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Original Article

Early Detection of Cerebral Palsy Using Sensorimotor Tract Biomarkers in Very Preterm Infants

Nehal A. Parikh, DO, MS [a, b, c, *], Alexa Hershey, BS [c], Mekibib Altaye, PhD [b, d]

[a] Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[b] Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, Ohio
[c] The Research Institute at Nationwide Children's Hospital, Columbus, Ohio
[d] Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

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ABSTRACT

Background: Our objectives were to evaluate the brain's sensorimotor network microstructure using diffusion magnetic resonance imaging (MRI) at term-corrected age and test the ability of sensorimotor microstructural parameters to accurately predict cerebral palsy in extremely-low-birth-weight infants.
Methods: We enrolled a prospective pilot cohort of extremely-low-birth-weight preterm infants (birth weight $\leq$ 1000 g) before neonatal intensive care unit discharge and studied them with structural and diffusion MRI at term-corrected age. Six sensorimotor tracts were segmented, and microstructural parameters from these tracts were evaluated for their ability to predict later development of cerebral palsy, diagnosed at 18 to 22 months corrected age.
Results: We found significant differences in multiple diffusion MRI parameters from five of the six sensorimotor tracts in infants who developed cerebral palsy (n = 5) versus those who did not (n = 36). When compared with structural MRI or individual diffusion MRI biomarkers, the combination of two individual biomarkers—fractional anisotropy of superior thalamic radiations (sensory component) and radial diffusivity of the corticospinal tract—exhibited the highest sensitivity (80%), specificity (97%), and positive likelihood ratio (28.0) for prediction of cerebral palsy. This combination of diffusion MRI biomarkers accurately classified 95% of the study infants.
Conclusions: Development of cerebral palsy in very preterm infants is preceded by early brain injury or immaturity to one or more sensorimotor tracts. A larger study is warranted to evaluate if a combination of sensorimotor microstructural biomarkers could accurately facilitate early diagnosis of cerebral palsy.
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Introduction

Cerebral palsy (CP) is the most common physical disability in children and a lifelong disorder that can worsen without treatment.[1,2] Infants born extremely preterm have a 50-fold higher risk of CP than infants born at term.[2] In most clinical settings, the average age at diagnosis of CP is typically two years or beyond, despite the etiologic role brain injury or abnormal brain development play in the development of CP.[3,4] This delay in diagnosis results in part because neuroimaging utilized in clinical decision making appears normal in up to 30% of CP cases.[5-8] There is wide consensus that earlier diagnosis, soon after birth, is urgently needed to take full advantage of critical windows of early brain development.[9,10] Earlier diagnosis would facilitate targeted delivery of early childhood interventions[11-13] and novel habilitative therapies during this optimal period.[9,14] Unfortunately, currently used tests for early detection of CP such as qualitative structural magnetic resonance imaging (MRI) (sMRI) or general movements assessment (GMA) are not sufficient on their own, and it is unknown if combining them improves prediction accuracy sufficiently to permit individual-level predictions.[15-17]

There is mounting evidence that advanced modes of MRI such as diffusion MRI (dMRI), brain morphometry, and magnetic resonance spectroscopy biomarkers can predict CP in very preterm infants.[18] When compared with sMRI, these advanced modes are quantitative, more sensitive, and more objective at detecting injury. In addition to the brain's macrostructure, they can query its

Competing interests: The authors declare no competing interests.

* Communications should be addressed to: Parikh; Professor of Pediatrics Cincinnati Children's Hospital; 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229.
E-mail address: Nehal.Parikh@cchmc.org (N.A. Parikh).

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microstructure and metabolites. dMRI exploits and is sensitive to the ubiquitous presence of water molecules in the brain's microarchitecture by measuring its diffusion properties. Water moves more freely along axonal paths (longitudinally) and is more restricted across axons (perpendicularly), hindered by axonal and myelin membranes. Thus diffusion properties are correlated with the brain's microstructural development (e.g., myelination and axonal integrity) and altered in the presence of brain injury due to the breakdown of organelles or membranes.[19] Diffusion tensor tractography is a three-dimensional rendering of dMRI that is produced by connecting voxels that exhibit the same local diffusion direction (i.e., fiber orientation), thereby inferring the presence of long-range white matter pathways or tracts *in vivo*.[20] This tool has highlighted the role various white matter tracts play in the pathophysiology of CP.[21] For example, in children with established CP, injury is observed not only in the corticospinal tract (CST) but also in other sensorimotor tracts such as the posterior subregions of the corpus callosum (CC) and posterior thalamic radiations (PTR).[22,23] A systematic review of dMRI in children with CP further highlighted the involvement of additional sensorimotor tracts such as the superior thalamic radiations (STR) in the pathophysiology of CP.[24] It is not known if microstructural abnormalities of all sensorimotor tracts can be reliably measured soon after birth in those with CP, and if so, can function as prognostic biomarkers of CP development in high-risk infants. We hypothesized that reduced structural connectivity of various sensorimotor tracts can be observed at term-corrected age in extremely-low-birth-weight infants (ELBW; $\leq$1000 g), and this reduced connectivity can be modeled to accurately predict later development of CP.

