



RESEARCH ARTICLE

Evidence for genetic correlation between human cerebral white matter microstructure and inflammation

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Abstract

White matter microstructure is affected by immune system activity via the actions of circulating pro-inflammatory cytokines. Although white matter microstructure and inflammatory measures are significantly heritable, it is unclear if overlapping genetic factors influence these traits in humans. We conducted genetic correlation analyses of these traits using randomly ascertained extended pedigrees from the Genetics of Brain Structure and Function Study ($N = 1862$, 59% females, ages 18–97 years; 42 ± 15.7). White matter microstructure was assessed using fractional anisotropy (FA) calculated from diffusion tensor imaging (DTI). Circulating levels (pg/mL) of pro-inflammatory cytokines (IL-6, IL-8, and TNF α) phenotypically associated with white matter microstructure were quantified from blood serum. All traits were significantly heritable (h^2 ranging from 0.41 to 0.66 for DTI measures and from 0.18 to 0.30 for inflammatory markers). Phenotypically, higher levels of circulating inflammatory markers were associated with lower FA values across the brain ($r = -.03$ to $r = -.17$). There were significant negative genetic correlations between most DTI measures and IL-8 and TNF α , although effects for TNF α were no longer significant when covarying for body mass index. Genetic correlations between DTI measures and IL-6 were not significant. Understanding the genetic correlation between specific inflammatory markers and DTI measures may help researchers focus questions related to inflammatory processes and brain structure.

KEYWORDS

diffusion tensor imaging, genetic correlation, interleukin-6, interleukin-8, tumor necrosis factor-alpha

1 | INTRODUCTION

The human brain is composed of structural networks that support brain function via white matter fiber connections (Kanai & Rees, 2011), making white matter microstructure essential to complex cognition (Kennedy & Raz, 2009; Madden et al., 2008), development (Barnea-Goraly et al., 2005; Giedd et al., 1999; Koenis et al., 2018; Nagy, Westerberg, & Klingberg, 2004), plasticity (Hofstetter, Tavor, Moryosef, & Assaf, 2013; Zatorre, Fields, & Johansen-Berg, 2012), and successful aging (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Gunning-Dixon & Raz, 2000). White matter microstructure is influenced by several factors, especially those associated with increased innate inflammatory activity (Porter, Leckie, & Verstynen, 2018). Inflammation affects white matter microstructure via elevating levels of circulating pro-inflammatory cytokines, which increase blood-brain barrier permeability (Stolp et al., 2009; Stolp, Dziegielewska, Ek, Potter, & Saunders, 2005; Varatharaj & Galea, 2017) and can trigger inflammatory processes in the brain (Konsman, Parinet, & Dantzer, 2002). Subsequent neuroinflammation has cascading effects that activate microglia (Sankowski, Mader, & Valdés-Ferrer, 2015), which contribute to white matter pathology in the form of volume reductions and loss of oligodendrocyte precursor cells (Li et al., 2017; McDonough, Lee, & Weinstein, 2017; Stolp et al., 2009). Local white matter damage can, in turn, send cytokine-mediated signals back to the periphery (Chen, Castro, Chow, & Reichlin, 1997; Chen & Reichlin, 1998; Romero, Kakucska, Lechan, & Reichlin, 1996), resulting in a reciprocal relationship between white matter microstructure and immune responses.

Evidence of these molecular interactions is observable *in vivo* using fractional anisotropy (FA) from diffusion tensor imaging (DTI), a sensitive but nonspecific marker of white matter microstructure (Alexander, Lee, Lazar, & Field, 2007). For example, prenatal exposure to high maternal serum levels of pro-inflammatory cytokines is associated with lower FA values at birth and disrupted white matter development throughout the first year of life (Rasmussen et al., 2018). In adulthood, higher levels of circulating cytokines are also associated with lower FA values along with age-related cognitive decline (Bettcher et al., 2014; Lim, Krajina, & Marsland, 2013). Furthermore, increased circulating levels of pro-inflammatory cytokines are associated with reduced FA in several disorders including schizophrenia (Najjar & Pearlman, 2015; Prasad, Upton, Nimgaonkar, & Keshavan, 2015), bipolar disorder (Benedetti et al., 2016), Parkinson's disease (Chiang et al., 2017), lipid metabolism disorders (Ryan et al., 2017), and tuberculosis meningitis (Yadav et al., 2010), possibly indicating joint impacts on a variety of illnesses.

While white matter microstructure, as quantified by DTI, and circulating pro-inflammatory cytokines are related at the phenotypic level, part of their relationship could be genetically mediated. Inflammation is typically conceptualized as a reaction to both acute and chronic environmental stimuli, but basal and reactionary cytokine levels are at least partially under genetic control (De Craen et al., 2005; Livshits, 2006; Sas et al., 2012). DTI white matter measures are, likewise, heritable (Kochunov et al., 2010; Kochunov et al., 2015; Kochunov et al., 2016), raising the possibility that shared genetic factors could impact both traits. Establishing partially overlapping genetic influences between white matter microstructure and innate

inflammatory responses is an important first step in understanding possible common biological mechanisms between these two seemingly disparate phenotypes. In other contexts, genetic correlation analyses have been successful for conceptualizing diagnostic specificity, particularly in neurological versus psychiatric disorders (Anttila et al., 2018), genetic links between depression and educational attainment (Peyrot et al., 2015), as well as joint genetic influences on brain volume and cognition (Posthuma et al., 2003).

We performed two types of quantitative genetic analyses in order to: (a) verify that DTI and inflammatory traits were heritable in our sample; and (b) estimate the shared variance attributable to overlapping genetic influences. Traits included global and regional FA measures of white matter microstructure from DTI and circulating measures of three commonly assayed pro-inflammatory cytokines that are negatively associated (phenotypically) with FA (IL-6, IL-8, and TNF α ; Benedetti et al., 2016; Prasad et al., 2015; Rasmussen et al., 2018). We hypothesized that both DTI and inflammatory traits are negatively phenotypically correlated and significantly heritable as in previous studies. We also hypothesized that there would be significant genetic correlations between them.

2 | MATERIALS METHODS

2.1 | Participants

Participants were from the Genetics of Brain Structure and Function Study, a subset of individuals recruited for the San Antonio Family Study. Recruitment details for this sample has been described elsewhere (McKay et al., 2014; Olvera et al., 2011); in short, participants were required to be of Mexican-American ancestry and part of a large extended family living in the San Antonio Area. One thousand eight hundred and sixty-two ($N = 1862$) individuals were included in our analyses (1105 females; age range 18–97 years; mean age (SD): 42.0 (15.7); 96 families total; family size range: 1–174; mean family size 19.3). All participants provided written informed consent in accordance with the institutional review board at the University of Texas Health Science Center, San Antonio and Yale University.

2.2 | DTI data acquisition and processing

MRI scanning was performed on a Siemens 3 T Trio scanner with a phase-array head coil at the Research Imaging Institute at the University of Texas Health Science Center at San Antonio (UTHSCSA). A single-shot, single refocusing spin-echo, echo-planar imaging sequence was used to acquire diffusion weighted images. Parameters for the diffusion sequence were as follows: spatial resolution $1.7 \times 1.7 \times 3.0$ mm, TE/TR = 87/8000 ms, FOV = 200 mm, 55 isotropically distributed diffusion weighted directions, two diffusion weighting values, $b = 0$ and 700 s/mm² and three $b = 0$ (nondiffusion-weighted) images. Sequence parameters, including number of diffusion directions, number of b_0 images, and b -value magnitudes were selected via an optimization procedure that accounted for the diffusivity of the cerebral white matter and T2 relaxation times (Jones, Horsfield, & Simmons, 1999).

Diffusion images were processed using FMRIB's Software Library (FSL; Smith et al., 2004). Preprocessing of diffusion weighted images included brain extraction (Smith, 2002), correction for subject motion and eddy currents (Andersson & Sotiropoulos, 2016), and diffusion tensor fitting resulting in individual FA maps. Preprocessed FA maps were then fed into the standard Tract-Based Spatial Statistics (TBSS) pipeline implemented in FSL (Smith et al., 2006). As part of the pipeline, preprocessed FA maps were aligned to the FMRIB58_FA template using nonlinear registration (Andersson, Jenkinson, & Smith, 2010). An average FA image was then calculated and thinned using an applied threshold of FA > 0.2 to create an average FA skeleton, which represents the center of white matter tracts common to all subjects. Each subject's aligned FA data was then projected onto the skeleton, resulting in one skeleton image per subject containing voxels with FA values across the brain within the skeleton boundaries.

