Title
Heritability of white matter microstructure in late middle age: A twin study of tract-based fractional anisotropy and absolute diffusivity indices

Journal
Human Brain Mapping, 38(4)

ISSN
1065-9471

Authors
Vuoksimaa, Eero
Panizzon, Matthew S
Hagler, Donald J
et al.

Publication Date
2017-04-01

DOI
10.1002/hbm.23502

Peer reviewed

◆ Human Brain Mapping 38:2026–2036 (2017) ◆

Heritability of White Matter Microstructure in Late Middle Age: A Twin Study of Tract-Based Fractional Anisotropy and Absolute Diffusivity Indices

Eero Vuoksimaa,[1,2,3]* Matthew S. Panizzon,[1,2] Donald J. Hagler Jr,[4] Sean N. Hatton,[1,2] Christine Fennema-Notestine,[1,4] Daniel Rinker,[1,4,5] Lisa T. Eyler,[1,6] Carol E. Franz,[1,2] Michael J. Lyons,[7] Michael C. Neale,[8] Ming T. Tsuang,[1,9,10] Anders M. Dale,[4,11] and William S. Kremen[1,2,12]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, California
[2]Center for Behavior Genetics of Aging University of California, San Diego, La Jolla, California
[3]Institute for Molecular Medicine Finland and Department of Public Health, University of Helsinki, Helsinki, Finland
[4]Department of Radiology, University of California, San Diego, La Jolla, California
[5]Imaging Genetics Center, Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles, California
[6]VA San Diego Healthcare System, Mental Illness Research Education and Clinical Center, San Diego, California
[7]Department of Psychology and Brain Sciences, Boston University, Boston, Massachusetts
[8]Virginia Commonwealth University School of Medicine, Virginia Institute for Psychiatric and Behavioral Genetics, Richmond, Virginia
[9]Center for Behavior Genomics, University of California, San Diego, La Jolla, California
[10]Institute for Genomic Medicine, University of California, San Diego, La Jolla, California
[11]Department of Neurosciences, University of California, San Diego, La Jolla, California
[12]VA San Diego Healthcare System, Center of Excellence for Stress and Mental Health, La Jolla, California

Abstract: There is evidence that differences among individuals in white matter microstructure, as measured with diffusion tensor imaging (DTI), are under genetic control. However, little is known about the relative contribution of genetic and environmental effects on different diffusivity indices among

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: NIA; Contract grant numbers: Grants R01 AG022381; R01 AG018384; R01 AG018386; R01 AG022982; K08 AG047903; Contract grant sponsor: EV was supported by the Academy of Finland grant; Contract grant number: 257075

CONFLICT OF INTEREST: Anders M. Dale is a founder and holds equity in CorTechs Laboratories, Inc., and also serves on its Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All other authors report no potential conflicts of interest.

*Correspondence to: Eero Vuoksimaa, Institute for Molecular Medicine Finland, P.O. Box 20 (Tukholmankatu 8), FI-00014 University of Helsinki, Finland.
E-mail: eero.vuoksimaa@helsinki.fi

Received for publication 24 July 2016; Revised 8 December 2016; Accepted 12 December 2016.

DOI: 10.1002/hbm.23502
Published online 29 December 2016 in Wiley Online Library (wileyonlinelibrary.com).

late middle-aged adults. Here, we examined the magnitude of genetic influences for fractional anisotropy (FA), and mean (MD), axial (AD), and radial (RD) diffusivities in male twins aged 56–66 years old. Using an atlas-based registration approach to delineate individual white matter tracts, we investigated mean DTI-based indices within the corpus callosum, 12 bilateral tracts and all these regions of interest combined. All four diffusivity indices had high heritability at the global level (72%–80%). The magnitude of genetic effects in individual tracts varied from 0% to 82% for FA, 0% to 81% for MD, 8% to 77% for AD, and 0% to 80% for RD with most of the tracts showing significant heritability estimates. Despite the narrow age range of this community-based sample, age was correlated with all four diffusivity indices at the global level. In sum, all diffusion indices proved to have substantial heritability for most of the tracts and the heritability estimates were similar in magnitude for different diffusivity measures. Future studies could aim to discover the particular set of genes that underlie the significant heritability of white matter microstructure. *Hum Brain Mapp 38:2026–2036, 2017*.

Key words: absolute diffusivity; diffusion tensor imaging; fractional anisotropy; genetic effects; twins

INTRODUCTION

Diffusion tensor imaging (DTI) has been widely used to study individual differences in white matter microstructure (often referred as white matter integrity, see [Jones et al., 2013]) in the context of cognitive and emotional function, neuropsychiatric disorders, brain development, and aging. Despite overwhelming evidence that macrostructural gray and white matter brain phenotypes are influenced to a large extent by genetic effects [Blokland et al. 2012; Strike et al., 2015], less is known about the genetic and environmental effects on the microstructure of white matter, especially in middle age. Specifically, there are no studies that have characterized the heritability of white matter microstructural properties in late middle age, an important transition period when aging-related cognitive decline may begin to emerge.

With DTI, it is possible to measure the diffusivity of water molecules within the brain to reconstruct white matter pathways. To determine the diffusion properties within a given voxel, the orientation (eigenvector; ϵ_1, ϵ_2, and ϵ_3) and diffusivity along the axes (eigenvalues; λ_1, λ_2, and λ_3) are calculated along the principal axis and two axes perpendicular to the principal axis. The fiber structure of white matter is commonly measured by fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).

FA represents directional diffusion and ranges from 0 to 1 with greater numbers indicating stronger directionality, often reflecting better white matter cohesion as a result of greater axonal coherence, density, or myelination. The mean diffusivity of all three axes ($[\lambda_1 + \lambda_2 + \lambda_3]/3$), is an absolute diffusivity measure and is independent of directionality. Within fiber tracts, lower MD is associated with better white matter integrity, and it is a sensitive marker of changes in myelin and variations in intra/extra cellular spaces. AD represents diffusion along the principle axis λ_1, whereas RD represents the mean diffusion perpendicular to the principle axis (i.e., the means of λ_2 and λ_3). The neurobiological mechanisms underlying AD and RD are less understood (Madden et al., 2012) and may reflect distinct anatomical properties that are sensitive to different pathological processes. AD is hypothesized to be related to axonal loss [Song et al., 2003] and Wallerian degeneration reflecting crushed or cut fibers [Pierpaoli et al., 2001], whereas RD is more reflective of alterations in myelination [Song et al., 2002, 2005].

Studying absolute diffusivity measures in the context of aging is important as it has been suggested that these measures are more sensitive than FA in detecting changes related to Alzheimer's disease [Acosta-Cabronero et al., 2010]. With regard to genetic effects on white matter microstructure, there are multiple studies on the heritability of FA, but few studies have investigated the genetic and environmental influences of absolute diffusivity indices.