Methods

Study design

For this prospective pilot cohort study, 50 consecutive ELBW infants were recruited from the neonatal intensive care unit of Children's Memorial Hermann Hospital before hospital discharge. The inclusion criteria for study infants were infants cared for in the neonatal intensive care unit with a birth weight of 1000 g or less and survival to 34 weeks postmenstrual age or greater. Infants were excluded if they had known congenital central nervous system anomalies. Dates of enrollment were May 2007 to July 2009. Per clinical protocol, a brain sMRI was performed in all hospitalized ELBW infants before hospital discharge or at term-corrected age, and those with study consent also underwent dMRI. Standardized developmental testing was performed at 18 to 22 months corrected age.

Standard protocol approvals, registrations, and patient consents

The institutional review board of Children's Memorial Hermann Hospital approved the study. Written informed consent was obtained from every parent or guardian of patients after the nature and possible consequences of the study were explained. All methods were carried out in accordance with the approved protocol and institutional guidelines.

Image acquisition

We performed all MRI scans on a 3T Philips Achieva scanner, equipped with a 32-channel receiver and a gradient system capable of producing gradient amplitudes of 80 mT/m with a slew rate of 200 T/m/s. An eight-channel phased array head coil was used for data acquisition. The dMRI protocol consisted of a single-shot, spin-echo planar sequence with repetition time (TR)/echo time (TE), 6000/61; in-plane resolution 1.6 $\times$ 1.6 mm^2, 2-mm contiguous slices, field of view 180 mm^2, and 128 $\times$ 128 matrix; and acquisition time four minutes. Fifteen directions of diffusion gradients were used with a b value of 800 s/mm^2 and SENSE factor = 2. The imaging parameters for the proton-density/T2-weighted scan were TE1/TE2, 9/175; TR, 10,000; flip angle = 90°; field of view, 180 mm^2; 256 $\times$ 256 mm^2 matrix; 2-mm contiguous slices; time, 2:20 m. Total scan time was approximately 30 minutes.

We imaged all infants during natural sleep without the use of any sedation. Infants were fed and swaddled before MRI using a MedVac Infant Vacuum Splint (CFI Medical Solutions, Fenton, MI, USA), and noise protection was provided using Insta-Puffy Silicone Earplugs (E.A.R. Inc, Boulder, CO, USA) and Natus Mini Muffs (Natus Medical Inc, San Carlos, CA, USA). A single magnetic resonance technologist performed all the scans; an experienced neonatologist and a neonatal research nurse supervised all scans. None of the patients experienced any adverse events during or after the MRI testing.

Image preprocessing

We preprocessed all dMRI images using FSL 5.0 software of FMRIB Software Library (Analysis Group, FMRIB, Oxford, UK) and DTIStudio 3.0.2 of MRI Studio (Johns Hopkins University, Baltimore, MD, USA) as previously described.[25] Briefly, after eddy current correction in FSL, we performed Automatic Image Registration and automatic outlier slice rejection in DTI Studio. Five infants had to be excluded owing to significant motion artifacts on dMRI. Next, in FSL, we performed tensor estimation and generated scalar maps (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD]). Last, we performed brain extraction and employed BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) to run probabilistic tractography.[26] The number of samples of probabilistic tracking was set at the default of 5000, the curvature threshold was set at 0.18, and a loop check was performed. The subsidiary threshold was set at 0.0 and step length at 0.4.

