploma, *n* (%)		14 (38)	14 (47)	
Bachelor's degree, *n* (%)		10 (28)	4 (13)	
Advanced degree, *n* (%)		8 (22)	7 (23)	
BSMSS, median (range)[c]	65	24 (4–41)	22 [6–40]	.69[f]

Barratt Simplified Measure of Social Status (BSMSS) is a proxy for socio-economic status (Barratt 2006). Scores range from three (unemployed single parent with middle school education) to 66 (two parents with graduate education and highly skilled professions). The mean population in this study corresponds grossly to a low-to-middle income distribution with few families in the middle-upper range. None would be considered upper range of incomes

BFMF Bimanual Fine Motor Function, *GA* gestational age, *GMFCS* Gross Motor Function Classfication Sysystem, *HINE* Hammersmith Infant Neurological Examination, *IQR* interquartile range, *N* number of non-missing values

[a]Percentages do not add up to 100% due to rounding

[b]BFMF, A and B categories within a class were collapsed into a single class

[c]Parents had the right to decline answering these socioeconomic questions

[d]Pearson test

[e]Wilcoxon test

[f]Two-tailed student's *t* test

processing of light touch on the more-affected UE at the contralateral electrode cluster, Cohen's $d = 0.53$. The direction of effect sizes was as expected, and all four variables indicated adaptive functioning favoring the intervention group.

To help interpret these differences, TD referenced z-scores for these four dependent variables are indicated in Table 4. Mean difference from 0 indicates degree of delay or advancement relative to the TD sample's SD units. For unimanual fine motor functioning and somatosensory processing, negative scores indicate delay and positive scores indicate advancement. For smoothness of reach, positive scores indicate delay and negative scores in advancement relative to TD functioning. Thus, smoothness of reach and unimanual fine motor functioning of the more-affected UE were still delayed in the intervention group but much less than in the control group. In contrast, somatosensory processing of the more-affected

Table 2 Dependent variable measures at pretest in intervention and waitlist control groups

Dependent variables	More- vs less-affected side	Intervention *(SD)*	Waitlist control M(SD)
Primary motor			
Movement units: kinematic measure of reach smoothness	More-affected arm	5.7(3.3)	6.4(3.6)
Bayley measure of unimanual fine motor capacity[a]	More-affected arm	9.6(5.7)	9.1(5.8)
Primary sensory			
N140 measure of attention to tactile stimulus at *contralateral* electrode cluster	More-affected hand	.68(.37)	.72(.44)
N140: measure of attention to tactile stimulus at *ipsilateral* electrode cluster	More-affected hand	.58(.32)	.54(.32)
P200: measure of tactile perception at *contralateral* electrode cluster	More-affected hand	.61(.28)	.72(.42)
P200: measure of tactile perception at *ipsilateral* electrode cluster	More-affected hand	.58(.29)	.54(.35)
Secondary			
Arc length: kinematics measure of reach	More-affected arm	219.8(78.4)	221.7(86.8)
Bayley measure of bimanual fine motor capacity[a]		4.2 (2.1)	3.8 (1.9)
Safety motor			
Movement units: kinematic measure of reach smoothness	Less-affected arm	3.8(1.9)	4.5(2.1)
Arc length: kinematics measure of reach	Less-affected arm	208.7(85)	220.6(81.9)
Bayley measure of gross motor capacity[a]		31.2(10)	30.6(11.2)
Safety sensory			
N140: measure of tactile perception at contralateral electrode cluster	Less-affected hand	.65(.34)	.69(.31)
N140: measure of tactile perception at ipsilateral electrode cluster	Less-affected hand	.60(.28)	.65(.29)
P200: measure of tactile perception at contralateral electrode cluster	Less-affected hand	.59(.36)	.57(.41)
P200: measure of tactile perception at ipsilateral electrode cluster	Less-affected hand	.59(.41)	.61(.28)

There were no significant differences between groups at pretest

[a]Bayley raw scores for a cohort of 52 age-matched typically developing children are provided for reference, with range indicative of age-dependent variability. Unimanual fine motor function: mean 19.2, SD 4.5, range 11–27; bimanual fine motor items: mean 6.5, SD 1.4, range 3–9; gross motor function: mean 44.4, SD 8.5, range 25–60

UE in the intervention group was more advanced than the TD infants' somatosensory processing but was slightly delayed in the control group.