We identified a total of 14 studies (8 twin and 6 family samples) that previously reported DTI heritability estimates: 14 for FA; 5 for AD; 5 for RD; and 3 for MD (Table I). As indicated in Table I and in reviews by Kanchibhotla et al. [2013] and Voineskos [2015], most of the studies on the heritability of white matter integrity examined children, adolescents or young adults or were family studies with a wide age range. Two twin studies had samples including individuals over 65 years old, but both of these studies looked only at the corpus callosum [Kanchibhotla et al., 2014; Pfefferbaum et al., 2001]. Notably, no studies have focused on late middle age.

Given well-documented changes in white matter microstructure during the lifespan [Lebel et al., 2012; Imperati et al., 2011], it is possible that genetic and environmental influences vary throughout the lifespan. Chiang et al. [2011] reported that the voxel-wise heritability of FA in some tracts was greater in adolescents (around 70%–80%) compared with young adults (around 30%–40%), which might suggest that the heritability of FA could be even

TABLE I. Diffusion tensor imaging twin and family studies investigating the heritability (h^2) of white matter microstructure as measured by fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)

Study	Age	N	Global h^2	Individual tracts h^2	Tracts
Twin studies					
University of North Carolina Early Brain Development Study Lee et al. [2015]	Neonates	356 48 MZ pairs 81 DZ pairs 98 unpaired	FA 0.33 AD 0.32 RD 0.30	FA 0.15–0.62 AD 0–0.61 RD 0.09–0.64	47 tracts
BrainSCALE Brouwer et al. [2010, 2012]	9 y	185 39 MZ pairs 43 DZ pairs 21 unpaired	FA 0.24	FA 0.07–0.54 AD 0.13–0.46 RD 0.17–0.64	FA 14 tracts in Brouwer et al. [2012] AD and RD: 6 tracts in Brouwer et al. [2010]
BrainSCALE Brouwer et al. [2012]	12 y	126 25 MZ pairs 27 DZ pairs 22 unpaired	FA 0.33	FA 0.15–0.49	14 tracts
The Queensland Twin Imaging study Chiang et al. [2011]	12–29 y	705 129 MZ pairs 165 DZ pairs 52 unpaired 43 siblings 15 triplets 7 singletons	FA 0.61[a]	FA ∼0.30–∼0.80	Voxel-wise
Netherlands Twin Register Kochunov et al. [2014][a]	18–45 y	246 72 MZ pairs 48 DZ pairs 6 siblings	FA 0.84	FA 0.53–0.88	14 tracts, left and right tracts combined in bilateral tracts
Human Connectome Project Kochunov et al. [2015]	22–36 y	481 57 MZ pairs 60 DZ pairs 246 siblings	FA 0.88	FA 0.53–0.90	14 tracts, left and right tracts combined in bilateral tracts
Institute of Psychiatry, King's College, London Budisavljevic et al. [2015, 2016]	20–62 y	86 26 MZ pairs 17 DZ pairs	–	FA 0.0–0.80 MD 0.1–0.78	13 tracts, 7 tracts in Budisavljevic et al. [2016], 6 tracts in Budisavljevic et al. [2015]
Older Australian Twins Study Kanchibhotla et al. [2014]	65–85 y	284 79 MZ pairs 63 DZ pairs	–	FA 0.32–0.56 MD 0.35–0.52 AD 0.07–0.37 RD 0.38–0.49	Whole corpus callosum, five corpus callosum subregions
National Heart, Blood, and Lung Institute longitudinal study of cardiovascular risk factors Pfefferbaum et al. [2001]	70–82 y	66 15 MZ pairs 18 MZ pairs	–	FA 0.49–0.85	Corpus callosum genu, corpus callosum splenium, corpus callosum callosal area
Family studies					
Teen Alcohol Outcomes Study Kochunov et al. [2014][a]	12–15 y	319	FA 0.49	FA 0.05–0.82	14 tracts, left and right tracts combined in bilateral tracts
Schizophrenia family study Bertisch et al. [2010]	13–56 y	114	–	FA 0–1.00	Voxel-wise
Older Order Amish Kochunov et al. [2016]	18–80 y	137	–	FA 0.67 AD 0.41 RD 0.72	Corpus Callosum
Genetics of Brain Structure and Function study Kochunov et al. [2010]	19–85 y	467	FA 0.52 AD 0.09 RD 0.37	FA 0.34–0.66 AD 0.13–0.25 RD 0.18–0.42	10 tracts, left and right tracts combined in bilateral tracts
Bipolar-Schizophrenia Network on Intermediate Phenotypes study Skudlarski et al. [2013]	M = 38.4 SD = 0.6	513	FA 0.45	FA 0.10–0.87	76 regions of interests
Diabetes Heart Study-Mind Cohort Raffield et al. [2015]	41–89 y	465	FA 0.64 MD 0.85	– –	Global white matter FA and MD

[a]Heritability estimates from these samples were taken from the mega-analytical work of the ENIGMA consortium as reported in the Kochunov et al. [2014]. Global FA heritability estimate for the Queensland Twin Imaging study is also from Kochunov et al. [2014]. Also BrainSCALE and Genetics of Brain Structure and Function study were included in the Kochunov et al. [2014] mega-analysis, but for these samples the heritability estimates are based on the original studies.

lower in older adults. Although some family studies have included older participants [Bertisch et al., 2010; Kochunov et al., 2010, 2016; Skudlarski et al., 2013], the samples had very wide age ranges, thus their reported heritabilities are not particularly informative about whether FA heritability is lower in older versus younger samples. One family study directly tested the association of age to genetic influences within their study sample, but did not find any interactions between age and genetic effects on global or tract specific FA [Glahn et al., 2013].

With regard to age-related diffusivity indices of AD and RD, there has also been interest in whether these two phenotypes are similar or different in the degree of genetic influence. In samples of neonates and children and adolescents, heritabilities of AD and RD were of similar magnitude to each other, for example tract-averaged AD and RD heritabilities of 32% and 30% in neonates, respectively [Brouwer et al., 2010, 2012; Lee et al., 2015]. Whether they are also similar to each other in adults is less clear. In two samples of adults of a wide age range, Kochunov et al. [2010, 2016] reported overall heritabilities of 37% and 72% for RD, and nonsignificant 9% and 41% for AD. Kanchibhotla et al. [2014] examined the corpus callosum in older adults and reported heritabilities of 49% for RD and 37% for AD. Although these adult studies did not provide confidence intervals, it seems likely that even the most discrepant values within studies would have overlapping confidence intervals, suggesting little strong evidence for greater heritability of RD compared with AD. However, further examination of this issue is warranted. To the extent that RD reflects demyelination and AD reflects axonal loss, significantly different heritabilities in adults could suggest age-related differential genetic and environmental influences on these processes.

The aim of the present study was to investigate the relative proportion of genetic and environmental influences on white matter microstructure in late middle-aged twins. We determined the average FA, MD, AD, and RD of 12 bilateral tracts and the mid-hemispheric corpus callosum using a probabilistic atlas-based approach. Subsequently, we elucidated the genetic and environmental components of these diffusion indices using the classical twin method.

