Brain stimulation and constraint for perinatal stroke hemiparesis

The PLASTIC CHAMPS Trial

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ABSTRACT

Objective: To determine whether the addition of repetitive transcranial magnetic stimulation (rTMS) and/or constraint-induced movement therapy (CIMT) to intensive therapy increases motor function in children with perinatal stroke and hemiparesis.

Methods: A factorial-design, blinded, randomized controlled trial (clinicaltrials.gov/NCT01189058) assessed rTMS and CIMT effects in hemiparetic children (aged 6–19 years) with MRI-confirmed perinatal stroke. All completed a 2-week, goal-directed, peer-supported motor learning camp randomized to daily rTMS, CIMT, both, or neither. Primary outcomes were the Assisting Hand Assessment and the Canadian Occupational Performance Measure at baseline, and 1 week, 2 and 6 months postintervention. Outcome assessors were blinded to treatment. Interim safety analyses occurred after 12 and 24 participants. Intention-to-treat analysis examined treatment effects over time (linear mixed effects model).

Results: All 45 participants completed the trial. Addition of rTMS, CIMT, or both doubled the chances of clinically significant improvement. Assisting Hand Assessment gains at 6 months were additive and largest with rTMS + CIMT (β coefficient = 5.54 [2.57–8.51], $p = 0.0004$). The camp alone produced large improvements in Canadian Occupational Performance Measure scores, maximal at 6 months (Cohen $d = 1.6$, $p = 0.002$). Quality-of-life scores improved. Interventions were well tolerated and safe with no decrease in function of either hand.

Conclusions: Hemiparetic children participating in intensive, psychosocial rehabilitation programs can achieve sustained functional gains. Addition of CIMT and rTMS increases the chances of improvement.

Classification of evidence: This study provides Class II evidence that combined rTMS and CIMT enhance therapy-induced functional motor gains in children with stroke-induced hemiparetic cerebral palsy. *Neurology*® 2016;86:1659–1667

GLOSSARY

AHA = Assisting Hand Assessment; **CIMT** = constraint-induced movement therapy; **COPM** = Canadian Occupational Performance Measure; **CP** = cerebral palsy; **PLASTIC CHAMPS** = Plastic Adaptation Stimulated by TMS and Induced Constraint for Congenital Hemiparesis After Perinatal Stroke; **RR** = relative risk; **rTMS** = repetitive transcranial magnetic stimulation; **TMS** = transcranial magnetic stimulation.

Cerebral palsy (CP) accounts for most lifelong physical disability, affecting >500,000 North American children and families.¹ Hemiparetic CP is a common subtype and is usually the result of perinatal stroke.² CP definitions imply a permanent neurologic condition³ and treatment options are limited. Perinatal strokes represent an ideal human model of developmental plasticity because they are focal injuries of defined timing in normal brains. Models of motor development following perinatal stroke developed from both animal⁴ and human^{5,6} studies suggest that the contralesional motor cortex influences function and is a potential therapeutic target.^{6–8}

Constraint-induced movement therapy (CIMT) may be effective in hemiparetic CP.⁹ CIMT restrains the better limb during therapy to promote affected limb function. In hemiparesis due

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to adult stroke, CIMT for 2 weeks produces gains lasting years.¹⁰ Noninvasive repetitive transcranial magnetic stimulation (rTMS) may produce lasting modulation of cortical activity. Randomized controlled trials suggest that short courses of inhibitory, contralesional rTMS improves function in hemiparesis due to adult stroke.^{11,12} A recent trial of contralesional rTMS in 19 participants with hemiparetic CP suggested favorable tolerability and functional short-term gains.¹³ Brain stimulation and CIMT have not been specifically evaluated in perinatal stroke.

We conducted a factorial design, randomized controlled trial of intensive therapy paired with rTMS and/or CIMT to evaluate their effects on upper limb motor function in children with hemiparesis due to perinatal stroke. We hypothesized that intervention would be associated with larger functional gains at 6 months.

METHODS Trial design and participants. PLASTIC CHAMPS (Plastic Adaptation Stimulated by TMS and Induced Constraint for Congenital Hemiparesis After Perinatal Stroke) was a randomized, blinded, single-center, controlled clinical trial. A factorial (2×2) design simultaneously evaluated 2 interventions: CIMT and rTMS.¹⁴ Recruitment, randomization, and flow are summarized in figure 1A. The primary research questions were whether rTMS or CIMT in addition to intensive therapy improves motor function in children with perinatal stroke and hemiparesis (current levels of evidence II for CIMT and III for rTMS).