Secondary Analyses

Table 5 indicates intercorrelations of the significantly different outcomes. Although the two primary motor dependent variables were associated, their intercorrelation was modest. The association of smoothness of reach between more- and less-affected UEs was notably strong.

Although not indicative of a treatment effect, clinicians may wish to know whether the waitlisted control group showed greater gains during their intervention period compared to an equal duration period just prior to intervention. The paired *t*-test comparing these raw change scores between these periods was significant, $t(23)=3.78$, $p=0.001$, favoring the treated period.

Discussion

This is the first study in infants under 2 years with CP specifically demonstrating effectiveness of an intervention in increasing reaching smoothness and unimanual fine motor skill in the more-affected UE, and safety for the somatosensory processing of a constrained-extremity. Between-group differences at posttest can be interpreted as treatment effects, due to the randomized control research design, use of blinded examiners, low attrition, and intent-to-treat analysis. The effects of the present study were not only statistically significant, but greatly reduced severity of delay of smoothness of reach and unimanual fine motor performance of the more-affected UE as evidenced by the TD-referenced z-scores on the primary motor dependent variables. We speculate that the enhanced sensory feedback in motor tasks (reinforcement during "sticky mitten"

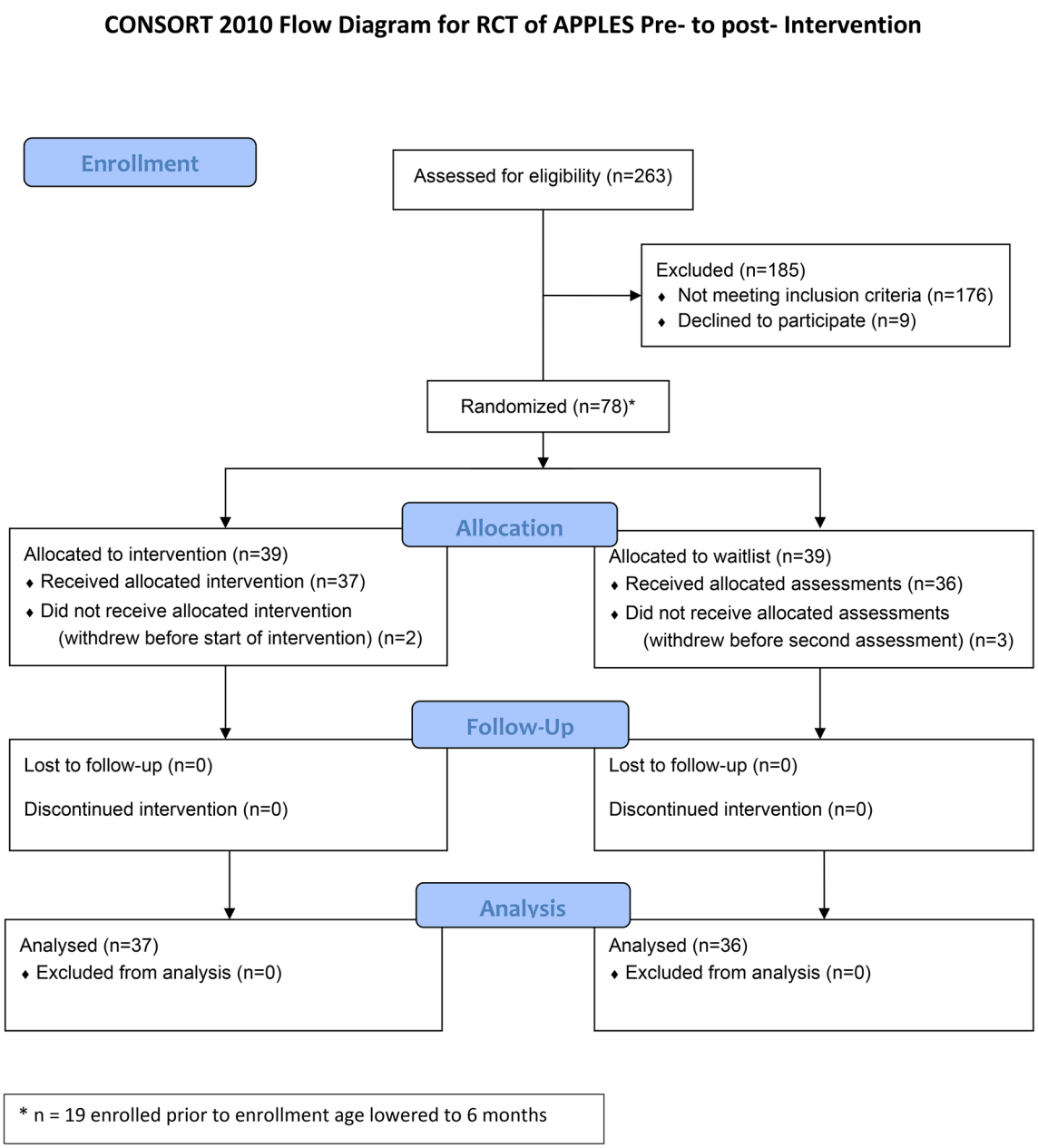

Fig. 2 CONSORT Flow diagram

task, reaching in textures, mirror neuron feedback) provided in our intervention was likely responsible for the observed results. In the current study, sensory enhancements have been complemented by the probable increased feedback resulting from more frequent exposure of the non-constrained UE during daily activities.

With regards to dosage, a current area of research interest (Eliasson et al. 2014), the 4-week intervention with daily training totaling 30–60 min/day in the current study was comparatively less-intensive than therapist-administered protocols that mandate 2–6 h/day training (NIH-RePORT 2018, 2019). Although therapist-coached, the current study's intervention was parent-administered and therefore did not have