White matter microstructure on diffusion tensor imaging is associated with conventional magnetic resonance imaging findings and cognitive function in adolescents born preterm

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ABBREVIATIONS
DTI Diffusion tensor imaging

AIM Diffusion tensor imaging (DTI) was used to evaluate white matter architecture after preterm birth. The goals were (1) to compare white matter microstructure in two cohorts of preterm- and term-born children; and (2) within preterm groups, to determine if sex, gestational age, birthweight, white matter injury score from conventional magnetic resonance imaging (MRI), or IQ was associated with DTI measures.

METHOD Participants (*n*=121; 66 females, 55 males) were aged 9 to 16 years. They comprised 58 preterm children (site 1, *n*=25; and site 2, *n*=33) born at less than 36 weeks' gestation (mean 29.4wks; birthweight 1289g) and 63 term children (site 1, *n*=40; site 2, *n*=23) born at more than 37 weeks' gestation. DTI was analyzed using tract-based spatial statistics. Diffusion measures were fractional anisotropy, axial, radial, and mean diffusivity.

RESULTS In no region of the white matter skeleton was fractional anisotropy lower in the preterm group at either site. Within the preterm groups, fractional anisotropy was significantly associated with white matter injury score, but not sex, gestational age, or birthweight. At site 1, fractional anisotropy was associated with IQ.

INTERPRETATION DTI contributes to understanding individual differences after preterm birth but may not differentiate a relatively high-functioning group of preterm children from a matched group of term-born children.

Infants born preterm are at high risk of cognitive disability and associated deficits that persist into adolescence and young adulthood.[1,2] These deficits have been attributed to a distinctive pattern of periventricular white matter injury within a global pattern of neonatal encephalopathy.[3] A cascade of adverse events begins with ischemia and/or hypoxia. Free radical-mediated injury to oligodendrocyte progenitors ultimately disrupts the maturation of myelin-producing cells.[4] Improvements in neonatal intensive care have led to a substantial reduction in the prevalence of cystic periventricular white matter injury.[4] However, evidence of non-focal white matter injury can be found on conventional magnetic resonance imaging (MRI) and is associated with adverse outcomes.[5]

Diffusion tensor imaging (DTI) is an MRI technique for characterizing the microstructural properties of white matter,[6] based on the rate and diffusion of water in the brain.[7] In white matter, water diffusion is anisotropic, relatively unimpeded in the direction of the axon, and restricted in directions perpendicular to the axon. The rate of diffusion along the principal axis is called axial diffusivity and the perpendicular rate of diffusion is called radial diffusivity. Fractional anisotropy is a value between zero and 1.0 derived from these measures that indicates the degree of anisotropy. Factors that reduce diffusion perpendicular to the orientation of the axon include dense axonal packing, large axonal diameters, and high levels of myelination. Because these factors increase with age and decrease with injury and illness, higher fractional anisotropy values are generally considered as an index of maturity and good health.[7,8] However, high fractional anisotropy values have also been found in clinical populations in which disruption of connectivity was expected.[9–11]

Many DTI studies in adolescents and adults who were born preterm have found lower fractional anisotropy values across many white matter regions.[12–15] However, a few studies do not replicate this pattern. Frye et al.[16] found no consistent differences in fractional anisotropy on association tracts when comparing 16-year-olds born preterm and at term. Kontis et al.[17] found no differences in fractional anisotropy or mean diffusivity in the corpus callosum between very preterm and term groups. A recent study by Allin et al.[18] found that, among

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adults who were born preterm, fractional anisotropy was lower in some tracts but higher in other tracts than among a comparison group. Discrepancies across studies may be related to the participants' degree of illness in the newborn period. Near-term imaging of children born preterm shows that complications of preterm birth, not pre term birth per se, are associated with injury to white matter.[19]

Many studies report positive associations between DTI measures and a variety of neurocognitive and neurobehavioral functions in preterm children.[9,10] Such findings are also inconsistent. Some studies find associations of function with white matter volume but not fractional anisotropy in preterm groups.[16]

The first goal of this study was to compare white matter microstructure in two cohorts of children and adolescents, one born preterm and one born at term. Distinctive features of this sample were that the participants were born across the spectrum of gestational age (24–36wks) and that the mean IQ was within the average range.[17,18] We hypothesized that we would find lower fractional anisotropy and higher radial diffusivity in children born preterm than in those born at term, controlling for age at DTI.[20]

The second goal was to understand the factors associated with microstructural properties of white matter within the preterm group. We hypothesized that fractional anisotropy values would be lower in males than in females;[14,21] that fractional anisotropy would be positively associated with gestational age/birthweight[12,15] and IQ;[12,14,15] and that fractional anisotropy would be negatively associated with the degree of injury on conventional MRI.

