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RESEARCH ARTICLE

Quantitative tract-based white matter heritability in 1- and 2-year-old twins

Seung Jae Lee[1,2] | Jingwen Zhang[3] | Michael C. Neale[4] | Martin Styner[1,5] | Hongtu Zhu[6,7,8] | John H. Gilmore[1,6]

[1]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[2]Department of Psychiatry, School of Medicine, Kyungpook National University, Daegu, South Korea

[3]Department of Biostatistics, UNC Gillings School of Global Public Health, Chapel Hill, North Carolina

[4]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia

[5]Department of Computer Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[6]Biomedical Research Imaging Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[7]Department of Biostatics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[8]Department of Biostatics, University of Texas, MD Anderson Cancer Center, Houston, Texas

Correspondence
Seung Jae Lee, Department of Psychiatry, School of Medicine, Kyungpook National University 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, South Korea.
Email: jayleemd@knu.ac.kr

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Abstract

White matter (WM) microstructure, as determined by diffusion tensor imaging (DTI), is increasingly recognized as an important determinant of cognitive function and is also altered in neuropsychiatric disorders. Little is known about genetic and environmental influences on WM microstructure, especially in early childhood, an important period for cognitive development and risk for psychiatric disorders. We studied the heritability of DTI parameters, fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) along 34 tracts, including 10 bilateral fiber pathways and the respective subdivision, using quantitative tractography in a longitudinal sample of healthy children at 1 year (N = 215) and 2 years (N = 165) of age. We found that heritabilities for whole brain AD, RD, and FA were 0.48, 0.69, and 0.72 at age 1, and 0.59, 0.77, and 0.76 at age 2 and that mean heritabilities of tract-averaged AD, RD, and FA for individual bundles were moderate (over 0.4). However, the heritability of DTI change between 1 and 2 years of age was not significant for most tracts. We also demonstrated that point-wise heritability tended to be significant in the central portions of the tracts and was generally spatially consistent at ages 1 and 2 years. These results, especially when compared to heritability patterns in neonates, indicate that the heritability of WM microstructure is dynamic in early childhood and likely reflect heterogeneous maturation of WM tracts and differential genetic and environmental influences on maturation patterns.

KEYWORDS

axial diffusivity, diffusion tensor imaging, fractional anisotropy, genetics, quantitative tractography, radial diffusivity

1 | INTRODUCTION

Recent evidence from diffusion tensor imaging (DTI) studies has shown a significant relationship between white matter (WM) microstructure and cognitive function in healthy subjects (Lee et al., 2017; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013; Schmithorst & Yuan, 2010; Short et al., 2013). Abnormalities of WM integrity are associated with cognitive impairments (Zhang et al., 2013), and neuropsychiatric disorders such as schizophrenia and autism spectrum disorder (Kuswanto, Teh, Lee, & Sim, 2012; Mueller, Keeser, Reiser, Teipel, & Meindl, 2012).

There is also evidence that the abnormal brain structure associated with psychiatric disorders arises in part during prenatal and early childhood development (Bale et al., 2010; Insel, 2010; NIMH Workgroup, 2008).

Early childhood is a period of rapid development of the basic structural and functional framework of the brain. During the first 2 years of life, DTI studies show that WM exhibits a significant increase in fractional anisotropy (FA) and decrease in radial diffusivity (RD) and axial diffusivity (AD), with rates of change faster in the first year than the second (Dubois et al., 2008; Dubois, Hertz-Pannier, Dehaene-Lambertz, Cointepas, & Le Bihan, 2006; Gao et al., 2009; Geng et al., 2012). These quantitative parameters are related to WM maturation, including bundle fasciculation, pre-myelination, and true myelination; AD is thought to be related to longitudinal fiber organization while RD is related to myelination (Dubois et al., 2008). However, very little is known about how genetic and environmental factors influence WM development during this period of rapid maturation, one that will likely affect future individual differences in cognition, behavior, and risk for psychopathology.

In adults and older children, WM microstructure has relatively high heritability: for example, additive genetic factors explain over 50% of inter-subject variance in FA values in most regions and heritability tends to increase with development (Kochunov et al., 2014), through longitudinal studies are still scarce (Brouwer et al., 2012). In neonates, we previously estimated whole brain mean genetic variance to be 0.60, 0.57, and 0.53 for FA, AD, and RD, respectively, with significant regional heterogeneity (Geng et al., 2012). A subsequent tract-based analysis in neonates found significant genetic influences in almost all tracts with similar mean genetic variances around 0.30 for FA, AD, and RD as well as positive relationships between these parameters and heritability, and demonstrated that commissural fibers tended to have the highest heritabilities for DTI parameters while association fibers tended to have the least (Lee et al., 2015). We recently studied the heritability of common factors extracted from 12 tracts for each DTI parameter from birth to 2 years and found that the factor structure develops complexity with an increase of the number of factors by 2 years of age and these factors were also moderately heritable (Lee et al., 2017). To the best of our knowledge, there has been no heritability report on WM tracts at 1 and 2 years of age. Moreover, WM maturation evolves dynamically at different times and speeds in different spatial locations within a bundle (Colby et al., 2012; Partridge et al., 2005). In turn, these dynamic changes in phenotypic variance within a tract may alter heritability. Thus, providing information about the spatial location of heritability along a given tract is of fundamental importance in understanding overall tract heritability.

To follow up on our tract-based study of WM microstructure heritability in neonates (Lee et al., 2015), we report a comprehensive study of heritability of WM DTI parameters along 10 bilateral bundles and their respective subdivisions in healthy twins with longitudinal data collected at ages 1 and 2 years, using the same quantitative tractography approach.

