Psychological Medicine

cambridge.org/psm

Original Article

*These authors equally contributed to this work

Cite this article: Prasad KM *et al* (2022). Heritable anisotropy associated with cognitive impairments among patients with schizophrenia and their non-psychotic relatives in multiplex families. *Psychological Medicine* **52**, 989–1000. https://doi.org/10.1017/S0033291720002883

Received: 12 February 2020
Revised: 17 July 2020
Accepted: 27 July 2020
First published online: 3 September 2020

Key words:
Brain connectivity; diffusion tensor imaging; familial risk; heritability; schizophrenia; neuroimaging; white matter fibers

Author for correspondence:
K. M. Prasad,
E-mail: PrasadKM@upmc.edu

CAMBRIDGE UNIVERSITY PRESS

Heritable anisotropy associated with cognitive impairments among patients with schizophrenia and their non-psychotic relatives in multiplex families

K. M. Prasad[1,*], J. Gertler[1,*], S. Tollefson[1], J. A. Wood[1], D. Roalf[2], R. C. Gur[2], R. E. Gur[2], L. Almasy[3], M. F. Pogue-Geile[4] and V. L. Nimgaonkar[1,5,6]

[1]Departments of Psychiatry and Bioengineering, University of Pittsburgh, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA; [2]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA; [5]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA, USA and [6]VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

Abstract

Background. To test the functional implications of impaired white matter (WM) connectivity among patients with schizophrenia and their relatives, we examined the heritability of fractional anisotropy (FA) measured on diffusion tensor imaging data acquired in Pittsburgh and Philadelphia, and its association with cognitive performance in a unique sample of 175 multigenerational non-psychotic relatives of 23 multiplex schizophrenia families and 240 unrelated controls (total = 438).

Methods. We examined polygenic inheritance (h^2r) of FA in 24 WM tracts bilaterally, and also pleiotropy to test whether heritability of FA in multiple WM tracts is secondary to genetic correlation among tracts using the Sequential Oligogenic Linkage Analysis Routines. Partial correlation tests examined the correlation of FA with performance on eight cognitive domains on the Penn Computerized Neurocognitive Battery, controlling for age, sex, site and mother's education, followed by multiple comparison corrections.

Results. Significant total additive genetic heritability of FA was observed in all three-categories of WM tracts (association, commissural and projection fibers), in total 33/48 tracts. There were significant genetic correlations in 40% of tracts. Diagnostic group main effects were observed only in tracts with significantly heritable FA. Correlation of FA with neurocognitive impairments was observed mainly in heritable tracts.

Conclusions:. Our data show significant heritability of all three-types of tracts among relatives of schizophrenia. Significant heritability of FA of multiple tracts was not entirely due to genetic correlations among the tracts. Diagnostic group main effect and correlation with neurocognitive performance were mainly restricted to tracts with heritable FA suggesting shared genetic effects on these traits.

Introduction

Schizophrenia is a chronic brain disorder with a 70%–90% heritability (I. I. Gottesman, 1991; Hilker *et al*., 2018; Sullivan, Kendler, & Neale, 2003). It is, therefore, instructive to estimate heritability for putative pathogenetic processes, such as brain connectivity (Kochunov *et al*., 2016), and associated cognitive impairments (Hubbard *et al*., 2016). Since schizophrenia may be a disconnection syndrome (Friston & Frith, 1995), impaired connectivity could be a heritable component. Diffusion tensor imaging (DTI) has been used extensively to investigate white matter (WM) connections. DTI characterizes anisotropy of water diffusion to examine anatomical connections using the principle that water diffuses preferentially along the longitudinal axis than along the transverse axes of axons. A commonly examined metric, fractional anisotropy (FA), is a relative diffusion along the longitudinal compared to transverse axes (Beaulieu, 2002; Beaulieu & Allen, 1994). Lower FA is associated with impaired axonal integrity (Beaulieu & Allen, 1994), decreased myelination (Kubicki *et al*., 2005) and tract coherence (Kubicki *et al*., 2005) that may contribute to impaired connectivity.