Participants were recruited via the Alberta Perinatal Stroke Project, a population-based research cohort from August 2010 to August 2013 (final outcomes March 2014). Recruitment was dependent on date of diagnosis and grouping by developmental level. Perinatal ischemic stroke diagnosis and type (arterial or venous) were assigned from clinically obtained MRI using validated classification.¹⁵ Participants were recruited in person with the opportunity to try rTMS before consenting.

Standard protocol approvals, registrations, and patient consents. All participants or their guardians provided written informed consent/assent. Institutional research ethics board approval was obtained. The trial was registered at clinicaltrials.gov (NCT01189058).

Inclusion criteria were as follows: (1) symptomatic hemiparesis (including perceived functional limitations by child and parent); (2) MRI-confirmed unilateral perinatal ischemic stroke; (3) age 6 to 19 years; (4) term birth (>35 weeks); and (5) written informed consent/assent. Exclusions were as follows: (1) additional neurologic abnormality; (2) multifocal stroke; (3) severe hemiparesis (Manual Ability Classification System V or $<20^\circ$ finger/wrist extension) or predominant dystonia; (4) developmental delay precluding compliance; (5) unstable epilepsy; (6) TMS contraindication¹⁶; or (7) CIMT within 6 months, upper limb surgery, or botulinum toxin within 12 months. Presence of stroke-side motor evoked potentials was not required.

Randomization and masking. Participants were randomized as a group before each camp (1:1) to rTMS/sham and 1:1 to CIMT/none. The statistician used random size blocks for group balance while accommodating camp sizes of 4 to 8 participants. Randomization was not stratified because of the sample size, unknown prognostic factors, and grouping by age to optimize psychosocial benefits. Study personnel, participants, and parents were blind to rTMS assignment. CIMT assignment was concealed from measuring occupational therapists. Subject estimation of rTMS assignment was recorded (days 1, 10).

Interventions. Motor learning therapy (all participants). Participants attended the Alberta Children's Hospital Rehabilitation Facility for 10 consecutive weekdays, completing a structured, child-centered, intensive motor learning therapy program. Study structure is summarized in figure 1B. Therapy totaled 80 hours per participant with form and intensity codified in a standard operating procedure manual. Therapy details by TIDieR (Template for Intervention Description and Replication) criteria are available in table e-1 on the *Neurology*[®] Web site at Neurology.org. Participants were grouped by developmental level in a peer-supported environment. Motor learning therapy was designed by pediatric neurorehabilitation experts based on best evidence. Each 8-hour day consisted of individualized (2 h/d) and group (5.5 h/d) activities. Target total therapy dose was 80 hours (20 individual, 55 group, 5 rTMS). Two hours of direct, one-on-one motor learning therapy each day was delivered by an experienced occupational therapist. Interventions were individualized to the specific goals of each child. Tasks were graded and selected according to relative function with increasing complexity and geared to age-appropriate activities of daily living. Assistive technologies including virtual reality and video games were used. Group activities incorporating upper extremity training were delivered by occupational therapists (1:3 ratio) and allied health professionals. Activities were sports, horticultural and music therapy, creative gaming (e.g., "Rock Band"), and therapeutic arts. During breaks (0.5 h/d), an upper extremity activity of the child's choice was encouraged, and activities of daily living were focused on during lunch/snack times (2 h/d).

During the 2-week intervention, participants were prescribed 60 min/evening of goal-directed upper limb activities. Following this, participants received a structured bimanual home program (15 min/d) based on evolution of their goals with a "transfer package" to promote integration into daily activities. Therapists met with families at 2 and 4 months and were available by phone to adjust therapy as needed.

rTMS or sham (1:1 randomization). Brain stimulation occurred at the Alberta Children's Hospital Pediatric Non-invasive Neuromodulation Laboratory immediately before daily 1:1 therapy. At baseline, the contralesional primary motor cortex was mapped (optimal location for stimulation of first dorsal interosseous using single-pulse TMS) to each participant's MRI (Brainsight2 neuronavigation, Rogue, Montreal). An air-cooled 70-mm rTMS coil (Airfilm; Magstim, Whitland, UK) was placed tangentially at 45° over this target. Inhibitory rTMS parameters based on evidence from controls and adult¹² and childhood stroke¹⁷ were as follows: intensity 90% resting motor threshold, frequency 1 Hz, and duration 20 minutes (1,200 stimuli). Sham participants underwent identical procedures but the coil was perpendicular (90°) to the skull, producing comparable sensations but no possible stimulation.^{17,18} Baseline single-pulse TMS determined corticospinal tract arrangement using established methods.¹⁹