The first objective of this study was to determine tract-averaged heritabilities of DTI parameters for individual tracts. We hypothesized that, relative to neonates, increase in heritability of WM DTI parameters would be observed at ages 1 and 2 years according to the general notion that heritability tends to increase with early brain development (Kochunov et al., 2014). As recently summarized (Gilmore, Knickmeyer, & Gao, 2018), we believe that this increase is not simply explained by a decreased measurement error in the developing brain, as heritability estimates are not higher in 9 and 12 years old compared to neonates. The second goal was to investigate the heritability of change between 1- and 2-year-old. Since myelination is largely complete in many WM fibers in the first year except in association fibers which are still developing (Dubois et al., 2014), we expected that the variation in WM microstructural change, and therefore the heritability of change would be subtle during the study period. If heritability did change, it would be more likely to occur in later maturing association fibers. The third aim was to visualize the distribution of spatial points with statistically significant heritability on tracts and to test whether this observation is statistically significant or not using cluster-based analysis.

2 | METHODS

2.1 | Participants

Children analyzed in this study are healthy twin and singleton subjects in the ongoing longitudinal University of North Carolina (UNC) Early Brain Development Studies (EBDS). Women with twin pregnancies were recruited from the outpatient OB-GYN clinics at UNC Hospitals and Duke University Medical Center. Exclusion criteria for mothers included major maternal illness or infection during pregnancy, and maternal diagnosis of a major psychiatric disorder; for infants exclusion criteria included chromosomal abnormalities, severe congenital abnormalities, and major medical illness or infection. Zygosity was determined with polymerase chain reaction-short tandem repeat (PCR-STR) analysis of 14 loci on DNA prepared from buccal swab cell collection (BRT Laboratories, Baltimore, MD). Written informed consent was obtained from a parent of all infant participants. This study was approved by the Institutional Review Boards of the UNC School of Medicine and Duke University Medical Center.

This study included 215 1-year-old with analyzable scans, including 74 monozygotic (MZ) twins, 88 dizygotic (DZ) twins, and 53 "single" twins for which an analyzable scan for the co-twin was not available. There were 165 2-year-old: 68 MZ twins, 56 DZ twins and 41 for "single" twins. One hundred one subjects had usable scans at both ages. All subjects participated in our previous study of heritability in neonates (Lee et al., 2015). Participants' median gestational age (interquartile range) at birth was 36 (34–37) weeks for 1-year-old and 36 (33–37) weeks for 2-year-old; their median chronological age (interquartile range) at scan was 57 (55–60) weeks for 1-year-old and 110 (107–113) weeks for 2-year-old. Demographic variables for each group are presented in Table 1.

2.2 | Image acquisition

Most MRI data were acquired on a 3 T Siemens Allegra head-only scanner (Siemens Medical System, Erlangen, Germany); comprising

TABLE 1 Demographic data for 1 and 2 years old

	1-year-old *N* = 215	2-year-old *N* = 165	Statistics	*p*
Zygosity				
MZ, paired twins	74	66	2.1[a]	.36
DZ, paired twins	88	56		
"Single" unpaired twins (MZ,DZ)	53(22,31)	43(18,25)		
Gender				
Male	114	83	2.8[a]	.60
Female	101	82		
Ethnicity				
Caucasian	153	99	6.7[b]	.03
African	61	62		
Asian	1	4		
Gestational age at birth (week, quartile)	36[34,37]	36[33,37]	0.26[c]	.80
Chronological age at scan (week, quartile)	57[55,60]	110[107,113]	–	–
MR scanner, gradient direction				
Allegro, 6 directions	62	46		
Allegro, 42 directions	113	72	5.5[a]	.63
Trio, 42 directions	40	47		

[a] Chi-square test.
[b] Fisher's exact test.
[c] Independent *t* test.

81% of the 1-year-old and 72% of the 2-year-old in this study. For earlier Allegra diffusion-weighted imaging (DWI) data, a single shot echo-planar imaging (EPI) spin-echo sequence was used with the following parameters: Repetition Time (TR)/Echo Time (TE) = 5,200/73 ms, slice thickness = 2 mm, in-plane resolution = 2 × 2 mm^2, with a total of 45 slices for six diffusion-weighted images using *b*-value of 1,000 s/mm^2 and one baseline image (*b*-value = 0) per sequence, repeated five times total to improve signal-to-noise. For the remaining Allegra DWI data, 42 directions of diffusion sensitization were acquired with a *b*-value of 1,000 s/mm^2 in addition to seven images with no diffusion weighting for reference. The parameters were as follows: TR/TE/Flip angle = 7680/82/90°, slice thickness = 2 mm, in-plane resolution = 2 × 2 mm^2, with a total of 60–72 slices. The rest of the study subjects were scanned using an upgraded Siemens model, the 3 T Tim Trio (Siemens Medical System, Erlangen, Germany), following the same sequencing parameters as the 42 direction Allegra sequence detailed above.

2.3 | Quantitative tractography

A study-specific quality control protocol was applied to all raw DWI data using DTIPrep (www.nitrc.org/projects/dtiprep) which included slice-wise and gradient-wise artifact detection, as well as eddy current and motion correction (Oguz et al., 2014). Skull and nonbrain tissue were masked out using brain extraction tool (Smith, 2002), followed by manual correction of the brain masks. Diffusion tensors were estimated using a weighted least squares algorithm (Goodlett, Fletcher, Gilmore, & Gerig, 2009). All diffusion tensor data was deformably mapped into the UNC EBDS combined pediatric (1–2 years) atlas space (www.nitrc/projects/dtiatlasbuilder) (Verde et al., 2014), where a total of 34 fiber tract segments had been previously defined using streamline tractography: rostrum, genu, body, and splenium of corpus callosum; bilateral prefrontal, premotor, motor, and parietal projections of the corticothalamic tract; cingulate and hippocampal cinguli; fornices; frontoparietal, frontotemporal, and temporoparietal parts of arcuate; uncinate; superior and inferior longitudinal fasciculi (SLF and ILF); inferior fronto-occipital fasciculi (IFOF); and optic tracts (see appendix in Lee et al., 2015 for details of tract identification and tractography parameters). Invertibility of the registration information permits mapping of these tracts from the pediatric DTI atlas space back to each original tensor image to sample diffusion measurements. This approach performs tractography only in atlas space and thus employs the atlas-defined tracts as curvilinear regions of interest. Tracts are then parameterized by length to represent diffusion properties as a function of location along the selected tracts. DTI property profiles for AD, RD, and FA are then extracted along these parameterized fibers at equally spaced points along the length of each fiber tract (see Verde et al., 2014 for details).