Prior DTI studies have reported that the WM FA is heritable and is correlated with cognitive performance in both pedigree and healthy twins (Bertisch, Li, Hoptman, & Delisi, 2010; Bohlken, Brouwer, Mandl, Kahn, & Hulshoff Pol, 2016; Kochunov *et al*., 2016; Lee *et al*., 2015; Shen *et al*., 2016). Global FA independently contributed to schizophrenia liability where frontal, thalamic and striatal connectivity contributed ≈85% variance (Bohlken *et al*., 2016) while global FA, cortical thickness, cortical surface area and intelligence quotient (IQ) shared

28% of genetic variance for schizophrenia (Bohlken *et al.*, 2016). These studies suggest that brain connectivity and morphometric phenotypes may explain genetic liability that is not shared by intelligence. The Human Connectome Project (HCP) and the Enhancing Neuroimaging Genetics for Meta-analysis (ENIGMA) cohorts showed heritability of FA in 11 major tracts that were between 0.53 (the fornix) and 0.90 (the corpus callosum) (Kochunov *et al.*, 2015).

Prior studies report impaired anatomical and functional connectivity among schizophrenia patients and first-degree relatives of schizophrenia patients. Two mega-analyses (Kanaan, Picchioni, McDonald, Shergill, & McGuire, 2017; Kelly *et al.*, 2018) and four meta-analyses (Bora *et al.*, 2011; Ellison-Wright & Bullmore, 2009; Vitolo *et al.*, 2017; Yang, Cao, Liang, & Zhao, 2017; Yao *et al.*, 2013) show decreased FA and increased mean diffusivity in schizophrenia compared to controls. Association of altered FA with impairments in neurocognitive (Alloza *et al.*, 2016; Knochel *et al.*, 2016; Roalf *et al.*, 2013) and social functioning (Hamoda *et al.*, 2019) in schizophrenia, and neurocognitive impairments in healthy controls (Ohtani *et al.*, 2017) supports the functional impact of impaired connectivity.

Existing studies have not examined the tracts based on the anatomical topology that broadly reflects the functions, namely the association, commissural and projection fibers (Catani & Thiebaut de Schotten, 2008; Schmahmann & Pandya, 2007). Association fibers connect brain regions within the hemisphere; commissural fibers connect between the hemispheres, and the projection fibers connect the brain with the spinal cord and other regions. Existing data do not specifically elucidate whether the diagnostic group-effect and associations with cognitive impairments are primarily associated with tracts with heritable FA or without heritable FA. This is important because shared genetic factors may affect heritability of schizophrenia, FA of WM fibers and cognitive performance. We examined the heritability of FA of 24 tracts in each hemisphere, diagnostic group-effects on FA and neurocognitive correlates of tract FA in a large sample of multigenerational multiplex schizophrenia families and unrelated psychiatrically healthy controls characterized under the Multiplex Genetics Investigation (MGI). Our primary goal was not identifying endophenotypes (Gottesman & Gould, 2003). Instead, we hypothesized that the tracts with significantly heritable FA show diagnostic group-effects and correlate with neurocognitive performance since heritability of FA, reduced FA in schizophrenia and association of FA with neurocognitive impairments are extensively reported. We further hypothesized that tracts without significantly heritable FA will not show diagnostic-group effects and correlations with cognitive impairments. Additionally, we studied genetic correlations between sets of traits and tested which genetic factors impacting on one trait overlapped with genetic factors impacting on the other trait under investigation.

Methods

Clinical

The sample consisted of 438 participants (Pittsburgh = 190, Philadelphia = 248) (multigenerational relatives of multiplex schizophrenia = 175; unrelated healthy volunteers = 240; schizophrenia patients = 23). Details of recruitment and ascertainment are published (Gur *et al.*, 2007). Briefly, participants were identified through mental health and consumer organizations in Pennsylvania and surrounding states. Participants who were ⩾18 years old at initial contact provided informed consent. Participants <18 years provided the assent, and their parent provided the consent. Relatives consisted of parents, siblings, offspring, maternal/paternal cousins, uncle, niece and nephews. The institutional review boards of both Universities approved the study. Trained interviewers with established reliability interviewed subjects under the supervision of experienced investigators. Consensus diagnosis was reached by two investigators blind to the subject group after reviewing data from the Diagnostic Interview for Genetic Studies (DIGS 2.0) (Nurnberger *et al.*, 1994), the Family Interview for Genetic Studies (FIGS) and medical records independently, and assigned DSM-IV lifetime diagnoses. Complex cases were discussed between the 2-sites. At each site, interrater reliability among investigators and interviewers was tested at regular intervals using videotaped interviews and bimonthly joint interviews. Inter-site reliability of psychiatric and neurocognitive assessments was maintained at κ>0.8.

