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Improved Myelination following Camp Leg Power, a Selective Motor Control Intervention for Children with Spastic Bilateral Cerebral Palsy: A Diffusion Tensor MRI Study

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ABSTRACT

BACKGROUND AND PURPOSE: Children with spastic cerebral palsy have motor deficits associated with periventricular leukomalacia indicating WM damage to the corticospinal tracts. We investigated whether practice of skilled lower extremity selective motor control movements would elicit neuroplasticity.

MATERIALS AND METHODS: Twelve children with spastic bilateral cerebral palsy and periventricular leukomalacia born preterm (mean age, 11.5 years; age range, 7.3–16.6 years) participated in a lower extremity selective motor control intervention, Camp Leg Power. Activities promoted isolated joint movement including isokinetic knee exercises, ankle-controlled gaming, gait training, and sensorimotor activities (3 hours/day, 15 sessions, 1 month). DWI scans were collected pre- and postintervention. Tract-Based Spatial Statistics was used to analyze changes in fractional anisotropy, radial diffusivity, axial diffusivity, and mean diffusivity.

RESULTS: Significantly reduced radial diffusivity ($P < .05$) was found within corticospinal tract ROIs, including 28.4% of the left and 3.6% of the right posterior limb of the internal capsule and 14.1% of the left superior corona radiata. Reduced mean diffusivity was found within the same ROIs (13.3%, 11.6%, and 6.6%, respectively). Additionally, decreased radial diffusivity was observed in the left primary motor cortex. Additional WM tracts had decreased radial diffusivity and mean diffusivity, including the anterior limb of the internal capsule, external capsule, anterior corona radiata, and corpus callosum body and genu.

CONCLUSIONS: Myelination of the corticospinal tracts improved following Camp Leg Power. Neighboring WM changes suggest recruitment of additional tracts involved in regulating neuroplasticity of the motor regions. Intensive practice of skilled lower extremity selective motor control movements promotes neuroplasticity in children with spastic bilateral cerebral palsy.

ABBREVIATIONS: ACR = anterior corona radiata; AD = axial diffusivity; ALIC = anterior limb of the internal capsule; CC = corpus callosum; CerPed = cerebral peduncle; CP = cerebral palsy; CST = corticospinal tract; EC = external capsule; FA = fractional anisotropy; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; MD = mean diffusivity; PLIC = posterior limb of the internal capsule; PVL = periventricular leukomalacia; RD = radial diffusivity; SCALE = Selective Control Assessment of the Lower Extremity; SCR = superior corona radiata; SMC = selective motor control; TBSS = Tract-Based Spatial Statistics

Children born prematurely are vulnerable to WM motor tract injury, with the resulting severity of motor impairment dependent on the extent of neuronal damage. The corticospinal tracts (CSTs) responsible for selective motor control (SMC) are particularly vulnerable to damage due to their anatomic location. Periventricular leukomalacia (PVL), indicating CST damage, is a common MR imaging finding in children with spastic bilateral cerebral palsy (CP).[1] Impaired SMC presents as a lack of isolated joint movement and may include flexor/extensor synergy patterns and mirror movements with reduced force, speed, and timing of movement.[2,3] SMC can be measured clinically using the Selective Control Assessment of the Lower Extremity (SCALE).[2] SCALE scores correlate with intralimb coordination[4] and knee

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extension acceleration during gait[5] and have a larger causal effect on gross motor function than strength, spasticity, contractures, and bony deformities.[6] SMC is considered a prognostic factor for surgical outcomes.[7,8]