What this paper adds

- Fractional anisotropy on DTI is not uniformly lower in individuals born preterm than in those who are born at term.
- Fractional anisotropy is highly associated with degree of injury on conventional MRI.
- Fractional anisotropy correlates with IQ in a relatively high-functioning group of preterm adolescents.

METHODS

Participants

The study population (n=121) consisted of a convenience sample of children born during the 1990s to 2001 at two sites: Stanford University (site 1, n=65; 35 females, 30 males) and University of Pittsburgh (site 2, n=56; 31 females, 25 males). Participants were aged 9 to 16 years (mean age 12y 8mo; SD 2y 1mo); preterm birth was defined as birth at a gestational age of less than 36 weeks (site 1: mean age 28.7wks; SD 2.6wks; site 2: mean age 29.6wks; SD 2.9wks) and a birthweight of less than 2500g (site 1: mean birthweight 1209g; SD 469g; site 2: mean birthweight 1349g; SD 516g). The comparison group comprised children and adolescents born at term (≥37wks) and recruited through recommendations of preterm and term participants, flyers posted throughout the community, and mailings to local schools.

Exclusion criteria for all participants included active seizures, complications of ventriculoperitoneal shunt for hydrocephalus, congenital malformation, meningitis or encephalitis; receptive vocabulary standard score <70; sensory impairments; and non-English speaker. Potential members of the comparison group were excluded by telephone pre-screening, which identified language, learning, or psychiatric disorders requiring medication, and grade retention after age 7 years, because these conditions could complicate the interpretation of significant associations between DTI measures and function. Table I summarizes the demographic data from each site.

Stanford University and University of Pittsburgh institutional review boards approved the study. A parent or legal guardian provided informed consent and children provided assent. Participants were compensated for participation.

Medical complications at birth in the preterm group at site 1 were as follows: eight had abnormal findings on brain ultrasound or MRI (grade 1 or 2 intraventricular hemorrhage, echodensities or cysts); 13 had respiratory distress syndrome and six developed chronic lung disease; one was small for gestational age (defined as lying at or below the third centile in birthweight for gestational age); and one had necrotizing enterocolitis. At site 2, five participants had abnormal findings on head ultrasound or MRI; nine had respiratory distress

Table I: Characteristics of participants at sites 1 and 2

	Site 1: Stanford University		Site 2: University of Pittsburgh	
	Comparison group (n=40)	Preterm group (n=25)	Comparison group (n=23)	Preterm group (n=33)
Males, n (%)	18 (45)	12 (48)	9 (39)	16 (48)
Females, n (%)	22 (55)	13 (52)	14 (61)	17 (52)
Injury on MRI,[a] n (%)				
None		13 (52)		12 (36)
Mild		10 (40)		19 (58)
Moderate		1 (04)		2 (6)
Severe		1 (04)		0 (0)
Age (y), mean (SD)	13.0 (2.2)	12.6 (2.1)	12.8 (2.0)	12.6 (2.1)
FIQ SS, mean (SD)	119.1 (14.9)	108.8 (15.5)	111.7 (9.4)	101.2 (14.0)
Gestational age (wks), mean (SD)	–	28.7 (2.6)	–	29.6 (2.9)
Birthweight (g), mean (SD)	–	1209 (469)	–	1349 (516)

[a]Magnetic resonance imaging (MRI) injury based 15-point scoring system following Inder et al.:[23] none, ≤6; mild, >6 and ≤9; moderate, >9 and ≤12; severe, >12. FIQ SS, Full-scale IQ standard score, measured on the Wechsler Abbreviated Scale of Intelligence.[22]

syndrome and one developed chronic lung disease; five were small for gestational age; and one had necrotizing enterocolitis. We did not include three participants from site 1 and one participant from site 2 who had moderate to severe ventriculomegaly because their scans distorted the patterns of the rest of the sample.