Image postprocessing

For the six sensorimotor tracts of interest (Fig 1), we employed color-coded tensor and FA maps to generate seed masks for the two CC tracts and seed masks and waypoint masks for the other four sensory and motor tracts of interest. We have previously described and published our mask regions of interest for the CST,[27] and posterior midbody (PMB) and isthmus of the CC.[25] Figure 2 displays the masks we used for the remaining three tracts—PTR, motor component of the STR (STRm), and sensory component of the STR (STRs). At least two orientations were used to select each region of interest. The connectivity distributions were generated from every voxel in the seed masks, and only those paths that went through the waypoint masks were retained. We imported each tract's seed point and waypoint masks into FSL's probabilistic tracking with crossing fibers (PROBTRACKX) tool to perform probabilistic tractography.[26] An exclusion mask was not required for any of the tracks except for the PTR. For the PTR, an exclusion mask was drawn on the axial slice superior to the CC, covering the frontal lobe and the motor cortex to remove possible projection fibers that may be captured due to the seed point location in the thalamus. Diffusion parameters (FA, MD, AD, and RD) were assessed for each tract. The individual performing the dMRI data (A.H.) was masked to all clinical information, sMRI readings, and CP diagnosis but, as would be expected, was able to visualize overt signs of brain injury on diffusion maps during region-of-interest placements. To ensure good intra-rater reliability, we segmented a different set of cases