Neurocognitive variables

Using the Penn Computerized Neurocognitive Battery (CNB), we assessed eight neurocognitive domains: complex cognition [abstraction and mental flexibility-Penn Conditional Elimination Test (PCET), logical reasoning-Penn Verbal Reasoning Test (PVRT)], sustained attention (Penn Continuous Performance Test, PCPT), working memory (Letter n-back), verbal memory (immediate/delayed components, Penn Word Memory Test), spatial processing (Penn Line Orientation Test), face memory (immediate/delayed components), visual memory (immediate/delayed components) and emotion processing. Accuracy and speed of processing were the outcome measures for all except the PCPT where sensitivity and specificity were examined. For the PCET, perseverative errors were used instead of accuracy. The test details are published (Almasy *et al.*, 2008; Prasad *et al.*, 2010; Roalf *et al.*, 2013).

Imaging

We examined DTI data collected on Siemens Tim Trio 3T MRI systems at both sites. Imaging parameters were: (b = 1000 s/mm^2, slices = 64, thickness = 2.4 mm, TE = 90 ms, TR = 6300 ms, flip angle = 90°, matrix = 128 × 128). Four regularly interspersed B_0 reference images were also acquired. The inter-scanner reliabilities were tracked using phantoms and test subjects with no significant differences (Roalf *et al.* 2014, 2015).

Diffusion data were pre-processed using FSL 4.1 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Diffusion scans were skull-stripped, manually checked for optimum brain extraction, and Eddy current corrected. FSL brain extraction tool generated a mask for each subject that was exported to DTI Studio. Linear registration was performed within Diffeomap using subject's B_0 as the reference image to set the noise threshold. Large Deformation Diffeomorphic Metric Mapping (LDDMM) was performed to morph DTI data in each subject's native brain space (Miller *et al.*, 2009). LDDMM runs a landmark distortion algorithm to minimize B_0 distortion (Beg, Miller, Trouve, & Younes, 2005). Within DTI studio, each subject's FA was estimated from the following tracts in both hemispheres in the Johns Hopkins University (JHU) atlas V2.0: corpus callosum (genu, body, splenium), corona radiata (anterior, posterior, superior), internal capsule (anterior, posterior, retrolenticular limbs),

https://doi.org/10.1017/S0033291720002883 Published online by Cambridge University Press

cerebellar peduncles (superior, middle, inferior), cerebral peduncle, uncinate fasciculus, fornix, stria terminalis, corticospinal tract, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior fronto-occipital fasciculus, posterior thalamic radiation, tapetum, external capsule, and medial lemniscus.

Statistical plan

Initially, polygenic inheritance (h^2r) of FA of each tract was examined using the Sequential Oligogenic Linkage Analysis Routines (SOLAR; www.solar-eclipse-genetics.org) (Almasy & Blangero, 1998), which uses multipoint identity-by-descent to compute heritability (h^2) phenotypes in complex pedigrees. SOLAR uses standard maximum likelihood variance component methods (Almasy & Blangero, 1998) to obtain model-estimated heritabilities. Specifically, we compared a matrix of observed covariances among family members with matrices that predicted what this sharing should look like based on shared deoxyribonucleic acid (DNA). The maximum likelihood methods estimated what portion of the population variance in the trait would be the result of additive genetic sharing. Thus, the FA of each tract from each individual was modeled as a function of measured covariates (age, sex, site and mothers' highest education), additive genetic effects estimated from correlations among family members, and individual-specific residual environmental factors. A likelihood ratio test was used to assess statistical significance. Variance component methods generally assume that traits are normally distributed and are particularly sensitive to kurtosis in the trait distribution (Allison *et al.*, 1999). All analyses reported in this study used the multivariate *t* distribution because it is robust to kurtosis in the trait distribution (Blangero, Williams, & Almasy, 2000). The details are published (Almasy *et al.*, 2008; Gur *et al.*, 2007; Prasad *et al.*, 2010). Data from controls were used to estimate the population mean of the phenotype and covariate effects so that the multigenerational relatives in the multiplex families could be evaluated in the context of the general population. Significance of heritability was corrected for false discovery rate (FDR) <0.05 using the Benjamini-Hochberg approach because FA was correlated among these tracts, and the Bonferroni approach is not appropriate.