CIMT or not (1:1 randomization). Methods were based on best evidence.^{20,21} The well-functioning limb was restrained by a

Figure 1 Recruitment, randomization, and flow

(A) Screening sampled the eligible population across the study period grouped by age and developmental level. Most were excluded by age or ability to attend the program. Intention-to-treat groups are shown as analyzed. (B) Study flow began with baseline motor function and neurophysiology outcome measures within 2 weeks of starting therapy. Daily programming for 2 weeks (days 1–10) included goal-directed, intensive motor learning therapy. Participants randomly received daily contralesional rTMS, CIMT, neither, or both. Outcome measures were repeated at 1 week, 2 months, and 6 months. APSP = Alberta Perinatal Stroke Project; CIMT = constraint-induced movement therapy; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

custom-fit, bivalved, removable cast from below the elbow to the distal interphalangeal joint, preventing grasp but allowing supportive use. The adherence target was 100% of the daily camp (8 hours) and 90% of waking hours. Treating occupational therapists fit the cast, confirmed compliance, and screened for complications.

Outcome measures. The primary outcome of upper extremity function was evaluated using the Assisting Hand Assessment (AHA), the evidence-based standard for bilateral upper extremity function in hemiparetic children.^{22,23} Structured application was performed by the same certified occupational therapist blinded to patient characteristics and treatment allocation. Baseline motor function measures within 2 weeks of trial initiation were repeated at 1 week, 2 months, and 6 months

postintervention (figure 1B). The principal subjective outcome was the Canadian Occupational Performance Measure (COPM),²⁴ a patient-centered measure in which performance and satisfaction scores (1–10) for each goal were averaged. Functional goals were set by agreement among participants, parents, and the therapist. The COPM is validated for pediatric hemiparesis trials with gains ≥ 2 points considered clinically significant.^{24–26} Details of these and the secondary functional outcomes (Melbourne Assessment, PedsQL [Pediatric Quality of Life Inventory] CP, ABILHAND-Kids, grip strength, and box and blocks test) are available in table e-2.

Safety and tolerability. The primary adverse outcome for rTMS was decreased function of either hand. A pediatric TMS tolerability measure was applied on days 1 and 10.²⁷ A data and safety monitoring board conducted interim safety analyses after 12 and 24