Average FA was calculated for the whole skeleton and 11 white matter tracts using the intersection between the average FA skeleton and the Johns Hopkins University (JHU) white matter tractography atlas (Hua et al., 2008). The JHU atlas contains 20 tracts, although we calculated bilateral FA measures by averaging the right and left

hemispheres except for the Forceps measures. We chose to use bilateral measures because genetic correlations between right and left measures of the same regions were approximately 0.90, indicating little unique genetic information determining right versus left FA measures. Tracts included the anterior thalamic radiation (ATR), cingulum bundle (CgC), cingulum hippocampal part (CgH), corticospinal tract (CST), forceps major (FMa), forceps minor (FMi), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), superior longitudinal fasciculus temporal part (tSLF), and the uncinate fasciculus (UF; See Figure 1).

2.3 | Measurement of inflammatory markers

Serum-based measures of IL-6, IL-8, and TNF α were isolated from participant's blood drawn via a venipuncture procedure after 12 hrs of fasting. Circulating cytokine levels were quantified using a Milliplex MAP Human Adipokine Magnetic Bead Panel 2-Endocrine Multiplex Assay (HADK2MAG-61 K) and were run on a Luminex 100 instrument. Ten percent of samples were run in duplicate on separate plates. Intra-assay coefficients of variation were <10% for all markers.

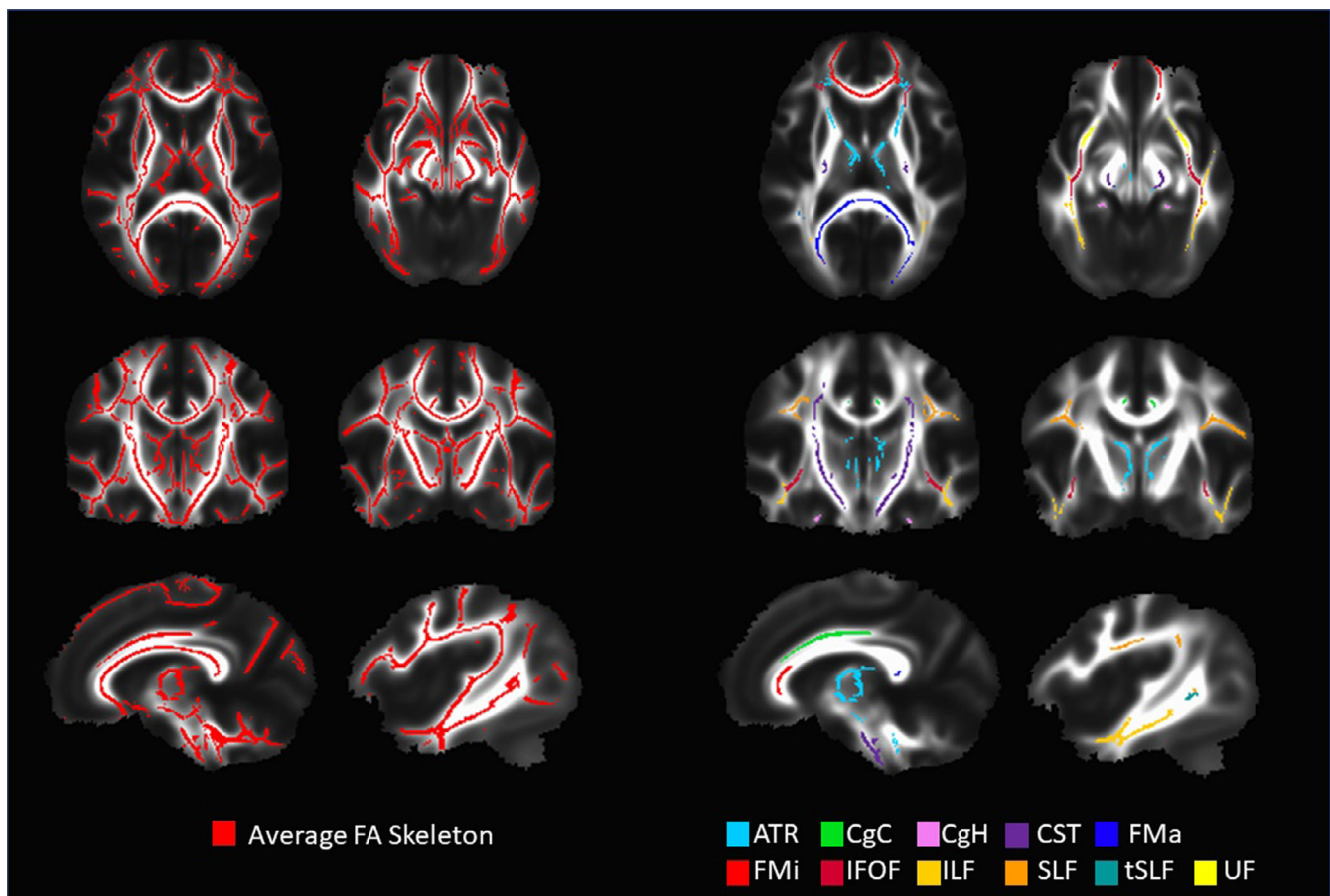


FIGURE 1 Skeletonized White matter tracts. Image shows the average FA skeleton (left) and the 11 skeletonized white matter tracts (right) used in the quantitative genetic analyses. Skeletonized data are overlaid on the average FA image created during DTI preprocessing and are in MNI space. ATR, anterior thalamic radiation; CgC, cingulum cortex; CgH, cingulum hippocampus; CST, corticospinal tract; FMa, forceps major; FMi, forceps minor; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; tSLF, superior longitudinal fasciculus temporal part; UF, Uncinate fasciculus [Color figure can be viewed at wileyonlinelibrary.com]

Minimum detectable concentration (pg/mL) was 0.2, 0.3, and 0.3 for IL-6, IL-8, and TNF α , respectively.

2.4 | Experimental design and analysis

Traits of interest for the quantitative genetic analyses (heritability and genetic correlations) were 12 DTI-derived FA measures (whole-skeleton average and individual tracts) and circulating levels of three pro-inflammatory cytokines (IL-6, IL-8, and TNF α). All quantitative genetic analyses were performed in SOLAR v8.1.1 (Almasy & Blangero, 1998), which employs maximum likelihood variance decomposition methods to determine the relative importance of genetic and environmental influences by modeling the covariance among family members as a function of genetic proximity. Before each analysis, an inverse-normal transformation was applied to DTI and inflammatory measures. Covariates common to all analyses included age, age squared, sex and their interactions (age \times sex and age squared \times sex). Two motion estimates calculated during DTI motion correction, the average amount of movement from the first volume and the average amount of movement from the previous volume, were used as covariates for DTI measures only. Given the known relationship between both circulating cytokine levels and FA and obesity (Bettcher et al., 2013; Verstynen et al., 2013), models were run with and without body mass index (BMI) as a covariate. For significant genetic correlations between cytokines and FA, we also test the effect of covarying for other cytokine measures as the levels of circulating cytokines are correlated (Li et al., 2016). This may provide information about the level of independence of a particular cytokine's effect on genotypic correlations with white matter.