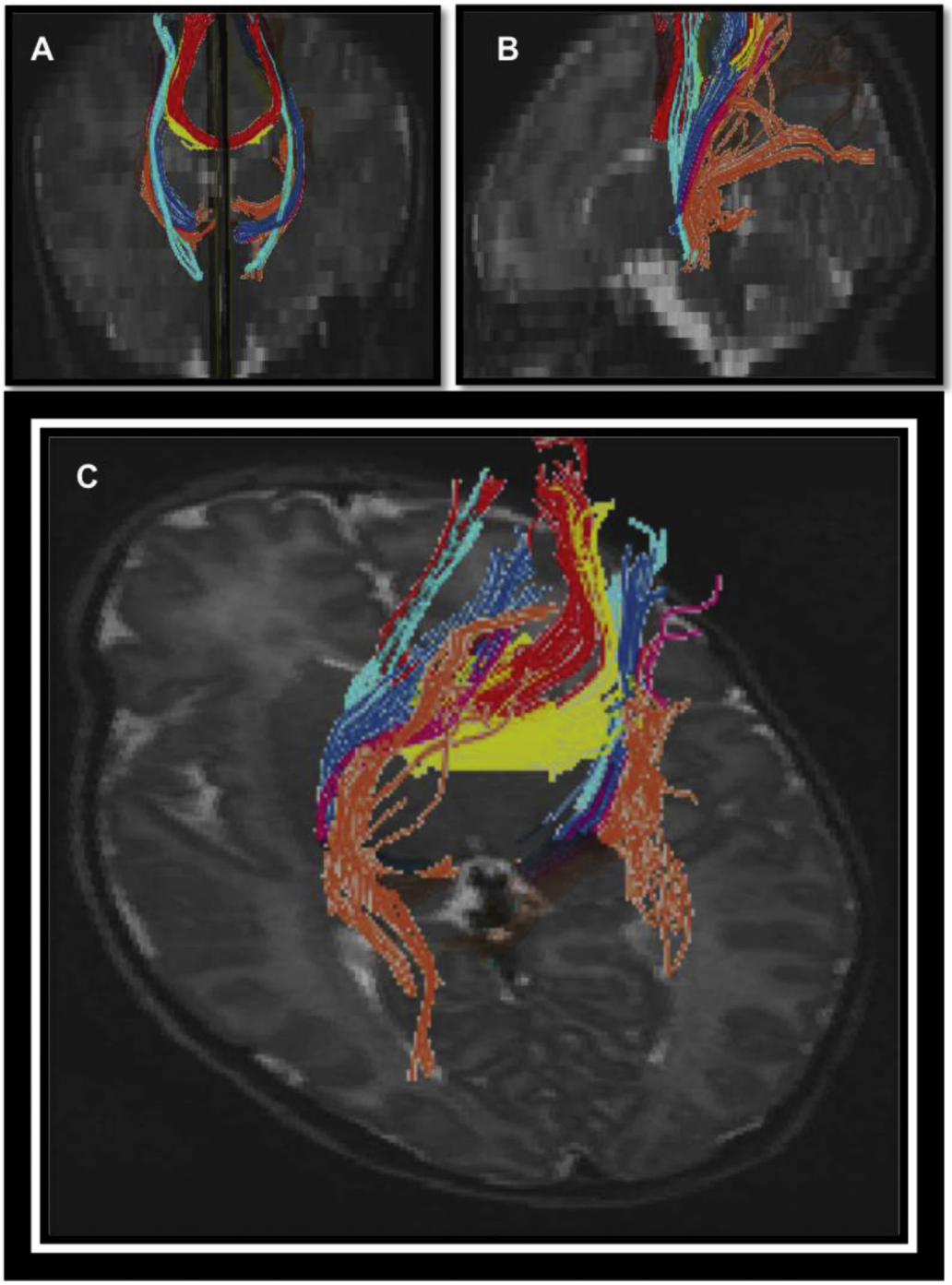

FIGURE 1. Sensorimotor network tractography superimposed on T2-weighted images in a very preterm infant. Coronal (A), sagittal (B), and axial (C) views of the corticospinal tract (light blue), posterior thalamic radiations (orange), superior thalamic radiations—motor segment (dark blue), superior thalamic radiations—sensory segment (pink), posterior midbody of the corpus callosum (CC; red), and isthmus of the CC (yellow).

before these study cases to establish consistency in methodology. The rater independently segmented the STRs, STRm, CST, and PTR of a random sample of 15 cases twice (separated by one month) to determine reliability. The mean ICC of the FA and MD for these four tracts ranged from 0.97 to 0.99. The ICC for the PMB and isthmus ranged from 0.87 to 0.92, as previously published.[25]

Structural MRI readings

In our institution, brain sMRI replaced ultrasound as the clinical standard of care for brain injury screening before discharge, at term-corrected age. A pediatric neuroradiologist read all sMRI studies unaware of the clinical data, diffusion MRI, and CP diagnosis. We used a data-driven standardized scoring system that was previously demonstrated as highly predictive of CP.[28] This study showed that infants with severe brain injury (diffuse cystic abnormalities, diffuse punctate white matter lesions, or severe ventriculomegaly) exhibited the highest accuracy for predicting CP. We used this prespecified definition of severe brain injury on sMRI to assess its ability to predict CP. We refrained from using a different definition that includes moderate degrees of white matter injury because although it increases

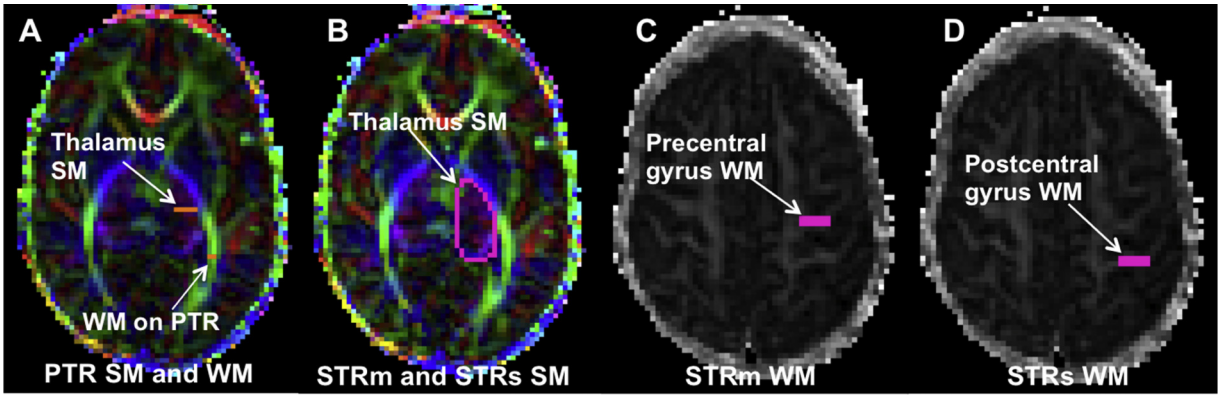

FIGURE 2. Axial color maps and fractional anisotropy maps displaying location of seed masks (SM) and waypoint masks (WM). (A) WM for the posterior thalamic radiations (PTR; seed mask placed in thalamus using coronal view); (B) common seed mask for superior thalamic radiations—motor (STRm) and sensory (STRs); (C) waypoint mask for STRm; and (D) WM for STRs.

test sensitivity, it concurrently lowers the specificity and positive likelihood ratio.