We conducted pleiotropy analysis to examine whether heritability of FA in multiple tracts would be secondary to the genetic correlation of FA among the examined tracts, using bivariate correlations within SOLAR. Observed genetic correlations of FA among the tracts were corrected at FDR<0.05.

Group differences in FA were examined using multivariate analysis of covariance (MANCOVA) controlling for age, sex, site and mother's education followed by Bonferroni-corrected between-subjects tests to investigate pairwise diagnostic group-effect on FA of each tract, and neurocognitive performance. Partial correlation tests were used to test the correlation of FA of heritable tracts with cognitive performance on the entire sample of patients, relatives and controls. Critical α was $p < 0.000063$ after applying Bonferroni correction for multiple tests (24 tests*33 tracts with significant heritability = 792 tests). Similar corrections were applied for correlation of neurocognitive performance with FA of tracts without significantly heritable FA (critical α $p < 0.00014$, 24 tests*15 tracts with non-significant FA heritability = 360 tests). In addition, since cognitive function is heritable and genetically correlated with schizophrenia, by regressing out mother's education there is a likelihood that the variance due to schizophrenia risk may also be regressed out. Therefore, the diagnostic group effect on FA in the above MANCOVA model was examined without including the mother's highest education.

Results

Demographic and clinical

The diagnostic groups significantly differed in age at scan ($p = 0.001$), sex ($p = 0.008$) with more male schizophrenia patients compared to relatives ($p = 0.014$) and controls ($p = 0.002$) but not between relatives and controls ($p = 0.24$), and duration of mother's education ($p < 0.001$). Education of mothers of relatives was intermediate between that of schizophrenia and controls. There were no site differences in age ($p = 0.08$) and sex ($p = 0.96$); however, mothers in the Pittsburgh cohort had 0.64 years of less education compared to mothers in the Philadelphia cohort ($p = 0.02$). Therefore, age, sex, site and mother's highest education were covaried in all analyses (Table 1).

Heritability

Total additive genetic heritability of FA was significant in all 3-classes of tracts after controlling for age, sex, mother's education and site. Of the 48 tracts (24/hemisphere), FA of 33 tracts was significantly heritable (FDR corrected $p < 0.05$). Among the association tracts, FA of bilateral stria terminalis, fornix, superior longitudinal fasciculi, left uncinate, left inferior fronto-occipital fasciculus, and right external capsule were significantly heritable ($h^2r = 0.27$–0.49). Among the commissural fibers, FA of bilateral body and splenium of the corpus callosum, bilateral superior cerebellar peduncles, left middle cerebellar peduncle and the right tapetum and genu of the corpus callosum were heritable ($h^2r = 0.38$–0.70). Projection fibers with significant heritability were: bilateral anterior, superior and posterior corona radiata, anterior and posterior limbs of the internal capsule, cerebral peduncles, and left corticospinal tract, right posterior thalamic radiation and right retrolenticular limb of the internal capsule ($h^2r = 0.28$–0.63) (Table 2).

Pleiotropy analysis revealed significant genetic correlation (Rhog) in 13 of the 33 tracts after FDR-correction. Genetic correlation was observed in all three-classes of tracts with greater genetic correlation among commissural fibers followed by association fibers (range 0.49–1.0). More tracts on the right and the corpus callosum regions showed significant genetic correlations (Fig. 1).