2.4 | Genetic analysis of twins

To estimate the variance components of tract-averaged diffusion parameters at ages of 1 year old and 2 years old simultaneously from the twin data, we fit a longitudinal ACE model. For subject *j* ($j \le 2$) of twin pair *i* at age *t* ($t = 1, 2$), we consider

$$y_{ij,t} = x_{ij,t}^{T}\beta + a_{ij,t} + c_{i,t} + e_{ij,t},$$

where $y_{ij,\,t}$ is the diffusion parameter, $x_{ij,\,t}$ is a vector of covariates including sex, gestational age at birth, postmenstrual age at scan, scanner type and number of gradient direction. β is composed of fixed effect coefficients, $a_{ij,t}$, $c_{i,t}$, and $e_{ij,t}$ are random effects representing additive genetic variation, common environmental variation, and unique environmental variation satisfying the following

$$\begin{bmatrix} a_{ij,1} \\ a_{ij,2} \end{bmatrix} \tilde{N}\left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{a,1} & \sigma_{a,12} \\ \sigma_{a,12} & \sigma^2_{a,2} \end{bmatrix} \right\}, \begin{bmatrix} c_{i,1} \\ c_{i,2} \end{bmatrix} \tilde{N}\left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{c,1} & \sigma_{c,12} \\ \sigma_{c,12} & \sigma^2_{c,2} \end{bmatrix} \right\},$$
$$\text{and} \begin{bmatrix} e_{ij,1} \\ e_{ij,2} \end{bmatrix} \tilde{N}\left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{e,1} & \sigma_{e,12} \\ \sigma_{e,12} & \sigma^2_{e,2} \end{bmatrix} \right\}.$$

For a DZ twin pair,

$$Var\left(\begin{bmatrix} a_{i1,1} \\ a_{i1,2} \end{bmatrix}, \begin{bmatrix} a_{i1,1} \\ a_{i1,2} \end{bmatrix} \right) = 0.5 \begin{bmatrix} \sigma^2_{a,1} & \sigma_{a,12} \\ \sigma_{a,12} & \sigma^2_{a,2} \end{bmatrix} \text{ and } Var\left(\begin{bmatrix} e_{i1,1} \\ e_{i1,2} \end{bmatrix}, \begin{bmatrix} e_{i1,1} \\ e_{i1,2} \end{bmatrix} \right) = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

For an MZ twin pair,

$$Var\left(\begin{bmatrix} a_{i1,1} \\ a_{i1,2} \end{bmatrix}, \begin{bmatrix} a_{i1,1} \\ a_{i1,2} \end{bmatrix} \right) = \begin{bmatrix} \sigma^2_{a,1} & \sigma_{a,12} \\ \sigma_{a,12} & \sigma^2_{a,2} \end{bmatrix} \text{ and } Var\left(\begin{bmatrix} e_{i1,1} \\ e_{i1,2} \end{bmatrix}, \begin{bmatrix} e_{i1,1} \\ e_{i1,2} \end{bmatrix} \right) = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

The heritability $h^2_{a,t}$ is defined as the proportion of additive genetic variation to total variation, that is, $h^2_{a,t} = \frac{\sigma^2_{a,t}}{\sigma^2_{a,t} + \sigma^2_{c,t} + \sigma^2_{e,t}}$. Similarly, we also calculate the proportion of common environmental variation

to total variation, that is, $h^2_{c,t} = \frac{\sigma^2_{c,t}}{\sigma^2_{a,t} + \sigma^2_{c,t} + \sigma^2_{e,t}}$, as well as the proportion of unique environmental variation to total variation, that is, $h^2_{e,t} = \frac{\sigma^2_{e,t}}{\sigma^2_{a,t} + \sigma^2_{c,t} + \sigma^2_{e,t}}$.

We used the OpenMx package implemented in R (Boker et al., 2011) to fit the longitudinal ACE model and to estimate the model coefficients. Correspondingly, the estimates of $h^2_{a,t}, h^2_{c,t}$, and $h^2_{e,t}$ were also calculated. The correlations between genetic components at 1-year-old and 2-year-old have been estimated as well. Loglikelihood ratio statistics is used to test the hypothesis of interests. Our primary interest is to test the significance of each variance components $\sigma^2_{a,t}, \sigma^2_{c,t}$, and $\sigma^2_{e,t}$. Additionally, we tested if genetic variations and environmental variations change significantly across time, which is given by the following hypotheses,

$$H_0 : Var(a_{ij,1} - a_{ij,2}) \triangleq \sigma^2_{\Delta a} = 0, H_1 : \sigma^2_{\Delta a} > 0,$$

$$H_0 : Var(c_{i,1} - c_{i,2}) \triangleq \sigma^2_{\Delta c} = 0, H_1 : \sigma^2_{\Delta c} > 0, \text{and}$$

$$H_0 : Var(e_{ij,1} - e_{ij,2}) \triangleq \sigma^2_{\Delta e} = 0, H_1 : \sigma^2_{\Delta e} > 0.$$

Through the above hypotheses, we actually tested the heritability and the environmental effects of DTI change after adjusting for covariates.

Point-wise heritability analysis is applied to each tract at 1-year-old and 2-year-old separately to further study the spatial pattern of heritability distribution using single time point ACE model. Permutation tests are performed to examine the significance of single points and adjusted P-values are calculated to control family-wise error rate along individual curve. Additionally, cluster-based inference (Salimi-Khorshidi, Smith, & Nichols, 2011) is also performed to identify significant clusters on each tract.

For demographic variables, frequency distributions were calculated for categorical variables, and the means and standard deviations were calculated for continuous variables. Pearson's correlations were used when studying the association between FA, AD, and RD heritability of all 34 tract segments.