Follow-up and developmental assessments

All EBLW infants underwent a comprehensive neurodevelopmental assessment at 18 to 22 months of age corrected for prematurity, as previously described.[29] Certified examiners, masked to dMRI results, performed a standardized neurological examination, and gross motor function was assessed using the Gross Motor Function Classification System.[30] We defined CP as abnormal tone or reflexes in at least one extremity and abnormal control of movement or posture that interferes with age-appropriate activity. Severity of CP was defined as per Kuban et al.[31]

Statistical analysis

We anticipated that it would not be possible to perform tractography for one or more sensorimotor tracts for infants with injury in those regions. This was indeed the case for one infant for delineation of the PMB, isthmus, left CST, and left STRm. An additional infant had right-sided injury where delineation of the right CST and right STRm was not possible. We also could not perform tractography of the bilateral STRs for these two and one additional infant. For such infants, we decided *a priori* to impute diffusion values that were four S.D. above (for MD, AD, RD) or below (for FA) the mean for our cohort. This strategy is akin to imputing a Bayley score of 46 (>4 S.D. below mean) for cognitive or language outcomes at age two years for infants that are too disabled for testing. Attempting to perform tractography in brain-injured infants also confirmed which infants with qualitatively defined brain injury had injury specifically to sensorimotor tracts. We compared diffusion parameters between children with and without CP using Wilcoxon rank sum test. We observed a significant difference in the postmenstrual age at MRI scan between the CP and no CP groups (Table 1). Because at least FA and RD are known to change significantly with increasing gestational age, all microstructural variables were adjusted for postmenstrual age at MRI scan.[24] For sensorimotor tract microstructural variables that were significantly different between groups, we further dichotomized these continuous measures at 2 S.D. above (for MD, AD, RD) or below (for FA) the mean for the non-CP group to create new categorical biomarkers. We selected this pre-specified standard cutoff because there is a lack of normative data and established thresholds for these potential biomarkers. We tested the prognostic properties of combining STRs FA with CST RD or combining STRs FA with STRm AD by creating two new combination biomarkers that was scored as positive if at least one of the single biomarkers was positive (using the 2 S.D. cutoff above) and negative when both biomarkers were negative. For categorical biomarkers, we performed Fischer's exact test and examined receiver operating characteristic curves to compare sensitivity, specificity, likelihood ratios (LRs), and area under the receiver operating characteristic curve. Two-sided *P*-values < 0.05 were considered to indicate statistical significance. All

TABLE 1.
Baseline Demographic and Clinical Characteristics of Extremely-Low-Birth-Weight Infants With and Without Cerebral Palsy

Clinical Variables	No CP (N = 36)	CP (N = 5)	*P* Value
Maternal age	26 (18, 38)	26 (21, 29)	0.576
Antenatal steroids given, N (%)	28 (77.8)	1 (20.0)	0.020
Gestational age at birth, weeks	25.5 (23.1, 30.1)	25.4 (23.0, 26.3)	0.510
Birth weight, g	765 (468, 1000)	720 (600, 909)	0.647
Male, N (%)	22 (61.1)	4 (80.0)	0.636
5-min Apgar score ≤5, N (%)	11 (30.6)	1 (20.0)	1.000
Small for gestational age, N (%)	2 (5.6)	0	0.594
Postnatal steroids, N (%)	8 (22.2)	2 (40.0)	0.580
Sepsis (culture positive), N (%)	10 (27.8)	2 (40.0)	0.620
Positive pressure ventilation duration before 36 weeks postmenstrual age, days	49 (3, 88)	67 (39, 90)	0.157
Postmenstrual age at MRI scan, weeks	38.5 (34.1, 43.9)	43.1 (38.1, 43.7)	0.038

Abbreviations:
CP = Cerebral palsy
MRI = Magnetic resonance imaging
All values are median (range) unless otherwise noted.

TABLE 2.
Baseline Characteristics, sMRI Findings at Term-Corrected Age, and CP Severity of the Five Extremely-LLow-Birth-Weight Infants Diagnosed With CP

Subject	Gestational Age (wks)	Birth Weight (g)	Sex	Severe sMRI Abnormality	sMRI Findings	CP Severity
1	23.0	720	Boy	Yes	Right encephalomalacia, S/P PVHI	Hemiparesis
2	25.4	468	Boy	No	No injury or abnormalities	Diaparesis
3	26.0	909	Boy	Yes	Bilateral encephalomalacia and ventriculomegaly, S/P PVHI	Quadraparesis
4	26.3	600	Girl	Yes	Diffuse multicystic PVL	Hemiparesis
5	23.6	665	Boy	No	Focal left-sided cyst	Quadraparesis

Abbreviations:
CP = Cerebral palsy
MRI = Magnetic resonance imaging
sMRI = Structural MRI
PVHI = Periventricular hemorrhagic infraction
PVL = Periventricular leukomalacia
S/P = Status-post

analyses were conducted in Stata 15.1 (STATA Corporation, TX, USA).