First, heritability estimates (h^2) of DTI and inflammatory measures were calculated using the polygenic command in SOLAR. Heritability is the proportion of variance within a trait that is explained by additive genetic factors and is estimated by partitioning the phenotypic covariance matrix into genetic and environmental components as $h^2 = \sigma_G^2 / (\sigma_G^2 + \sigma_E^2)$, where σ_G^2 represents additive genetic variance and σ_E^2 represents random environmental effects. The covariance matrix, Ω , is composed of the $n \times n$ kinship matrix (R) and an $n \times n$ identity matrix (I) as follows: $\Omega = 2R\sigma_E^2 + I\sigma_E^2$. Tests of heritability are performed using standard likelihood ratio tests in which the \ln likelihood of the null model (where the focal variance component is forced to be zero) is compared to that of the alternative model (where the focal variance component is explicitly estimated from the data). Twice the difference in these \ln likelihoods yields a likelihood ratio test statistic that is asymptotically distributed as a 50:50 mixture of a chi-square variate with one degree of freedom and a point mass at zero. Second, bivariate polygenic analyses were performed in order to estimate the genetic correlations between DTI and inflammatory measures. Genetic correlations estimate how much of the variance shared between two traits is due to shared genetic variance and is based on decomposing the phenotypic variance as follows: $\rho_p = \rho_g \sqrt{(h^2_1)(h^2_2)} + \rho_e \sqrt{(1 - h^2_1)(1 - h^2_2)}$, where h^2_1 and h^2_2 are the heritabilities of the two traits, ρ_g is the genetic correlation, and ρ_e is the environmental correlation. Significance of correlations are tested by comparing the \ln likelihood for two restricted

models (with either ρ_g or ρ_e constrained to 0) against the \ln likelihood for the model in which these parameters were estimated. Genetic correlations that are significantly different from 0 indicate that the two traits are influenced by shared genetic effects (Almasy, Dyer, & Blangero, 1997).

False discovery rate (FDR) (Benjamini & Hochberg, 1995) was used in all quantitative genetic analyses to account for false positives due to multiple testing. For heritability analyses, corrections were applied within BMI condition (with or without BMI as a covariate) and within trait type (inflammatory marker or DTI). For genetic correlations, corrections were applied within BMI condition (with or without BMI as a covariate), within marker (IL-6, IL-8, or TNF α), and within rho estimate (ρ_p , ρ_g , or ρ_e).

3 | RESULTS

Descriptive statistics for each trait in the quantitative genetic analyses are reported in Table 1. Sample sizes in Table 1 reflect all available data for a given variable. Because BMI is associated with circulating cytokines and FA, we also report phenotypic and genotypic correlations between each trait and BMI. There were significant phenotypic correlations between BMI and IL-6, TNF α , and some white matter tracts. There were only significant genetic correlations between BMI and IL-6.

All DTI and inflammatory traits were significantly and moderately heritable (FDR corrected $p < .05$), with h^2 ranging from 0.41 to 0.66 and 0.18 to 0.30 respectively (See Table 2). Estimates remained significant when BMI was included as a covariate, although BMI was a significant covariate in the h^2 model for 2 out of 12 DTI measures (CgH and FMI) and 2 out of 3 inflammatory markers (IL-6 and TNF α).

Results of the genetic correlation analyses are shown in Table 3 and summarized in Figure 2. Phenotypic correlations between DTI and inflammatory measures were negative and significant with the exception of the correlation between CgH and IL-6. Genetic correlations were also negative, but significance varied across inflammatory markers and covariate inclusion. IL-8 levels were significantly and moderately genetically correlated with whole-skeleton FA and FA in most individual tracts, regardless of whether BMI was included as a covariate in the bivariate model. TNF α was similarly genetically correlated with whole-skeleton and tract-level FA, but these associations were no longer significant when covarying for BMI. While genetic correlations between TNF α and FA measures were slightly reduced when including BMI as a covariate, this reduction was not significant (see Table S4). Lastly, there were no significant genetic correlations between any DTI measures and IL-6 with or without including BMI as a covariate. Cytokine levels were phenotypically correlated in our analysis (see Table 4), suggesting that genetic correlations should be tested in a model where other cytokines are considered as covariates. When adding IL-6 and TNF α as covariates in the bivariate model including whole-skeleton FA and IL-8 (the only model to show unequivocal significant genetic association), genetic correlations were reduced but remained significant (IL-8: $\rho_g = -.23$, $p = .04$).

TABLE 1 Descriptive statistics for traits used in the quantitative genetic analyses

BMI (kg/m ²), n = 1,635	Mean	SD	Range	Correlation with BMI	
				ρ_p (p)	ρ_g (p)
Inflammatory markers (p _g /mL), n = 1,817					
IL-6	3.86	16.70	588.89	0.27 (8.8 × 10 ⁻²⁶)*	0.41 (.002)*
IL-8	3.34	5.06	98.32	-0.03 (0.27)	0.03 (.78)
TNF α	2.51	1.92	23.22	0.13 (1.4 × 10 ⁻⁰⁶)*	0.05 (.64)
DTI measures (FA), n = 1,320					
Whole skeleton	0.46	0.03	0.26	-0.05 (0.14)	-0.19 (.03)
Anterior thalamic radiation (ATR)	0.50	0.04	0.34	-0.02 (0.56)	-0.21 (.05)
Cingulum bundle (CgC)	0.61	0.05	0.33	0.003 (0.92)	-0.13 (.17)
Cingulum hippocampal part (CgH)	0.45	0.06	0.60	0.19 (5.4 × 10 ⁻⁰⁹)*	0.01 (.94)
Corticospinal tract (CST)	0.62	0.04	0.49	0.02 (0.54)	-0.10 (.27)
Forceps major (FMa)	0.68	0.05	0.38	-0.06 (0.07)	-0.21 (.02)
Forceps minor (FMi)	0.57	0.05	0.35	-0.09 (0.006)*	-0.17 (.06)
Inferior fronto-occipital fasciculus (IFOF)	0.53	0.04	0.33	-0.07 (0.03)	-0.25 (.01)
Inferior longitudinal fasciculus (ILF)	0.51	0.03	0.35	-0.02 (0.53)	-0.24 (.01)
Superior longitudinal fasciculus (SLF)	0.51	0.04	0.28	-0.08 (0.009)*	-0.23 (.01)
Superior longitudinal fasciculus temporal part (tSLF)	0.58	0.04	0.37	-0.01 (0.79)	-0.11 (.29)
Uncinate fasciculus (UF)	0.52	0.05	0.41	-0.002 (0.95)	-0.13 (.21)

Note: Inflammatory markers are serum-based measures of IL-6, IL-8, and TNF α . DTI measures are bilateral FA values obtained from averaging the right and left hemispheres (excluding the forceps major and minor) of tracts in the JHU white matter atlas. Table shows mean, standard deviation, and range for each measure included in the quantitative genetic analyses. Genetic correlation analyses were used to estimate the phenotypic and genetic correlations between each measure and BMI. Reported *p*-values are uncorrected (FDR corrected *p*-values are listed in Table S1).

*Significant correlation with BMI, FDR corrected *p* < .05.

4 | DISCUSSION

White matter microstructure and innate inflammatory responses are associated both phenotypically and genetically. At the phenotypic level, we found negative correlations between FA and circulating pro-inflammatory cytokine levels, consistent with prior reports (Bettcher et al., 2014; Lim et al., 2013; Rasmussen et al., 2018). By observing significant genetic correlations, we demonstrated that at least a portion of these phenotypic associations is due to shared genetic control of cerebral white matter FA and circulating levels of pro-inflammatory cytokines.

Like their phenotypic correlations, genetic correlations between FA and circulating pro-inflammatory cytokines were primarily negative, which could result from several scenarios. One, is that the same gene or genetic factor positively influences one phenotype and negatively influences another. Genome-wide association (GWA) analyses could identify these genes or variants. There are several GWA studies of FA (Elliott et al., 2017; Lopez et al., 2012; Sprooten et al., 2013, 2014) and inflammatory measures (Ahola-Olli et al., 2017; Emilsson et al., 2018; Folkersen et al., 2017; Kim et al., 2012; Larsen et al., 2013; Li et al., 2016; Sun et al., 2018). While these analyses successfully identify loci underlying individual variation in these traits, they fail to identify variants common to both. Furthermore, most significant associations from these studies are related to variations in

IL-6, which was not genetically correlated with white matter measures in our study. It is likely that more targeted approaches or larger sample sizes will be necessary to find shared variants between specific cytokines and white matter FA rather than independent GWA analyses of these traits. Another possibility is that the same genetic factor acts on a third trait, which has opposing effects on two phenotypes. A likely candidate may be the genes that regulate pro-inflammatory nuclear factor (NF)- κ B, a transcription factor that is activated by inflammation. Upon activation, (NF)- κ B induces cytokine gene expression, which contributes to circulating cytokine levels (Baker, Hayden, & Ghosh, 2011). It also appears to play an integral role in CNS reactive astrogliosis, which contributes to axon loss when inflammatory processes are not resolved (Saggu et al., 2016). Still another possible explanation is that different variants are responsible for the opposing effects on two phenotypes, but these variants are in linkage disequilibrium with each other.