All the data were analyzed using SPSS for Windows, version 20.0 (SPSS, Inc.; Chicago, IL), R and in-house programs written in MATLAB. In hypothesis testing, a p value <.05 will be considered as significant.

3 | RESULTS

3.1 | Tract-averaged values of DTI parameters and their relationships at age 1 and 2

A summary of the values of DTI parameters at age 1 and 2 and their distributions for individual tracts were shown in Figure 1 and Supporting Information Table S1. As previously reported (Geng, Gouttard, et al., 2012), every bundle showed a small but significant increase of FA and decrease of AD and RD from 1 to 2 years of ages. Unlike other bundles, the fornix and optic tracts showed higher and more widely distributed AD and RD values and the least FA values. This is likely due to local misalignments and partial volume effect that can be exaggerated when analyzing fibers with fine tubular or curved structures like the fornix and optic tract (Bach et al., 2014; Szczepankiewicz et al., 2015). Thus, results of these two tracts should be interpreted cautiously.

Further subgroup analysis of subjects with usable scans at both time periods found that DTI values had moderate to strong relationships between two-time points (e.g., .67 ≤ r ≤ .90 for FA; Supporting Information Table S1). Note that mean (±SD) scores in this subgroup were almost the same as those in the whole group. On the other hand, correlation analyses between DTI parameters showed that most bundles had positive relationships between AD and RD yet negative relationships between RD and FA; mixed relationships between AD and FA varying from negative to positive coefficients (Supporting Information Figure S1).

3.2 | Heritability of whole brain DTI parameters

Heritability estimates for whole brain (from all points in all tracts studied) FA, AD, and RD at age 1 and 2 are presented in Figure 2 (also see Supporting Information Table S2 and S3). Heritabilities and their 95% confidence interval (CI) for whole brain AD, RD, and FA were 0.48, 0.69, and 0.72 at age 1, and 0.59, 0.77, and 0.76 at age 2. The heritability was significant for all DTI parameters except that of AD at age 1, which was slightly above the significance level (p = .09). However, the heritability/genetic variation of DTI change from 1-year-old to 2-year-old in the whole brain was not significant for all three parameters (Supporting Information Table S4).

3.3 | Heritability of tract-averaged values of DTI parameters for individual tracts

Tract-averaged heritabilities are also presented in Figure 2. We observed that mean heritabilities of tract-averaged AD, RD and FA for individual bundles were 0.37, 0.53, and 0.55 at age 1, and 0.46, 0.53, and 0.51 at age 2. For AD, 35% (12/34) of tracts had significant heritability at age 1, while at age 2, this increased to 53% (18/34). For RD, 71% (24/34) had significant heritability, while at age 2, this decreased to 53% (18/34). For FA, 74% (25/34) had significant heritability, while at age 2, this decreased to 35% (12/34). Reduced sample size at age 2 compared to age 1 year may have contributed to overall reduction in number of tracts with significant heritability, as in many tracts, heritability estimates were similar at each age. Relative to the stability of DTI values between the two-time points, heritability ranks were less stable during this period (Supporting Information Table S5).

In 1-year-old, tracts with higher heritability for AD included the splenium of the corpus callosum, bilateral premotor and left parietal corticothalamic tracts, bilateral cingulate portion of the cingulum, right frontotemporal segment of the arcuate, right SLF, bilateral ILF, and left IFOF. In 2-year-old, these tracts tended to remain heritable, with significant heritabilities emerging in other tracts of the corpus callosum, corticothalamic tracts, as well as in the fornix bilaterally.

Tracts with high heritability for RD in 1-year-old include all the tracts of the corpus callosum, several corticothalamic tracts, bilateral cingulate portion of the cingulum, several portions of the arcuate fasciculus, bilateral uncinate fasciculus, bilateral frontoparietal, bilateral frontoparietal and frontotemporal portions of the arcuate tract,