METHODS

Participants

Participants in this study were from the ongoing Vietnam Era Twin Study of Aging (VETSA) [Kremen et al., 2006, 2013]. They were middle-aged twin men 51–59 years old at the time of recruitment. The primary VETSA sample had 1,237 participants in the first wave of data collection. The VETSA participants were randomly selected from the Harvard Twin Study of Drug Abuse and Dependence (a study with no specific inclusion criteria), which in turn was based on the Vietnam Era Twin registry [Goldberg et al., 2002]. All VETSA participants were twin pairs who served in the United States military at sometime between 1965 and 1975. VETSA participants are representative of US men of similar age with respect to health and lifestyle characteristics [Kremen et al., 2006; Lyons et al., 2009; Schoenborn and Heyman, 2009]. VETSA participants were veterans but most of them (~80%) were not in combat.

The participants of this study were 56–66 year-old VETSA twins who participated in a second wave of data collection conducted in 2009–2014. The full MRI sample consisted of 435 twins. For the present study, we used 393 cases from our MRI cohort [Kremen et al., 2010] for whom we had adequate DTI data from the second wave of data collection.

Participants in the present study were mostly Caucasian (88.8%). The mean age of the sample at the second wave of the study was 61.8 (SD 2.6) with mean education of 13.8 (SD = 2.1) years. The sample included 85 full pairs of monozygotic (MZ) and 58 full pairs of dizygotic (DZ) twins. Zygosity was determined from DNA for 92% of twin pairs whereas questionnaire-based and blood group information (a method with 95% agreement with the DNA-based zygosity determination) was used for the rest of the participants. Data collection in VETSA was done at the University of California, San Diego (UCSD) and Boston University (BU), with MRI data collection at the latter site taking place at the Massachusetts General Hospital (MGH). All participants gave written informed consent before their participation. The study protocol was approved by Institutional Review Boards at the participating institutions.

Image Acquisition

T1-weighted and diffusion-weighted images were acquired on 3T scanners at UCSD and MGH as previously reported [McEvoy et al., 2015]. At UCSD, images were acquired on a GE 3T Discovery 750 scanner (GE Healthcare, Waukesha, WI, USA) with an eight-channel phased array head coil. The imaging protocol included a sagittal 3D fast spoiled gradient echo (FSPGR) T1-weighted image (TE = 3.164 ms, TR = 8.084 ms, TI = 600 ms, flip angle = 8°, pixel bandwidth= 244.141, FOV = 24 cm, frequency = 256, phase = 192, slices = 172, slice thickness = 1.2 mm), and a diffusion-weighted image with 51 diffusion directions, b value = 1,000 s/mm^2, integrated with a pair of b = 0 images with opposite phase-encode polarity, TR = 9,700 ms, TE 80–84 ms, pixel bandwidth 3,906.25. Acquisition resolution for diffusion scans was 2.5 mm isotropic, but images written by the scanner had a nominal resolution of 1.875 × 1.875 × 2.5 mm.

At MGH, images were acquired with a Siemens Tim Trio, (Siemens USA, Washington, DC) with a 32-channel head coil. The imaging protocol included a 3D magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted image (TE = 4.33 ms, TR = 2,170 ms, TI = 1,100 ms, flip

angle = 7°, pixel bandwidth= 140, slices = 160, slice thickness = 1.2 mm), and a diffusion-weighted image consisting two separate b = 0 images with opposite phase-encode polarity, followed by two scans with 30 diffusion directions, b value = 1,000 s/mm^2 (and one b = 0 image), TR = 9,500 ms, TE 94 ms, pixel bandwidth 1,371. Acquisition resolution for diffusion scans was 2.5 mm isotropic, and images written by the scanner had the same resolution.

DTI Data

In order to avoid the potential confounding effects of scanner differences on estimates of genetic and environmental effects, twin pairs were always assessed at the same site and on the same scanner. Following data quality control procedures, 42 individuals were excluded from the analyses due to processing errors, anatomical abnormalities, motion artifact, poor image quality, inability to visualize individual white matter tracts, or errors in the data acquisition protocol. In addition, outliers with FA, MD, AD, or RD values consistently more than 3.5 SDs above/below the mean were removed. In total, DTI data were utilized from 393 VETSA participants.

Image Processing

Image files in DICOM format were processed with an automated stream written in MATLAB and C++ by the UCSD Multimodal Imaging Laboratory. All images were visually inspected to exclude data with severe scanner artifacts or excessive head motion. T_1-weighted (T1) structural images were corrected for distortions due to gradient nonlinearities [Jovicich et al., 2006] and B1 field inhomogeneity [Sled et al., 1998]. T1 images were rigidly resampled into alignment with an atlas brain derived from an average of all VETSA cases for a common, standard orientation across participants.

Diffusion-weighted images (DWI) were corrected for eddy current distortion [Zhuang et al., 2006], head motion [Hagler et al., 2009], B0-susceptibility distortions [Holland et al., 2010], and gradient nonlinearity distortions [Jovicich et al., 2006]. DWIs were automatically registered to T1 images using mutual information [Wells et al., 1996] and then rigidly resampled into the standard T1-based orientation at a 2 × 2 × 2 mm resolution using cubic interpolation for all resampling steps.

Conventional DTI methods were used, modeling the diffusion tensor as an ellipsoid where eigenvalues λ_1, λ_2, and λ_3 define the three primary axes [Basser, 1995; Basser et al., 1994; Le Bihan et al., 2001; Pierpaoli et al., 1996]. FA (a scalar value of the degree of anisotropic/directional diffusion within a voxel) and MD (the average diffusion of all directions, or eigenvalues) were calculated using the standard formulas:

$$FA = \sqrt{\frac{3}{2}} * \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}},$$

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

We also calculated axial (AD; 1st eigenvalue, λ_1) and radial (RD; average diffusion of 2nd and 3rd eigenvalues, λ_2 and λ_3) diffusivity in each voxel.

We used a previously constructed probabilistic atlas containing information about the locations and orientations of 25 white matter fiber tracts (12 in each hemisphere plus corpus callosum) plus 10 sub-tracts for three of the main tracts (Table III, Supporting Information Fig. 1) to estimate the *a posteriori* probability that a voxel belongs to a particular fiber tract [Hagler et al., 2009]. Based on separate anatomical processing streams using FreeSurfer [Fischl et al., 2002], cortical, basal ganglia, and thalamic gray matter as well as all cerebrospinal fluid (CSF) voxels were excluded during the fiber tract atlas application to ensure that tracts coursed only through white matter regions. Average FA, MD, AD, and RD was calculated for each fiber tract, weighted by the fiber probability at each voxel. In addition to the individual fiber tract and subtract measures, we also created five composite indices based on the union of all fiber tracts, with or without the corpus callosum, both bilaterally and for each hemisphere, using the maximum probability in the case of overlap (Table III). As shown in Table III, there were a total of 40 different white matter regions of interest for each of the four diffusion measures.