Genetic correlations also differed across the three circulating pro-inflammatory cytokines measured. FA across the white matter skeleton showed significant genetic overlap with IL-8 and TNF α , although for TNF α this relationship was dependent on covarying for BMI. In contrast, FA showed no evidence for genetic overlap with IL-6 in our sample. IL-6, IL-8, and TNF α are pro-inflammatory cytokines with different roles in the body's response to inflammation and could, therefore, impact white matter microstructure via different genetic mechanisms. Both IL-6 and

TABLE 2 Heritability (h^2) estimates for traits with and without BMI as a covariate

Covariates	Age/sex h^2 (se), p -value	Age/sex/BMI h^2 (se), p -value, BMI p -value
Inflammatory markers		
IL-6	0.18 (0.05), $p = -2.0 \times 10^{-06}$	0.18 (0.05), $p = 2.4 \times 10^{-05}$, BMI $p = 5.9 \times 10^{-29}$ *
IL-8	0.30 (0.05), $p = -4.0 \times 10^{-14}$	0.25 (0.05), $p = 2.3 \times 10^{-08}$, BMI $p = .28$
TNF α	0.23 (0.05), $p = -1.4 \times 10^{-09}$	0.25 (0.05), $p = 2.9 \times 10^{-09}$, BMI $p = 1.26 \times 10^{-07}$ *
DTI measures		
Whole skeleton	0.60 (0.06), $p = 8.1 \times 10^{-31}$	0.56 (0.06), $p = 8.8 \times 10^{-24}$, BMI $p = .59$
ATR	0.41 (0.06), $p = 1.3 \times 10^{-13}$	0.33 (0.07), $p = 1.4 \times 10^{-08}$, BMI $p = .87$
CgC	0.54 (0.06), $p = 2.5 \times 10^{-22}$	0.53 (0.07), $p = 3.5 \times 10^{-19}$, BMI $p = .37$
CgH	0.41 (0.07), $p = 5.6 \times 10^{-13}$	0.40 (0.08), $p = 5.6 \times 10^{-09}$, BMI $p = 3.5 \times 10^{-13}$ *
CST	0.55 (0.06), $p = 6.7 \times 10^{-26}$	0.50 (0.06), $p = 3.0 \times 10^{-19}$, BMI $p = .18$
FMa	0.64 (0.06), $p = 4.8 \times 10^{-31}$	0.60 (0.07), $p = 1.7 \times 10^{-23}$, BMI $p = .38$
FMi	0.58 (0.06), $p = 7.1 \times 10^{-30}$	0.57 (0.06), $p = 1.4 \times 10^{-24}$, BMI $p = .03$ *
IFOF	0.56 (0.06), $p = 4.0 \times 10^{-23}$	0.51 (0.07), $p = 1.8 \times 10^{-17}$, BMI $p = .20$
ILF	0.53 (0.06), $p = 1.8 \times 10^{-22}$	0.48 (0.07), $p = 6.3 \times 10^{-17}$, BMI $p = .66$
SLF	0.66 (0.06), $p = 1.5 \times 10^{-29}$	0.60 (0.07), $p = 8.4 \times 10^{-22}$, BMI $p = .08$
tSLF	0.44 (0.06), $p = 4.1 \times 10^{-16}$	0.40 (0.07), $p = 4.4 \times 10^{-13}$, BMI $p = .84$
UF	0.49 (0.07), $p = 1.7 \times 10^{-17}$	0.44 (0.07), $p = 3.3 \times 10^{-13}$, BMI $p = .56$

Note: Heritability estimates (h^2) for circulating levels of inflammatory markers and bilateral tract FA measures with and without BMI as a covariate in the model. Estimates listed are from the full polygenic model, which included all covariates: age, age², sex and their interactions, motion parameters for DTI measures, and BMI where indicated. All estimates were significant before and after correction for multiple comparisons using FDR. Reported p -values are uncorrected (corrected p -values are listed in Table S2). Significance of BMI as a covariate in the h^2 model and its respective p -value is also reported. ATR, anterior thalamic radiation; CgC, cingulum bundle; CgH, cingulum hippocampal part; CST, corticospinal tract; FA, fractional anisotropy; FMa, forceps major; FMi, forceps minor; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; tSLF, superior longitudinal fasciculus temporal part; UF, uncinata fasciculus.

*BMI was significant as a covariate in the model at $p < .05$.

TNF α are early players in the inflammatory response and initiate a broad spectrum of processes. IL-6 induces B-cell differentiation into antibody producing cells, hematopoiesis, and stimulation of acute phase proteins (Heinrich, Castell, & Andus, 1990), whereas TNF α influences monocyte recruitment and T-cell proliferation (Strieter, Kunkel, & Bone, 1993). IL-8 has a more specific function as a chemotactic cytokine that recruits phagocytotic neutrophils to the sight of inflammation (Baggiolini, Walz, & Kunkel, 1989; Bickel, 1993). It also has an effect on neutrophil degranulation, which results in the release of cytotoxins that can cause tissue damage (Nathan, 2006; Smith, 1994). Our observation of common genetic factors influencing FA and IL-8 and, to some extent, TNF α , but not IL-6, suggests an intriguing level of specificity. This specificity was further supported for IL-8, whose relationship to whole-skeleton FA could not be fully accounted for by other cytokine measures. However, it is also possible that the pattern of results here reflect methodological or measurement differences between the various pro-inflammatory cytokines, as described below.

For example, we failed to find a significant genetic association with IL-6, but this result should be interpreted with caution. The range of IL-6 measures in our sample was substantially larger than the other two cytokines measured. This could be the result of actual variation in the sample (potentially due to environmentally important variation) or

an increase in measurement error. If the latter is the case, this could have contributed to our lack of findings. Furthermore, failure to find a significant genetic correlation between FA and IL-6 could reflect the low heritability estimate of IL-6, which was the least heritable of the three cytokines measured. Given that IL-6 was still significantly phenotypically correlated with FA measures, it is also possible that the impact of IL-6 on white matter microstructure is more under the influence of environmental rather than genetic factors, although we did not observe a significant environmental correlation between IL-6 and whole-skeleton FA.

BMI is often associated with reduced white matter microstructure (Ryan et al., 2017; Spieker et al., 2015; Stanek et al., 2011) and higher circulating levels of IL-6, IL-8, and TNF α (Bruun, Pedersen, Kristensen, & Richelsen, 2002; Bruun, Verdich, Toubro, Astrup, & Richelsen, 2003; Straczkowski et al., 2002), making it an important factor to consider in genetic correlation models. Indeed, in our sample BMI was phenotypically correlated with IL-6, TNF α , and a few white matter tracts and genetically correlated with IL-6. Release of pro-inflammatory cytokines from adipose tissue contributes to elevations in cytokine serum levels, producing a chronic inflammatory state (Fain, 2006; Makki, Froguel, & Wolowczuk, 2013), which could be responsible for white matter alterations. Genetic correlations between FA and

TABLE 3 Results of the genetic correlation analyses between inflammatory markers and DTI measures with and without BMI as a covariate

