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# Heritability of DTI and MTR in nine-year-old children

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ABSTRACT

Overall brain size is strikingly heritable throughout life. The influence of genes on variation in focal gray and white matter density is less pronounced and may vary with age. This paper describes the relative influences of genes and environment on variation in white matter microstructure, measured along fiber tracts with diffusion tensor imaging and magnetization transfer imaging, in a sample of 185 nine-year old children from monozygotic and dizygotic twin pairs. Fractional anisotropy, a measure of microstructural directionality, was not significantly influenced by genetic factors. In contrast, studying longitudinal and radial diffusivity separately, we found significant genetic effects for both radial and longitudinal diffusivity in the genu and splenium of the corpus callosum and the right superior longitudinal fasciculus. Moreover, genetic factors influencing the magnetization transfer ratio (MTR), putatively representing myelination, were most pronounced in the splenium of the corpus callosum and the superior longitudinal fasciculi, located posterior in the brain. The differences in the extent to which genetic and environmental factors influence the various diffusion parameters and MTR, suggest that different physiological mechanisms (either genetic or environmental) underlie these traits at nine years of age.



## Introduction

Around the onset of puberty, individual differences in global brain volumes are already mainly determined by genes (Peper et al., 2009; Wallace et al., 2006). Heritability estimates are over 90% for total brain volume, and around 80% for gray and white matter volume, comparable to heritability estimates found in adults (Peper et al., 2007, review). The influence of genetic factors on focal variation in gray and white matter density in children seems limited to a few brain areas: these include areas containing the posterior fronto-occipital and superior longitudinal fasciculus and splenium and genu of the corpus callosum in white matter, and amygdala and superior frontal and temporal cortices in gray matter (Peper et al., 2009). Moderate influences of genetic factors on cortical thickness have been found in children between 5 and 19 years of age, mainly in frontal and temporal regions (Lenroot et al., 2009). In adults, the heritability estimates for some gray (Thompson et al., 2001; Wright et al., 2002; Hulshoff Pol et al., 2006) and white matter areas (Hulshoff Pol et al., 2006) are more pronounced than in children. Thus, heritability of focal brain densities, as well as heritability of cortical thickness (Lenroot et al., 2009), may increase with age.

Previous findings regarding heritability of white matter brain structure in children are based on T1-weighted magnetic resonance images, but these T1-weighted MRI scans do not provide microstructural information of the white matter fiber tracts in the brain. In this study, white matter cortico-cortical fibers were investigated by means of diffusion tensor imaging (DTI) and magnetization transfer imaging. DTI (Le Bihan et al., 2001) provides directional information on the diffusion of water molecules in (brain) tissue. In the highly directional white matter tracts in the brain, water diffusion in the directions perpendicular to axons will be more restricted than diffusion parallel to axons. Magnetization transfer imaging makes it possible to study another aspect of fiber bundles: myelination. Magnetization transfer imaging can be used to compute the magnetization transfer ratio (MTR), which provides a measure of the amount of macromolecules in tissue, including myelin (Wolff and Balaban, 1994). Both these techniques supply complementary information on white matter microstructure.

There are two studies in adult twin pairs that investigated heritability of diffusion parameters. Recently, the heritability of fractional anisotropy (FA) – a measure of microstructural directionality (Basser and Pierpoali, 1996) – was investigated in healthy adult twin pairs, using voxel-based-morphometry. Significant contributions of genetic factors were found in areas covering the splenium and genu of the corpus callosum, the right cerebral peduncle, the right inferior longitudinal fasciculus, the anterior limbs of the internal capsule

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bilaterally, the left posterior thalamic radiation, the superior longitudinal fasciculus bilaterally, and the superior and posterior corona radiata bilaterally (Chiang et al., 2009). In an elderly twin sample, strong genetic effects on FA in the corpus callosum were found (Pfefferbaum et al., 2001). The influence of genes and environment on white matter microstructure in children, as measured with DTI or MTR, has not been examined so far.

White matter microstructure has functional relevance. In healthy development, associations have been found between FA and the apparent conduction speed of the visual pathways in infants (Dubois et al., 2008) and between FA and working memory and reading ability (Nagy et al., 2004). IQ is positively associated with FA in white matter association areas in children between 5 and 18 (Schmithorst et al., 2005). In adults, Chiang et al. (2009) showed an association between IQ scores and FA values, which originates from a common genetic factor. In both children (e.g. Carter et al., 2009) and adults (e.g. Klingberg et al., 2000) with dyslexia, reduced FA values have been found in regions containing the left superior longitudinal fasciculus. White matter abnormalities have been reported in several childhood-onset neuropsychiatric diseases, such as attention deficit/hyperactive disorder (Ashtari et al., 2005; Pavuluri et al., 2009), pediatric bipolar disorder (Pavuluri et al., 2009) and schizophrenia in adolescents (Kumra et al., 2005; Ashtari et al., 2007). Thus, as diffusion parameters are linked to both pathological and healthy development, it is important to establish the influence of genes and environment on these traits.