Statistical Analysis

We used publicly available OpenMx [Boker et al., 2011] structural equation modeling software to determine the relative proportion of genetic and environmental influences on DTI indices. We used maximum-likelihood methods with raw data. In ACE twin analysis, the phenotypic variance is decomposed into additive genetic (A), common environmental (C), and unique environmental (E) effects. The A effects correlate 1.0 in MZ twin pairs, who are assumed to share all of their genes, whereas in DZ twin pairs who share on average half of their segregating genes, the assumed correlation of A effects is 0.5. The C effects correlate 1.0 both in MZ and DZ twin pairs, since these effects refer to all environmental effects that make both members of a twin pair alike. The E effects are uncorrelated both in MZ and DZ twin pairs because these refer to all environmental effects that make members of twin pair different. Measurement error is also included in the E effects. Twin modeling assumes that the means and variances do not differ between MZ and DZ or between first and second members of twin pairs. The fit of the ACE model is compared against a fully saturated model that does not have these assumptions.

Here, we fitted univariate ACE models to both all-fiber tract and tract-specific FA, MD, AD, and RD measures. The effects of age and scanner were taken into account in all models. In addition to ACE models, it is also possible to test the relative fit of the reduced model by dropping either the A or C component. The dropping of a component is reasonable in cases where the estimate is zero or close to zero. Dropping the E estimate is not possible because the measurement error is included in the E effects. Model comparisons are based on the likelihood-ratio chi-square test, where the goodness of fit is based on the change in negative two log likelihood from the full model to reduced model. Non-significant *P*-values greater than 0.05 indicate that the reduced model does not yield a significant change in the model fit.

Under certain regularity conditions, the likelihood-ratio chi-square test is distributed as a chi-square with degrees of freedom (df) equal to the difference in the number of parameters between the two models [Steiger et al., 1985]. But since there is a predefined lower bound of zero for variance components, the distribution of the test statistics for the A and C parameters is distributed as a 50:50 mixture of zero and chi-square with df = 1 [Dominicus et al., 2006; Self and Liang, 1987]. If this mixed distribution is not taken into account, the produced *P*-values are too large. This problem can be solved by dividing the *P*-values obtained from the naïve chi-square distribution (with df = 1) by two. When the A and C parameters are tested simultaneously, the resulting distribution is a mixture of zero, chi-square with df = 1, and chi-square with df = 2 [Dominicus et al., 2006]. Also here, an adjusted *P*-value can be obtained by halving the *P*-value generated from a chi-square with df = 1 distribution [Dominicus et al., 2006]. The effects of age and scanner were regressed out of the DTI measures prior to twin analyses; that is, residual scores, after covarying for age and scanner, were used in the ACE models.

RESULTS

Descriptive Results

Table II presents the means and standard deviations of average FA, MD, AD, and RD of all fiber tracts. There was a significant site/scanner effect on MD, AD, and RD indices, and subsequent models included adjustment for scanner differences in the means. Comparing diffusion indices between left and right hemispheres (results not presented) showed that the means and SDs were similar in both hemispheres, and in most cases identical to values observed when left and right were averaged together as in Table II. Older individuals had lower FA and higher MD, RD, and AD (Table II).

TABLE II. Average values for all-tracts diffusion measures and associations with age and study site

			Site effect		Age effect	
	Mean	SD	*t*	*P*	*r*	*P*
Fractional Anisotropy	0.46	0.02	1.79	0.0757	−0.12	0.0069
Mean Diffusivity	0.84	0.03	4.59	<0.0001	0.24	<0.0001
Axial Diffusivity	1.30	0.03	4.99	<0.0001	0.24	<0.0001
Radial Diffusivity	0.61	0.03	2.98	0.0034	0.22	<0.0001

Site and Age effects are based on mixed model results that adjust for the correlated nature of twin data. Total $N = 393$.

Fractional Anisotropy

Additive genetic effects explained 80% (95% confidence interval [CI]: 47%; 86%) of the variance in all-fiber tract FA. Non-significant C effects accounted only for 1% (95%CI: 0%; 33%) of the variance in all-fiber tract FA. Excluding corpus callosum, there was significant heritability for all-fiber tract FA in the left (73%, [95%CI: 35%; 83%]) and right (70%, [95%CI: 34%; 84%]) hemispheres. The heritability of corpus callosum FA was 79% (95%CI's: 45%; 85%) and C effects were 0% (95%CI: 0%; 32%). Based on the ACE models, genetic effects accounted for a significant proportion of the variance for all but three of the tract measures. Heritability estimates ranged from 0% to 82% (Table III).

Non-significant common environmental effects varied from 0% to 28% for individual tracts. Unique environmental effects varied from 18% to 75% for individual tracts, accounting for a significant proportion of variance for all tracts. Supporting Information Table 1 presents the MZ and DZ within-pair correlations and the standardized A, C, and E estimates for the all-fiber tract FA values as well as for the individual fiber tracts. *P*-values for fixing A or C, or A and C components to zero are also shown in Supporting Information Table 1.

Mean Diffusivity

Most of the variance in all-fiber tract MD was explained by genetic effects (73% [95%CI: 54%; 81%]); the C effects were 0% (95%CI: 0%; 16%). Excluding corpus callosum, genetic effects accounted for 76% of the variance in all-fiber tract MD both in the left (95%CI: 56%; 83%) and right (95%CI: 44%; 83%) hemispheres. The heritability of corpus callosum MD was 70% (95%CI: 44%; 78%) and C effects were 0% (95%CI: 0%; 22%). Based on the ACE models, genetic effects accounted for a significant proportion of the variance in all but four tracts. Heritability estimates ranged from 0% to 81% (Table III). All individual tracts had non-significant C estimates for MD. Supporting Information Table 2 presents the same measures for MD as presented in Supporting Information Table 1 for FA.

Axial and Radial Diffusivity

Additive genetic effects explained 72% (95%CI: 56%; 81%) of the variability in all-fiber tract AD. Similarly,

TABLE III. Heritability estimates for diffusion indices by individual fiber tracts (sub-tracts indented) and average values of all tracts

