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Quantitative tract-based white matter heritability in twin neonates

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ABSTRACT

Studies in adults indicate that white matter microstructure, assessed with diffusion tensor imaging (DTI), has high heritability. Little is known about genetic and environmental influences on DTI parameters, measured along fiber tracts particularly, in early childhood. In the present study, we report comprehensive heritability data of white matter microstructure fractional anisotropy (FA), radial diffusion (RD), and axial diffusion (AD) along 47 fiber tracts using the quantitative tractography in a large sample of neonatal twins (n = 356). We found significant genetic influences in almost all tracts with similar heritabilities for FA, RD, and AD as well as positive relationships between these parameters and heritability. In a single tract analysis, genetic influences along the length of the tract were highly variable. These findings suggest that at birth, there is marked heterogeneity of genetic influences of white matter microstructure within white matter tracts. This study provides a basis for future studies of developmental changes in genetic and environmental influences during early childhood, a period of rapid development that likely plays a major role in individual differences in white matter structure and function.

Introduction

Recent diffusion tensor imaging (DTI) studies have found abnormalities of white matter microstructure in neuropsychiatric disorders such as schizophrenia, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder (Dennis and Thompson, 2013; Kuswanto et al., 2012; Mueller et al., 2012; Nortje et al., 2013). It is becoming clear that most of these neurodevelopmental and psychiatric disorders are the result of abnormal trajectories of prenatal and early childhood brain development (Bale et al., 2010; Insel, 2010; NIMH Workgroup, 2008). The abnormal developmental trajectories that underlie these disorders are likely contributed to by the additive and interactive effects of multiple genetic and environmental factors, each with small individual effects.

Early childhood is a period of very rapid development of the basic structural and functional frameworks of the brain, including global tissue volumes (Knickmeyer et al., 2011), cortical thickness and surface area (Lyall et al., 2014), white matter tract microstructure (Dubois et al., 2006, 2008; Gao et al., 2009a; Geng et al., 2012a; Gilmore et al., 2007) and resting state functional networks (Gao et al., 2009b, 2011, 2013; Lin et al., 2008). During the first 2 years of life in particular, DTI studies show that white matter exhibits significantly increasing fractional anisotropy (FA) and decreasing radial diffusivity (RD) and axial diffusivity (AD), with rates of change faster in the first year than the second (Dubois et al., 2006, 2008; Gao et al., 2009a; Geng et al., 2012a). Very little is known about how genetic and environmental factors influence white matter development during this period, one that will likely determine individual differences in cognition and behavior, as well risk for psychiatric disease.

Twin DTI studies in adults have reported high heritability of regional FA in the splenium and genu corpus callosum (Pfefferbaum et al., 2001), and of lobar FA in bilateral frontal, parietal, and left occipital lobes (Chiang et al., 2009). Whole brain white matter FA and RD were found to have significant genetic variability, with heritability values of .52 and .37 respectively, while genetic variation in AD was non-significant (Kochunov et al., 2010). A recent multi-site study found additive genetic factors explaining over 50% of inter-subject variance in FA values across multiple white matter regions (Kochunov et al., 2014). Studies in older children indicate that the heritability of FA decreases significantly from adolescence (70–80%) to adulthood (30–40%) (Chiang et al., 2011b),

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while studies of 9 year olds find no significant heritability of FA with little change between 9 and 12 years (Brouwer et al., 2010, 2012). In neonates, we found rather high heritability of FA in neonates, compared to the study of 9 year olds (Brouwer et al., 2010), that tended to decrease with tract maturation (Geng et al., 2012b).

Studies to date suggest that heritability of white matter microstructure changes with development. Twin studies of white matter in childhood will allow a better understanding of when specific structures and circuits are more or less amendable to environmental and experimental influence, identifying periods of heightened plasticity that can be targeted by early environmental interventions to reduce risk and improve long term developmental outcomes. These studies also provide temporal and regional targets with high genetic influence for future genetic studies of development in early childhood, allowing the field to gain traction in the face of the enormous genetic complexity of psychiatric disorders. It has been proposed that structural endophenotypes used in genetics studies be highly heritable (Glahn et al., 2012; Medland et al., 2014). Blokland et al. (2012) concluded in a meta-analysis that twin studies are "the first step to determine whether it is worthwhile to perform gene finding analyses on a given imaging phenotype."

Irrespective of the scarcity of heritability studies in early childhood, previous studies only provide us limited information by reporting only one diffusion parameter (Chiang et al., 2009; Pfefferbaum et al., 2001), global diffusion measurements (Gilmore et al., 2010; Kochunov et al., 2010), or measurements in several discrete sites along fiber pathways (Geng et al., 2012b). In the current work, we have extended our previous region-of-interest (ROI) based analysis in neonates to a quantitative tract-based analysis in a large sample, in which anatomically informed curvilinear regions are used to analyze diffusion at specific locations all along fiber (Goodlett et al., 2009; Verde et al., 2014). Using this quantitative tractography, we report a comprehensive heritability data of white matter DTI measures along 12 bilateral fiber pathways and the respective subdivision in the largest sample of pediatric twin subjects to date (n = 365).