Diagnostic group-effect on FA

MANCOVA model consisting of FA of 33 tracts with heritable FA, age, sex, site and mother's education was significant (Wilk's $\lambda = 0.752$, $F(86\ 744) = 1.32$, $p = 0.034$). Tests of between-subjects effects showed diagnosis main effect in 7 of the 33 tracts (left posterior corona radiata, and bilateral stria terminalis, fornix and body of corpus callosum). Post-hoc pairwise Bonferroni-corrected comparisons revealed that FA was significantly decreased among patients compared to controls and relatives, but not between controls and relatives (Table 3). Effect sizes for schizophrenia-relatives and for schizophrenia-control comparisons were small to large whereas relatives-control comparison was small (Table 3). The MANCOVA model that did not include mother's education was, also, significant (Wilk's $\lambda = 0.746$, $F(86, 778) = 1.43$, $p = 0.009$) but showed diagnostic group-effect on posterior thalamic radiation, additionally (online Supplemental Table 1).

https://doi.org/10.1017/S0033291720002883 Published online by Cambridge University Press

Table 1. Demographic and clinical characteristics of the study sample

Diagnostic group	Schizophrenia			Relatives			Healthy controls			Statistics for the entire group
Site	Penn	Pitt	All	Penn	Pitt	All	Penn	Pitt	All	
Sample Size	13	10	23	100	75	175	135	105	240	
Sex (M/F)	11\2	7\3	18/5	48/52	41/34	89/86	63/72	45/60	108/132	
	$\chi^2 = 0.71$, df = 1,23, $p = 0.40$			$\chi^2 = 0.76$, df = 1,175, $p = 0.38$			$\chi^2 = 0.35$, df = 1, 240, $p = 0.56$			$\chi^2 = 9.66$, df = 2, $p = 0.008$[a]
Age (Years)	51.92 ± 13.48 Range: 25–66	57.40 ± 12.18 Range: 28–78	54.30 ± 12.94 Range:25–78	44.77 ± 16.48 Range: 65–83	40.24 ± 19.79 Range: 12–84	42.83 ± 18.06 Range: 12–84	41.36 ± 16.14 Range: 16–85	38.69 ± 16.54 Range: 16–85	40.20 ± 16.34 Range: 16–85	
	$F(1, 21) = 1.01$, $p = 0.33$			$F(1, 173) = 2.72$, $p = 0.10$			$F(1, 228) = 1.54$, $p = 0.22$			$F(2, 436) = 7.67$, $p = 0.001$[b]
Mothers Highest education	12.25 ± 2.10 Range: 8–16	12.50 ± 1.84 Range: 9–16	12.36 ± 1.94 Range: 8–16	12.34 ± 2.77 Range: 8–18	12.87 ± 3.26 Range: 3–18	12.57 ± 2.98 Range: 3–18	13.33 ± 2.34 Range: 6–18	14.06 ± 2.83 Range: 6–20	13.65 ± 2.59 Range: 6–20	
	$F(1, 21) = 0.09$, $p = 0.77$			$F(1, 173) = 1.35$, $p = 0.25$			$F(1, 228) = 4.59$, $p = 0.03$[a]			$F(2, 419) = 8.68$, $p < 0.001$[c]
Age at onset (years)	24.23 ± 13.39	23.47 ± 10.37	23.90 ± 11.91							
Duration of Illness (years)	27.69 ± 14.16	33.93 ± 12.96	30.40 ± 13.71							
GAS in the past month	54.75 ± 22.58	58.92 ± 15.46	57.33 ± 18.06							

[a]There were no site differences in sex (Pittsburgh: M/F 93/97; Philadelphia: M/F 122/126; $\chi^2 = 0.003$, $p = 0.96$). There more male schizophrenia patients compared to relatives ($\chi^2 = 6.15$, $p = 0.014$) and controls ($\chi^2 = 9.30$, $p = 0.002$) but there was no difference in sex distribution between relatives and controls ($\chi^2 = 1.39$, df = 1, $p = 0.24$).
[b]There were no site differences in age (Pittsburgh: 43.29 ± 16.31 years; Philadelphia: 40.30 ± 18.12 years; $t = 1.78$, $p = 0.08$).
[c]Mothers in the Pittsburgh cohort had 12.87 ± 2.6 years of education compared to mothers in the Philadelphia cohort, which was statistically significant (13.51 ± 3.01 years; $t = 2.32$, $p = 0.02$).