Table 1 Patient characteristics by treatment group

Characteristic	Treatment group			
	Neither (n = 12)	CIMT only (n = 11)	rTMS only (n = 10)	CIMT + rTMS (n = 12)
Demographics, stroke				
Age, y, mean (SD)	10.34 (3.5)	10.57 (3.7)	12.20 (4.2)	13.23 (3.7)
Range	6.32-18.22	6.23-17.63	6.32-18.48	8.26-19.79
Sex, male, n (%)	7 (58)	6 (55)	5 (50)	10 (83)
Stroke type: Arterial, PVI	10, 2	5, 6	7, 3	7, 5
Stroke side: Left, right	5, 7	8, 3	4, 6	8, 4
Baseline function				
COPM satisfaction, mean (SD)	4.42 (2.0)	3.37 (1.1)	3.69 (2.6)	3.90 (1.7)
COPM performance, mean (SD)	3.44 (1.3)	2.94 (1.0)	2.77 (1.7)	3.85 (1.5)
AHA logit, mean (SD)	63.92 (15.6)	68.36 (18.3)	53.20 (21.3)	62.50 (16.6)
Median (range)	61.50 (46-100)	66.00 (37-100)	47.50 (33-100)	61.00 (39-84)
MA, %, mean (SD)	74.72 (18.7)	85.19 (16.2)	61.69 (24.3)	76.50 (22.4)
Median (range)	79.78 (34.8-100)	91.01 (51.69-100)	53.37 (32.6-100)	82.58 (40.5-98.9)
PedsQL parent, mean (SD)	76.55 (19.6)	64.41 (21.2)	71.36 (27.2)	76.85 (21.3)
PedsQL child, mean (SD)	80.55 (21.0)	75.04 (17.8)	75.18 (24.8)	85.19 (15.8)
ABILHAND-Kids, mean (SD)	2.69 (2.3)	1.96 (1.9)	2.18 (2.2)	3.62 (2.4)
Grip affected, kg, mean (SD)	15.93 (10.7)	16.97 (12.9)	15.15 (16.3)	16.88 (13.4)
Box and blocks, mean (SD)	19.58 (14.5)	25.18 (12.9)	17.90 (16.4)	24.58 (15.4)
PSOM total, mean (SD)	2.08 (1.3)	1.64 (0.7)	2.25 (1.6)	2.13 (1.1)
PSOM nonmotor delays	Mild 2, Mod 5	Mild 3, Mod 1	Mild 2, Mod 2	Mild 0, Mod 5
Normal hand function				
Grip unaffected, mean SD	35.70 (23.3)	40.27 (25.9)	42.60 (23.1)	39.47 (15.2)
Box and blocks, mean (SD)	46.58 (10.7)	43.09 (14.3)	47.20 (16.1)	52.33 (11.6)
Neurophysiology				
No stroke side resting MEP, n (%)	5 (42)	3 (27)	6 (60)	4 (33)
Ipsilateral orientation, ^a n (%)	5 (42)	4 (36)	6 (60)	5 (42)
Stroke-side RMT, mean (SD) ^b	67.3 (17.2)	76.6 (19.2)	55.5 (15.7)	68.1 (17.9)
Stroke-side AMT, mean (SD) ^b	63.7 (23.9)	60.5 (15.4)	46.0 (11.6)	58.9 (20.0)
Nonstroke RMT, mean (SD)	60.7 (16.4)	67.2 (15.6)	58.4 (22.3)	52.8 (16.6)
Nonstroke AMT, mean (SD)	55.0 (17.1)	57.4 (17.3)	40.3 (12.6)	42.3 (16.1)

Abbreviations: AHA = Assisting Hand Assessment; AMT = active motor threshold; CIMT = constraint-induced movement therapy; COPM = Canadian Occupational Performance Measure; MA = Melbourne Assessment; MEP = motor evoked potential; Mod = moderate; PedsQL = Pediatric Quality of Life Inventory; PSOM = Pediatric Stroke Outcome Measure; PVI = periventricular venous infarction; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation.

^aIpsilateral orientation: >5/20 TMS stimulations of nonlesioned M1 at 120% RMT produce ipsilateral MEP >0.5 mV.

^bMean data from only those participants with obtainable stroke-side MEP as indicated.

participants. Stopping rules were significant decrease in function of either limb or serious adverse event associated with rTMS.

Sample size and analysis. Sample size was estimated using 2-way analysis of variance to detect a clinically significant change at 6 months of 5 AHA logit units (smallest detectable difference of 5),^{26,28} $\alpha = 0.05$, and power of 90%. We estimated 11 participants per group (n = 44), a sample larger than existing adult stroke stimulation¹² and pediatric CIMT trials.^{20,29}

The primary outcome of change in AHA from baseline to 6 months was analyzed on an intention-to-treat basis using a 2-way analysis of variance to explore effects of rTMS and CIMT

using an “at the margins” approach.¹⁴ We used a linear mixed effects model with repeated measures to examine interactions of time (change at 1 week, 2 months, and 6 months) with treatment group for each outcome expressed as β coefficient (95% confidence intervals). A secondary per-protocol analysis was conducted using the same methods. Dichotomous variables for smallest detectable difference in COPM and AHA, safety and blinding outcomes were assessed using χ^2 /Fisher exact tests and reported as relative risk (RR) (95% confidence intervals). Normally distributed continuous variables were compared using 2-sample independent *t* tests. Statistical analyses were completed using R-Project version 3.1.2.

RESULTS Population. During the enrollment period (August 2010 to August 2013), 199 children were screened (figure 1A). Of these, 154 (77%) were excluded (including 3 families for personal reasons only) and 45 were consented and randomized (table 1). Treatment groups were not significantly different in any baseline characteristics. All participants completed all interventions and outcomes. Two participants randomized to rTMS crossed over and were reassigned to sham because of high resting motor thresholds ($>90\%$) precluding rTMS. None of the following intention-to-treat analysis findings or conclusions were altered by the secondary per-protocol analysis.