Procedures

IQ

Full-scale IQ was estimated using the Wechsler Abbreviated Scale of Intelligence,[22] a nationally standardized test of intellectual ability that measures verbal and non-verbal cognitive ability.

MRI data acquisition

Site 1. MRI data were acquired on a 3T Signa Excite (GE Medical Systems, Milwaukee, WI, USA) at Stanford University. For DTI, a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence was used to acquire 60 slices of 2mm thickness in 30 different diffusion directions (b=900s/mm^2). For additional details, see the supplementary material (MRI data acquisition).

Site 2. Structural magnetic resonance imaging and DTI data were acquired with a Siemens 3T Magnetom Allegra (Erlangen, Germany) system with a standard circularity-polarized head coil. For DTI, a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence was used to acquire 29 axial slices of 4mm thickness in six directions (b=850s/mm^2). For additional details, see supplementary material (MRI data acquisition).

T1 and T2 image evaluation

A neuroradiologist unaware of the child's medical conditions evaluated the T1- and T2-weighted MRI of the preterm group, using the white matter scoring system of Inder et al.[23] Each scan was scored from 5 to 15, based on a 3-point scale for five white matter features: white matter signal abnormality, periventricular white matter volume loss, cystic abnormalities, ventricular dilation, and thinning of the corpus callosum. We further classified the scans as injury none (score ≤6), mild (>6 and ≤9), moderate (>9 and ≤12), or severe (>12).

DTI processing

We analyzed white matter properties using the voxelwise tract-based spatial statistics method from the Oxford Centre for Functional MRI of the Brain Diffusion Toolbox.[24] This method identifies a core white matter 'skeleton' that is anatomically equivalent across participants. By analyzing only voxels of core white matter, it minimizes partial volume effects that occur when more than one tract goes through a voxel.[24]

In the initial analysis of DTI for the purposes of group comparison, we analyzed fractional anisotropy. We also analyzed axial diffusivity, radial diffusivity, and mean diffusivity.

DTI was corrected for eddy current distortions by affine registration to a non-diffusion-weighted volume. A tensor model was fitted to each voxel, and fractional anisotropy images were calculated. Because we were analyzing children,[24] the fractional anisotropy image of the most representative participant in the study (target) was chosen based on the minimum necessary warping, with Functional MRI of the Brain Software Library's non-linear registration tool.[24] The target image was sampled to 1mm^3 resolution and aligned by affine transformation to the Montreal Neurological Institute template (MNI152), allowing us to use standard space coordinates for describing regions. Each participant's image was aligned to the target. We found no difference between preterm and comparison groups in the degree of non-linear warping, using an independent samples t-test, indicating that the tract-based spatial statistics methods did not require additional warping to fit preterm brains to the target.

Using a threshold of fractional anisotropy ≤0.2 to restrict analyses to white matter, a mean fractional anisotropy image was generated and thinned to create the mean fractional anisotropy skeleton, a representation of the centers of all major white matter tracts common to the group. Finally, each participant's maximum local fractional anisotropy, axial and radial diffusivity were orthogonally projected onto the fractional anisotropy skeleton. The resulting data was fed into voxelwise cross-participant statistics.

Statistical analysis

Chi-square tests (for categorical variables) and independent t-tests (for continuous variables) were used to evaluate between-group differences on demographic variables and IQ.

Analysis of the fractional anisotropy values of the fractional anisotropy skeleton at the voxel level was conducted using a permutation-based approach.[24] These analyses controlled for age and set significance at p<0.05, after non-parametric permutation testing, corrected for multiple comparisons. Statistical maps were obtained for each voxelwise test in both the positive and negative directions. To determine if we would find differences in fractional anisotropy, axial, radial, or mean diffusivity between preterm participants and the comparison group, we analyzed group differences across the entire fractional anisotropy skeleton for preterm versus term participants from the two sites separately.

To determine if fractional anisotropy was associated with other factors within the preterm group only, we analyzed the fractional anisotropy skeleton for differences as a function of sex using the t-statistic and for associations with age, gestational age, birthweight, score on conventional MRI, and IQ. We set the statistical threshold at p<0.05, after non-parametric permutation testing, corrected for multiple comparisons. We also correlated fractional anisotropy and IQ in the term-born group.