Materials and methods

Participants

Pregnant women with twin fetuses were recruited from the outpatient OB–GYN clinics as part of the UNC Early Brain Development Studies (www.earlybrainresearch.org) between 2004 and 2014. Exclusion criteria for mothers included major maternal illness or infection during pregnancy, and maternal diagnosis of a major psychiatric disorder; those for neonates were chromosomal abnormalities, severe congenital abnormalities, major medical illness or infection, abnormalities on MRI other than small intracranial hemorrhages which are common in neonates (Looney et al., 2007). 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 University of North Carolina School of Medicine and Duke University Medical Center.

A total of 356 of twin neonates were included in the final analysis: 129 twin pairs and 98 unrelated "singleton" twins — a single unpaired twin subject in which a usable scan was not obtained from the co-twin. Demographic variables are presented in Table 1. Data from these participants has been published previously in a ROI-based study of heritability (Geng et al., 2012b).

Table 1
Demographic characteristics.

	MZ twins	DZ twins	Single twin	Total
Number of subject	96	162	98	356
Biological sex				
Male (%)	40 (41.7)	91 (55.5)	59 (60.2)	190 (53.4)
Female (%)	56 (58.3)	73 (44.5)	39 (39.8)	166 (46.6)
Birth weight[a] (g)	2202.6 (562.3)	2407.7 (491.1)	2434.3 (551.7)	2361.4 (534.7)
Gestational age at birth[b] (week)	35 [32,36]	36 [35,37]	36 [35,37]	36 [34,37]
Postmenstrual age at MRI[b] (week)	40 [39,42]	41 [39,42]	41 [40,42]	41 [39,42]
NICU admission				
Number of subject (%)	43 (44.8)	45 (27.8)	28 (28.6)	116 (32.6)
Days of admission[b] (%)	8.2 (13.8)	3.6 (8.1)	4.6 (10.3)	5.2 (10.7)
Intubation (%)	8 (8.3)	8 (4.9)	5 (5.1)	21 (5.9)
Scanner type				
Allegra (%)	90 (93.8)	136 (84.0)	78 (79.6)	304 (85.4)
Trio (%)	6 (6.3)	26 (16.0)	20 (20.4)	52 (14.6)
Diffusion gradient directions				
6 (%)	66 (68.8)	62 (38.3)	42 (42.9)	170 (47.8)
42 (%)	31 (31.3)	100 (61.7)	56 (57.1)	186 (52.2)
Ethnicity				
Caucasian (%)	70 (72.9)	118 (72.8)	77 (78.6)	264 (74.2)
African American (%)	22 (22.9)	44 (27.2)	18 (18.4)	85 (23.9)
Other (%)	4 (4.2)	0 (0)	3 (3.2)	7 (2.0)

NICU, neonatal intensive care unit.
[a] Represents means and standard deviations.
[b] Represents median ages with interquartile ranges.

Image acquisition

Most (N = 304, 85%) of MRI were acquired on a 3 T Siemens Allegra head only scanner (Siemens Medical System, Erlangen, Germany). For the 170 (56%) subjects scanned with the Allegra model, diffusion weighted images (DWIs) were acquired using a single shot echo-planar imaging (EPI) spin-echo sequence with the following parameters: Time to Repeat [TR]/Time to Echo [TE] = 5200/73 ms, slice thickness = 2 mm, in-plane resolution = 2×2 mm^2, and 45 slices. For each EPI sequence, a total of 6 diffusion weighted images with a b value = 1000 s/mm^2 and one reference image without diffusion sensitization (b value = 0) were acquired. The diffusion gradients were applied in six non-collinear directions, (1,0,1), (−1,0,1), (0,1,1), (0,1,−1), (1,1,0), and (−1,1,0) for each sequence, with each sequence repeated 5 times for a total 35 diffusion weighted images per scan session to improve signal-to-noise. For the other 134 (44%) subjects scanned on the Allegra, DWIs were acquired with the following parameters: TR/TE/Flip angle = 7680/82/90°, acquisition matrix = 128×96, voxel resolution = $2 \times 2 \times 2$ mm^3, field of view [FOV] = 256×192 mm^2, 42 non-collinear diffusion gradients with 7 $b = 0$ scans (60 axial slices), and diffusion weighting $b = 1000$ s/mm^2.

The remaining 52 (15%) were scanned on a new 3 T Siemens Tim Trio scanner (Siemens Medical System, Erlangen, Germany). DWIs were acquired with acquisition protocol similar to the second Allegra DWI protocol: TR/TE = 7200/83 ms, acquisition matrix = 128×96, voxel resolution = $2 \times 2 \times 2$ mm^3, FOV = 256×192, 42 non-collinear diffusion gradients, with 7 $b = 0$ scans (62 axial slices), and diffusion weighting $b = 1000$ s/mm^2.

Diffusion tensor imaging analysis

A study specific quality control protocol was performed for all raw diffusion-weighted images (DWI) using DTIPrep (http://www.nitrc.org/projects/dtiprep) for slice-wise and gradient-wise artifact detection, as well as eddy current and motion correction (Oguz et al., 2014). Removal of the skull and other non-brain tissue was performed using FSL's Brain Extraction Tool (Smith, 2002) to generate a binary brain mask from the baseline image (average of all $b = 0$ images) for use in limiting tensor field estimation to only brain tissue included within the mask. The tensors were estimated from the DWI with the binary brain mask applied by using the weighted least squares fitting method (DTIEstim, Goodlett et al., 2009). For further visual quality control, the