DTI has been used to assess WM damage in children with spastic CP.[9-12] Relative to normative data, reduced fractional anisotropy (FA) has been interpreted as a marker of disruption of local tissue structural anisotropy; higher radial diffusivity (RD), as decreased myelination; lower axial diffusivity (AD), as axonal injury; and higher mean diffusivity (MD), as greater overall diffusion.[13-18] Lower FA,[9-12] higher RD and MD,[10,12] and bidirectional results for AD[10,12] have been reported for children with spastic bilateral CP compared with children with typical development. In children with spastic bilateral CP, significant correlations between DTI measures and the Gross Motor Function Classification System (GMFCS) levels,[10,11] Gross Motor Function Measure (GMFM),[12] and SCALE scores[12] have been found. SCALE scores were found to correlate positively with FA and negatively with RD in more motor regions of the brain compared with GMFM.[12]

Neuroplasticity as evidenced by changes in the microstructural properties of WM motor tracts in spastic CP is not well-understood. DTI studies examining the response to exercise interventions are limited, and improvements have yet to be clearly demonstrated. Most have focused on upper extremity therapy in children with unilateral CP with contrasting results.[19-21] No significant changes were found in any DTI measure in cohorts of children and young adults with unilateral CP following constraint-induced therapy[19] and constraint-induced therapy preceded by transcranial direct current stimulation.[21] In contrast, Kim et al[20] found increased FA following a task-specific upper extremity exercise intervention in infants with CP, suggesting that microstructural changes may be more likely in younger participants with greater plasticity.

DTI changes of WM motor regions in children with spastic CP in response to a lower extremity exercise intervention have received little attention. Researchers in India examined FA using tractography following 6 months of daily physical therapy (1.5 hours/day for 24 weeks) that was preceded by botulinum toxin injections and casting for children born full-term with bilateral spastic CP (GMFCS levels I–IV).[22] Physical therapy included strengthening, gait training, and stretching. They found significant increases in FA of motor and sensory bundles and GMFM, regardless of botulinum toxin assignment, supporting the efficacy of intensive lower extremity physical therapy. Improved FA, which has not been reported in other studies of lower extremity motor intervention in this population, may be related to the high physical therapy dosage. This dosage is not feasible in most settings and may place a considerable burden on a child and his or her family. Jain et al[23] reported that neither FA nor the apparent diffusion coefficient increased following botulinum toxin injections and 6 months of physical therapy in a cohort of children with spastic bilateral CP. ROIs, however, were defined differently (on the basis of WM perfusion). Most studies of lower extremity interventions in spastic CP to date have not included RD or MD.

While previous CP studies used DTI to observe specific isolated WM motor tracts, full tract reconstruction can be difficult in cohorts with impaired WM leading to exclusion of participants.[20,24,25] Additionally, focusing on a priori WM tracts may limit the scope of analysis and underestimate the global extent of WM neuroplasticity. Tract-Based Spatial Statistics (TBSS), a whole-brain voxel-based approach, can be used to observe an intervention effect on all WM tracts, including motor regions of the brain,[26] circumventing these issues.

The effect of an intensive lower extremity SMC intervention on WM motor tract microstructure has not been studied in children with spastic bilateral CP born prematurely with PVL. We hypothesized the following: 1) DTI measures would improve following intensive task-specific SMC intervention, and 2) participants with greater baseline SCALE scores would have greater improvement.

MATERIALS AND METHODS

Participants

This study was conducted in an outpatient clinical research setting (Center for CP at the University of California Los Angeles/Orthopaedic Institute for Children and Ahmanson-Lovelace Brain Mapping Center). The institutional review board of the University of California Los Angeles provided ethics approval. Informed assent and consent for research were obtained from the children and their parents or guardians.

Inclusion criteria for all participants were the following: 1) between 5 and 18 years of age, 2) history of prematurity, 3) diagnosis of spastic bilateral CP and PVL as evidenced by a brain scan, 4) the ability to understand and follow verbal directions, 5) the ability to lie still, and 6) the ability to walk with or without assistive devices.

Exclusion criteria were the following: 1) metal implants not verified as MR imaging–safe, 2) programmable implants including ventriculoperitoneal shunts and intrathecal baclofen pumps, 3) dental braces, 4) seizures not controlled by medication, 5) orthopedic surgery or neurosurgery within 1 year of starting the study, and 6) botulinum toxin or casting within 3 months of starting the study.