The aim of this study was to disentangle influences of genetic and environmental factors on variation in diffusion parameters and MTR in a sample of 185 nine-year-old twins. Twins provide us with a unique opportunity to do so, by modeling the (co)-variance structure within monozygotic and dizygotic twin pairs. The narrow age-range of our sample (between 9.0 and 9.6 years) provided us with an opportunity to assess heritability in a sample of children on the brink of puberty, without age-confounding factors. The fact that all children included in this study were nine years of age is important in the light of the considerable age-related white matter changes taking place during puberty (e.g. Giedd et al., 1999; Paus et al., 1999; Thompson et al., 2000; Barnea-Goraly et al., 2005; Schmithorst et al., 2005; Eluvathingal et al., 2007; McLaughlin et al., 2007; Giorgio et al., 2008; Lebel et al., 2008). We chose to investigate several major fiber tracts (genu and splenium of the corpus callosum, superior longitudinal fasciculi and uncinate fasciculi bilaterally), with different developmental trajectories (e.g. Lebel et al., 2008). The influence of genetic factors influencing diffusion parameters and MTR may act differently in these fibers, possibly through different timing of fiber maturation and myelination.

## Methods

### Participants

Participating in this study were 185 twins from 103 families, recruited from the Netherlands Twin Registry (Boomsma et al., 2006). Exclusion criteria consisted of having any metal material in the head, having a pacemaker, a known history of any major medical condition or psychiatric illness. Medical and psychiatric status was confirmed by a medical questionnaire filled in by the parents at the time of the MRI scan. DTI measurements were available in 82 complete pairs – 39 monozygotic pairs (20 male), 33 dizygotic same-sex pairs (16 male) and 10 dizygotic opposite-sex pairs – and 21 children (7 male) whose co-twin either did not complete the scanning protocol (11) or whose scans were not processable due to gross motion artifacts. From all but three of these children (1 monozygotic male, 1 dizygotic male and 1 dizygotic female), MTR measurements were available. At time of scanning, all children were 9 years of age (mean age 9.2, range 9.0–9.6). Zygosity was determined based on DNA polymorphisms, using 8–11 highly polymorphic di-, tri- and tetranucleotide genetic markers. Pubertal status was assessed through physical examination (no self-report) by an experienced researcher (J.S.P) according to the Tanner stages of development (Marshall and Tanner, 1969, 1970). Due to ethical restrictions (i.e. children could not be asked to undress twice, or be rated by more than one person), intra- or inter-rater reliability statistics were not available. However, the data thus obtained was comparable with earlier studies (Herman-Giddens et al., 1997, 2001). As our sample was relatively young, we created a combined variable indicating that the child showed no signs of secondary sexual characteristics (0), or showed signs of secondary sexual characteristics on one or more scales (1). Both parents and children gave written informed consent to participate in the study. The study was approved by the Central Committee on Research involving Human Subjects of the Netherlands (CCMO) and was in agreement with the Declaration of Helsinki (Edinburgh amendments).

Diffusion Tensor Imaging scans were acquired as part of a larger protocol, which included several MRI scans and a cognitive task battery (Peper et al., 2009; van Leeuwen et al., 2008).

### MRI acquisition and preprocessing

Structural magnetic resonance images of the whole brain were made on a 1.5 T Achieva scanner (Philips, Best, The Netherlands). A three-dimensional T1-weighted scan (Spoiled Gradient Echo; TE = 4.6 ms; TR = 30 ms; flip angle 30°; 160–180 contiguous coronal slices of 1.2 mm; in-plane resolution $1 \times 1$ mm$^2$; acquisition matrix $256 \times 256$) and a three-dimensional Magnetization Transfer Imaging scan (60 transverse slices of 2.5 mm; no gap; $128 \times 96$ acquisition matrix; FOV 240 mm; flip angle 8°; TE = 4.5 ms; TR = 37.5 ms, with and without off-resonance prepulse (frequency offset 1100 Hz; 620 degrees, three-lobe sync-shaped)) of the whole head was made of each subject. Two Single Shot Echo Planar Imaging (SS-EPI) DTI scans were acquired (32 diffusion-weighted volumes with diffusion weighting $b = 1000$ s/mm$^2$ and 32 non-collinear diffusion gradient directions; 7 diffusion-unweighted ($b = 0$ s/mm$^2$) scans; TE = 78 ms, SENSE factor 2.5; flip angle 90°; 60 transverse slices of 2.5 mm, no gap, FOV 240 mm; in-plane resolution $1.875 \times 1.875$ mm$^2$; $128 \times 96$ acquisition matrix, no cardiac gating). The DTI scans were combined and corrected for geometric distortions (Andersson and Skare, 2002). Subsequently, the diffusion pattern in each voxel was fitted to a tensor matrix using a robust M-estimator (Chang et al., 2005), providing three eigenvectors (representing the three principal directions of diffusion) and corresponding eigenvalues ($\lambda_1 > \lambda_2 \approx \lambda_3$, in white matter).