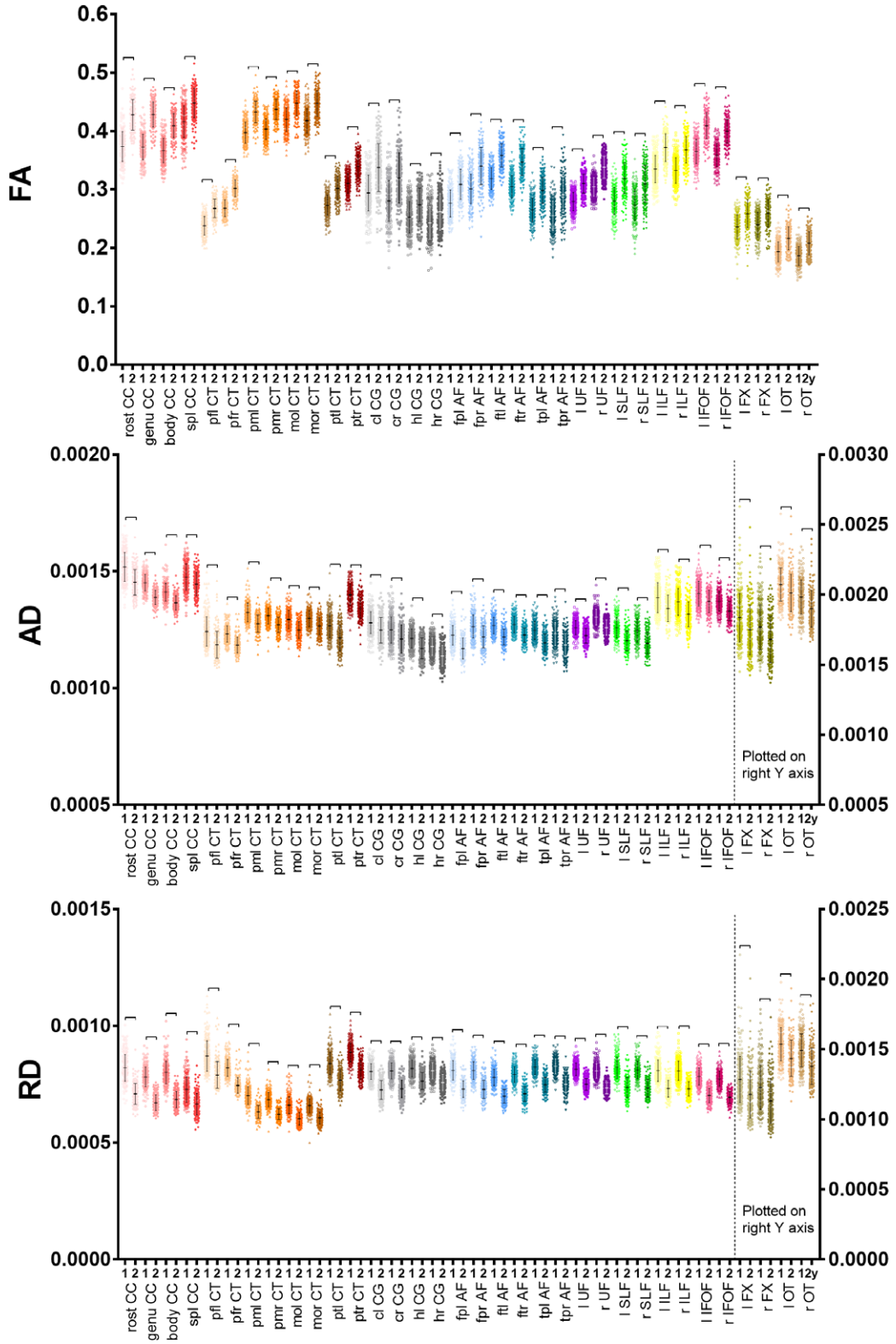

FIGURE 1 Changes in tract-averaged DTI values for individual bundles from 1 to 2 years of age. A pair of the same bundles at each age is illustrated side by side with the same color yet the vacant and solid symbols for 1 and 2 years old, respectively. All of the pairs showed significant differences between the two time periods (down square bracket). Abbreviations: Rostrum (rost), genu, body, and splenium (spl) of corpus callosum (CC); left (l) and right (r) prefrontal (pf), premotor (pm), motor (mo), and parietal (pt) projections of the corticothalamic tract (CT); cingulate (c) and hippocampal (h) cinguli (CG); fornices (FX); frontoparietal (fp), frontotemporal (ft), and temporoparietal (tp) parts of arcuate fasciculi (AF); uncinate fasciculi (UF); superior and inferior longitudinal fasciculi (SLF and ILF); inferior fronto-occipital fasciculi (IFOF); and optic tracts (OT)

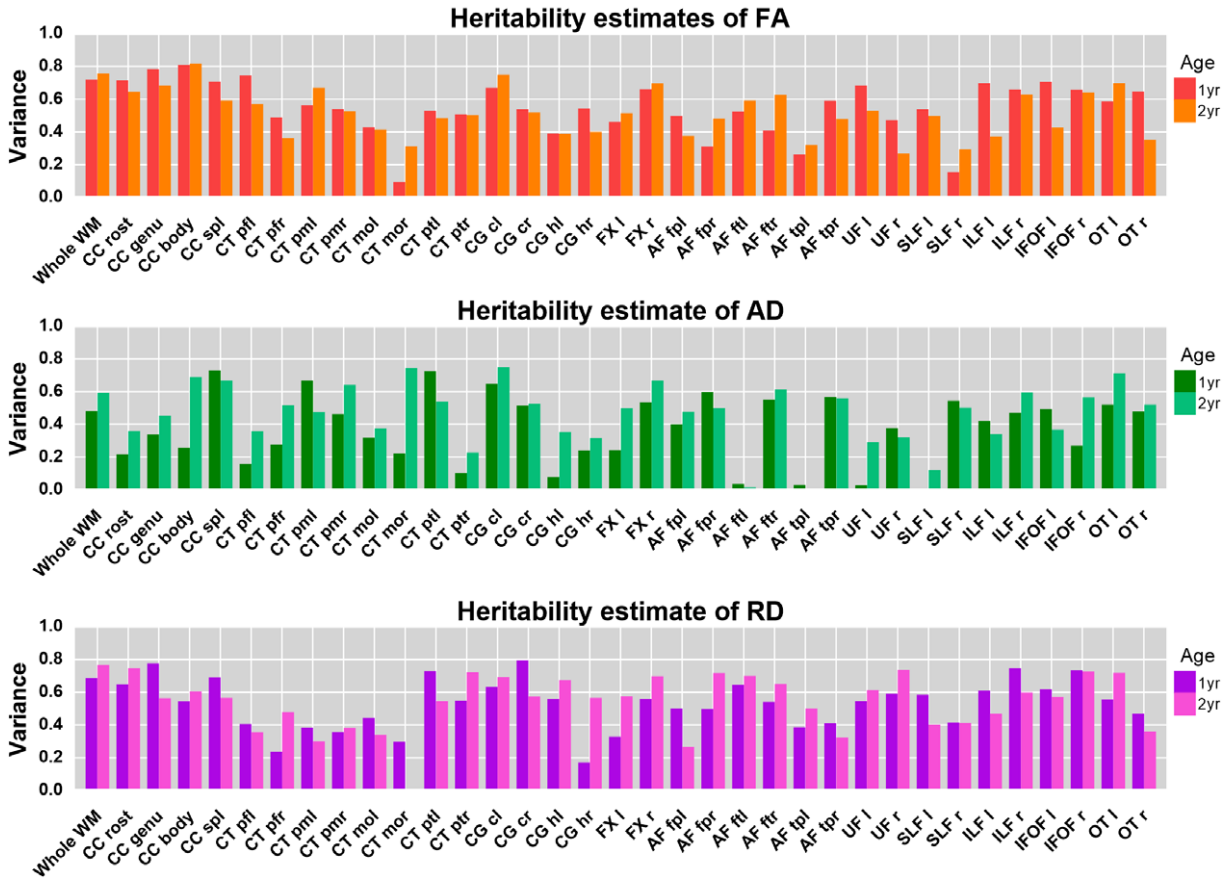

FIGURE 2 Genetic estimates of whole and individual tract-averaged FA, AD, and RD in 1 and 2 years old. Abbreviations: Rostrum (rost), genu, body, and splenium (spl) of corpus callosum (CC); left (l) and right (r) prefrontal (pf), premotor (pm), motor (mo), and parietal (pt) projections of the corticothalamic tract (CT); cingulate (c) and hippocampal (h) cinguli (CG); fornices (FX); frontoparietal (fp), frontotemporal (ft), and temporoparietal (tp) parts of arcuate fasciculi (AF); uncinate fasciculi (UF); superior and inferior longitudinal fasciculi (SLF and ILF); inferior fronto-occipital fasciculi (IFOF); and optic tracts (OT)