RESULTS

Group differences

We found no location on the fractional anisotropy skeleton at which fractional anisotropy was lower in the preterm group than in the term group at either site. The following tracts showed significantly higher fractional anisotropy in the preterm group than in the comparison group at site 1: right corticospinal, right inferior fronto-occipital/inferior longitudinal, and

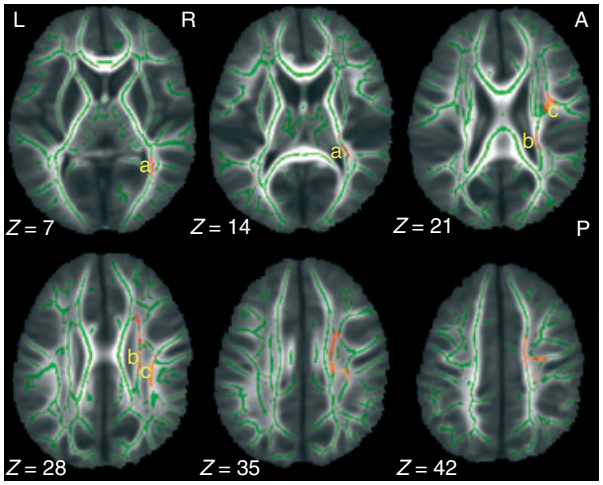

Figure 1: White matter regions (red–yellow heat map) on the fractional anisotropy skeleton (green) of statistically significant increased fractional anisotropy ($p<0.05$; non-parametric permutation test, corrected for multiple comparisons) in the preterm group at site 1 overlaid on the mean fractional anisotropy image (grayscale). The tracts in which differences are found include (a) the right inferior fronto-occipital/inferior longitudinal (posterior region), (b) the right corticospinal, and (c) the right superior longitudinal fasciculi. L, left; R, right; A, anterior; P, posterior.

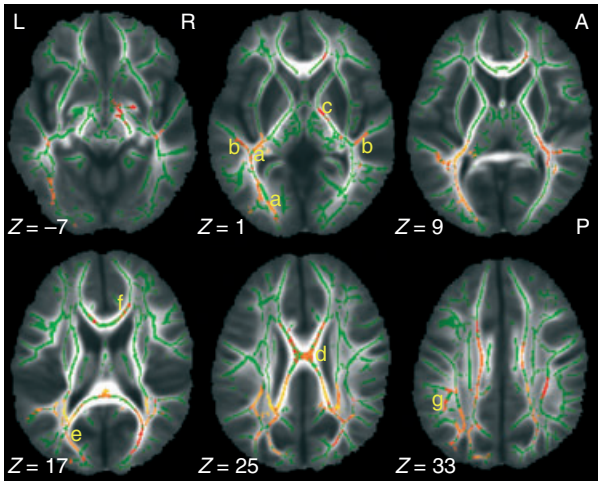

Figure 2: White matter regions (red–yellow heat map) on the fractional anisotropy skeleton (green) of statistically significant negative associations between fractional anisotropy and white matter injury score ($p<0.05$; non-parametric permutation test, corrected for multiple comparisons) within the preterm group at sites 1 and 2 overlaid on the mean fractional anisotropy image (grayscale). The tracts in which differences are found include (a) the bilateral inferior fronto-occipital fasciculi, (b) the bilateral inferior longitudinal fasciculi, (c) the bilateral anterior thalamic radiations, (d) the corpus callosum, (e) forceps major, (f) forceps minor, and (g) the bilateral superior longitudinal fasciculi. L, left; R, right; A, anterior; P, posterior.

right superior longitudinal fasciculi (Fig. 1). We found no significant group differences in axial, radial, or mean diffusivity at site 1. The following tracts showed higher axial diffusivity in the preterm group than in the comparison group at site 2: bilateral corticospinal, bilateral inferior fronto-occipital/uncinate (anterior), right superior longitudinal, corpus callosum and forceps minor, and bilateral anterior thalamic radiations. We found no statistically significant differences in fractional anisotropy, radial, or mean diffusivity at site 2.