The largest eigenvalue $\lambda_1$, called longitudinal diffusivity, represents the amount of diffusion in the direction of the longest axis of the tensor. The mean of $\lambda_2$ and $\lambda_3$, or radial diffusivity, represents the amount of diffusion in directions perpendicular to the principal axis. In highly organized white matter tracts, longitudinal diffusivity coincides with the direction parallel to the axons. Similarly, radial diffusivity may be thought of as diffusivity perpendicular to axons.

Longitudinal and radial diffusivity may provide information on different physiological processes (Budde et al., 2007). Therefore, we chose to study them separately. FA values were calculated in each voxel as a measure of microstructural directionality from the eigenvalues (Basser and Pierpoali, 1996). The Magnetic Transfer Ratio (MTR) was computed as the difference between the MRI signal without and with magnetization prepulse, relative to the signal without magnetization prepulse. The MTR image was realigned with the average of the diffusion-unweighted scans (b0), based on the optimization of a mutual information metric (Maes et al., 1997).

### Fiber tractography and creation of average fibers

We followed the procedure as described in (Mandl et al., 2010) for fiber tracking of the genu and splenium of the corpus callosum, the uncinate fasciculi and the superior longitudinal fasciculi (SLF) (Fig. 1).

All possible fibers in the brain were reconstructed in individual space using the FACT algorithm (Fiber Assignment by Continuous Tracking; Mori and van Zijl, 2002), with 8 seed points per voxel, an FA threshold of 0.2 and maximal angle of 26° (except for the uncinate fasciculi, where the maximal angle was 60°, necessary because of the anatomy of the tract). Per subject, tracts were superimposed with MTR, FA, longitudinal diffusivity and radial diffusivity values. Subsequently, fibers were warped into model space. First, the b0 scan was linearly registered to the T1-weighted scan, based on the optimization of a mutual information metric (Maes et al., 1997). Second, the T1-weighted images were nonlinearly warped into model space up to a scale of 4 mm full-width-at-half maximum (FWHM) (Collins et al., 1995). The concatenated transformation was applied to the fiber bundles in native space, obtaining fibers in a standardized model space. In model space, regions of interest (ROIs) were manually defined by one of the authors (R.M.B) to specify the particular tracts according to (Mori et al., 2002; Mandl et al., 2010). Because tracts were selected in model space, this was done only once for each tract. No assessment of consistency was done. See Supplementary Material, Fig. 4, for placement of the ROIs. The genu of the corpus callosum was defined by two ROIs placed in the left and right frontal lobe. The splenium of the corpus callosum was defined on the mid-sagittal slice, as the posterior 1/5 of the corpus callosum (Witelson, 1989). The uncinate fasciculi were defined by two ROIs in the temporal and frontal lobe. The superior longitudinal fasciculi were defined by an ROI that was outlined on a DTI-based color map. Spurious tracts were removed by placing ROIs that fiber tracts should not cross according to the anatomy of the tract.

We created average fiber bundles as described in (Mandl et al., 2010; Gerig et al., 2004), per individual. In short, the middle points of all fibers in the bundle were determined. The (spatial) average of these points served as a starting point for the average fiber. The $n$th coordinate of the average fiber was subsequently computed as the spatial average of the points on the fibers in the bundle at distance $2n$ millimeter from the starting point. This initial average fiber was smoothed and resampled to its original resolution. This procedure provided us with individual averages, which could be averaged again, providing the parts of the tract that were common to all subjects. We obtained the FA, MTR, and longitudinal and radial diffusivity along the average fiber in each subject by superimposing the FA, MTR, and longitudinal and radial diffusivity on the average fiber. Subsequently, the mean values of diffusion parameters and MTR in these average fibers were computed. This tract-based approach allows us to investigate subtle effects that occur along a fiber bundle.

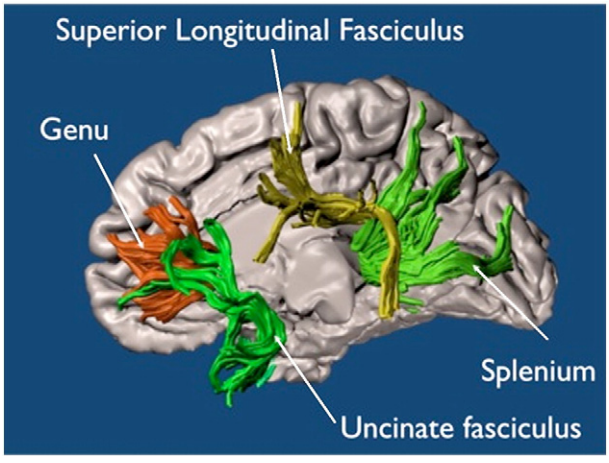


**Fig. 1.** Fiber tracking results for a typical subject (first-born monozygotic female). Visible are the fiber bundles in the left hemisphere.