	Age/sex			Age/sex/BMI			p
	ρ_p (se)	p	ρ_g (se)	ρ_p (se)	p	ρ_g (se)	
IL-6							
Whole skeleton	-0.10 (0.03)	$8.7 \times 10^{-04*}$	-0.16 (0.12)	-0.09 (0.03)	.002*	-0.03 (0.14)	.84
ATR	-0.09 (0.03)	.003*	-0.23 (0.15)	-0.09 (0.03)	.002*	-0.09 (0.18)	.61
CgC	-0.08 (0.03)	.003*	-0.23 (0.13)	-0.09 (0.03)	.002*	-0.19 (0.14)	.19
CgH	0.01 (0.03)	.74	0.23 (0.16)	-0.03 (0.03)	.25	0.29 (0.19)	.12
CST	-0.05 (0.03)	.12	-0.06 (0.13)	-0.06 (0.03)	.05	0.07 (0.15)	.64
FMa	-0.11 (0.03)	$1.8 \times 10^{-04*}$	-0.15 (0.12)	-0.10 (0.03)	.001*	0.01 (0.14)	.97
FMI	-0.07 (0.03)	.01*	-0.09 (0.13)	-0.06 (0.03)	.05	-0.02 (0.14)	.91
IFOF	-0.11 (0.03)	$1.6 \times 10^{-04*}$	-0.18 (0.13)	-0.11 (0.03)	$2.3 \times 10^{-04*}$	-0.10 (0.15)	.51
ILF	-0.09 (0.03)	.0002*	-0.20 (0.13)	-0.10 (0.03)	$5.4 \times 10^{-04*}$	-0.11 (0.15)	.50
SLF	-0.09 (0.03)	.001*	-0.17 (0.12)	-0.08 (0.03)	.007*	-0.03 (0.15)	.86
tSLF	-0.08 (0.03)	.004*	-0.07 (0.15)	-0.09 (0.03)	.002*	0.001 (0.16)	.99
UF	-0.09 (0.30)	.003*	-0.18 (0.14)	-0.10 (0.03)	.001*	-0.10 (0.16)	.53
IL-8							
Whole skeleton	-0.17 (0.03)	$4.7 \times 10^{-09*}$	-0.32 (0.10)	-0.17 (0.03)	$4.7 \times 10^{-08*}$	-0.36 (0.12)	.004*
ATR	-0.15 (0.03)	$6.2 \times 10^{-07*}$	-0.34 (0.12)	-0.14 (0.03)	$4.0 \times 10^{-06*}$	-0.39 (0.15)	.01*
CgC	-0.16 (0.03)	$1.5 \times 10^{-08*}$	-0.35 (0.10)	-0.16 (0.03)	$1.4 \times 10^{-07*}$	-0.45 (0.12)	$5.0 \times 10^{-04*}$
CgH	-0.07 (0.03)	.01*	-0.05 (0.13)	-0.06 (0.03)	.05	-0.11 (0.16)	.48
CST	-0.14 (0.03)	$1.5 \times 10^{-06*}$	-0.29 (0.10)	-0.14 (0.03)	$4.0 \times 10^{-06*}$	-0.30 (0.13)	.02*
FMa	-0.14 (0.03)	$2.7 \times 10^{-06*}$	-0.22 (0.10)	-0.13 (0.03)	$1.2 \times 10^{-05*}$	-0.23 (0.12)	.07
FMI	-0.17 (0.03)	$7.9 \times 10^{-09*}$	-0.31 (0.10)	-0.16 (0.03)	$5.2 \times 10^{-08*}$	-0.36 (0.12)	.004*
IFOF	-0.18 (0.03)	$1.9 \times 10^{-09*}$	-0.31 (0.10)	-0.17 (0.03)	$1.8 \times 10^{-08*}$	-0.39 (0.12)	.003*
ILF	-0.18 (0.03)	$2.3 \times 10^{-09*}$	-0.30 (0.11)	-0.17 (0.03)	$1.3 \times 10^{-08*}$	-0.36 (0.13)	.01*
SLF	-0.16 (0.03)	$9.2 \times 10^{-08*}$	-0.25 (0.10)	-0.15 (0.03)	$5.6 \times 10^{-07*}$	-0.30 (0.12)	.02*
tSLF	-0.14 (0.03)	$3.1 \times 10^{-06*}$	-0.31 (0.12)	-0.14 (0.03)	$4.7 \times 10^{-06*}$	-0.39 (0.14)	.01*
UF	-0.16 (0.03)	$4.1 \times 10^{-08*}$	-0.28 (0.11)	-0.15 (0.03)	$2.7 \times 10^{-07*}$	-0.27 (0.14)	.06
TNF α							
Whole skeleton	-0.15 (0.03)	$2.4 \times 10^{-07*}$	-0.30 (0.11)	-0.14 (0.03)	$3.9 \times 10^{-06*}$	-0.26 (0.12)	.03
ATR	-0.11 (0.03)	$1.4 \times 10^{-04*}$	-0.28 (0.13)	-0.11 (0.03)	$5.7 \times 10^{-04*}$	-0.24 (0.15)	.11
CgC	-0.10 (0.03)	$5.9 \times 10^{-04*}$	-0.34 (0.11)	-0.09 (0.03)	.004*	-0.33 (0.12)	.01*
CgH	-0.06 (0.03)	.003*	-0.25 (0.13)	-0.09 (0.03)	.003*	-0.23 (0.15)	.13

(Continues)

TABLE 3 (Continued)

	Age/sex				Age/sex/BMI			
	ρ_p (se)	p	ρ_g (se)	p	ρ_p (se)	p	ρ_g (se)	p
CST	-0.12 (0.03)	5.5×10^{-05} *	-0.18 (0.12)	.13	-0.12 (0.03)	9.6×10^{-05} *	-0.11 (0.12)	.37
FMa	-0.13 (0.03)	1.3×10^{-05} *	-0.20 (0.11)	.07	-0.11 (0.03)	4.5×10^{-04} *	-0.13 (0.12)	.28
FMI	-0.16 (0.03)	4.7×10^{-08} *	-0.36 (0.10)	.001*	-0.15 (0.03)	1.9×10^{-06} *	-0.35 (0.11)	.003*
IFOF	-0.16 (0.03)	8.2×10^{-08} *	-0.32 (0.11)	.007*	-0.15 (0.03)	1.2×10^{-06} *	-0.31 (0.12)	.02
ILF	-0.15 (0.03)	5.2×10^{-07} *	-0.28 (0.11)	.02*	-0.15 (0.03)	2.5×10^{-06} *	-0.24 (0.13)	.07
SLF	-0.14 (0.03)	2.3×10^{-06} *	-0.23 (0.11)	.04	-0.12 (0.03)	8.0×10^{-05} *	-0.21 (0.12)	.09
tSLF	-0.16 (0.03)	1.1×10^{-07} *	-0.36 (0.12)	.005*	-0.16 (0.03)	1.6×10^{-07} *	-0.35 (0.13)	.01*
UF	-0.13 (0.03)	8.3×10^{-06} *	-0.30 (0.12)	.02*	-0.13 (0.03)	2.1×10^{-05} *	-0.26 (0.13)	.06

Phenotypic (ρ_p), genotypic (ρ_g), and environmental (ρ_e) correlation estimates from the full polygenic model, which included all covariates: age, age², sex and their interactions, motion parameters for DTI measures, and BMI where indicated. Reported p -values are uncorrected (corrected p -values are listed in Table S3). ATR, anterior thalamic radiation; CgC, cingulum bundle; CgH, cingulum hippocampal part; CST, corticospinal tract; FA, fractional anisotropy; FMa, forceps major; FMI, forceps minor; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; tSLF, superior longitudinal fasciculus temporal part; UF, uncinate fasciculus.
*Significant after FDR correction.

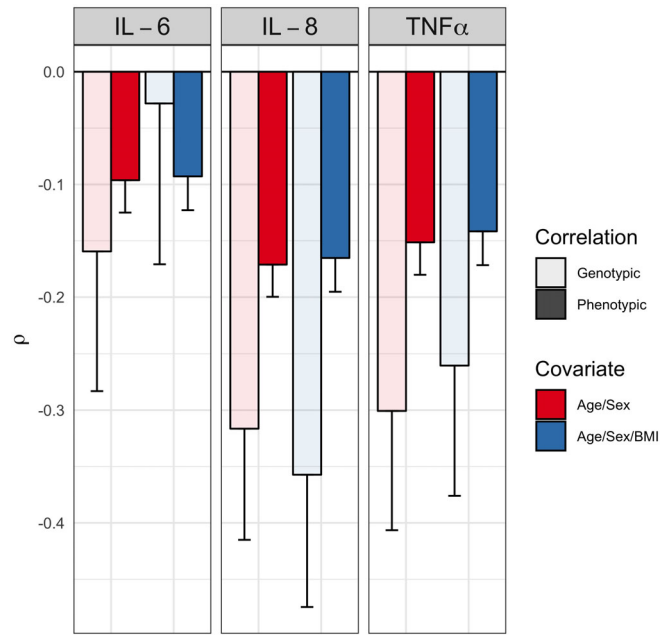


FIGURE 2 Phenotypic and genotypic correlations between inflammatory markers and the average FA skeleton. Image shows the results of the genetic correlation analysis between each inflammatory marker and the average FA skeleton. Blue bars show rho values using age and sex (in addition to their interactions and motion for DTI measures) along with BMI as covariates; red bars show the same excluding BMI as a covariate. Dark shaded bars show the phenotypic correlation and light shaded bars show the genotypic correlation as estimated by the genetic correlation analysis for each covariate condition. Error bars represent standard errors [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Phenotypic correlations (ρ_p) between inflammatory markers

	IL-6	IL-8	TNFα
IL-6	1		
IL-8	0.36*	1	
TNFα	0.37*	0.51*	1

Phenotypic correlations were estimated with a bivariate polygenic model to account for interdependence due to family structure.
*Significant phenotypic correlation $p < .0001$.