The participants in the current study were included in a previous publication examining the correlation between baseline DTI outcomes and SCALE in CP and DTI differences relative to a group of children with typical development.[12]

Clinical Assessments

Children with CP were evaluated by experienced physical therapists using standardized protocols. SCALE was used to assess SMC.[2] Specific isolated movement patterns at the hip, knee, ankle, and subtalar and toe joints were evaluated bilaterally. SCALE scores for each limb ranged from 0 (absent SMC) to 10 (normal SMC). Left and right limb scores were summed for a total possible SCALE score of 20 points.

Lower Extremity SMC Intervention

Camp Leg Power, the lower extremity SMC intervention, included practice of skilled, isolated joint movements, isokinetic knee exercises at variable speeds, ankle-controlled video gaming, gait and functional training, and sensory enrichment using a summer camp format. Under the supervision of experienced physical

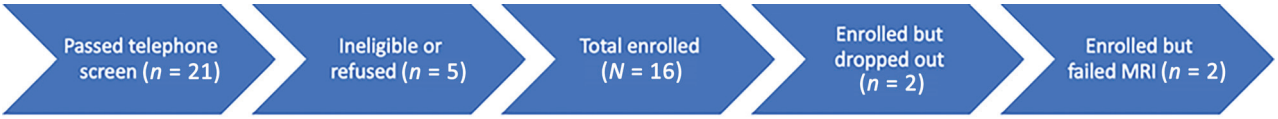

FIG 1. Flowchart detailing the recruitment and screening process leading to the total number of participants included in the study.

therapists, each participant had 15 camp sessions for 3 hours/day during a 1-month period. Skilled, isolated movements of the hip, knee, ankle, and subtalar and toe joints were practiced. By means of a Biodex System 4 Pro Dynamometer (Biodex Medical Systems), isokinetic knee extension and flexion exercises were performed bilaterally for a minimum of 10 sessions. Each participant was trained at speeds up to 300°/s, depending on his or her initial ability to produce torque and was progressed to higher speeds on the basis of ability during each session. Participants operated video games using ankle dorsiflexion and plantar flexion movements on a robotic device[27] for at least 5 minutes per limb for a minimum of 10 sessions. Additionally, gait and functional training in activities that emphasized intra- and interlimb control were practiced. These included kicking, navigating obstacles, stair climbing, and treadmill/overground walking encouraging maximal step length. Barefoot sensory enrichment activities were performed including walking on different surfaces.

MR Imaging Protocols

Before MR imaging sessions, children viewed a slide presentation describing procedures and practiced lying still while listening to recordings of scanner sounds. All T1WI and DWI scans were acquired using a 32-channel coil on a 3T Magnetom Prisma MR imaging scanner (Siemens) without sedation. T1-weighted MPRAGE images were obtained using TR = 2500 ms; TE = 1.8, 3.6, 5.39, and 7.18 ms; FOV = 256 × 256 mm^2; and isotropic voxel resolution = 0.8 × 0.8 × 0.8 mm^3. DWI scans were obtained using a single-shot, spin-echo, echo-planar acquisition with 6 reference images (b = 0 s/mm^2), 52 gradient directions (b = 1500 s/mm^2), TR = 3231 ms, TE = 89.6 ms, FOV = 210 × 210 mm^2, echo spacing = 0.69 ms, and isotropic voxel resolution = 1.5 × 1.5 × 1.5 mm^3. All DWI scans were corrected for EPI susceptibility and eddy current distortions using FSL's topup tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup/ExampleTopupFollowedByApplytopup) and eddy tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy), respectively, and FA, RD, AD, and MD maps were generated using DTIFit (http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/fdt_dtifit.html).[28] All DTI maps underwent a nonlinear registration to the standard space. Subsequently, the mean FA image was projected in the standard space FMRIB58_FA (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA) and thresholded at FA = 0.2 to create a skeletonized version.[26] The nonlinear transformations were applied to the FA, RD, AD, and MD maps and projected on the mean FA skeleton in preparation for statistical analysis.[29]