*Structural equation modeling*

Monozygotic (MZ) twins share 100% of their segregating genes whereas dizygotic (DZ) twins share on average 50% of their segregating genes. The relative influences of heritable, genetic factors and subject-specific (environmental) factors on a certain trait can be examined by comparing within-pair correlations between zygosity groups. An MZ correlation that is twice as large as a DZ correlation indicates that the trait is largely influenced by genetic factors. An MZ correlation larger than, but not twice as large as a DZ correlation, indicates that common environmental factors, such as upbringing, nutrition or mutual friends, also play a role. We estimated heritability, defined as the proportion of variance explained by genetic factors, in each fiber bundle for each diffusion parameter. The contributions of genetic factors (A — heritability), common environmental factors (C) and subject-specific factors (E, including unique environmental factors and measurement error) to variation of diffusion parameters were assessed with structural equation modeling (Neale and Cardon, 1992), implemented by the program Mx (Neale et al., 2006). Note that this type of analysis distinguishes heritable from non-heritable influences: epigenetic factors and de novo copy number variations which involve genes, but are not inherited from parents to offspring, are not included in A. For each diffusion parameter and MTR, information from all fibers was combined in a multivariate analysis, using Cholesky decomposition to separate genetic and environmental sources of variance (Neale and Cardon, 1992). Significance of genetic and common environmental factors was determined by the 95% confidence intervals of the estimates of A and C, respectively. To correct for multiple comparisons, 99.9% confidence intervals ($0.05/(2*24)=0.00104$) were computed. In all analyses, sex and handedness were added as covariates for the means. Further, possible effects of a gradient set replacement of the scanner were modeled by an additional dummy variable (before = 0, after = 1).

## Results

There were no differences in age or handedness between monozygotic and dizygotic twins ($p=0.12$; $p=0.83$) or between boys and girls ($p=0.06$; $p=0.82$) (Table 1). Girls were in a slightly more advanced pubertal stage than boys ($p=0.03$): 41% of the girls showed first signs of secondary sexual characteristics, opposed to 19% of the boys. Fractional anisotropy in the genu of the corpus callosum was higher in girls than in boys ($p=0.04$). Girls showed lower radial diffusivity in both the left SLF ($p=0.03$) and the right SLF ($p<0.001$) and lower longitudinal diffusivity in the right SLF ($p=0.001$). There were no other significant sex differences in diffusion parameters or MTR. Mean values for diffusion parameters and MTR can be found in Supplementary Table 6. Average fibers on individual (combined for all subjects) and group level are shown in Fig. 2.

Correlations between MTR and FA were around 0.15 in the genu of the corpus callosum, the SLF bilaterally and the right uncinate fasciculus (all $p<0.007$). Exceptions were the left uncinate fasciculus ($r=0.30$, $p<0.001$), and the splenium of the corpus callosum, where

**Table 1**
Demographics.

| | MZM | DZM | MZF | DZF | DOS-M | DOS-M |
|---|---|---|---|---|---|---|
| Number of subjects | 41 | 38 | 42 | 38 | 10 | 16 |
| Age in years (s.d.) | 9.2 (0.1) | 9.2 (0.1) | 9.2 (0.1) | 9.2 (0.1) | 9.3 (0.2) | 9.3 (0.2) |
| First/second born | 20/21 | 19/19 | 20/22 | 18/20 | 4/6 | 9/7 |
| Right/non-right handed | 35/6 | 31/7 | 34/8 | 34/4 | 8/2 | 13/3 |
| Tanner stage 0/1 | 33/8 | 33/5 | 33/9 | 24/14 | 9/1 | 11/5 |

MZM: monozygotic male; DZM: dizygotic male; MZF: monozygotic female; DZF: dizygotic female; DOS-M: male from opposite-sex pair; DOS-F: female from opposite-sex pair.

there was no association between MTR and FA ($r = 0.05$, $p = 0.35$). MTR correlated negatively with radial diffusivity in all fibers studied, with correlations between $-0.10$ in the right SLF and $-0.34$ in the left uncinate fasciculus ($p = 0.06$ for the right SLF, all other $p < 0.001$). MTR correlated negatively with longitudinal diffusivity in the splenium ($r = -0.30$, $p < 0.001$) and genu ($r = -0.16$, $p = 0.004$) of the corpus callosum and in the right uncinate fasciculus ($r = -0.11$, $p = 0.04$). Correlations between the diffusion parameters and MTR can be found in Supplementary Material, Table 7.