Primary objective outcome: AHA. On the primary outcome of change in AHA logit units at 6 months, the combined rTMS + CIMT group improved by 5.91 (3.4) units compared to 0.62 (1.9) units in those receiving neither (β coefficient = 5.54 [2.57–8.51], $p = 0.0004$; figure 2A). Gains were evident at 1 week (β coefficient = 3.46 [0.49–6.44], $p = 0.02$) and 2 months (β coefficient = 5.92 [2.95–8.90], $p = 0.0002$). Effects of rTMS and CIMT were additive with no detectable interaction between treatment types. There were treatment-specific increases over time. The CIMT-only group showed AHA improvements at 1 week (β coefficient = 6.50 [3.11–9.89], $p = 0.0003$) and 2 months (β coefficient = 6.30 [2.91–9.69], $p = 0.0004$) but not at 6 months (β coefficient = 2.8 [–0.59 to 6.19], $p = 0.11$). The rTMS-only group demonstrated gains at 1 week (β coefficient = 5.22 [1.65–8.80], $p = 0.005$) that were not evident at 6 months (β coefficient = 3.11 [–0.46 to 6.69], $p = 0.09$).

Nineteen participants (42%) achieved the smallest detectable difference in AHA (≥ 5 logit units). Addition of any intervention approximately doubled the chances of achieving a clinically significant improvement: neither (17%), CIMT (45%, RR 2.2 [0.7–6.8]), rTMS (50%, RR 1.9 [0.6–6.6]), CIMT + TMS (58%, RR 2.4 [0.9–7.6]). For all rTMS vs sham, the primary outcome was achieved in 52% vs 33% (RR 1.4 [0.8–2.6], $p = 0.13$) and for CIMT vs no CIMT, the primary outcome was achieved in 52% vs 32% (RR 1.6 [0.8–3.4], $p = 0.10$). Effect sizes (Cohen d) were in the direction of benefit for both CIMT (0.64) and rTMS (0.71).

Primary subjective outcome: COPM. COPM scores increased over time across the entire group (figure 2B). Both performance and satisfaction scores increased at 1 week (6.1 [1.7] and 6.3 [2.2], $p < 0.001$). Effects were sustained or increased over time with maximal gains at 6 months (performance 6.7 [1.6], satisfaction 7.3 [1.8]). Most achieved clinically significant gains (≥ 2 points) in both elements at 6 months: 31 (69%)

Figure 2 Primary outcomes

(A) AHA scores across time and treatment. Largest changes at 6 months were observed with rTMS + CIMT. Top dashed line indicates clinically significant change of ≥ 5 logit units. (B) COPM satisfaction and performance increased at 1 week with sustained or further elevations at 2 and 6 months across all participants. (C) Change in COPM by treatment group. Clinically significant gains (≥ 2 units, top dashed line) were associated with CIMT, rTMS, or both. Open circles = outliers. AHA = Assisting Hand Assessment; CIMT = constraint-induced movement therapy; COPM = Canadian Occupational Performance Measure; rTMS = repetitive transcranial magnetic stimulation.

satisfaction, 38 (84%) performance. Clinical examples are presented in table e-3. The effect size of the camp itself was large, regardless of additional treatments (Cohen $d > 1.3$; figure 2C). Addition of CIMT and/or rTMS increased the proportion achieving significant gains with satisfaction/performance proportions of neither (33%/67%), CIMT (64%/73%), rTMS (100%/100%), and CIMT + rTMS (83%/100%). CIMT was associated with significant gains in satisfaction ($p = 0.04$) but not performance ($p = 0.21$). Treatment with rTMS was associated with significant gains in satisfaction ($p = 0.01$) and performance ($p = 0.02$).

Secondary outcomes. Melbourne scores were increased at 1 week (figure 3A). Gains were larger in the rTMS-only group ($F = 5.62$, $p = 0.003$). Melbourne scores were unchanged at 6 months (figure 3B). Parents reported treatment-related improvements in quality-of-life measures including daily activity, school activity, and movement/balance subscores at 6 months (figure 3, C and D). Subscales of pain/hurt, fatigue, eating, and speech/communication did not change. Child and parent reports agreed across 6 of 7 subscales. No changes in ABILHAND-Kids scores were observed.