Statistical Analysis

TBSS, a whole-brain voxel-based approach, was used to assess pre- and postdifferences in FA, RD, AD, and MD.[26] The mean WM skeleton used was derived from and overlaid on the FMRIB58 standard-space FA template. Statistical analyses were performed using paired t tests (5000 permutations). In addition, correlation analyses between pre- and post-DTI differences within each voxel and total SCALE score were performed. All results were corrected for multiple comparisons using the threshold-free cluster enhancement procedure implemented in Randomise (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide).[30] Voxels with significant findings ($P < .05$) were displayed on the mean WM skeleton.

ROI analyses were performed to quantify voxels with significant postintervention differences ($P < .05$). Using the Johns Hopkins University ICBM-DTI-81 WM atlas labels (http://neuro.debian.net/pkgs/fsl-jhu-dti-whitematter-atlas.html),[31] we transferred ROIs to all images produced in the TBSS pipeline after nonlinear warping to the standard Montreal Neurological Institute 152 space and skeletonization. Significant pre- and postdifferences ($P < .05$) within ROIs were quantified by performing voxel counts in FSL (http://www.fmrib.ox.ac.uk/fsl). ROIs located along the descending pathways of the CSTs were parcellated bilaterally to analyze WM motor regions: 1) area inferior to the cerebral peduncle (sub-CerPed), 2) cerebral peduncle (CerPed), 3) posterior limb of the internal capsule (PLIC), and 4) superior corona radiata (SCR). Secondary ROIs were the anterior limb of the internal capsule (ALIC), external capsule (EC), anterior corona radiata (ACR), and the corpus callosum (CC) genu and body. The percentages of significant voxels ($P < .05$) in relation to the total number of voxels within ROIs were calculated.

RESULTS

Twelve children with spastic bilateral CP (2 females, 10 males; mean age, 11.5 [SD, 2.8] years; age range, 7.3–16.6 years) participated. They were born preterm with a mean gestational age of 28.9 weeks, ranging from 24 to 33 weeks. Using baseline T2WI scans, a neurologist or neuroradiologist examined CST brain regions between the cortex and medulla. All demonstrated findings consistent with clinical findings of spastic bilateral CP, namely PVL and/or ventricular enlargement, particularly in the posterior horns of the lateral ventricles. GMFCS levels were the following: I (n = 3), II (n = 1), III (n = 7), and IV (n = 1). Total SCALE scores ranged from 1 to 18. Five participants were right-handed, and 7 participants were left-handed. Figure 1 details the recruitment and screening process leading to the total number of participants included in the study.

The mean WM skeleton used is shown in Fig 2*A*. Significant postintervention decreases in RD ($P < .05$) were found throughout major WM tracts, including the CSTs, ALIC, EC, ACR, and CC (Fig 2*B*). Within the CSTs, RD decreased in the bilateral PLIC and left SCR as seen on the coronal and axial views. In the