bilateral uncinate fasciculus, left SLF, bilateral ILF, and bilateral IFOF. In 2-year-old, many of these tracts continued to have significant heritabilities or nonsignificant heritabilities similar to those in 1-year-old.

Tracts with significant heritability of FA in 1-year-old were generally similar to those significant for RD and AD. In 2–year-old, as with RD, many of these tracts continued to have significant heritabilities or nonsignificant heritabilities similar to those in 1-year-old.

While there were apparent age-related differences in the number of tracts with significant heritability for AD, RD, and FA, these findings did not reflect the change between two heritabilities at two-time points, but only showed the statistical significance of heritability value itself for a given tract at a single time point. When we specifically tested heritability of DTI change in individual bundles from 1 to 2 years, no tracts showed a significant change in their genetic component variation, with two exceptions—the right motor segment of the corticothalamic tract and the right ILF (Supporting Information Table S4). In addition, the genetic correlation revealed how consistent the genetic variations are at the two-time points. The genetic correlation estimates in most bundles were very close to 1.0, indicating that the gene sets contributing to the variations at the two-time points are likely to be the same or have large proportion of overlap at least (Supporting Information Table S6).

To validate these main results, a range of sub-analysis data for 101 subjects with scans at both 1 and 2 years of age is shown in Supporting Information Table S7 and S8. The sub-analysis results were largely similar to the main findings when considering that the estimation accuracy and testing power might be low since a sample size of 101 was relatively small for an ACE model.

3.4 | Common environmental estimate of the tract-averaged values of DTI parameters for individual bundles

Common environmental estimates for tract-averaged FA, AD, and RD at age 1 and 2 are presented in Supporting Information Table S2 and S3 and Figure S2. We found that mean common environmental estimates for tract-averaged FA, AD, and RD were 0.05, 0.20, and 0.09 at age 1, and 0.08, 0.15, and 0.09 at age 2. As for individual bundles, most bundles showed almost zero environmental estimates for FA and RD: for AD, several bundles projecting to the frontal lobe had significant environmental estimates including the anterior part of the corpus callosum, the prefrontal segments of the corticothalamic tract, and the left uncinate fasciculus at age 1. Although the prefrontal segment of the corticothalamic tract still maintained relatively high

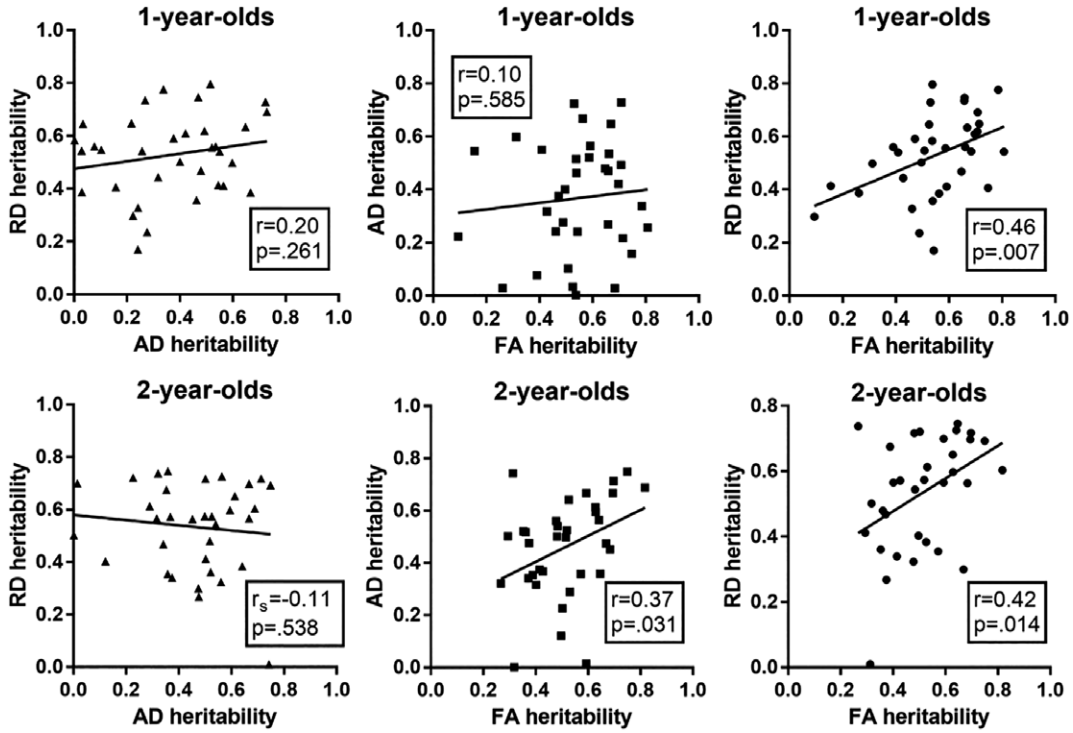

FIGURE 3 Relationship between heritability estimates of FA, AD, and RD for 34 bundles. Each point represents heritability estimate of tract-averaged DTI parameters for individual tracts

common environmental estimates, only a few segments reached the statistical significance across DTI parameters at 2 years of age. A longitudinal model revealed that no tracts showed significant change in common environmental variation from 1 to 2 years of age. Note, in contrast, that every tract showed significant change in unique environmental variation partly due to reduced measurement error (Supporting Information Table S4).