the same degree of adherence to protocols that trials in older children may have achieved. Even so, for 6–24 month-old infants, 30 min/day is relatively intensive in our opinion. In addition, the treatment package also included 6 h of soft-constraint use, resulting in the more-affected UE performing daily activities for an average of 38 h with only limited assist from the less-affected UE over 28 days. This is consistent with the effective dosage in improving upper limb motor ability in children with unilateral CP (40 h) and those with all typographies (15–20 h) reported in a recent systematic

Table 3 Post-intervention outcomes

Dependent variables	Affected side	Intervention M(SD)	Waitlist control M(SD)	*F*	df,df	Unadjusted *P*
Primary motor						
Movement units* (reach smoothness)	More	4.1(2.9)	6.5(3.5)	16.9	1,56	**< .001** **
Bayley unimanual fine motor	More	11.7(5.7)	10.1(6.3)	8.9	1,70	**.004** **
Sensory						
N140 *contralateral*	More			3.8	1,60	.06
N140 *ipsilateral*	More			.002	1,60	.97
P200 *contralateral*	More	.74(.36)	.55(.35)	4.6	1,60	**.04**
P200 *ipsilateral*	More			3.35	1,60	.07
Secondary						
Arc length (reach)	More			.42	1,45	.12
Bayley bimanual fine motor				N/A	N/A	N/A
Safety motor						
Movement units* (reach smoothness)	Less	3.1(1.3)	4.5(2.1)	7.0	1,41	**.01** **
Arc length (reach)	Less			.83	1,41	.37
Bayley gross motor				2.06	1,70	.16
Safety sensory						
N140 *contralateral*	Less			1.2	1,60	.27
N140 *ipsilateral*	Less			.35	1,60	.56
P200 *contralateral*	Less			.67	1,60	.42
P200 *ipsilateral*	Less			.02	1,60	.88

Statistically significant values ($p < 0.05$) are given in bold

We report pretest-adjusted immediate posttest means, standard deviations, tests of significance, and *p*-values

Adjusted means, F, and *p* for groups of dependent variable outcomes post-intervention

N/A not applicable because homogeneity of slopes assumption was violated. Treatment effect and pretest-moderated treatment effect was tested in separate analysis

*For movement units, a lesser number indicates a smoother reach, as a perfectly smooth reach would have only 1–2 movement units

**$p < .01$ on significance testing after Benjamini–Hochberg adjustment for multiple significance testing

Table 4 Mean (SD) for typically developing referenced z-scores on significant outcomes at immediate post-intervention