	FA		MD		AD		RD	
Fiber Tract	a^2	(95% CI)	a^2	(95% CI)	a^2	(95% CI)	a^2	(95% CI)
Fornix-R	0.09	(0.00; 0.50)	0.11	(0.00; 0.56)	0.08	(0.00; 0.56)	0.13	(0.00; 0.56)
Fornix-L	0.00	(0.00; 0.42)	0.56	(0.33; 0.68)	0.61	(0.41; 0.72)	0.52	(0.27; 0.65)
Cingulate Portion of the Cingulum-R	0.69	(0.31; 0.82)	0.66	(0.43; 0.76)	0.71	(0.47; 0.80)	0.74	(0.48; 0.81)
Cingulate Portion of the Cingulum-L	0.50	(0.10; 0.76)	0.61	(0.34; 0.72)	0.59	(0.22; 0.70)	0.65	(0.25; 0.79)
Parahippocampal Portion of the Cingulum-R	0.28	(0.00; 0.56)	0.21	(0.00; 0.57)	0.40	(0.11; 0.56)	0.11	(0.00; 0.55)
Parahippocampal Portion of the Cingulum-L	0.51	(0.22; 0.65)	0.68	(0.49; 0.78)	0.51	(0.19; 0.64)	0.71	(0.50; 0.80)
Corticospinal/Pyramidal Tract-R	0.37	(0.00; 0.73)	0.00	(0.00; 0.34)	0.43	(0.05; 0.59)	0.00	(0.00; 0.43)
Corticospinal/Pyramidal Tract-L	0.52	(0.02; 0.65)	0.23	(0.00; 0.42)	0.38	(0.00; 0.54)	0.09	(0.00; 0.46)
Anterior Thalamic Radiation-R	0.46	(0.00; 0.67)	0.53	(0.19; 0.65)	0.62	(0.35; 0.73)	0.55	(0.12; 0.67)
Anterior Thalamic Radiation-L	0.45	(0.16; 0.60)	0.53	(0.27; 0.66)	0.67	(0.47; 0.76)	0.48	(0.22; 0.62)
Uncinate-R	0.64	(0.22; 0.80)	0.51	(0.08; 0.75)	0.57	(0.18; 0.70)	0.43	(0.03; 0.76)
Uncinate-L	0.43	(0.01; 0.72)	0.47	(0.11; 0.79)	0.52	(0.13; 0.65)	0.47	(0.14; 0.80)
Inferior Longitudinal Fasciculus-R	0.73	(0.49; 0.80)	0.80	(0.63; 0.86)	0.70	(0.44; 0.79)	0.79	(0.63; 0.85)
Inferior Longitudinal Fasciculus-L	0.69	(0.36; 0.78)	0.76	(0.52; 0.83)	0.66	(0.30; 0.81)	0.73	(0.51; 0.81)
Inferior Fronto-Occipital Fasciculus-R	0.73	(0.52; 0.81)	0.71	(0.54; 0.80)	0.69	(0.50; 0.78)	0.71	(0.52; 0.79)
Inferior Fronto-Occipital Fasciculus-L	0.69	(0.27; 0.77)	0.68	(0.41; 0.77)	0.65	(0.39; 0.75)	0.68	(0.38; 0.77)
Corpus Callosum	0.79	(0.45; 0.85)	0.70	(0.44; 0.78)	0.67	(0.41; 0.76)	0.72	(0.45; 0.80)
Forceps Major	0.72	(0.42; 0.79)	0.75	(0.55; 0.82)	0.57	(0.27; 0.68)	0.77	(0.57; 0.84)
Forceps Minor	0.74	(0.55; 0.81)	0.63	(0.20; 0.75)	0.54	(0.12; 0.67)	0.71	(0.34; 0.79)
Superior Longitudinal Fasciculus-R	0.77	(0.48; 0.84)	0.76	(0.52; 0.83)	0.75	(0.58; 0.82)	0.74	(0.42; 0.81)
Superior Longitudinal Fasciculus-L	0.82	(0.64; 0.87)	0.78	(0.58; 0.84)	0.64	(0.22; 0.79)	0.79	(0.54; 0.85)
Temporal Superior Longitudinal Fasciculus-R	0.82	(0.55; 0.87)	0.77	(0.57; 0.84)	0.70	(0.52; 0.79)	0.79	(0.53; 0.85)
Temporal Superior Longitudinal Fasciculus-L	0.81	(0.60; 0.87)	0.77	(0.53; 0.84)	0.55	(0.14; 0.78)	0.79	(0.53; 0.85)
Parietal Superior Longitudinal Fasciculus-R	0.73	(0.43; 0.80)	0.74	(0.52; 0.81)	0.74	(0.56; 0.82)	0.71	(0.37; 0.79)
Parietal Superior Longitudinal Fasciculus-L	0.81	(0.66; 0.87)	0.77	(0.54; 0.84)	0.70	(0.44; 0.79)	0.79	(0.59; 0.85)
Superior Corticostriate-R	0.63	(0.30; 0.85)	0.68	(0.41; 0.77)	0.70	(0.50; 0.79)	0.72	(0.32; 0.81)
Superior Corticostriate-L	0.58	(0.23; 0.82)	0.76	(0.63; 0.84)	0.71	(0.55; 0.80)	0.77	(0.59; 0.84)
Frontal Superior Corticostriate-R	0.53	(0.21; 0.84)	0.66	(0.41; 0.76)	0.70	(0.50; 0.79)	0.74	(0.36; 0.81)
Frontal Superior Corticostriate-L	0.66	(0.29; 0.83)	0.78	(0.63; 0.84)	0.75	(0.59; 0.83)	0.77	(0.55; 0.84)
Parietal Superior Corticostriate-R	0.64	(0.29; 0.84)	0.68	(0.42; 0.77)	0.69	(0.48; 0.78)	0.73	(0.33; 0.81)
Parietal Superior Corticostriate-L	0.64	(0.26; 0.81)	0.69	(0.53; 0.79)	0.68	(0.48; 0.77)	0.72	(0.51; 0.80)
Striatal Inferior Frontal Cortex-R	0.66	(0.23; 0.75)	0.68	(0.25; 0.77)	0.69	(0.42; 0.78)	0.53	(0.09; 0.74)
Striatal Inferior Frontal Cortex-L	0.53	(0.13; 0.77)	0.71	(0.46; 0.79)	0.72	(0.51; 0.80)	0.68	(0.39; 0.77)
Inferior Frontal Superior Frontal Cortex-R	0.70	(0.31; 0.81)	0.69	(0.41; 0.78)	0.73	(0.49; 0.81)	0.68	(0.37; 0.77)
Inferior Frontal Superior Frontal Cortex-L	0.79	(0.53; 0.85)	0.81	(0.65; 0.87)	0.77	(0.57; 0.84)	0.80	(0.62; 0.86)
All Fiber Tracts	0.80	(0.47; 0.86)	0.73	(0.54; 0.81)	0.72	(0.56; 0.81)	0.74	(0.51; 0.82)
All Fiber Tracts (excluding Corpus Callosum)-R	0.70	(0.34; 0.84)	0.76	(0.44; 0.83)	0.76	(0.60; 0.83)	0.69	(0.33; 0.83)
All Fiber Tracts (excluding Corpus Callosum)-L	0.73	(0.35; 0.83)	0.76	(0.56; 0.83)	0.78	(0.64; 0.85)	0.75	(0.48; 0.82)
All Fiber Tracts-R (including Corpus Callosum)-R	0.74	(0.38; 0.84)	0.71	(0.49; 0.79)	0.72	(0.55; 0.80)	0.71	(0.41; 0.79)
All Fiber Tracts-L (including Corpus Callosum)-L	0.81	(0.50; 0.86)	0.72	(0.52; 0.80)	0.64	(0.44; 0.75)	0.75	(0.53; 0.82)

FA, Fractional Anisotropy; MD, Mean Diffusivity; AD, Axial Diffusivity; RD, Radial Diffusivity; a^2, Heritability Estimate; 95% CI, 95% Confidence Interval; R, right; L, left; All results are based on ACE univariate models. See Supporting Information Tables 1–4 (FA, MD, AD, and RD, respectively) for common and unique environmental estimates, within pair twin correlations, fits of the univariate models and *P*-values when excluding genetic and common environmental effects.

additive genetic effects accounted 74% of the variance in all-fiber tract RD (95%CI: 51%; 82%). C effects were 0% for both AD and RD (with zero as the lower bound of the CI for both measures). Excluding corpus callosum, heritabilities of all-fiber tract AD in left and right hemispheres separately were 78% (95%CI: 64%; 85%) and 76% (95%CI: 60%; 83%), respectively. For the similar hemispheric RD measures, genetic effects explained 75% (95%CI: 48%; 82%) and 69% (95%CI: 33%; 83%) of the variance in left and right hemispheres, respectively.