Table 2. Heritability of FA of white matter fiber tracts

Tract name	h^2r	95% CI	Uncorrected *p*-value	[a]FDR corrected *p*	Tract name	h^2r	95% CI	Uncorrected *p*-value	[a]FDR corrected *p*
Association fibers (Tracts that connect brain regions within the same hemisphere)									
L. Stria Terminalis	0.42	0.72–0.12	0.004	0.022	R. Stria Terminalis	0.47	0.79–0.16	0.002	0.020
L. Fornix Body	0.36	0.69–0.02	0.016	0.032	R. Fornix Body	0.42	0.68–0.16	0.0006	0.014
L. Superior Longitudinal Fasciculus	0.36	0.65–0.06	0.005	0.023	R. Superior Longitudinal Fasciculus	0.43	0.73–0.13	0.002	0.017
L. Inferior Fronto-Occipito Fasciculus	0.27	0.56–0.01	0.016	0.031					
L. Uncinate	0.49	0.85–0.13	0.005	0.024					
					R. External Capsule	0.39	0.71–0.07	0.007	0.027
Commissural fibers (Tracts that connect brain regions between the two hemispheres)									
L. Body of the Corpus Callosum	0.54	0.84–0.25	0.00025	0.007	R. Body of the Corpus Callosum	0.49	0.76–0.23	8.7E-05	0.006
L. Splenium of the Corpus Callosum	0.70	1.04–0.36	0.0003	0.009	R. Splenium of the Corpus Callosum	0.70	0.99–0.39	3.6E-05	0.004
L. Superior Cerebellar Peduncle	0.61	0.94–0.27	0.0003	0.010	R. Superior Cerebellar Peduncle	0.43	0.72–0.14	0.001	0.016
L. Middle Cerebellar Peduncle	0.38	0.74–0.02	0.019	0.033					
					R. Genu of the Corpus Callosum	0.44	0.77–0.10	0.005	0.025
					R. Tapetum	0.38	0.74–0.02	0.013	0.030
Projection fibers (Tracts that connect the cortical/subcortical regions with spinal cord)									
L. Superior Corona Radiata	0.62	0.86–0.37	3E-07	0.001	R. Superior Corona Radiata	0.37	0.61–0.12	0.0007	0.015
L. Posterior Corona Radiata	0.63	0.90–0.36	2.5E-06	0.002	R. Posterior Corona Radiata	0.40	0.71–0.08	0.006	0.026
L. Anterior Limb Internal Capsule	0.62	0.91–0.33	5.6E-06	0.003	R. Anterior Limb Internal Capsule	0.44	0.71–0.16	0.0004	0.013
L. Posterior Limb Internal Capsule	0.39	0.73–0.05	0.009	0.028	R. Posterior Limb Internal Capsule	0.61	0.92–0.30	4.7E-05	0.005
L. Cerebral Peduncle	0.39	0.66–0.13	0.0004	0.011	R. Cerebral Peduncle	0.40	0.70–0.09	0.003	0.021
L. Anterior Corona Radiata	0.28	0.59–0.04	0.032	0.034	R. Anterior Corona Radiata	0.57	0.88–0.25	0.0003	0.008
L. Corticospinal Tract	0.38	0.73–0.03	0.011	0.029					
					R. Posterior Thalamic Radiation	0.47	0.79–0.14	0.002	0.017
					R. Retrolenticular Limb	0.52	0.87–0.17	0.002	0.019

[a]Corrected significance at 5% False Discovery Rate using the Benjamini-Hochberg procedure. CI refers to confidence interval.