Results

Of the original cohort of 50 ELBW infants, two infants died and two did not return for follow-up. An additional five infants were excluded owing to significant motion artifacts on dMRI. Of the final cohort of 41 ELBW infants, five (12.2%) were diagnosed with CP at 18 to 22 months corrected age. The baseline characteristics of the cohort of infants that developed CP were similar to those that did not, except mothers of infants who developed CP received antenatal steroids less frequently and infants with CP had a significantly higher median age at MRI scan (Table 1). These same baseline characteristics of infants in the final cohort (n = 41) were not significantly different than those not included in the study cohort (n = 9). The sMRI findings and severity of CP for the five ELBW infants diagnosed with CP are presented in Table 2. Two infants without severe abnormalities on sMRI also developed CP (false-negatives), and one diagnosed with severe abnormality (left-sided moderate ventriculomegaly and cystic periventricular leukomalacia) did not develop CP (false-positive). Overall, severe injury on sMRI exhibited 60.0% sensitivity and 97.1% specificity in predicting CP ($P = 0.004$).

All six segmented sensorimotor tracts are displayed in Fig 1. We found significant differences in multiple diffusion microstructural parameters from these tracts in infants that developed CP versus those that did not (Table 3). As expected, the CST and STRm were the most closely associated with the development of CP. However, we also identified significant differences in the STRs and the motor subregions of the CC (PMB and isthmus). We did not observe any significant group differences in diffusion parameters from the PTR.

Three individual sensorimotor tract biomarkers—STRs FA, CST RD, and STRm AD—exhibited low sensitivity (40% to 60%) but high specificity (97% to 100%) in predicting CP (Table 4; Fig 2). An abnormal STRs FA exhibited 100% specificity for development of CP. Both CST RD and STRm AD categorical biomarkers classified CP and non-CP cases similarly. Combining STRs FA with CST RD (or STRm AD) achieved the best sensitivity, negative LR, and area under the receiver operating characteristic curve of 80.0%, 0.21, and 0.886, respectively (Table 4). The combination of STRs FA and CST RD biomarkers correctly classified 95% of the ELBW infants (one false-negative and one false-positive).

Discussion

We identified several dMRI sensorimotor parameters that were significantly different in ELBW infants who later developed CP, suggesting the importance of a variety of sensorimotor tracts in the etiology and pathophysiology of CP. Moreover, three of these microstructural biomarkers were highly specific in diagnosing CP and additionally demonstrated enhanced sensitivity for prediction of CP when combined. For example, a combination of two of these biomarkers correctly classified 95% of the ELBW infants. The individual risk of developing CP for an ELBW infant with a baseline risk of 12.2% (prevalence of CP in this cohort used as prior probability) is 80% (posterior probability) for a positive biomarker combination test and 3% for a negative test.[32] The key limitation of our prognostications, however, was that we only had five cases of CP and therefore our 95% confidence limits for these prognostic properties were quite wide.

The combination of FA from the STRs and RD from the CST yielded the most accurate prediction of CP. Furthermore, the combination of FA from the sensory and AD from the motor

TABLE 3.
Sensorimotor Tract Diffusion Parameters That Were Significantly Different Between Five Extremely-Low-Birth-Weight Infants Diagnosed With CP and 36 Without CP

Sensorimotor Tract	No CP (N = 36)*	CP (N = 5)*	*P* Value†
Posterior midbody			
FA	0.18 (.028)	0.12 (.024)	0.006
Isthmus			
FA	0.19 (.005)	0.13 (.025)	0.027
STR—sensory			
FA (B)	0.18 (.004)	0.14 (.025)	0.039
MD (B)	1.33 (.033)	1.64 (.016)	0.015
MD (L)	1.36 (.021)	1.75 (.191)	0.031
AD (L)	1.59 (.021)	1.97 (.181)	0.023
AD (B)	1.56 (.037)	1.87 (.151)	0.017
RD (L)	1.24 (.022)	1.76 (.267)	0.037
RD (B)	1.20 (.031)	1.62 (.221)	0.018
STR—motor†			
MD (L)	1.33 (.016)	1.48 (.058)	0.017
MD (B)	1.32 (.013)	1.47 (.070)	0.020
AD (L)	1.58 (.017)	1.73 (.045)	0.008
AD (B)	1.57 (.012)	1.72 (.055)	0.011
Corticospinal tract‡			
FA (R)	0.23 (.005)	0.14 (.042)	0.019
RD (R)	1.13 (.017)	1.41 (.159)	0.028

Abbreviations:
AD = Axial diffusivity
B = Bilateral
FA = Fractional anisotropy
L = Left
MD = Mean diffusivity
R = Right
RD = Radial diffusivity
SE = Standard error
STR = Superior thalamic radiations
* Mean (SE); all MD, AD, and RD values should be multiplied by 10^{-3}
† P value determined using Wilcoxon rank sum test.
‡ dMRI data not available for one baby from no CP group due to localized motion artifacts.