Dependent variables	Upper extremity tested	Intervention M(SD)	Waitlist control M(SD)
Primary motor			
Movement units: kinematic measure of reach smoothness	More-affected arm	1.38(2.6)	3.95(3.2)
Bayley measure of fine motor capacity	More-affected arm	− 1.64(1.3)	− 2.1(1.4)
Primary sensory			
P200: measure of tactile perception at *contralateral* electrode cluster	More-affected hand	.48(1.1)	− .18(1.1)
Safety motor			
Movement units: kinematic measure of reach smoothness	Less-affected arm	.58(1.1)	2.2(2)

review of UE interventions (Jackman et al. 2020). Because parents delivered positive reinforcement and validation of their infant's efforts on a daily basis, with routines and social-emotional exchanges unperturbed by intrusions into the home, therapy was likely provided in multiple contexts throughout the day, which may maximize generalization.

The largest effect was on smoothness of reach of the more-affected UE. The intervention resulted in decreased number of movement units per reach by more than half (mean 2.7), greatly reducing the delay relative to that of TD infants (Fallang et al. 2003). This improvement differed greatly from reported kinematic measures of smoothness

Table 5 Intercorrelation of dependent variables post-intervention

	Side	Kinematic measure of reach smoothness	Kinematic measure of reach smoothness	P200 somatosensory processing contralateral
		More-affected	Less-affected	More-affected
Bayley measure of unimanual fine motor capacity	More-affected	− .327*	− .234	.286*
Kinematic measure of reach smoothness	More-affected		.609***	− .109
Kinematic measure of reach smoothness	Less-affected			.018

Only those variables on which significant effects were present were analyzed

*$p < .05$ Pearson's correlation;

*** $p < .001$ Pearson's correlation

of reach in untreated infants with CP (Boxum et al. 2017). Increased smoothness of reach in a more-affected UE could reflect ability of the developing brain to integrate new and more accurate sensory information (Körding and Wolpert 2006). Although the current report does not examine long-term effects, these infants may have more pronounced effects from increased and more precise UE use as their experience grows (Kurz et al. 2014). This will be a topic of future analyses.

Additionally, a large treatment effect on smoothness of reach of the less-affected (constrained) UE was noted. This measure correlated strongly with smoothness of reach of the more-affected UE. As indicated by the waitlist control group's TD-referenced kinematic smoothness of reach of the less-affected UE, the degree of delay relative to TD performance of the constrained extremity was improved by the intervention, but less in the unconstrained limb. Our study was not designed to investigate why the intervention positively affected the less-affected extremity, but the bimanual aspects of the intervention, in the context of improved somatosensory feedback from the more-affected UE, may explain this unexpected finding. The multiple components of the intervention leverage both adaptive (experience-dependent plasticity that can be modified by training) and reactive plasticity (influenced by sensory deprivation/enrichment) induction (Ismail et al. 2017). These mechanisms of acquiring neural function are less dependent on lesion type, as they recruit multisensory or sensorimotor pathways and associations; thus, they can benefit infants with hemiplegic CP resulting from infarcts as well as those with asymmetric quadriplegia after preterm white matter insults (Jackman et al. 2020).

Fine motor development of the more-affected hand demonstrated small, but significant and clinically important, improvements that are due to intervention. The small size of these unimanual effects on the downstream outcome may be due to brevity of the intervention and the relative insensitivity of the Bayley unimanual items to skills the intervention affected. Even so, the link between the direct outcome (smoothness of reach of the more-affected UE) and this downstream outcome strengthen the logic that the change was due to the intervention. With only two sampling times at a one-month interval, it is difficult to accurately predict a trajectory of motor development. In the case of developmental evolution of handedness in reach and grasp in infants, monthly evaluations over the course of 6–8 months revealed a non-linear trajectory (Ferre et al. 2010). However, gains in smoothness of reach may be relevant to the broader motor development context for these children with CP, as reach is a proxy measure for injury, recovery, and rehabilitation of underlying cellular, molecular, and brain circuitry impairments (Boyd et al. 2017a). Smoothness of reach is indicative of developmental maturity, suggesting that study subjects receiving the intervention may have trajectories that are "catching up "to those of their TD peers. The early gains demonstrated in this study through objective measures of movement quality may also allow later acquisition of more complex skills as a compounding relationship exists between practicing a skill with better coordination, and attainment of new skills (Bakker et al. 2010; Machado et al. 2019). Nonetheless, downstream effect monitoring is needed. The study of long-term trajectories throughout the first three-years is an aim we intend to address in future analyses of motor performance at later measurement periods in this sample.