TNFα were reduced when covarying for BMI, although this was not a significant reduction. Regardless, these slight reductions may be consistent with the observation that TNFα is produced by adipose tissue, although it is restricted to certain tissue (Fried, Bunkin, & Greenberg, 1998; Hube, Birgel, Lee, & Hauner, 1999) and cell types (Hoch et al., 2008). BMI, on the other hand, had virtually no effect on the significance of genetic correlations with FA and IL-8. BMI was not significantly phenotypically correlated with IL-8 nor was it a significant covariate in the IL-8 heritability model. The association between BMI and IL-8 has not been as extensively studied as it has for TNFα, although IL-8 is the only cytokine of the three measured that has been shown to increase after weight loss/reductions in BMI (Bruun et al., 2002, 2003).

This could indicate a more complex relationship between BMI and IL-8 and could explain why BMI had no effect on any of our IL-8 genetic models.

Inflammatory activity drives levels of circulating pro-inflammatory cytokines, which fluctuate in response to acute insults, like infection or injury, and/or chronic disruptions in homeostasis and tissue function (Cohen et al., 2012; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012; Hotamisligil, 2017; Scriver, Vasile, Bartosiewicz, & Valesini, 2011). This gives inflammatory processes wide berth to impact brain structure, evidence of which is reflected in both early development and adulthood (Bettcher et al., 2013, 2014; Favrais et al., 2011; Jiang, Cowan, Moonah, & Petri Jr., 2018; Lim et al., 2013; Rasmussen et al., 2018) and in health and illness (Benedetti et al., 2016; Chiang et al., 2017; Najjar & Pearlman, 2015; Prasad et al., 2015; Yadav et al., 2010). Our study aimed to evaluate common genetic influences on white matter microstructure, as measured by DTI, and markers of inflammation, as measured by circulating pro-inflammatory cytokines in humans. Despite significant phenotypic correlations between all DTI measures and inflammatory markers, significant genotypic correlations were variable across markers and only readily identifiable for IL-8. Identifying genetic correlations between white matter microstructure and immune markers is the first step in characterizing common biological mechanisms underlying both traits. Further determining what parts of the immune response are genetically related to alterations in brain structure could provide insight into the complex interplay between central and peripheral nervous systems. Such insights may then point to possible pathways to disease and help in the development of more targeted treatments for many disorders in which white matter microstructure and immune function are altered.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

- Ahola-Olli, A. V., Würzt, P., Havulinna, A. S., Aalto, K., Pitkänen, N., Lehtimäki, T., ... Raitakari, O. T. (2017). Genome-wide association study identifies 27 loci influencing concentrations of circulating cytokines and growth factors. *The American Journal of Human Genetics*, 100(1), 40–50. <https://doi.org/10.1016/j.ajhg.2016.11.007>
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316–329. <https://doi.org/10.1016/j.nurt.2007.05.011>
- Almasy, L., & Blangero, J. (1998). Multipoint quantitative-trait linkage analysis in general pedigrees. *American Journal of Human Genetics*, 62(5), 1198–1211.
- Almasy, L., Dyer, T. D., & Blangero, J. (1997). Bivariate quantitative trait linkage analysis: Pleiotropy versus co-incident linkages. *Genetic Epidemiology*, 14(6), 953–958.
- Andersson, J. L. R., Jenkinson, M., & Smith, S. (2010). Non-linear registration, aka spatial normalization. FMRIB technical report TR07JA2.
- Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, 125, 1063–1078. <https://doi.org/10.1016/j.neuroimage.2015.10.019>
- Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., ... Malik, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, 360(6395), eaap8757.
- Baggiolini, M., Walz, A., & Kunkel, S. (1989). Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. *The Journal of Clinical Investigation*, 84(4), 1045–1049.
- Baker, R. G., Hayden, M. S., & Ghosh, S. (2011). NF- κ B, inflammation, and metabolic disease. *Cell Metabolism*, 13(1), 11–22. <https://doi.org/10.1016/j.cmet.2010.12.008>
- Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., ... Reiss, A. L. (2005). White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. *Cerebral Cortex*, 15(12), 1848–1854. <https://doi.org/10.1093/cercor/bhi062>
- Benedetti, F., Poletti, S., Hoogenboezem, T. A., Mazza, E., Ambrée, O., de Wit, H., ... Drexhage, H. A. (2016). Inflammatory cytokines influence measures of white matter integrity in bipolar disorder. *Journal of Affective Disorders*, 202, 1–9. <https://doi.org/10.1016/j.jad.2016.05.047>
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 57, 289–300.
- Bettcher, B. M., Walsh, C. M., Watson, C., Miller, J. W., Green, R., Patel, N., ... Kramer, J. H. (2013). Body mass and white matter integrity: The influence of vascular and inflammatory markers. *PLoS One*, 8(10), e77741. <https://doi.org/10.1371/journal.pone.0077741>
- Bettcher, B. M., Watson, C. L., Walsh, C. M., Lobach, I. V., Neuhaus, J., Miller, J. W., ... Kramer, J. H. (2014). Interleukin-6, age, and corpus callosum integrity. *PLoS One*, 9(9), e106521. <https://doi.org/10.1371/journal.pone.0106521>
- Bickel, M. (1993). The role of interleukin-8 in inflammation and mechanisms of regulation. *Journal of Periodontology*, 64(5 Suppl), 456–460.
- Bruun, J. M., Pedersen, S. B., Kristensen, K., & Richelsen, B. (2002). Opposite regulation of Interleukin-8 and tumor necrosis factor- α by weight loss. *Obesity Research*, 10(6), 499–506.
- Bruun, J. M., Verdich, C., Toubro, S., Astrup, A., & Richelsen, B. (2003). Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men. *European Journal of Endocrinology*, 148(5), 535–542.
- Chen, G., Castro, W. L., Chow, H.-H., & Reichlin, S. (1997). Clearance of 125I-labeled Interleukin-6 from brain into blood following Intracerebroventricular injection in rats*. *Endocrinology*, 138(11), 4830–4836. <https://doi.org/10.1210/endo.138.11.5533>
- Chen, G., & Reichlin, S. (1998). Clearance of [125I]-tumor necrosis factor-alpha from the brain into the blood after intracerebroventricular injection in rats. *Neuroimmunomodulation*, 5(5), 261–269. <https://doi.org/10.1159/000026346>
- Chiang, P.-L., Chen, H.-L., Lu, C.-H., Chen, P.-C., Chen, M.-H., Yang, I. H., ... Lin, W.-C. (2017). White matter damage and systemic inflammation in