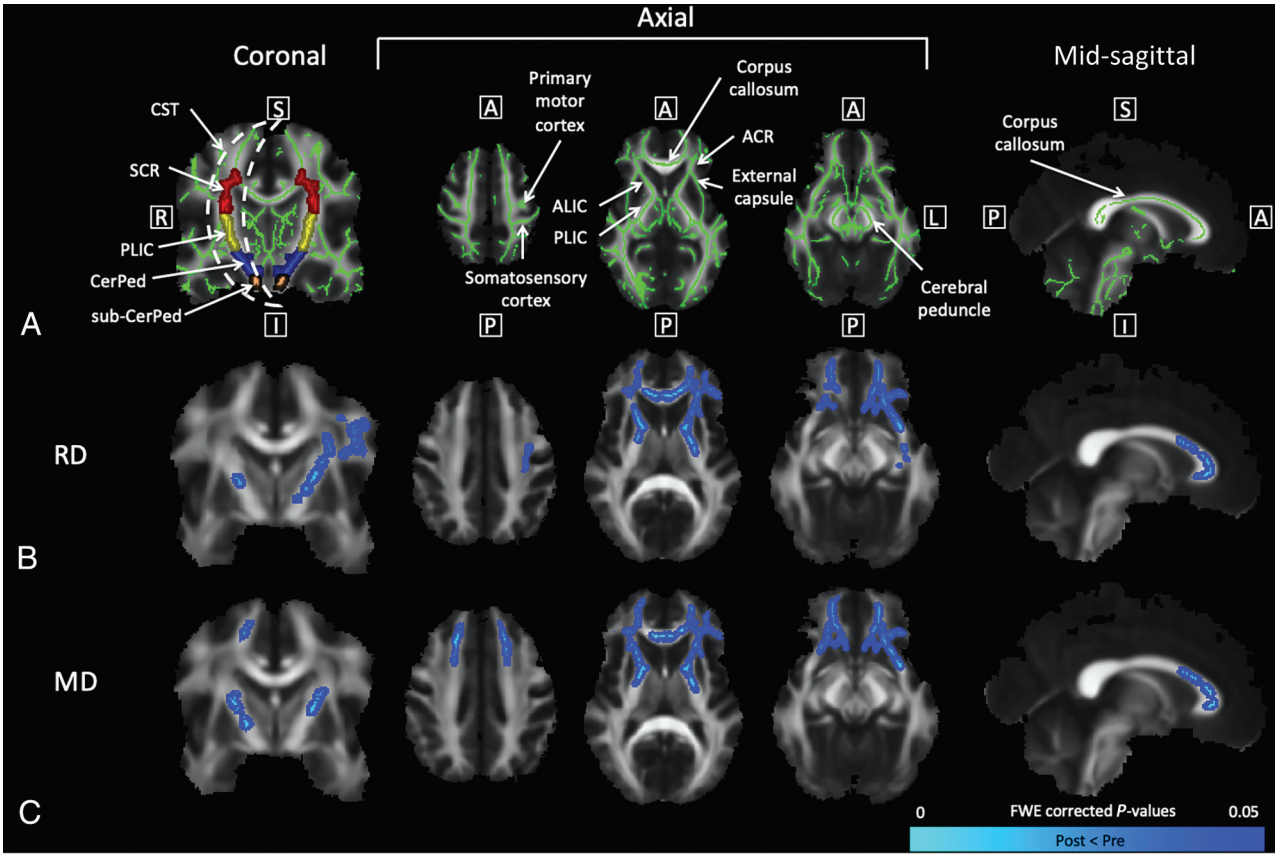

FIG 2. TBSS results show significant reductions in RD and MD ($P < .05$) after lower extremity SMC intervention. Coronal slices were selected at the level of the CSTs. From left to right, axial slices were selected at the level of the primary motor cortex, PLIC, and CerPed, respectively. Mid-sagittal slices were selected at the level of the CC. *A*, The WM skeleton is shown in green with additional *arrows* labeling the somatosensory cortex, ALIC, ACR, and EC. In the coronal view, ROIs for the SCR (red), PLIC (yellow), CerPed (blue), and sub-CerPed (orange) are shown. Significant pre- and postdifferences for the CP group ($P < .05$) are shown for RD (*B*) and MD (*C*). The colormap (blue-light blue) denotes a significant decrease in the DTI measure ($P < .05$). A indicates anterior; FWE, family-wise error; I, inferior; L, left; P, posterior; R, right; S, superior.

superior axial section, decreased RD can be viewed in the left motor and somatosensory cortices. Significant decreases in MD ($P < .05$) were found in similar regions of the brain (Fig 2*C*): the CSTs (bilateral PLIC and left SCR), ALIC, EC, ACR, and CC. In addition, decreased MD was apparent in both frontal lobes. No significant increases in RD or MD ($P < .05$) were found, and no significant changes in FA or AD ($P < .05$) were found in either direction. Significant correlations ($P < .05$) were not found between changes in DTI measures and total SCALE scores.