Safety of the intervention was demonstrated through positive effects or non-effects on measurements involving the constrained, less-affected UE. Not only did smoothness of reach of this extremity increase, but there were non-significant differences on other safety measures, including gross motor skill level.

Current published neuroscientific theory and research suggest that improvements in somatosensory processing would be greatest in the contralateral somatosensory cortex. Ipsilateral reorganization of somatosensory representations from the affected UE have not been demonstrated (Nevalainen et al. 2014). Previous research also suggests that complex processing of tactile information (P200, 200–400 ms post-stimulus) correlates with behavioral measures such as stereognosis and is most likely to change after interventions (Matusz et al. 2018). In the current study, the

between-group posttest difference on the P200 ERP measure of somatosensory processing in the contralateral representation of the more-affected UE was significant before, but not after, alpha adjustment for multiple between-group comparisons on ERP measures. Supporting the need to test for replicated treatment effects in future studies, the intervention group's posttest P200 contralateral ERP measure of somatosensory processing was slightly better than that of the TD group, while waitlisted controls remained delayed compared to the TD group.

In addition to providing a representation of the external world, the somatosensory cortex has recently been shown in animal models to integrate convergent streams of motor and sensory stimuli, dependent on behavioral state during a task, see (Schneider 2020; Sofroniew et al. 2015). Inputs from locomotion, position and sensation are integrated in the primary murine somatosensory cortex, but this process appears more effective during active behaviors rather than passive (as opposed to auditory and visual stimuli, which can be integrated effectively in passive and active states). Furthermore, the human somatosensory system benefits from long stimulus time frames (up to 600 ms) during active exploration tasks, in order to integrate tactile and proprioceptive information for decision making (Hernández-Pérez et al. 2020). While this has been shown in adults, it is likely that this time frame may be even longer in infants with insults in which tactile processing is less efficient. The repeated, active and goal-oriented sensorimotor tasks of the intervention may contribute to this integrative process, along with the use of sticky mittens which allow positive sensory reinforcement of successful reach. This hypothesis can be further strengthened by results previously demonstrated in TD infants using the sticky mittens, who showed earlier development of reaching than those who did not play with the mittens (Needham et al. 2017). Consistent with this finding, infants with CP who received the treatment had somatosensory processing that appeared slightly improved compared to that of TD children who did not receive any treatment. Therefore, our tasks combining repeated longer sensory exposures, with active learning and successful reaches may promote optimal integration of tactile and proprioceptive information during goal-directed movements, even in infants with somatosensory and motor deficits at baseline.

The ERP findings are also intriguing because they are novel to the literature. One component of the current study's intervention is bimanual play, derived from HABIT, a very successful UE motor intervention for older children with CP (Kuo et al. 2016). Even when combined with tactile enrichment, HABIT did not show improvements on behavioral-based somatosensory assessments. However, behaviorally-based measures may not have been reliable or sensitive enough to measure intervention effects on somatosensory processing. In the current study, intervention effects on somatosensory processing were measured with brain-based testing. In addition, our study included infants with three main types of neural insults (neonatal encephalopathy, encephalopathy of prematurity, and term infarct/thrombosis), representing a mixed population compared to studies of HABIT. While somatosensory effects may be more pronounced in infants with one type of lesion compared to another, the current study's goal was to provide a generalizable intervention for all affected infants and was not powered to answer hypotheses centered on lesion type.

Thus, among the contributions of the current study is the demonstration that ERP measures of somatosensory processing were sensitive to change and may be sensitive to short-term intervention effects in infants and toddlers. Future confirmatory work may replicate the between-group difference on the somatosensory responses observed in the P200 time window measured from the frontal region contralateral to the more-affected hand's light-touch stimulation. One advantage of the current ERP procedure is that it does not require active attention to a task, in contrast to some earlier paradigms tested in older children and more similar to those used in newborn infants. In infants, sustained attention to a repetitive and uninteresting stimulus would have been almost impossible to maintain for 10 min, and thus was not supplemented by a directive scenario (Maitre et al. 2017).