- Parkinson's disease. *BMC Neuroscience*, 18, 48. <https://doi.org/10.1186/s12868-017-0367-y>
- Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., & Turner, R. B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America*, 109(16), 5995–5999. <https://doi.org/10.1073/pnas.1118355109>
- De Craen, A., Posthuma, D., Remarque, E., Van Den Biggelaar, A., Westendorp, R., & Boomsma, D. (2005). Heritability estimates of innate immunity: An extended twin study. *Genes and Immunity*, 6(2), 167–170.
- Elliott, L., Sharp, K., Alfaro-Almagro, F., Douaud, G., Miller, K., Marchini, J., & Smith, S. (2017). The genetic basis of human brain structure and function: 1,262 genome-wide associations found from 3,144 GWAS of multimodal brain imaging phenotypes from 9,707 UKbiobank participants. *BioRxiv*, 178806. <https://doi.org/10.1101/178806>
- Emilsson, V., Ilkov, M., Lamb, J. R., Finkel, N., Gudmundsson, E. F., Pitts, R., ... Aspelund, T. (2018). Co-regulatory networks of human serum proteins link genetics to disease. *Science*, 361(6404), 769–773.
- Fain, J. N. (2006). Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitamins & Hormones* (Vol. 74, pp. 443–477). Academic Press.
- Favrais, G., van de Looij, Y., Fleiss, B., Ramanantsoa, N., Bonnin, P., Stoltenberg-Didinger, G., ... Gressens, P. (2011). Systemic inflammation disrupts the developmental program of white matter. *Annals of Neurology*, 70(4), 550–565. <https://doi.org/10.1002/ana.22489>
- Folkersen, L., Fauman, E., Sabater-Lleal, M., Strawbridge, R. J., Frånberg, M., Sennblad, B., ... Rauramaa, R. (2017). Mapping of 79 loci for 83 plasma protein biomarkers in cardiovascular disease. *PLoS Genetics*, 13(4), e1006706.
- Fried, S. K., Bunkin, D. A., & Greenberg, A. S. (1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: Depot difference and regulation by glucocorticoid. *The Journal of Clinical Endocrinology & Metabolism*, 83(3), 847–850.
- Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., ... Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, 2, 861–863. <https://doi.org/10.1038/13158>
- Gouin, J. P., Glaser, R., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. (2012). Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*, 31(2), 264–268. <https://doi.org/10.1037/a0025536>
- Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: A review of MRI findings. *International Journal of Geriatric Psychiatry: A Journal of the Psychiatry of Late Life and Allied Sciences*, 24(2), 109–117.
- Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, 14(2), 224–232.
- Heinrich, P. C., Castell, J. V., & Andus, T. (1990). Interleukin-6 and the acute phase response. *Biochemical Journal*, 265(3), 621–636.
- Hoch, M., Eberle, A. N., Peterli, R., Peters, T., Seboek, D., Keller, U., ... Linscheid, P. (2008). LPS induces interleukin-6 and interleukin-8 but not tumor necrosis factor- α in human adipocytes. *Cytokine*, 41(1), 29–37. <https://doi.org/10.1016/j.cyto.2007.10.008>
- Hofstetter, S., Tavor, I., Moryosef, S. T., & Assaf, Y. (2013). Short-term learning induces white matter plasticity in the fornix. *Journal of Neuroscience*, 33(31), 12844–12850.
- Hotamisligil, G. S. (2017). Inflammation, metaflammation and immunometabolic disorders. *Nature*, 542(7640), 177–185.
- Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., ... Mori, S. (2008). Tract probability maps in stereotaxic spaces: Analyses of White matter anatomy and tract-specific quantification. *NeuroImage*, 39(1), 336–347. <https://doi.org/10.1016/j.neuroimage.2007.07.053>
- Hube, F., Birgel, M., Lee, Y., & Hauner, H. (1999). Expression pattern of tumour necrosis factor receptors in subcutaneous and omental human adipose tissue: Role of obesity and non-insulin-dependent diabetes mellitus. *European Journal of Clinical Investigation*, 29(8), 672–678.
- Jiang, N. M., Cowan, M., Moonah, S. N., & Petri, W. A., Jr. (2018). The impact of systemic inflammation on neurodevelopment. *Trends in Molecular Medicine*, 24(9), 794–804. <https://doi.org/10.1016/j.molmed.2018.06.008>
- Jones, D. K., Horsfield, M. A., & Simmons, A. (1999). Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magnetic Resonance in Medicine*, 42(3), 515–525.
- Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nature Reviews Neuroscience*, 12(4), 231–242.
- Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*, 47(3), 916–927.
- Kim, D. K., Cho, M. H., Hersh, C. P., Lomas, D. A., Miller, B. E., Kong, X., ... Silverman, E. K. (2012). Genome-wide association analysis of blood biomarkers in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, 186(12), 1238–1247. <https://doi.org/10.1164/rccm.201206-1013OC>
- Kochunov, P., Fu, M., Nugent, K., Wright, S., Du, X., Muellerklein, F., ... Jahanshad, N. (2016). Heritability of complex white matter diffusion traits assessed in a population isolate. *Human Brain Mapping*, 37(2), 525–535.
- Kochunov, P., Glahn, D. C., Lancaster, J. L., Winkler, A. M., Smith, S., Thompson, P. M., ... Blangero, J. (2010). Genetics of microstructure of cerebral white matter using diffusion tensor imaging. *NeuroImage*, 53(3), 1109–1116. <https://doi.org/10.1016/j.neuroimage.2010.01.078>
- Kochunov, P., Jahanshad, N., Marcus, D., Winkler, A., Sprooten, E., Nichols, T. E., ... Van Essen, D. C. (2015). Heritability of fractional anisotropy in human white matter: A comparison of human Connectome project and ENIGMA-DTI data. *NeuroImage*, 111, 300–311. <https://doi.org/10.1016/j.neuroimage.2015.02.050>
- Koenis, M. M. G., Brouwer, R. M., Swagerman, S. C., van Soelen, I. L. C., Boomsma, D. I., & Hulshoff Pol, H. E. (2018). Association between structural brain network efficiency and intelligence increases during adolescence. *Human Brain Mapping*, 39(2), 822–836. <https://doi.org/10.1002/hbm.23885>
- Konsman, J. P., Parnet, P., & Dantzer, R. (2002). Cytokine-induced sickness behaviour: Mechanisms and implications. *Trends in Neurosciences*, 25(3), 154–159. [https://doi.org/10.1016/S0166-2236\(00](https://doi.org/10.1016/S0166-2236(00)
- Larsen, M. H., Albrechtsen, A., Thøner, L. W., Werge, T., Hansen, T., Gether, U., ... Ullum, H. (2013). Genome-wide association study of genetic variants in LPS-stimulated IL-6, IL-8, IL-10, IL-1ra and TNF- α cytokine response in a Danish cohort. *PLoS One*, 8(6), e66262. <https://doi.org/10.1371/journal.pone.0066262>
- Li, Y., Oosting, M., Deelen, P., Riccaño-Ponce, I., Smeekens, S., Jaeger, M., ... Netea, M. G. (2016). Inter-individual variability and genetic influences on cytokine responses to bacteria and fungi. *Nature Medicine*, 22(8), 952–960. <https://doi.org/10.1038/nm.4139>
- Li, Y., Zhang, R., Hou, X., Zhang, Y., Ding, F., Li, F., ... Wang, Y. (2017). Microglia activation triggers oligodendrocyte precursor cells apoptosis via HSP60. *Molecular Medicine Reports*, 16(1), 603–608.
- Lim, A., Krajina, K., & Marsland, A. L. (2013). Peripheral inflammation and cognitive aging. In *Inflammation in psychiatry* (Vol. 28, pp. 175–187). Karger Publishers, Basel, Switzerland.
- Livshits, G. (2006). Quantitative genetics of circulating molecules associated with bone metabolism: A review. *Journal of Musculoskeletal and Neuronal Interactions*, 6(1), 47–61.
- Lopez, L. M., Bastin, M. E., Maniega, S. M., Penke, L., Davies, G., Christoforou, A., ... Deary, I. J. (2012). A genome-wide search for genetic influences and biological pathways related to the brain's white matter integrity. *Neurobiology of Aging*, 33(8), 1847 e1841–1847 e1814. <https://doi.org/10.1016/j.neurobiolaging.2012.02.003>

- Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., ... Huettel, S. A. (2008). Cerebral white matter integrity mediates adult age differences in cognitive performance. *Journal of Cognitive Neuroscience*, 21(2), 289–302.
- Makki, K., Froguel, P., & Wolowczuk, I. (2013). Adipose tissue in obesity-related inflammation and insulin resistance: Cells, cytokines, and chemokines. *ISRN Inflammation*, 2013, 1–12.
- McDonough, A., Lee, R. V., & Weinstein, J. R. (2017). Microglial interferon signaling and White matter. *Neurochemical Research*, 42(9), 2625–2638. <https://doi.org/10.1007/s11064-017-2307-8>
- McKay, D. R., Knowles, E. E., Winkler, A. A., Sprooten, E., Kochunov, P., Olvera, R. L., ... Glahn, D. C. (2014). Influence of age, sex and genetic factors on the human brain. *Brain Imaging and Behavior*, 8(2), 143–152. <https://doi.org/10.1007/s11682-013-9277-5>
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, 16(7), 1227–1233.
- Najjar, S., & Pearlman, D. M. (2015). Neuroinflammation and white matter pathology in schizophrenia: Systematic review. *Schizophrenia Research*, 161(1), 102–112. <https://doi.org/10.1016/j.schres.2014.04.041>
- Nathan, C. (2006). Neutrophils and immunity: Challenges and opportunities. *Nature Reviews Immunology*, 6(3), 173–182.
- Olvera, R. L., Bearden, C. E., Velligan, D. I., Almasy, L., Carless, M. A., Curran, J. E., ... Glahn, D. C. (2011). Common genetic influences on depression, alcohol, and substance use disorders in Mexican-American families. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 156b(5), 561–568. <https://doi.org/10.1002/ajmg.b.31196>
- Peyrot, W. J., Lee, S. H., Milaneschi, Y., Abdellaoui, A., Byrne, E. M., Esko, T., ... Social Science Genetic Association Consortium Collaborator. (2015). The association between lower educational attainment and depression owing to shared genetic effects? Results in ~25,000 subjects. *Molecular Psychiatry*, 20(6), 735–743. <https://doi.org/10.1038/mp.2015.50>
- Porter, A., Leckie, R., & Verstynen, T. (2018). White matter pathways as both a target and mediator of health behaviors. *Annals of the New York Academy of Sciences*, 1428(1), 71–88.
- Posthuma, D., Baaré, W. F., Pol, H. E. H., Kahn, R. S., Boomsma, D. I., & De Geus, E. J. (2003). Genetic correlations between brain volumes and the WAIS-III dimensions of verbal comprehension, working memory, perceptual organization, and processing speed. *Twin Research and Human Genetics*, 6(2), 131–139.
- Prasad, K. M., Upton, C. H., Nimgaonkar, V. L., & Keshavan, M. S. (2015). Differential susceptibility of white matter tracts to inflammatory mediators in schizophrenia: An integrated DTI study. *Schizophrenia Research*, 161(1), 119–125. <https://doi.org/10.1016/j.schres.2014.09.043>
- Rasmussen, J. M., Graham, A. M., Entringer, S., Gilmore, J. H., Styner, M., Fair, D. A., ... Buss, C. (2018). Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. *NeuroImage*, 185, 825–835. <https://doi.org/10.1016/j.neuroimage.2018.04.020>
- Romero, L. I., Kakucska, I., Lechan, R. M., & Reichlin, S. (1996). Interleukin-6 (IL-6) is secreted from the brain after intracerebroventricular injection of IL-1 beta in rats. *The American Journal of Physiology*, 270(3 Pt 2), R518–R524. <https://doi.org/10.1152/ajpregu.1996.270.3.R518>
- Ryan, M., Kochunov, P., Rowland, L. M., Mitchell, B. D., Wijtenburg, S. A., Fieremans, E., ... Adhikari, B. (2017). Lipid metabolism, abdominal adiposity, and cerebral health in the Amish. *Obesity*, 25(11), 1876–1880.
- Saggu, R., Schumacher, T., Gerich, F., Rakers, C., Tai, K., Delekate, A., & Petzold, G. C. (2016). Astroglial NF- κ B contributes to white matter damage and cognitive impairment in a mouse model of vascular dementia. *Acta Neuropathologica Communications*, 4(1), 76. <https://doi.org/10.1186/s40478-016-0350-3>
- Sankowski, R., Mader, S., & Valdés-Ferrer, S. I. (2015). Systemic inflammation and the brain: Novel roles of genetic, molecular, and environmental cues as drivers of Neurodegeneration. *Frontiers in Cellular Neuroscience*, 9, 28. <https://doi.org/10.3389/fncel.2015.00028>
- Sas, A. A., Jamshidi, Y., Zheng, D., Wu, T., Korf, J., Alizadeh, B. Z., ... Snieder, H. (2012). The age-dependency of genetic and environmental influences on serum cytokine levels: A twin study. *Cytokine*, 60(1), 108–113.
- Scrive, R., Vasile, M., Bartosiewicz, I., & Valesini, G. (2011). Inflammation as “common soil” of the multifactorial diseases. *Autoimmunity Reviews*, 10(7), 369–374. <https://doi.org/10.1016/j.autrev.2010.12.006>
- Smith, J. (1994). Neutrophils, host defense, and inflammation: A double-edged sword. *Journal of Leukocyte Biology*, 56(6), 672–686.
- Smith, S. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143–155. <https://doi.org/10.1002/hbm.10062>
- Smith, S., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T., Mackay, C. E., ... Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>
- Smith, S., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., ... Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23, S208–S219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>
- Spieker, E. A., Kochunov, P., Rowland, L. M., Sprooten, E., Winkler, A. M., Olvera, R. L., ... Blangero, J. (2015). Shared genetic variance between obesity and white matter integrity in Mexican Americans. *Frontiers in Genetics*, 6, 26.
- Sprooten, E., Fleming, K. M., Thomson, P. A., Bastin, M. E., Whalley, H. C., Hall, J., ... McIntosh, A. M. (2013). White matter integrity as an intermediate phenotype: Exploratory genome-wide association analysis in individuals at high risk of bipolar disorder. *Psychiatry Research*, 206(2–3), 223–231. <https://doi.org/10.1016/j.psychres.2012.11.002>
- Sprooten, E., Knowles, E. E., McKay, D. R., Göring, H. H., Curran, J. E., Kent, J. W., ... Glahn, D. C. (2014). Common genetic variants and gene expression associated with white matter microstructure in the human brain. *NeuroImage*, 97, 252–261. <https://doi.org/10.1016/j.neuroimage.2014.04.021>
- Stanek, K. M., Grieve, S. M., Brickman, A. M., Korgaonkar, M. S., Paul, R. H., Cohen, R. A., & Gunstad, J. J. (2011). Obesity is associated with reduced White matter integrity in otherwise healthy adults*. *Obesity*, 19(3), 500–504. <https://doi.org/10.1038/oby.2010.312>
- Stolp, H. B., Dziegielewska, K. M., Ek, C. J., Potter, A. M., & Saunders, N. R. (2005). Long-term changes in blood-brain barrier permeability and white matter following prolonged systemic inflammation in early development in the rat. *The European Journal of Neuroscience*, 22(11), 2805–2816. <https://doi.org/10.1111/j.1460-9568.2005.04483.x>
- Stolp, H. B., Ek, C. J., Johansson, P. A., Dziegielewska, K. M., Bethge, N., Wheaton, B. J., ... Saunders, N. R. (2009). Factors involved in inflammation-induced developmental white matter damage. *Neuroscience Letters*, 451(3), 232–236. <https://doi.org/10.1016/j.neulet.2009.01.021>
- Strackowski, M., Dzienis-Strackowska, S., Stępień, A., Kowalska, I., Szelachowska, M., & Kinalska, I. (2002). Plasma Interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor- α system. *The Journal of Clinical Endocrinology & Metabolism*, 87(10), 4602–4606. <https://doi.org/10.1210/jc.2002-020135>
- Strieter, R. M., Kunkel, S. L., & Bone, R. C. (1993). Role of tumor necrosis factor-alpha in disease states and inflammation. *Critical Care Medicine*, 21(10 Suppl), S447–S463.
- Sun, B. B., Maranville, J. C., Peters, J. E., Stacey, D., Staley, J. R., Blackshaw, J., ... Surendran, P. (2018). Genomic atlas of the human plasma proteome. *Nature*, 558(7708), 73–79.
- Varatharaj, A., & Galea, I. (2017). The blood-brain barrier in systemic inflammation. *Brain, Behavior, and Immunity*, 60, 1–12. <https://doi.org/10.1016/j.bbi.2016.03.010>

- Verstynen, T. D., Weinstein, A., Erickson, K. I., Sheu, L. K., Marsland, A. L., & Gianaros, P. J. (2013). Competing physiological pathways link individual differences in weight and abdominal adiposity to white matter microstructure. *NeuroImage*, *79*, 129–137. <https://doi.org/10.1016/j.neuroimage.2013.04.075>
- Yadav, A., Chaudhary, C., Keshavan, A. H., Agarwal, A., Verma, S., Prasad, K. N., ... Gupta, R. K. (2010). Correlation of CSF Proinflammatory cytokines with MRI in Tuberculous meningitis. *Academic Radiology*, *17* (2), 194–200. <https://doi.org/10.1016/j.acra.2009.09.017>
- Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: Neuroimaging changes in brain structure during learning. *Nature Neuroscience*, *15*, 528–536. <https://doi.org/10.1038/nn.3045>

SUPPORTING INFORMATION

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

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