Safety and tolerability. All participants completed all stages with no dropouts or adverse events. No decrease in unaffected extremity function occurred (figure 4). Box and blocks scores in the unaffected limb increased at 6 months with greater gains associated with CIMT ($p = 0.03$). Grip strength in the unaffected limb also improved with greater gains associated with rTMS ($p = 0.008$). Unimanual function

(Melbourne scores) in participants with ipsilateral corticospinal arrangements ($n = 20$) did not decrease with rTMS (scores were higher, $p = 0.03$; figure 4C). Tolerability was favorable with mean rTMS scores of 4.2 (0.1) ranking between a birthday party and long car ride and comparable to sham (4.0 [1.0]/4.0 [1.4], $p = 0.9$). Headache reported in 11% was mild and self-limiting. Additional side effects (tingling, nausea) were reported in $<3\%$ of sessions. There was no association between participant guess and rTMS treatment received. On an exit survey, 96% of families said they would recommend the program to others.

DISCUSSION We simultaneously evaluated rTMS and CIMT within an intensive motor learning program among children with hemiparesis due to perinatal stroke. Addition of rTMS or CIMT doubled the chances of significant improvement with additive effect. The effect of the camp itself was large with most children showing sustained functional gains at 6 months.

Our study advances noninvasive neuromodulation in children. Two pediatric rTMS studies in childhood stroke¹⁷ and CP¹³ reported favorable safety and tolerability across 10 and 19 children, respectively. The hemiparetic CP trial¹³ was dominated by perinatal stroke, providing preliminary evidence of safety and efficacy. Children without stroke-side motor evoked potentials were excluded because of theoretical concern of inhibiting contralesional motor cortex. This appropriate consideration added complexity while reducing

Figure 3 Secondary outcomes

(A) Mean MA scores increased from baseline at 1 week with greater effects in the rTMS group. (B) By 6 months, no change in mean MA score was observed across groups. PedsQL CP-measure parent scores for child daily activity (C) and school activity (D) increased at 6 months with treatment effects similar to those seen in motor function scores (* $p < 0.05$). Open circles = outliers. CIMT = constraint-induced movement therapy; CP = cerebral palsy; MA = Melbourne Assessment; PedsQL = Pediatric Quality of Life Inventory; rTMS = repetitive transcranial magnetic stimulation.

Figure 4 Safety

Unaffected hand function did not decrease with any interventions. (A) Box and blocks performance at 6 months was unchanged except for an increase in function associated with CIMT ($p = 0.03$). (B) Grip strength of the unaffected hand was maintained and increased in those receiving rTMS ($p = 0.008$). (C) In participants with prominent ipsilateral corticospinal tract arrangements ($n = 20$), no decrease in hand function was associated with rTMS where MA gains were actually larger. Open circles = outliers. CIMT = constraint-induced movement therapy; MA = Melbourne Assessment; rTMS = repetitive transcranial magnetic stimulation.

eligibility for children with greater disability.^{5,6} Consistent with current models,^{5,6,8} we instead considered this interhemispheric balance as a spectrum, rather than a dichotomy, and included participants without stroke-side motor evoked potentials. This approach was in keeping with adult stroke neuromodulation whereby such “pushing” of motor control toward the lesioned hemisphere has been hypothesized. Our results suggest contralesional rTMS is a promising rehabilitation approach in children with CP, including those with more severe hemiparesis.

How low-frequency rTMS of contralesional M1 might facilitate motor learning after perinatal stroke is poorly understood. Animal and human evidence suggest maximizing motor control in the lesioned hemisphere is associated with better function.^{5,6} Early injury affects the ability of upper motor neurons to compete with their contralateral counterparts (equally present at birth) to innervate spinal lower motor neurons.⁸ Inhibition of contralesional M1 with 1-Hz rTMS³⁰ might enhance lesioned hemisphere function to facilitate therapy-induced motor learning. Although models differ, this approach has demonstrated efficacy in adult stroke rehabilitation.¹² With

few pediatric studies and emerging exceptions to these “rules” of neuromodulation,³¹ the need for safety-oriented trials and establishment of neuromodulation principles in children remains.³² With lifelong morbidity, limited therapeutic options, and substantial safety evidence, we suggest further trials of noninvasive neuromodulation in CP are warranted.