Several limitations of the current study exist. First, as some parents randomized to the intervention group inconsistently used the restraint (< 4 h/per week), the observed effect size may be lower than when parents use the restraint more consistently. This may be why the effect size for the downstream motor outcome was rather small and the somatosensory perception outcome was significant only prior to multiple-comparison adjustment. Additionally, using amplitude of the P200 to measure somatosensory processing incompletely characterizes the complexities of topographic and time-dependent changes of underlying source generators. More complex ERP analyses that focus on mechanistic underpinnings of somatosensory changes in response to the intervention may more fully quantify treatment effects on somatosensory processing, and are the topic of a future paper. Third, we were unable to test for maintenance of between-group differences several months after intervention ended. In future work, the trajectories of all children who received the intervention in both groups will be compared to those of a matched cohort of TD children until the age of 3, to determine if changes in motor or somatosensory processing exhibit amplified effects over time. Fourth, we were unable to assess specific contributions of individual intervention components due to study design. Finally, our study was not powered to examine whether constraint-dosage was associated with increases in somatosensory processing after multiple-comparison adjustment. Future ancillary studies using ERP measures of somatosensory processing that are

more sensitive to treatment effects may be able to address this question.

While acknowledging the limitations of this intervention, its generalizability and feasibility remain high. An approach that includes weekly one-hour therapist interactions, with coaching of parents and home exercise plans, administered by parents and integrated into family routines, is consistent with current early intervention models. It does not require extensive therapist involvement (although therapist expertise is necessary) in settings where early intervention programs and parents have limited resources. Tools and toys used were inexpensive and readily available, with the entire kit costing less than $25 (US) per child, making it feasible and easily scalable. To limit the considerable costs of therapy devices incurred by families of children with CP (Berry et al. 2018), the patent for the C-Mitt harness design was made freely available after optimization (https://www.nationwidechildrens.org/research/areas-of-research/center-for-perinatal-research/maitre-lab), with materials commonly available for less than $4 (US).

Conclusion

A multi-component therapist-coached, parent-administered UE intervention is safe for developing somatosensory and motor systems, is effective in improving reaching ability and fine motor skills, and may improve somatosensory processing. Studies in progress comparing parent-administered single constraint versus bimanual training in infants with CP (Boyd et al. 2017b) will further answer which components of these interventions may best benefit infants with CP, while others will investigate dosage, and long-term effects of the treatment.

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Author Contributions NLM conceived and designed the study, acquired and analyzed the data, drafted the manuscript created the figures, and obtained funding. AJ acquired and analyzed EEG data and created figures. PJY designed the trial data analysis, analyzed data, created tables, and drafted a significant portion of the manuscript. APK helped conceptualize the study and the EEG analysis, monitored EEG data reliability, and drafted a significant portion of the manuscript. JCS contributed to the study design, analyzed data, and drafted a significant portion of the manuscript. HC acquired data, designed fidelity measures, and drafted a significant portion of the manuscript. AN helped conceptualize the study intervention, designed the sticky mittens, and drafted a significant portion of the manuscript. MMM helped conceptualize the study and the EEG analysis and drafted a significant portion of the manuscript. JH helped conceptualize the study kinematics, analyzed the kinematics data and drafted a significant portion of the manuscript and figures.

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Data Availability All reasonable requests from qualified scientists for unique research resources (ERP paradigms, protocols and expertise) developed with NIH funds for research purposes will be honored. We will fill requests in a timely manner. We will adhere to the NIH Grant Policy on Sharing of Unique Research Resources including the Sharing of Biomedical Research Resources Principle and Guidelines for Recipients of NIH Grants and Contracts. There is no unique biological information that could be made available to the scientific community. De-identified ERP raw data will be retained on the Abigail Wexner Research Institute at Nationwide Children's Hospital server, and assessment data will be retained in REDCap. These data will be made available to investigators who make specific inquiry for good cause 5 years after the conclusion of the final outcomes.

Compliance with Ethical Standards

Conflict of interest Dr. Maitre reports USPTO 29/577,142 (C-MITT, Soft Constraint Harness for Infants 6–27 months—for filing design application), pending. The remaining authors report no conflict of interest.

Ethical Approval This research was approved by the Nationwide Children's Hospital Institutional Review Board on June 18, 2015.

Informed Consent Written informed consent was obtained for each subject included in the study. Consent for publication of non-identifiable results is included in the written informed consent.

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