*Heritability of MTR*

A significant influence of genetic factors was found in the genu and splenium of the corpus callosum and the SLFs bilaterally. Heritability estimates in the uncinate fasciculi and genu of the corpus callosum ranged from 14% to 31%, heritability estimates superior longitudinal fasciculi and splenium of the corpus callosum were estimated at 47% to 61% (Table 2 and Fig. 3).

*Heritability of fractional anisotropy*

Heritability estimates of FA ranged from 15% the splenium of the corpus callosum to 32% in the genu of the corpus callosum, but significant genetic influences could not be established. Common environmental factors, explaining 20% of variation of FA in the splenium of the corpus callosum, were found to be significant (Table 3).

*Heritability of radial diffusivity*

Genetic factors had a significant influence on radial diffusivity in all fiber bundles studied, apart from the right uncinate fasciculus. Heritability estimates were around 30%, except in the left SLF where genetic factors explained 64% of variance, and the right uncinate fasciculus (17%) (Table 4).

*Heritability of longitudinal diffusivity*

Genetic factors significantly explained variation in longitudinal diffusivity in the genu (33%) and splenium (46%) of the corpus callosum and the right SLF (35%) (Table 5).

## Discussion

At nine years of age, genetic factors exert different influences on variation in MTR and the diffusion parameters. Presence of genetic influences is most widespread for radial diffusivity, for which significant influences of genetic factors were found in the genu and splenium of the corpus callosum, the SLF bilaterally and the left uncinate fasciculus. Significant influences of genetic factors on variation in longitudinal diffusivity were found in the genu and splenium of the corpus callosum and the right SLF. In contrast, significant influences of genetic factors could not be established for FA in all fiber bundles studied. Genetic factors influencing MTR, and thus possibly myelination, were most pronounced in the splenium of the corpus callosum and the superior longitudinal fasciculi, located posteriorly in the brain.

In our young sample, heritability estimates of FA were lower than those reported in adults (Chiang et al., 2009). This difference could possibly arise from the difference in age and development. The finding that heritability estimates for longitudinal and radial diffusivity were