3.5 | Correlations between heritability values of three DTI parameters

Significant relationships were found between genetic contribution estimates of three DTI parameters at age 1 (r = .46, p = .007 for FA vs. RD) and age 2 (r = .37, p = .031 for FA vs. AD; r = .42, p = .014 for FA vs. RD; Figure 3).

3.6 | Distribution of heritably significant data points along the tract

Figure 4 represents statistically significant heritability estimates of FA along each tract for representative bundles in 1- and 2-year-old (also see Supporting Information Figure S3). In general, regions with significant heritability in individual tracts tended to be centrally located, regardless of DTI parameters. Moreover, the visualization of genetically significant points along each tract demonstrated that anatomically similar regions were significant in both 1- and 2-year-old (Supporting Information Figure S3). Cluster analysis revealed that there were some overlaps between the clusters at age 1 and 2 (Supporting Information Figure S4 and S5).

4 | DISCUSSION

To the best of our knowledge, this is the first comprehensive report of WM heritability in the large cohort sample of healthy twins at ages 1 and 2 years using the quantitative tractography approach. We found that heritabilities for whole tract-averaged AD, RD, and FA were 0.48, 0.69, and 0.72 at age 1, and 0.59, 0.77, and 0.76 at age 2 and that mean heritabilities of tract-averaged AD, RD, and FA for individual bundles were moderate (over 0.4). However, the heritability of DTI change between 1 and 2 years of ages was not significant for most tracts. We also demonstrated that point-wise heritability tended to be significant in the central portions of the tracts and was generally spatially consistent at ages 1 and 2 years.

4.1 | Heritability for whole brain DTI parameters

In the current study, heritability for whole brain DTI parameters varied from 0.48 to 0.77. Both FA and RD heritability (about 0.7) were higher than AD heritability (about 0.5) at both time periods. For FA, a multisite study reported that heritability estimates for the whole-brain average FA values ranged from 0.27 to 0.82, which tended to be lower in adolescent cohorts than in adult cohorts although there were no significant differences between cohorts (Kochunov et al., 2014). Our result is comparable to high FA heritability from adult cohorts and this finding suggests that FA and RD heritability may reach and maintain at their peak early in the brain development, that the fact that unique environment variance is over 30% may be attributed mainly to measurement error in this and other studies (Blokland, de Zubicaray, McMahon, & Wright, 2012).

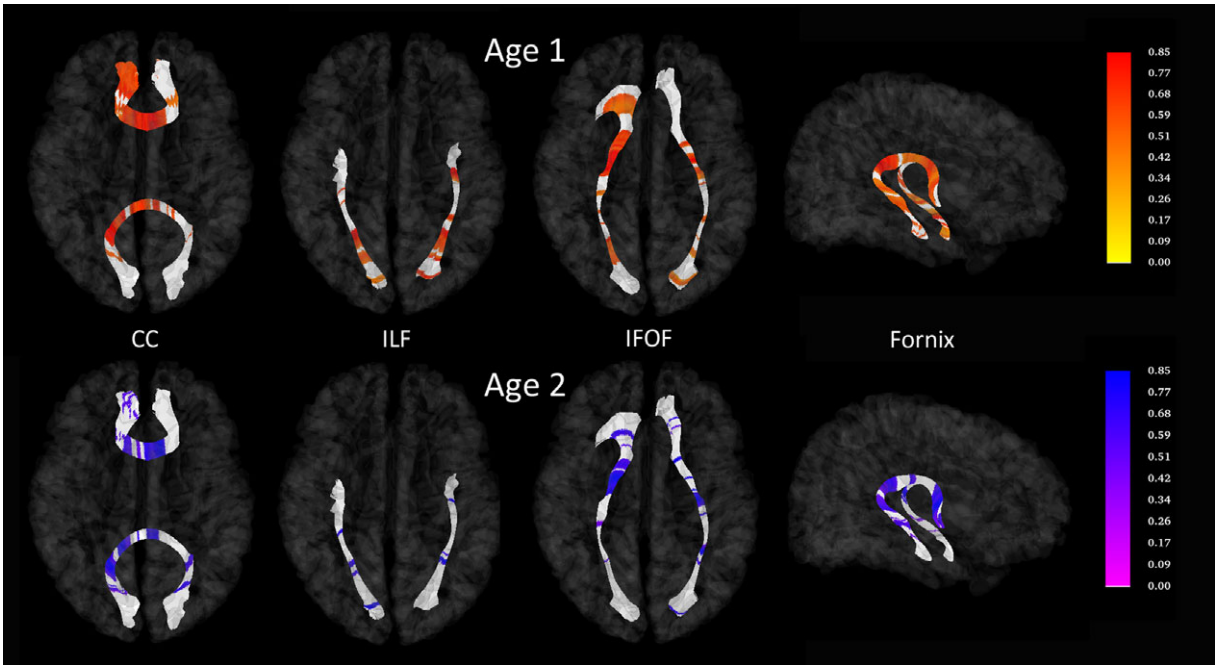

FIGURE 4 Statistically significant heritability estimates of FA along the genu and splenium of the corpus callosum (CC), the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus (IFOF), and the fornix in 1 and 2 years old. The color bar shows heritability estimates of the FA. Heritability estimates with significance are highlighted; nonsignificant portions are white

4.2 | Heritability for individual tracts

The mean heritabilities across tracts in this study were 0.37, 0.53, and 0.55 at age 1, and 0.46, 0.53, and 0.51 at age, for AD, RD, and FA, respectively. As expected, heritabilities for individual tracts were lower than that for whole tract-averaged heritability partly because heritability estimates increase with increased region size of interest (Eyler et al., 2014), but heritabilities for individual tracts also showed a trend that both FA and RD heritability tended to be higher than AD heritability at both time periods. Moreover, the pattern of change in AD heritability from 1 and 2 years of age was different from that of RD and FA. While heritability for RD was significant in most individual tracts at age 1 and decreased to 53% at age 2, heritability for AD was significant in 35% of tracts at age 1 and increased to 53% of tracts at age 2 even in the face of a smaller sample size. This suggests that the emerging genetic influences on AD (related to longitudinal fiber organization) and RD (related to myelination) in this period may differ. Moreover, this and previous studies (Geng, Gouttard, et al., 2012) show that both AD and RD decrease with age in this time frame, suggesting that for AD heritability may increase with maturation, while for RD heritability may decrease with maturation. RD is thought to reflect myelination, and it may be that environmental influences and individual variability decrease overall heritability of RD, while increasing it for AD.