Generally, the heritability estimates of AD and RD were similar in magnitude in individual tracts (Table III). The magnitude of genetic effects in the corpus callosum was 67% (95%CI: 41%; 76%) for AD, and 72% (95%CI: 45%; 80%) for RD. C effects in the corpus callosum were 0% for both AD and RD.

All but one tracts had a significant heritability for AD measures. For RD, all but four tracts had significant heritability estimates. Heritabilities ranged from 8% to 77% for AD and from 0% to 80% for RD (Table III).

Common environmental effects on AD were non-significant for all individual tracts. For RD, all but one tract had non-significant C effects. Supporting Information Tables 3 (for AD) and 4 (for RD) parallel the measures delineated in Supporting Information Tables 1 and 2.

DISCUSSION

Heritability Estimates

Our results provide evidence that white matter microstructure is substantially heritable in late middle age. These results extend findings on the importance of genetic effects on white matter microstructure into late middle age, adding to the pattern earlier detected in younger adults and in children [Brouwer et al., 2010; Brouwer et al., 2012; Chiang et al. 2011; Geng et al., 2012; Kochunov et al. 2014, 2015; Lee et al., 2015]. Genetic effects accounted for about three-quarters of the variance (72%–80%) in all-fiber tract DTI indices, but the proportion of heritability varied among individual fiber tracts. Importantly, we demonstrated that in addition to FA, all absolute diffusivity indices (MD, AD, and RD) had substantial heritability for almost all tracts. Indeed, based on *P*-values, 92% of all 160 DTI measures were significantly heritable. Consistent with other twin literature, we used uncorrected *P*-values. In the framework of a univariate twin model, we were testing how variance is partitioned across three factors (genetic, common environment and unique environment). If the *P*-values for the heritability estimates would be adjusted downward by implementing multiple comparison corrected *P*-values, it would result in the incorrect conclusion that the environmental influences would be of increased importance (the variance across the factors must sum to the phenotypic variance).

Although the genetic effects could be fixed at zero for some individual tracts, fixing both A and C effects to zero resulted in a poor model fit for all individual tracts. This result reflects the fact that there is a substantial familiality for all of the tracts, although we were underpowered to distinguish between genetic and common environmental effects for a few individual tracts. The right fornix was the only tract for which genetic effects could be fixed to zero in all four diffusivity indices, but also in this case, fixing both A and C effects to zero resulted in a poor model fit. Prior work has demonstrated that this small tract is prone to errors in alignment; the fornix is a thin tract surrounded by CSF in an area with varied morphology [Kuroki et al., 2006; Lee et al., 2012; Nir et al., 2014]. Thus, the fornix may be more prone to measurement error for diffusivity indices compared with other tracts. MZ within-pair correlations for FA were substantially lower for the fornix compared with other tracts. However, MZ within-pair correlations for MD, AD, and RD for the fornix were more comparable to other tracts (see Supporting Information Tables).

Although it is tempting to infer tract-based differences in heritability from the wide range of heritability estimates of individual tracts, it should be noted that most of the estimates had large and overlapping confidence intervals. The overlapping confidence intervals of heritability estimates suggest that the magnitudes of genetic effects in different tracts were not significantly different from each other, even for most comparisons between significant and non-significant heritabilities. Variation in the degree of genetic effects in individual tracts did not seem to be explained by any particular anatomical or developmental characteristic. For example, there was generally no meaningful difference in the magnitude of the genetic effects between early versus late myelinating fibers, or based on the location of the tracts.

Aging-Related Effects

Age was associated with all DTI indices when we examined all-fiber tracts. Based on earlier studies, FA has been shown to be negatively related to age, whereas MD, AD, and RD are positively related to age from young adulthood/middle age onward [Sexton et al., 2014]. Our findings were thus consistent with these age-related associations. Moreover, it is striking that during late midlife, age is an important factor in white matter microstructure even within the narrow (10-year) age range represented in our sample. It is also noteworthy that the age-related associations observed in our middle-aged sample are not complicated by aging-related dementias that are more prevalent after 65 years of age.

Chiang et al. [2011] suggested the heritability of FA is greater in adolescence compared with young adulthood. In addition, a family study covering the adult life span from 18 to 83 years suggested that the heritability of FA may differ as a function of age, with environmental factors playing a greater role in older age [Glahn et al., 2013]. Although our study did not include old age participants, we found high heritability for all four DTI indices in late middle age. Thus, our heritability estimates were comparable to those reported in younger age groups [Kochunov et al., 2014] and indicate substantial heritability of white matter microstructure across adulthood at least before old age.

In our late middle-aged adults, the heritability estimates for AD and RD were similar in magnitude both for all-fiber tracts (72% vs. 74%) and individual tracts, and almost all were significantly heritable. Thus, our results for AD and RD are similar to findings in newborns and children [Brouwer et al., 2010; Lee et al., 2015], but different from the adult studies of Kochunov et al. [2010, 2016] who reported non-significant heritability estimates for AD. The

age range in our sample was 10 years compared with over 60 years in the studies of Kochunov et al., but whether that might account for the discrepant results requires systematic evaluation.

Limitations

One of the limitations of our study was the all-male sample. Studying adolescents and young adults, Chiang et al. [2011] reported that the genetic influences on the FA in external capsule and in the genu and splenium of the corpus callosum were greater in males than in females. However, another study in young adults indicated similar magnitude of genetic effects in FA between males and females [Kochunov et al., 2015]. Whether quantitative sex differences in the heritability of FA or other DTI indices exist in middle-aged adults is not known. It is also possible that different genes contribute to individual differences among males and females.

Another limitation is that MRI scans were performed at two sites. As reported here, we observed a large effect of scanning site for all DTI measures. Although there was a substantial difference in the mean values of MD, AD, and RD in different scanning sites, the variances did not differ between the two sites. The similar variances indicate that the distribution of values was shifted while the shape of the distribution was similar between sites. We accounted for site effects in our twin modeling and as part of the study design made sure that twin pairs that were always both scanned at the same site. Thus, the differences in means across scanners should not impact the heritability estimates.

Strengths

The sample size was reasonably large for a DTI study, and we reported the genetic and environmental contributions of four different DTI indices in multiple tracts. Although it might be viewed as a limitation, we think the fact that our results were based on a sample with a narrow age range is a strength in that it adds to and complements prior studies. Prior large-scale DTI twin studies have been conducted in children, adolescents or young adults. Our report extends knowledge of genetic contributions to white matter microstructure into middle age. Our study provides a detailed examination of a particular age group, one that is at the transition from middle age to old age. In that regard, our findings also complement prior family studies that have been conducted in samples with a very wide age range of adults.