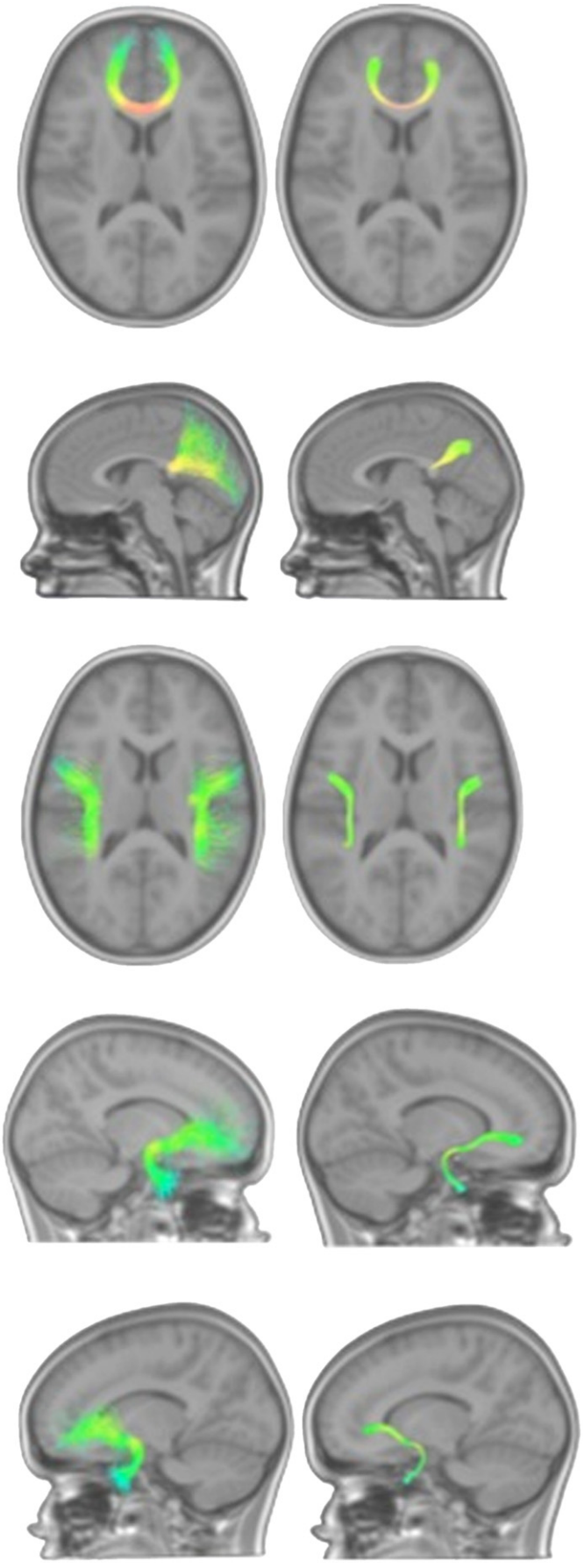

**Fig. 2.** Average fibers for all individuals combined (left) and group average (right). Top to bottom: genu of the corpus callosum, splenium of the corpus callosum, superior longitudinal fasciculi bilaterally, left uncinate fasciculus, right uncinate fasciculus. Fibers are colored with FA values.

**Table 2**
Relative contributions of genetic (A), common environmental (C) and unique environmental (E) factors to variation in *MTR*.

| | A (%) | C (%) | E (%) |
|---|---|---|---|
| Genu of corpus callosum | **31** [5–60] | 12 [0–38] | 57 [38–78] |
| Splenium of corpus callosum | **47** [17–70]* | 10 [0–39] | 43 [31–81] |
| Left uncinate fasciculus | 20 [0–55] | 22 [0–49] | 48 [39–80] |
| Right uncinate fasciculus | 14 [0–38] | 6 [0–24] | 80 [61–95] |
| Left SLF | **61** [30–88]* | 23 [0–51] | 16 [9–27] |
| Right SLF | **50** [16–71]* | 7 [0–37] | 43 [28–63] |

Columns 2–4 present estimated contributions of A, C and E and 95% confidence intervals.
SLF = superior longitudinal fasciculus. Significant contributions of genetic factors (A) or common environmental factors (C) are printed in bold.
* Significant after Bonferroni correction for multiple comparisons, uncorrected $p<0.001$.

**Table 3**
Relative contributions of genetic (A), common environmental (C) and unique environmental (E) factors to variation in *fractional anisotropy*.

| | A (%) | C (%) | E (%) |
|---|---|---|---|
| Genu of corpus callosum | 32 [0–62] | 13 [0–48] | 55 [35–82] |
| Splenium of corpus callosum | 15 [0–45] | **20** [1–41] | 65 [44–87] |
| Left uncinate fasciculus | 27 [0–55] | 4 [0–30] | 69 [43–97] |
| Right uncinate fasciculus | 18 [0–50] | 12 [0–40] | 70 [47–94] |
| Left SLF | 30 [0–58] | 3 [0–26] | 67 [42–95] |
| Right SLF | 21 [0–51] | 9 [0–32] | 70 [44–69] |

Columns 2–4 present estimated contributions of A, C and E and 95% confidence intervals.
SLF = superior longitudinal fasciculus. Significant contributions of genetic factors (A) or common environmental factors (C) are printed in bold.

higher in the callosal tracts and SLFs than in the uncinate fasciculi supports this explanation: these fibers are the first to reach full development whereas the uncinate fasciculi are not fully developed until 25 years of age (Lebel et al., 2008). Further evidence supporting the idea that heritability may increase with development is the finding that genetic factors explain variation in MTR mostly in fiber bundles that are located in the back of the brain — in line with the back-to-front developmental pattern (Yakovlev and Lecours 1967; Gogtay et al., 2004). It must be noted however, that although the back-to-front pattern seems to be a rather general principle in brain development, growth of the corpus callosum follows a rostral–caudal pattern. In early childhood (3–6 years) growth rates are largest in the frontal circuits of the corpus callosum, while the posterior parts are growing rapidly in later childhood (Thompson et al., 2000). Another possibility for the difference in heritability estimates found between our study and Chiang et al. (2009) could be the difference in methodology: we investigated mean FA along fiber tracts in children, compared to voxel-based morphometry results on FA in adults. Nevertheless, our results are supported by a voxel-based morphometry (VBM) study in this sample (Peper et al., 2009), which showed moderate to high heritability estimates of white matter density in areas covering the SLF, and genu and splenium of the corpus callosum. In general, white matter density seemed more under genetic control in the back than in the front of the brain (Peper et al., 2009). The MTR measurements, if indeed representing myelin, may be expected to be similar to the white matter in T1-weighted scans. Indeed, the MTR results are more similar to previous findings regarding white matter density in children, than the FA results.