TABLE 4.
Prognostic Test Properties for Prominent Diffusion MRI Sensorimotor Biomarkers

Biomarker	Threshold	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	*P*
STRs FA	0.1383	0.800 (0.560, 1.000)	60.0% (14.7%, 95.7%)	100.0% (90.3%, 100.0%)	∞	0.40 (0.14, 1.17)	<0.001
CST RD	0.00135	0.686 (0.444, 0.927)	40.0% (5.3%, 85.3%)	97.1% (85.1%, 99.9%)	14.0 (1.54, 127.6)	0.62 (0.30, 1.27)	0.036
STRm AD	0.00172	0.686 (0.444, 0.927)	40.0% (5.3%, 85.3%)	97.1% (85.1%, 99.9%)	14.0 (1.54, 127.6)	0.62 (0.30, 1.27)	0.036
Combined*	See above	0.886 (0.688, 1.000)	80.0% (28.4%, 99.5%)	97.1% (85.1%, 99.9%)	28.0 (3.9, 203.0)	0.21 (0.04, 1.19)	<0.001

Abbreviations:
AD = Axial diffusivity
AUC = Area under receiver operating characteristic curve
CST = Corticospinal tract
FA = Fractional anisotropy
LR = Likelihood ratio
RD = Radial diffusivity
STRm = Superior thalamic radiations, motor
STRs = Superior thalamic radiations, sensory
* Combination of STRs FA and CST RD biomarkers or STRs FA and STRm AD biomarkers.

component of the STR yielded identical prediction of CP. Using either combination biomarker approach, we demonstrated higher sensitivity and positive LR to enhance identification of CP over sMRI when one or both biomarkers are positive and low negative LR to largely rule out diagnosis of CP when both biomarkers are negative. Our prognostic values are difficult to compare to prior published dMRI studies because most have not reported prognostic test properties.[18] However, they readily outperform sMRI prediction of CP as demonstrated in a recent meta-analysis of all eligible sMRI studies up to 2013 in very preterm infants and a 2015 published larger (N = 445) multicenter study in ELBW infants.[7,15] The presence of moderate or severe white matter abnormalities in the meta-analysis exhibited a positive LR of 8.1 and negative LR of 0.36,[15] whereas the multicenter study reported a lower positive LR of 2.8 and negative LR of 0.62 (sensitivity, 48%, specificity, 83%) for prediction of CP.[7] For a given very preterm infant with moderate or severe white matter abnormality sMRI, a positive LR of 8.1 translates to a posterior probability of 37% for developing CP (using the meta-analysis CP pretest probability or prevalence of 6.7%).[32] These data suggest an unmet research and possible clinical need for additional prognostic biomarkers that could be met with dMRI biomarkers.

There has been strong interest and an emerging consensus to diagnose CP early, within a few months after birth in high-risk populations.[9,10] Such progress would mean that early intervention therapies could be targeted far earlier for the highest risk infants than is currently possible or the highest risk infants can be selected for neuroprotective trials. A prior systematic review of GMA and Hammersmith Infant Neurological Examination studies at three months corrected age for CP prediction reported summary estimates of sensitivity, specificity, and positive LR for GMA of 98%, 91%, 10.9, respectively, and for Hammersmith Infant Neurological Examination of 88%, 87%, 6.8, respectively.[33] However, a large pragmatic study since that time suggests a much lower accuracy for the GMA during the fidgety period.[16] This multicenter study of GMA use in routine clinical practice, reported a much lower sensitivity of 56% and specificity of 87% (LR+ 4.3; LR− 0.50). Furthermore, current evidence suggests that combining sMRI with GMA does not increase sensitivity or accuracy in predicting CP,[34] possibly because these two tests are significantly correlated.[35] Even if sMRI was readily available in all centers, this suggests that individual-level accurate prediction of CP is not yet possible with such tests. If our results can be validated in an independent large prospective study, as we are currently doing,[36] dMRI sensorimotor tract biomarkers could facilitate early, accurate risk stratification for CP by term-corrected age, which would represent a significant advance for testing neuroprotective interventions.