The MZ within-pair correlations (Supporting Information Tables) indicated that our DTI measures have good reliabilities. MZ within-pair correlations provide a lower limit for the test-retest reliability, that is, MZ correlations cannot be higher than the test–retest correlation. In the case of average diffusivity measure of all tracts, MZ within-pair correlations ranged from 0.68 to 0.80. Also, many of the individual tracts had MZ within-pair correlation greater than 0.70.

CONCLUSIONS

White matter microstructure as measured with directional and non-directional water diffusivities is substantially heritable in late middle-aged men. The magnitude of heritability estimates was similar across FA, MD, AD, and RD measures. Notably, even with the narrow age range of this sample, greater age was associated with poorer white matter microstructural properties. This suggests that prominent aging-related changes occur in middle age and before the typical age of onset of dementias, and that these DTI indices may be more age-sensitive than traditional structural measures.

REFERENCES

Acosta-Cabronero J, Williams GB, Pengas G, Nestor PJ (2010): Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. Brain 133:529–539.

Basser PJ (1995): Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed 8:333–344.

Basser PJ, Mattiello J, Le Bihan D (1994): MR diffusion tensor spectroscopy and imaging. Biophys J 66:259–267.

Bertisch H, Li D, Hoptman MJ, Delisi LE (2010): Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. Am J Med Genet B Neuropsychiatr Genet 153B:885–894.

Blokland GA, de Zubicaray GI, McMahon KL, Wright MJ (2012): Genetic and environmental influences on neuroimaging phenotypes: A meta-analytical perspective on twin imaging studies. Twin Res Hum Genet 15:351–371.

Boker S, Neale MC, Maes HH, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T, Mehta PH, Fox J (2011): OpenMx: An open source extended structural equation modeling framework. Psychometrika 76:306–317.

Brouwer RM, Mandl RC, Peper JS, van Baal GC, Kahn RS, Boomsma DI, Hulshoff Pol HE (2010): Heritability of DTI and MTR in nine-year-old children. Neuroimage 53:1085–1092.

Brouwer RM, Mandl RC, Schnack HG, van Soelen IL, van Baal GC, Peper JS, Kahn RS, Boomsma DI, Hulshoff Pol HE (2012): White matter development in early puberty: A longitudinal volumetric and diffusion tensor imaging twin study. PloS One 7:e32316.

Budisavljevic S, Dell'Acqua F, Rijsdijk FV, Kane F, Picchioni M, McGuire P, Toulopoulou T, Georgiades A, Kalidindi S, Kravariti E, Murray RM, Murphy DG, Craig MC, Catani M (2015): Age-related differences and heritability of the perisylvian language networks. J Neurosci 35:12625–12634.

Budisavljevic S, Kawadler JM, Dell'Acqua F, Rijsdijk FV, Kane F, Picchioni M, McGuire P, Toulopoulou T, Georgiades A, Kalidindi S, Kravariti E, Murray RM, Murphy DG, Craig MC, Catani M (2016): Heritability of the limbic networks. Soc Cogn Affect Neurosci 11:746–757.

Chiang MC, McMahon KL, de Zubicaray GI, Martin NG, Hickie I, Toga AW, Wright MJ, Thompson PM (2011): Genetics of white matter development: A DTI study of 705 twins and their siblings aged 12 to 29. Neuroimage 54:2308–2317.

Dominicus A, Skrondal A, Gjessing HK, Pedersen NL, Palmgren J (2006): Likelihood ratio tests in behavior genetics: Problems and solutions. Behav Genet 36:331–340.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002): Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.

Geng X, Prom-Wormley EC, Perez J, Kubarych T, Styner M, Lin W, Neale MC, Gilmore JH (2012): White matter heritability using diffusion tensor imaging in neonatal brains. Twin Res Hum Genet 15:336–350.

Glahn DC, Kent JW, Jr, Sprooten E, Diego VP, Winkler AM, Curran JE, McKay DR, Knowles EE, Carless MA, Göring HH, Dyer TD, Olvera RL, Fox PT, Almasy L, Charlesworth J, Kochunov P, Duggirala R, Blangero J (2013): Genetic basis of neurocognitive decline and reduced white-matter integrity in normal human brain aging. Proc Natl Acad Sci U S A 110: 19006–19011.

Goldberg J, Curran B, Vitek ME, Henderson WG, Boyko EJ (2002): The Vietnam era twin registry. Twin Res 5:476–481.

Hagler DJ, Jr, Ahmadi ME, Kuperman J, Holland D, McDonald CR, Halgren E, Dale AM (2009): Automated white-matter tractography using a probabilistic diffusion tensor atlas: Application to temporal lobe epilepsy. Hum Brain Mapp 30:1535–1547.

Holland D, Kuperman JM, Dale AM (2010): Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. Neuroimage 50:175–183.

Imperati D, Colcombe S, Kelly C, Di Martino A, Zhou J, Castellanos FX, Milham MP (2011): Differential development of human brain white matter tracts. PloS One 6:e23437.

Jones DK, Knösche TR, Turner R (2013): White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. Neuroimage 73:239–254.

Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, Kennedy D, Schmitt F, Brown G, Macfall J, Fischl B, Dale A (2006): Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. Neuroimage 30:436–443.

Kanchibhotla SC, Mather KA, Wen W, Schofield PR, Kwok JBJ, Sachdev PS (2013): Genetics of ageing-related changes in brain white matter integrity – A review. Ageing Res Rev 12:391–401.

Kanchibhotla SC, Mather KA, Thalamuthu A, Zhuang L, Schofield PR, Kwok JB, Ames D, Wright MJ, Trollor JN, Wen W, Sachdev PS (2014): Genetics of microstructure of the corpus callosum in older adults. PloS One 9:e113181.

Kochunov P, Glahn DC, Lancaster JL, Winkler AM, Smith S, Thompson PM, Almasy L, Duggirala R, Fox PT, Blangero J (2010): Genetics of microstructure of cerebral white matter using diffusion tensor imaging. Neuroimage 53:1109–1116.

Kochunov P, Jahanshad N, Sprooten E, Nichols TE, Mandl RC, Almasy L, Booth T, Brouwer RM, Curran JE, de Zubicaray GI, Dimitrova R, Duggirala R, Fox PT, Hong LE, Landman BA, Lemaitre H, Lopez LM, Martin NG, McMahon KL, Mitchell BD, Olvera RL, Peterson CP, Starr JM, Sussmann JE, Toga AW, Wardlaw JM, Wright MJ, Wright SN, Bastin ME, McIntosh AM, Boomsma DI, Kahn RS, den Braber A, de Geus EJ, Deary IJ, Hulshoff Pol HE, Williamson DE, Blangero J, van 't Ent D, Thompson PM, Glahn DC (2014): Multi-site study of additive genetic effects on fractional anisotropy of cerebral white matter: Comparing meta and megaanalytical approaches for data pooling. Neuroimage 95:136–150.