Associations of factors and fractional anisotropy within the preterm group

We found no difference in fractional anisotropy values between males and females at either site. We found no association of either gestational age or birthweight and fractional anisotropy at either site. Thirteen participants in the preterm group at site 1 and 12 in the preterm group at site 2 had white matter injury scores ≤6, indicating no injury. At both sites, injury scores were predominantly mild and moderate; one child at site 1 had severe injury (Table I). At both sites, lower fractional anisotropy values were associated with higher white matter injury scores (Fig. 2 and Table II). The regions of significant association tended to be in the corpus callosum and in posterior and periventricular tracts, sites of known white matter injury in preterm children. In no tracts was there a positive association between fractional anisotropy and white matter injury score. At site 2 there were also significant positive associations between injury score and axial, radial, and mean diffusivity.

We found positive associations of fractional anisotropy and IQ in the preterm group at site 1 (Fig. 3). The tracts in which these associations were significant included bilateral anterior thalamic radiations, bilateral corticospinal tracts, left cingulum, forceps minor, right inferior fronto-occipital/inferior longitudinal, bilateral superior longitudinal fasciculi, and bilateral fronto-occipital/uncinate. We found no region of negative association between fractional anisotropy and IQ. At site 1 we found significant positive associations of axial and mean diffusivity and IQ. At site 2, the association of fractional anisotropy and IQ in the preterm group showed a trend ($p<0.15$); tracts with this level of significance were the bilateral inferior fronto-occipital/inferior longitudinal fasciculi and the uncinate. We found no significant association of axial, radial, and mean diffusivity and IQ. Correlations of fractional anisotropy and IQ in the term group at both sites were not statistically significant.

DISCUSSION

Contrary to our hypothesis, we did not find lower fractional anisotropy values in the preterm than in the term group. As we replicated this finding at two independent sites, we could not readily dismiss it as chance. At site 1, we found higher fractional anisotropy values in selected tracts in the right hemisphere, and at site 2 higher axial diffusivity in multiple bilateral tracts in the preterm groups.

Increased fractional anisotropy among children born preterm has been reported in similar tracts at term age[25] and in adolescence and adulthood.[18] One possible explanation for our findings is that study participants at both sites were

Table II: Tracts in which fractional anisotropy on diffusion tensor imaging was significantly associated with injury score from conventional magnetic resonance imaging at the two sites

Site 1: Stanford University	Site 2: University of Pittsburgh
Bilateral anterior thalamic radiations	Bilateral anterior thalamic radiations
Bilateral inferior fronto-occipital/inferior longitudinal fasciculus	Bilateral inferior fronto-occipital/inferior longitudinal fasciculus
Bilateral superior longitudinal fasciculus	Left superior longitudinal fasciculus
Corpus callosum	Corpus callosum
Forceps major	Forceps major
Forceps minor	Forceps minor
	Bilateral corticospinal tracts
	Bilateral uncinate/inferior longitudinal fasciculus

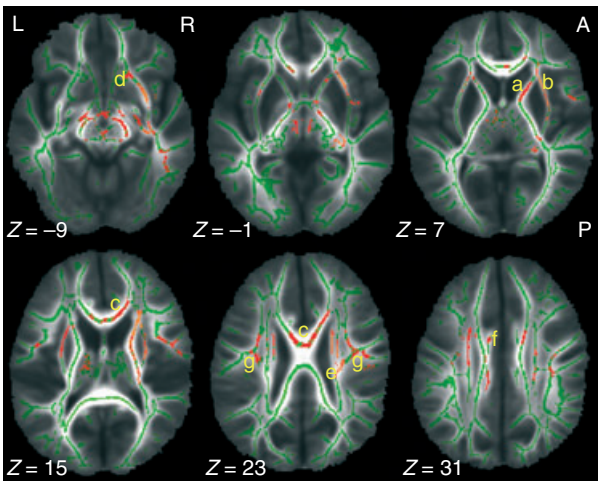

Figure 3: White matter regions (red–yellow heat map) on the fractional anisotropy skeleton (green) of statistically significant positive associations between fractional anisotropy and IQ ($p<0.05$; non-parametric permutation test, corrected for multiple comparisons) within the preterm group at site 1 overlaid on the mean fractional anisotropy image (grayscale). The tracts in which these associations are significant include (a) the bilateral anterior thalamic radiations, (b) the right inferior fronto-occipital fasciculus, (c) the corpus callosum and forceps minor, (d) the uncinate, (e) the bilateral corticospinal tracts, (f) the left cingulum, and (g) the bilateral superior longitudinal fasciculi.) L, left; R, right; A, anterior; P, posterior.