The number of voxels with significant decreases in RD and MD ($P < .05$) within motor and nonmotor WM ROIs is shown in the Table. RD and MD decreased within ROIs for the bilateral ALIC, bilateral PLIC, bilateral EC, bilateral ACR, left SCR, and CC genu and body. In all bilateral ROIs presented, a greater percentage change was seen in the left hemisphere of the brain compared with the right for both RD and MD, with the exception of MD in the bilateral ALIC. Additional ROIs containing voxels with significant decreases in RD ($P < .05$) are shown in the Online Supplemental Data.

DISCUSSION

This study showed significantly decreased RD and MD ($P < .05$) in the WM motor regions after an intensive lower extremity SMC intervention in children with spastic bilateral CP. No significant postintervention increases in RD or MD ($P < .05$) were found. Few studies of children with spastic CP have analyzed postintervention DTI changes beyond FA. Following the intervention, RD and MD decreased in key CST regions, including the bilateral PLIC, left SCR, and left primary motor cortex. While decreased RD of the WM tracts is indicative of improved myelination,[16,18] the meaning of decreased MD is less clear.[17,32] We suggest, however, that the decreased MD is driven by intervention-guided neuroplastic changes related to altered uniformity in microstructural tissue complexity.[17,32-34] In children with typical development, myelination is rapidly developed during infancy[35] and is dynamically regulated throughout adolescence,[36] but deficits have been widely reported for children with spastic CP and PVL.[12,37-39] It has been theorized that task-based interventions focused on practicing new complex motor skills, as performed in this study, promote myelination.[40-43] Others have reported improved CST myelination (using DTI tract-based quantitative susceptibility mapping) in children with spastic CP following cord blood stem cell therapy and usual rehabilitation therapy,[44-46] precluding direct comparisons.

Our current findings of improved myelination of the CC genu and body are consistent with potential neuroplastic

Voxel counts of WM ROIs[a]

ROI	Voxel Count	Voxels with Significant Pre- and Post-Decreases	
		RD (%)	MD (%)
R ALIC	792	278 (35.1)	400 (50.5)
L ALIC	819	341 (41.6)	205 (25.0)
R PLIC	845	30 (3.6)	98 (11.6)
L PLIC	858	244 (28.4)	114 (13.3)
R EC	1331	19 (1.4)	41 (3.1)
L EC	1431	320 (22.4)	164 (11.5)
R ACR	1619	365 (22.5)	569 (35.1)
L ACR	1613	897 (55.6)	802 (49.7)
L SCR	1279	180 (14.1)	84 (6.6)
Genu of CC	1758	914 (52.0)	710 (40.4)
Body of CC	3138	201 (6.4)	256 (8.2)

Note:— R indicates right; L, left.
[a] Significance set at ($P < .05$).

changes in response to SMC-focused therapy activities. In a study of rats trained in a spatial learning and memory task, WM changes in the CC as evidenced by DTI changes in FA and apparent diffusion coefficient were accompanied by increased myelin basic protein expression.[47] These findings support the association between acquisition of new complex motor skills and increased CC myelination. The CC is an important WM structure that is believed to play a role in bilateral coordination,[48] especially inhibition of physiologic mirroring that normally diminishes with age during early childhood.[49] Loss of transcallosal inhibition is one proposed cause of acquired obligatory mirror movements in patients with upper motor neuron lesions.[50-52] These abnormal mirror movements in CP contribute to SMC deficits and lower SCALE scores.[2] Lower FA in transcallosal fibers in the CC body has been associated with upper extremity mirroring in children with spastic CP and PVL.[53] We previously demonstrated a correlation between SCALE scores and DTI indices in the CC in a cross-sectional analysis of this cohort.[12]