Throughout this paper, we have interpreted FA as "fiber integrity" and MTR as "myelin". However, we must note that the interpretation of FA, MTR, and longitudinal and radial diffusivity is not straightforward. In general, FA is thought to provide information about the degree of fiber organization. High levels of FA are thought to represent coherently bundled, myelinated fibers, whereas low levels may indicate poorly developed, or structurally unorganized white matter. However, the relation between FA and myelin is not clear: it has been shown that FA does not necessarily correspond to myelin (Beaulieu, 2002; Mädler et al., 2008). Nevertheless, myelin is expected to have an effect on radial diffusivity, acting as an obstacle for water molecules in the direction perpendicular to the axons and in that sense, myelin does act as moderator for FA (Gulani et al., 2001). In this sample, we found a negative correlation between MTR and radial diffusivity in all fibers studied. Apart from myelin, other factors, like axonal density, axonal diameter, and compactness and organization of fiber bundles influence diffusion parameters (e.g. McGraw et al., 2002; Alexander et al., 2001). Further we note that, although MTR measurements are used as a proxy for myelination, other macromolecules contribute to the MTR signal. In fact, the contribution of myelin may be limited to explaining up to 50% (Norton and Cammer, 1984).

Although the exact physiology of diffusion parameters and MTR measurements remains unclear, it is important to study their genetic origin, especially in children, as white matter deficits have been found

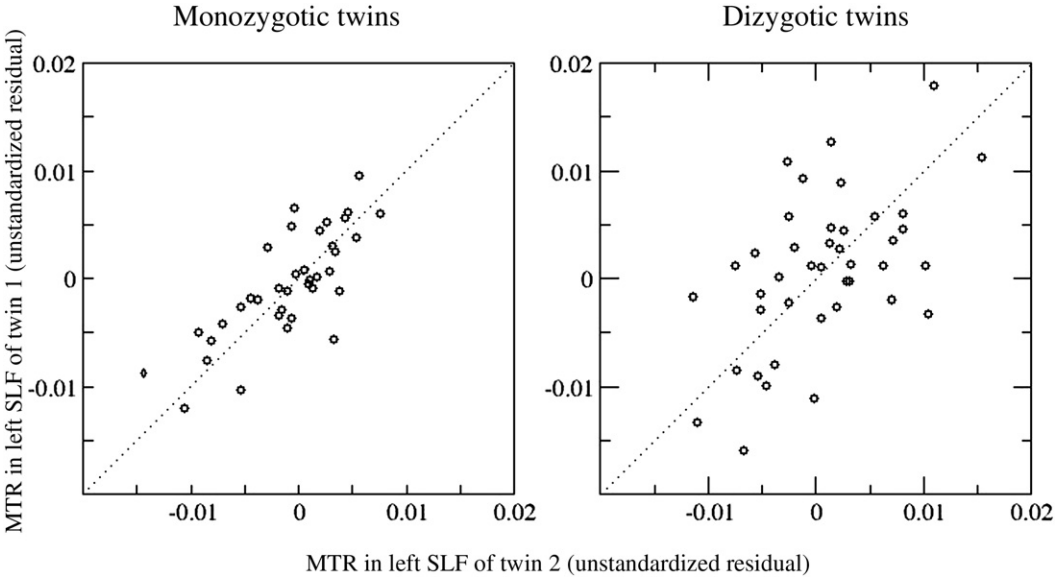


**Fig. 3.** Twin pair correlations for MTR in the left SLF. MTR values were corrected for sex and handedness.

**Table 4**
Relative contributions of genetic (A), common environmental (C) and unique environmental (E) factors to variation in radial diffusivity.

| | A (%) | C (%) | E (%) |
|---|---|---|---|
| Genu of corpus callosum | **32** [2–66] | 18 [0–43] | 50 [35–75] |
| Splenium of corpus callosum | **33** [5–60] | 14 [0–37] | 53 [34–76] |
| Left uncinate fasciculus | **29** [2–53] | 1 [0–24] | 70 [47–93] |
| Right uncinate fasciculus | 17 [0–55] | 20 [0–42] | 63 [41–87] |
| Left SLF | **64** [30–81] | 0 [0–14] | 36 [19–68] |
| Right SLF | **27** [5–52] | 8 [0–27] | 65 [43–91] |

Columns 2–4 present estimated contributions of A, C and E and 95% confidence intervals.
SLF = superior longitudinal fasciculus. Significant contributions of genetic factors (A) or common environmental factors (C) are printed in bold.

in a range of highly heritable neuropsychiatric illnesses that have their onset before or around puberty, such as schizophrenia (Ashtari et al., 2005, 2007; Pavuluri et al., 2009; Kumra et al., 2005) and pediatric bipolar disorder (Pavuluri et al., 2009). MTR deficits have been found in adults with schizophrenia (Foong et al., 2001; Kubicki et al., 2005; Mandl et al., 2010) and bipolar disorder (Bruno et al., 2004). Knowledge about the influence of genetic factors on white matter microstructure in a healthy population might provide insight on the identification of genes that are involved in brain pathology. For example, the neuregulin 1 (NRG1) gene that is associated with schizophrenia (Stefansson et al., 2002) has been shown associated with reduced fractional anisotropy in the anterior limb of the internal capsule (McIntosh et al., 2008).