However, the longitudinal ACE model revealed that almost all tracts showed no statistically significant changes in genetic variation in the tract-averaged values from 1 to 2 years of age. These findings may be explained by the fact that the changes in the diffusion parameters are much smaller in the second year than the first year (Geng, Gouttard, et al., 2012). Moreover, the peak of myelination occurs during the first year of life (Fields, 2008) and a number of WM fibers complete the bulk of their myelination by end of the first year (Dubois et al., 2014). Although the subjects were adolescents, a twin study using a similar quantitative tractography approach found no significant change between 9 and 12 years (Brouwer et al., 2012). However, this negative finding may be due to small sample size not identifying potential changes.

When compared to our previous study of our twin neonate cohorts using the same analysis method (Lee et al., 2015), heritability estimates in this study are somewhat higher than those of neonates (around 0.32). Another notable difference between neonates in the previous study and 1- or 2-year-old in this study is that heritabilities in neonates were relatively similar across tracts whereas those in 1- and 2-year-old were more heterogeneous across tracts. Almost all tracts showed significant genetic influence in neonates whereas a considerable number of tracts in this study did not reach significance. We believe that these changes from birth to 2 years of age may reflect differential maturational processes across WM bundles. This is consistent with our recent study that found a single factor describes variance across WM tracts at birth, and that this increases to 3 factors by age 2 years; heritability of these factors was consistent at birth and variable at age 2 (Lee et al., 2017). Third, we did not observe the differential pattern of heritability in relation to functional fiber categorization, which shows increasing heritability from association to projection to commissural fibers in neonates (Lee et al., 2015).

4.3 | Distribution of heritably significant data points along the tract

Point-wise heritability information along the entire tract uncovered several novel findings. First, regions of significant heritability were

usually located in the central region of a given tract. It has been proposed that regional differences typically follow a "high FA in core and low FA in peripheral WM" rule (Zhai, Lin, Wilber, Gerig, & Gilmore, 2003) and that changes in microstructure near cortical regions generally appear smaller than in central regions, during the first two postnatal years (Geng, Gouttard, et al., 2012). However, these findings could be explained by the fact that observed higher heritability in the center of tracts reflects the consequences of averaging noise across individuals and a decline in signal to noise toward the periphery of the tracts. Other potential explanations are; DTI parameters may be more reproducible across subjects in these regions or there may be lower partial volume effects with other interrupting tracts. For example, FA appears to increase more with age in noncompact tracts (corona radiata and peripheral WM) compared to compact tracts (corpus callosum, internal capsule, cerebral peduncle) across the first three postnatal years (McGraw, Liang, & Provenzale, 2002). We demonstrated that these compact regions with high FA also showed high heritability along the corticofugal bundles in neonates (Lee et al., 2015). Second, some regions of significant heritability were similar in 1- and 2-year olds. Cluster-based analyses confirmed that regions of significant heritability were centrally located and some of them overlapped across two age groups in many bundles. However, little is known about highly heritable regions within individual fiber bundles, especially association fibers. These segments showing consistent heritability would be good candidate regions to identify genes that influence WM microstructure.

4.4 | Common environmental contribution estimates

The tract-averaged DTI values along the tract in this study showed approximately 10% common environment variation, with a considerable number of bundles having near zero. Changes in common environmental estimates from 1 to 2 years of age seemed variable and small. Like genetic estimates, the change in common environmental variation across time was not significant in every tracts. However, it is noteworthy that about 20% of the bilateral prefrontal corticothalamic tracts has significant common environmental variance, especially for AD and RD at age 1 and 2; this is much higher than other corticothalamic tracts. In fact, the prefrontal cortex is known to be susceptible to early life experiences and displays remarkable plasticity over the life course [for review, McEwen & Morrison, 2013]. This finding is consistent with a high environmental variance of prefrontal WM in neonates (Gilmore et al., 2010) and cortical thickness in the dorsolateral prefrontal cortex in early childhood (Schmitt et al., 2014).

Some methodological issues should be considered. First, this study showed that heritability is heterogeneous across and within tracts: for some tracts, heritability was not even statistically significant. This pattern may stem from methodological limitations such as sample size, DTI data preparation, tractography, and twin analysis model. Second, though we used the same analysis method with controlling for the same covariates, the reduced sample size and loss of power in 2 years old may result in fewer points in each tract having significant heritability. As noted above, there were more tracts with significant heritability for AD at age 2 compared to age 1, indicating an exception to this limitation. Subjects were lost from 1 to 2 years old not only due to drop-outs over time but also due to failure to get the child to sleep and enter the scanner at the start as well as movement once in the scanner. MRI scanners changed and scan sequences improved from 6 to 42 directions during the course of the study, potentially impacting estimates of heritability. Each twin in a twin pair was scanned in the same way at each age, and scanner type and sequence direction were covariates in our statistical models, which would control for these changes over time.

In conclusion, mean heritabilities for tract-averaged FA, AD, and RD across tracts were moderate and the heritabilities of DTI changes from 1 to 2 years were not significant for most tracts. Central regions of tracts tended to have the highest heritability regardless of age or DTI parameter. There appears to be a complex relationship between the genetic influence on AD and RD at least in the tracts studies during this developmental period. Future studies are needed to determine better understand these relationships in early and later childhood.

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ORCID

Seung Jae Lee https://orcid.org/0000-0003-3648-9824

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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