Kochunov P, Jahanshad N, Marcus D, Winkler A, Sprooten E, Nichols TE, Wright SN, Hong LE, Patel B, Behrens T, Jbabdi S, Andersson J, Lenglet C, Yacoub E, Moeller S, Auerbach E, Ugurbil K, Sotiropoulos SN, Brouwer RM, Landman B, Lemaitre H, den Braber A, Zwiers MP, Ritchie S, van Hulzen K, Almasy L, Curran J, deZubicaray GI, Duggirala R, Fox P, Martin NG, McMahon KL, Mitchell B, Olvera RL, Peterson C, Starr J, Sussmann J, Wardlaw J, Wright M, Boomsma DI, Kahn R, de Geus EJ, Williamson DE, Hariri A, van 't Ent D, Bastin ME, McIntosh A, Deary IJ, Hulshoff Pol HE, Blangero J, Thompson PM, Glahn DC, Van Essen DC (2015): Heritability of fractional anisotropy in human white matter: A comparison of human connectome project and ENIGMA-DTI data. Neuroimage 111:300–311.

Kochunov P, Fu M, Nugent K, Wright SN, Du X, Muellerklein F, Morrissey M, Eskandar G, Shukla DK, Jahanshad N, Thompson PM, Patel B, Postolache TT, Strauss KA, Shuldiner AR, Mitchell BD, Hong LE (2016): Heritability of complex white matter diffusion traits assessed in a population isolate. Hum Brain Mapp 37:525–535.

Kremen WS, Thompson-Brenner H, Leung YM, Grant MD, Franz CE, Eisen SA, Jacobson KC, Boake C, Lyons MJ (2006): Genes, environment, and time: The Vietnam era twin study of aging (VETSA). Twin Res Hum Genet 9:1009–1022.

Kremen WS, Prom-Wormley E, Panizzon MS, Eyler LT, Fischl B, Neale MC, Franz CE, Lyons MJ, Pacheco J, Perry ME, Stevens A, Schmitt JE, Grant MD, Seidman LJ, Thermenos HW, Tsuang MT, Eisen SA, Dale AM, Fennema-Notestine C (2010): Genetic and environmental influences on the size of specific brain regions in midlife: The VETSA MRI study. Neuroimage 49:1213–1223.

Kremen WS, Franz CE, Lyons MJ (2013): VETSA: The vietnam era twin study of aging. Twin Res Hum Genet 16:399–402.

Kuroki N, Kubicki M, Nestor PG, Salisbury DF, Park HJ, Levitt JJ, Woolston S, Frumin M, Niznikiewicz M, Westin CF, Maier SE, McCarley RW, Shenton ME (2006): Fornix integrity and hippocampal volume in male schizophrenic patients. Biol Psychiatry 60:22–31.

Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C (2012): Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage 60:340–352.

Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H (2001): Diffusion tensor imaging: Concepts and applications. J Magn Reson Imaging 13:534–546.

Lee DY, Fletcher E, Carmichael OT, Singh B, Mungas D, Reed B, Martinez O, Buonocore MH, Persianinova M, Decarli C (2012): Sub-regional hippocampal injury is associated with fornix degeneration in Alzheimer's Disease. Front Aging Neurosci 4:1.

Lee SJ, Steiner RJ, Luo S, Neale MC, Styner M, Zhu H, Gilmore JH (2015): Quantitative tract-based white matter heritability in twin neonates. Neuroimage 111:123–135.

Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Schaie KW, Panizzon MS, Boake C, Xian H, Toomey R, Eisen SA, Kremen WS (2009): Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. Psychol Sci 20:1146–1152.

Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW (2012): Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochim Biophys Acta 1822:386–400.

McEvoy LK, Fennema-Notestine C, Eyler LT, Franz CE, Hagler DJ, Jr, Lyons MJ, Panizzon MS, Rinker DA, Dale AM, Kremen WS (2015): Hypertension-related alterations in white matter microstructure detectable in middle age. Hypertension 66:317–323.

Nir TM, Jahanshad N, Busovaca E, Wendelken L, Nicolas K, Thompson PM, Valcour VG (2014): Mapping white matter integrity in elderly people with HIV. Hum Brain Mapp 35: 975–992.

Pfefferbaum A, Sullivan EV, Carmelli D (2001): Genetic regulation of regional microstructure of the corpus callosum in late life. Neuroreport 12:1677–1681.

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996): Diffusion tensor MR imaging of the human brain. Radiology 201:637–648.

Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, Virta A, Basser P (2001): Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. Neuroimage 13:1174–1185.

Raffield LM, Cox AJ, Hugenschmidt CE, Freedman BI, Langefeld CD, Williamson JD, Hsu FC, Maldjian JA, Bowden DW (2015): Heritability and genetic association analysis of neuroimaging measures in the Diabetes Heart Study. Neurobiol Aging 36: 1602.e7–1615.

Schoenborn CA, Heyman KM (2009): Health characteristics of adults aged 55 and over: United States 2004–2007. National Health Statistics Reports no. 16, National Center for Health Statistics, MD: Hyatsville. http://www.cdc.gov/nchs/data/nhsr/nhsr016.pdf

Self SG, Liang KY (1987): Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J Am Stat Assoc 82:605–610.

Sexton CE, Walhovd KB, Storsve AB, Tamnes CK, Westlye LT, Johansen-Berg H, Fjell AM (2014): Accelerated changes in white matter microstructure during aging: A longitudinal diffusion tensor imaging study. J Neurosci 34:15425–15436.

Skudlarski P, Schretlen DJ, Thaker GK, Stevens MC, Keshavan MS, Sweeney JA, Tamminga CA, Clementz BA, O'Neil K, Pearlson GD (2013): Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. Am J Psychiatry 170:886–898.

Sled JG, Zijdenbos AP, Evans AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17:87–97.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002): Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 17:1429–1436.

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH (2003): Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20:1714–1722.

Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, Armstrong RC (2005): Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 26:132–140.

Steiger JH, Shapiro A, Browne MW (1985): On the multivariate asymptotic distribution of sequential Chi-square statistics. Psychometrika 50:253–264.

Strike LT, Couvy-Duchesne B, Hansell NK, Cuellar-Partida G, Medland SE, Wright MJ (2015): Genetics and brain morphology. Neuropsychol Rev 25:63–96.

Voineskos AN (2015): Genetic underpinnings of white matter 'connectivity': Heritability, risk, and heterogeneity in schizophrenia. Schizophr Res 161:50–60.

Wells WM, 3rd Viola P, Atsumi H, Nakajima S, Kikinis R (1996): Multi-modal volume registration by maximization of mutual information. Med Image Anal 1:35–51.

Zhuang J, Hrabe J, Kangarlu A, Xu D, Bansal R, Branch CA, Peterson BS (2006): Correction of eddy-current distortions in diffusion tensor images using the known directions and strengths of diffusion gradients. J Magn Reson Imaging 24:1188–1193.