relatively high functioning. The preterm groups scored within the average range on the test of intelligence. Many preterm participants had no apparent white matter injury on conventional MRI. The high proportion of high-functioning children in a sample of this size may have reduced our ability to detect small group differences in fractional anisotropy. A recent study of near-term DTI in preterm infants that found no group differences in fractional anisotropy comparing preterm and term participants noted that fractional anisotropy was more highly associated with complications of preterm birth than with preterm birth per se.[19]

Increased fractional anisotropy has also been found in various white matter tracts in other clinical populations of children in whom impaired connectivity was observed or anticipated, including Williams syndrome,[9] attention-deficit–hyperactivity disorder,[10] and poor reading.[11] Possible explanations for these unexpected results have included decreased white matter volume,[18] decreased dendritic branching or crossing fibers,[9] and fewer but larger axons,[11] all of which would contribute to relative increases in fractional anisotropy. The physiological properties that contribute to fractional anisotropy are likely to vary across different clinical populations. The interpretation of fractional anisotropy may therefore vary in different clinical populations, and even in different white matter tracts within a population.

Alternative explanations for increased fractional anisotropy in the preterm group may relate to the pathophysiology of injury and recovery in this population.[6] Studies on diffusion measurements on myelin-deficient and demyelinated fibers[25] suggest that fractional anisotropy and mean diffusivity arise predominantly from axonal density rather than from myelin content. If the primary pathology of white matter injury in preterm birth is loss of myelin-producing cell lines, then fractional anisotropy may not be the ideal measure to index injury. Measures currently under development that would more specifically assess myelin content might be able to show group differences more consistently than the non-specific DTI measures currently in use. It is also possible that some of the participants born preterm may have experienced recovery such that the usual signs of injury had resolved by adolescence.[6] White matter is known to respond to experiences such as training.[26] The participants in these cohorts have received considerable intervention since infancy and are currently functioning in the average range of intelligence. Therefore, white matter properties may have changed over time. The participants from site 1 had higher intelligence scores than those from site 2, a factor that may explain differences in the pattern of results from the two locations.

Fractional anisotropy was sensitive to individual differences within the preterm group, even though it was not sensitive to group differences. First, fractional anisotropy was associated with white matter injury scores from conventional MRI. The tracts in which the association was statistically significant overlap the regions known to be vulnerable to white matter injury in preterm children: posterior periventricular tracts, including the inferior fronto-occipital and inferior longitudinal fasciculi, superior longitudinal fasciculi, and the corpus callosum and its extensions to the forceps major and minor.[3–5] Second, fractional anisotropy was also significantly associated with IQ within the preterm group at site 1 and a trend was found at site

2. Other studies report similar associations of fractional anisotropy and functional outcomes.[12,13,15] The sensitivity to within-group individual differences may be greater than the sensitivity to between-group factors because the pathological processes that affect white matter in the preterm group are similar across individuals.

A limitation of the current study was that it used a convenience sample rather than a birth cohort. The scans were done at two different sites using different DTI sequences, a feature that may account for group differences. However, the main results were similar at two independent sites, increasing our confidence in the findings. Another limitation was that the sample was relatively high functioning. This study shows that the associations of fractional anisotropy with outcomes within the preterm population are not limited to samples with severe impairment. The sample had a range of gestational ages at birth and ages at scanning, which may introduce variability to the results. However, increased variation may also facilitate finding associations, particularly between structure and function. Tract-based spatial statistics (TBSS) is a conservative method for detecting group differences because it assesses only the core of the white matter tract. However, TBSS has shown focal areas of reduced fractional anisotropy on DTI from infants born preterm, obtained near term[25,26] and in adulthood.[15] Moreover, TBSS was sufficiently sensitive in detecting associations of fractional anisotropy and IQ in this sample.

These findings support the concept that white matter injury contributes to adverse neurodevelopmental outcomes in children born preterm. Future directions include attempting to replicate these findings, using other methods of DTI analysis that may be more sensitive to group differences. In addition, we plan to evaluate structure–function relations in other developmental domains known to be affected by preterm birth.

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SUPPORTING INFORMATION

The following additional information may be found online:

MRI data acquisition: site 1 and site 2.

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