Of the six sensorimotor tracts examined, we identified significant differences in infants with and without CP in all but one tract (PTR). Although injury or immaturity of the CST is well established in the etiology and pathophysiology of CP, our findings also highlight the importance of the sensory and motor components of the STR and subregions of the CC. Widespread sensorimotor abnormalities in FA, AD, or RD suggest injury or immaturity of white matter myelination and axonal integrity. Our findings are consistent with those of other dMRI studies performed at term-corrected age identified in a recent systematic review of advanced MRI to predict neurodevelopmental outcomes in very preterm infants.[18] This review identified three tractography studies that reported that microstructural connectivity parameters from either the posterior limb of the internal capsule (part of the CST)[37,38] or CC[39] were predictive of motor outcomes at 2 years corrected age. Other dMRI studies that did not perform tractography but queried regions of interest (two-dimensional) also reported significant associations between FA or MD in sensorimotor regions such as the posterior limb of the internal capsule,[40-45] CC subregions,[43-45] or basal nuclei,[46] and development of CP or abnormal gross motor scores. A 2013 systematic review of diffusion MRI studies also highlighted the aberrant development and involvement of several sensorimotor tracts other than the CST in older children with established CP.[24] These dMRI studies examined and identified the involvement of one or two regions or biomarkers, whereas comprehensive study of most of the major sensorimotor tracts permitted us to uncover significant differences in five such tracts in very preterm infants with CP. In addition, examination of prognostic test properties permitted determination of the clinical value of such biomarkers for individualized prognostication. Our study verifies the findings of this systematic review that CP results from brain injury or immaturity of structural connectivity in one or more regions of the sensorimotor network. Importantly, we also extended this data by identifying these abnormalities in preterm infants soon after birth and combining biomarkers to improve CP prediction accuracy.

Similar to the systematic review findings from Schenk et al.[24] in older children with CP, we observed that CP is preceded by the presence of microstructural injury or immaturity soon after birth in one or more sensorimotor tracts. In addition, our findings of abnormal FA, AD or RD in these tracts suggest that the type of injury or immaturity may also be heterogeneous. Overall, an increase in radial (perpendicular) diffusivity suggests underlying demyelination or delayed myelination, whereas aberrant axial (parallel) diffusivity is closely associated with axonal injury or immaturity or necrosis and decrease in FA is typically observed when one or both of these pathological processes are present.[47] When examined histopathologically, this heterogeneous CP injury phenotype results

in a range of pathological outcomes, including focal necrosis with loss of cellular elements, including axons, and diffuse non-necrotic injury characterized by arrested pre-oligodendrocyte maturation with resulting delays in myelination.[48,49] The five infants with CP in our study exhibited a similar range of macrostructural injuries (Table 2) with resulting microstructural changes, as shown on dMRI and sensorimotor tract biomarkers. Depending on the underlying types of CP represented in the cohort, another study may yield somewhat different results. Therefore a much larger cohort study that is representative of the most common CP phenotypes will provide the most robust assessment of the ultimate value of sensorimotor tract prognostic biomarkers.

Our study has several limitations. Studies using small sample sizes are more prone to prognostic overoptimism, as reflected in our wide confidence intervals, and therefore independent validation in a larger cohort will be required. We only used 15 diffusion directions and a single shell, which limited our ability to fully exploit the power of this technology. We are addressing these limitations in our current ongoing study. The addition of brain morphometric biomarkers such as brain volumes and cortical surface measures may further enhance our ability to predict motor outcomes.[18] Because the focus of our study was prediction of CP, we limited our analyses to sensorimotor tracts; however, it is also important to examine additional white matter tracts that subserve additional important functions that are known to be abnormal in some children with CP (e.g., cognitive, visual). We and others have previously published region-of-interest-based analyses of these tracts and shown significant correlations with cognitive and language scores.[43,50] Current availability of neonatal structural atlases is making it easier to perform whole-brain structural connectivity, which may replace manual parcellation methods. We are currently conducting a large prospective, population-based cohort study designed to address these limitations and to externally validate our promising findings.[36]

Conclusions

Development of CP in very preterm infants is preceded by early brain injury or immaturity to one or more sensorimotor tracts that can be identified as early as term-corrected age using diffusion tractography. In this single-center pilot cohort study, combined microstructural parameters from these tracts predicted later diagnosis of CP with good accuracy. Larger population-based, structural and functional connectivity studies are needed to determine the value of sensorimotor connectivity parameters as robust prognostic biomarkers for early, accurate diagnosis of CP.

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Author contributions: N.A.P. conceived the study and wrote the initial draft of the manuscript. A.H. performed the image processing and figures. N.A.P. and M.A. analyzed all the data. All authors reviewed the manuscript.

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