Significant postintervention decreases in RD and MD ($P < .05$) in other WM regions, including the ALIC, ACR, EC, sensorimotor cortex, and frontal lobes suggest recruitment of neighboring WM tracts directly adjacent or within close proximity to the CSTs. Prior studies of adults recovering from stroke have demonstrated significant changes in functional connectivity among the primary motor cortices,[54,55] as well as postintervention (repetitive transcranial magnetic stimulation and occupational therapy) changes in similar WM regions.[56] Although motor improvement in children with spastic CP is made more complex by ongoing processes in the developing brain, similar patterns and principles of neuroplasticity likely apply. These neighboring WM regions with reduced RD and MD are areas of the brain that contain rich interconnections among the cortex, thalamus, and association regions.[57-61] Therefore, it is plausible that coactivation and improved myelination of these additional WM tracts are necessary in regulating neuroplasticity of the brain motor regions.

Lower extremity interventions aimed specifically at developing and improving SMC in CP are limited and have primarily focused on the ankle joint.[27,62] DTI changes following more generalized lower extremity rehabilitation have focused on FA. Two studies with botulinum toxin and 6 months of general lower extremity exercise in children with CP reported increased FA in the PLIC of the CSTs[63] and in motor fiber bundles,[22] regions where we found decreased RD and MD. Additionally, increased FA was found in 2 motor tracts (CSTs and PLIC) and 5 association tracts (CC, inferior and superior longitudinal fasciculus, uncinate, and cingulum) following intensive voice treatment (14 weeks) in children with CP and secondary dysarthria.[64] While the DTI measures analyzed did not include RD, these studies support the ideas in the present study that recruitment and activation of the CSTs play a critical role in responsiveness to intensive lower extremity intervention and practicing new complex motor skills. It is possible that improved myelination preceded or accompanied improvements in FA in these previous studies, but RD was not assessed. A longer intervention duration and a younger CP cohort may be required to promote improvements in FA.

Significant postintervention decreases in RD and MD ($P < .05$) were not associated with SCALE scores in this analysis, despite the significant correlation between RD and SCALE at baseline.[12] Isolated, skilled movements require good CST function; therefore, we hypothesized that children with higher SCALE scores would have greater capacity to learn and perform skilled movements, resulting in greater myelination. One explanation may be that children with lower SCALE scores are more likely to move in synergistic patterns, have lower levels of physical activity, and experience ankle and foot constraints due to greater dependence on orthotics. Therefore, the Camp Leg Power intervention was more novel for these participants, and greater motor learning may have occurred than was expected.

This study was limited by a relatively small sample size due to MR imaging exclusion criteria. Children with spastic CP commonly have shunts, baclofen pumps, and orthopedic surgery requiring metal implants.[65] In addition, involuntary movements are common and sometimes exaggerated by noise, further limiting a good MR imaging acquisition. The inclusion of a control group of children with spastic bilateral CP who did not undergo the Camp Leg Power intervention would strengthen these findings. Trivedi et al[63] included a control group of children with typical development and did not find significant within-group differences in FA or MD over a much longer time period. A randomized, controlled trial with a larger cohort would confirm our results. An additional limitation was that ROI analyses of the CSTs at the level of the primary motor cortex were not performed because this region is not included in the Johns Hopkins University WM atlas labels. Younger children with greater potential for plasticity[66] may be more likely to show improvement but are more difficult to scan without sedation. Efforts are currently underway to adapt SCALE and develop a lower extremity SMC intervention for infants and toddlers.

CONCLUSIONS

Intensive practice of skilled lower extremity SMC movements by children with spastic bilateral CP and PVL born prematurely was associated with increased myelination of WM motor tracts, including the CSTs and CC. Improved myelination of neighboring WM tracts suggests additional neuroplasticity associated with

skilled lower extremity SMC learning. A longer intervention duration at earlier ages may optimize WM neuroplasticity.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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