A strength of the present study is that all children were 9 years of age at time of scanning, so that our results are not confounded by age-related factors. This becomes even more important as both cross-sectional studies on heritability of brain volumes (Wallace et al., 2006) and cortical thickness (Lenroot et al., 2009) suggest that heritability changes with age. However, conclusive evidence of changing heritabilities should follow from longitudinal measurements. Despite the narrow age range, developmental factors may play a role explaining our results: as FA has been shown to increase with age (e.g. Snook et al., 2005; Lebel et al., 2008) the higher FA in the genu of the corpus callosum and the lower radial diffusivity in the bilateral SLFs found in girls all suggest that these fiber tracts are more matured in girls. Brain developmental trajectories in girls have been shown to precede those in boys by several years (Giedd et al., 1999; Lenroot et al., 2008). Hence, this finding might reflect the more advanced pubertal status of the girls in our study.

The different heritability patterns for FA and MTR, and the low correlations between the two, suggest that possibly, different mechanisms (either genetic or environmental) influence these traits at the age of nine. Thus, FA and MTR measurements may provide complementary information. Similarly, genetic influences seem higher on radial and longitudinal diffusivity than on fractional anisotropy. This should not be surprising, FA essentially being a function of the other two, and therefore a less direct measure. In the light of our findings, considering longitudinal and radial diffusivity separately when studying diffusion in the brain may provide more information than FA. Conclusive evidence for different (or common) genetic factors influencing these traits can be provided by a bivariate analysis, incorporating both FA and MTR measurements. Although our study design was set up to investigate just that, it requires high heritabilities of the individual traits, higher than estimated in our sample (or a larger sample size) (Posthuma and Boomsma, 2000). The power for determining whether different or common genetic factors play a role can be increased considerably by longitudinal measurements, which are currently underway. Nevertheless, regardless of the underlying genetic mechanisms, FA and MTR (but also longitudinal and radial diffusivity) seem to provide different types of information.

Several methodological considerations need to be discussed. The choice of tract-based analyses over a voxel-based approach was driven by the fact that voxel-based morphometry (VBM) methods are a mixture of shape aspects and the quantity measured: if twin pairs have similar brain morphometry then it is likely that shape plays a role in establishing heritability. Our approach, although limited to the major fiber tracts only, suffers less from shape aspects. Further, it has been shown that the size of the blurring kernel considerably influence results from a VBM study on FA (Jones et al., 2005). A similar argument holds for the choice of studying DTI and MTR measurements based on a group average instead of individual fiber tracts: as the result of fiber tracking can vary between individuals we will not be certain that we are looking at the same part of the tract in each individual when using fiber tracts (or averages) at an individual level. Heritability estimates will be less meaningful. Therefore, we chose to create group averages. Admittedly, the projection on the group fiber may be more alike in twin pairs. However, using averages at the individual level suffers from a similar problem: tracking results may also be more alike in twin pairs. In our opinion, creating a group average and therefore being certain that we investigate the same part of the tract in each person is the better of the two. Finally, subtle effects that occur everywhere along a fiber bundle might not be detected when considering one voxel only. However, averaging along a tract reduces noise, making detection of subtle effects possible.

In conclusion, at 9 years of age, genetic factors explained a limited amount of variation in FA. Studying longitudinal and radial diffusivity separately, we found significant genetic effects for both radial and longitudinal diffusivity in the genu and splenium of the corpus callosum and the right SLF. Genetic factors also significantly influenced radial diffusivity in the left SLF and left uncinate fasciculus. The heritability estimates of the MTR signal, likely representing myelin, are largest in the posterior part of the brain. The different patterns indicate that at nine years of age, genetic factors might differentially influence distinctive aspects of white matter microstructure.

**Table 5**
Relative contributions of genetic (A), common environmental (C) and unique environmental (E) factors to variation in *longitudinal diffusivity*.

| | A (%) | C (%) | E (%) |
|---|---|---|---|
| Genu of corpus callosum | **33** [6 –59] | 13 [0–36] | 54 [36–78] |
| Splenium of corpus callosum | **46** [13–72] | 17 [0–45] | 37 [27–64] |
| Left uncinate fasciculus | 38 [0–56] | 15 [0–49] | 47 [31–69] |
| Right uncinate fasciculus | 23 [0–69] | 19 [0–49] | 58 [40–79] |
| Left SLF | 13 [0–49] | 20 [0–48] | 67 [47–90] |
| Right SLF | **35** [0.1–60] | 5 [0–41] | 59 [40–82] |

Columns 2–4 present estimated contributions of A, C and E and 95% confidence intervals.
SLF = superior longitudinal fasciculus. Significant contributions of genetic factors (A) or common environmental factors (C) are printed in bold.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.03.017.

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