A recent meta-analysis of CIMT hemiparetic CP trials described modest effect sizes with substantial variability.⁹ We adhered to established principles including dose-equivalent comparison groups and medium-term follow-up. CIMT effects were modest compared to well-powered adult stroke studies and pediatric studies in congenital hemiplegia.¹⁰ Our study is unique in the potentially additive benefits observed by combining CIMT with rTMS. Combined, multimodal approaches require additional exploration.³³

Most children experienced sustained improvements regardless of treatment with implications for CP neurorehabilitation. Short-duration, intensive models are increasingly utilized in both adult and pediatric populations.^{9,10} Our results complement this evidence and emphasize the need for comparative

studies with intermittent therapy models. Such approaches are resource intensive, requiring skilled, multidisciplinary teams. Dosage and intensity may be important determinants of therapy-induced plastic change. Optimal timing of follow-up for clinically relevant change has not been determined although immediate changes may preclude functional integration while very long-term outcomes (years) limit trial completion. The persistent gains we observed at 6 months may relate to lasting synaptic change. Positive effects on child psychology including peer support, realization of potential, or enhanced self-confidence may also alter developmental trajectories.

Limitations include a single-center trial and modest sample size that precluded examination of covariates such as age, stroke type, and baseline disability. A ceiling effect for the AHA (3 participants scored 100) may have limited discriminatory ability in higher-functioning children. The AHA is also unable to specifically characterize what “clinically significant” improvement looks like across children with variable function and goals. The randomization imposed by peer grouping may be an unavoidable requirement to optimize psychosocial benefits in such trials. Quality-of-life measures improved but likely failed to capture meaningful psychosocial changes observed anecdotally. Most had never met another child with hemiparesis. They worked closely and intensively with age-matched peers, often in group settings. They shared goals, faced similar challenges, supported each other, and realized successes together. Such examples of personal growth were consistently reported by participants and parents. Measures to capture these effects in future interventional studies would enhance the quality of the data and associated conclusions.

Disease specificity was a major advantage of our study. Nonspecific historical definitions of CP are no longer adequate to understand what multiple brain disorders are causing congenital hemiparesis. We applied validated, evidence-based imaging criteria to define the most common and specific disease state. Such specificity facilitated the direct translation of preclinical studies that predicted motor reorganization following early injury^{4–6} and identified the nonlesioned motor cortex as a potential therapeutic target.⁸ Attention to such disease specificity may facilitate translation of our results to other forms of CP where our results suggest neuromodulation to affect meaningful gains in function is possible.

AUTHOR CONTRIBUTIONS

A.K.: principal investigator, all elements of study design, funding, execution, data collection, analysis, primary author of manuscript. J.A.: study design including rehabilitation methods, motor outcome measures, analysis, clinical interpretation, and manuscript review. M.H.: occupational therapy methods, interventional applications, outcome measurement design and interpretation, and manuscript review. A.N.-A.: primary statistician, statistical methodology, data analysis, randomization, and manuscript review. L.

C.: study design and execution including child life interventions, day camp methods and interventions, psychosocial outcome analysis, and manuscript review. O.D.: study design and execution including TMS methodology, applications, quality assurance, safety outcomes, and manuscript review. J.K.: study design and execution including case ascertainment, recruitment, consenting, treatment delivery, and manuscript review. A.M.: participant diagnosis and recruitment, study design and execution, and manuscript review. J.H.: study execution including recruitment, data management and analysis, and manuscript review. M.D.H.: senior author including study design, data monitoring and safety, clinical trial methodology, statistical analysis, and manuscript review.

ACKNOWLEDGMENT

The authors gratefully acknowledge the following contributors: Helen Carlson, PhD (Neurosciences, Alberta Health Services, Alberta Children's Hospital, neuroimaging methods development); Lorelea Schwed, BScOT (Neurosciences, Alberta Health Services, Alberta Children's Hospital, pediatric occupational therapy, outcome measure scoring); Colleen Lane, BScOT (Neurosciences, Alberta Health Services, Alberta Children's Hospital, pediatric occupational therapy, camp methods); Kathleen O'Grady, MSc (Glenrose rehabilitation hospital, pediatric occupational therapy, outcome measure scoring); Gillian Hoyt-Hallett, MSc (Neurosciences, Alberta Health Services, Alberta Children's Hospital, pediatric occupational therapy, senior management); Conny Betuzzi, BA (Neurosciences, Alberta Health Services, Alberta Children's Hospital, resource management).

STUDY FUNDING

Supported by the Heart and Stroke Foundation of Canada, Alberta Children's Hospital Foundation. The funder had no role in study design, data collection, analysis or interpretation, or writing of the report. The corresponding author had full access to the data and final responsibility for the decision to submit.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 12, 2015. Accepted in final form December 17, 2015.

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