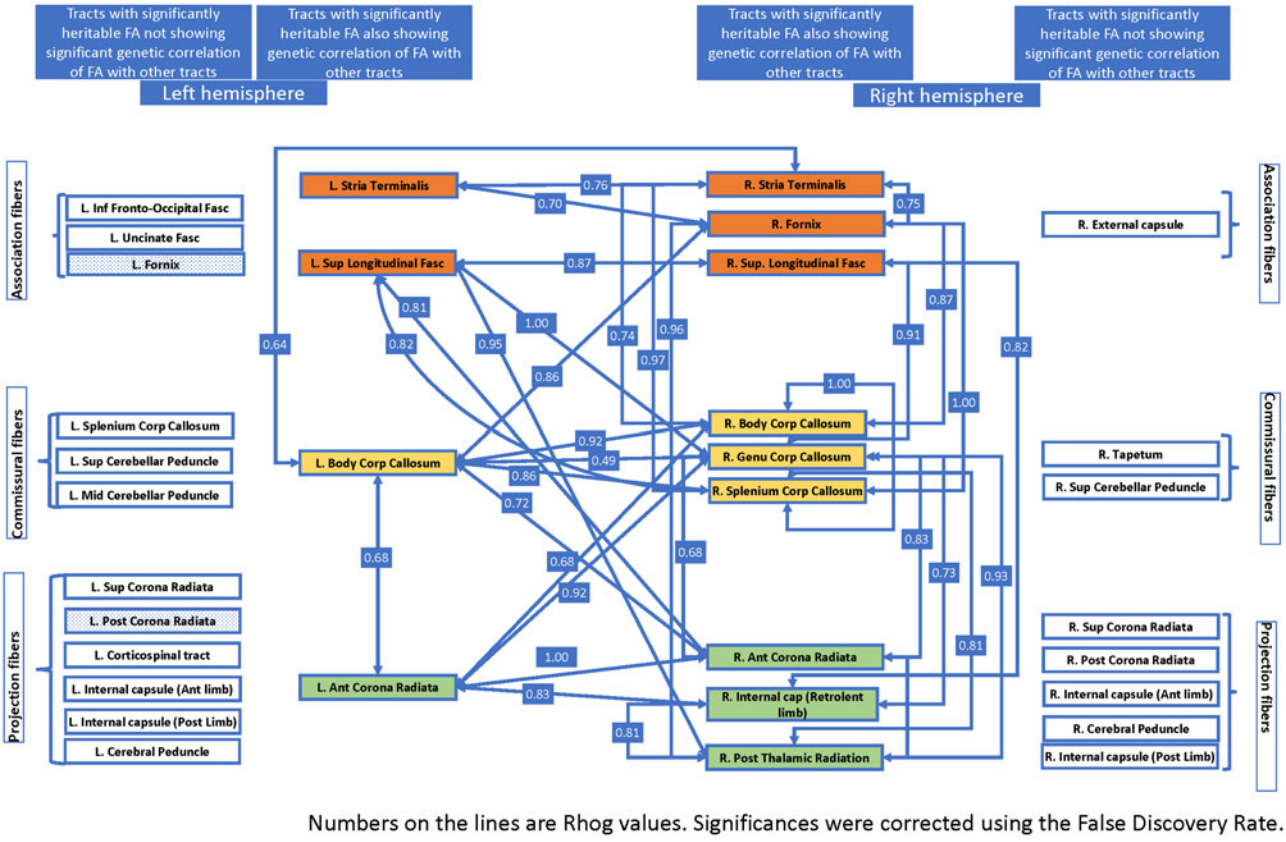

Fig. 1. Pleiotropy analysis showing genetic correlation among tracts with heritable FA.

A similar MANCOVA model for 15 tracts that did not show heritable FA, revealed no diagnosis main effect (Wilk's $\lambda = 0.92$, F = 1.07, $p = 0.37$) or between-subjects effects for any tract.

Diagnostic group-effects on neurocognitive performance

Neurocognitive impairments significantly differed among the groups controlling for age, sex, site and mother's education (MANCOVA; Wilk's $\lambda = 0.70$, F = 2.59, $p < 0.001$) on the accuracy of two tasks (letter n-back and verbal reasoning) and processing time of seven tasks [face memory (immediate and delayed), word memory (immediate and delayed), and emotion recognition, conditional elimination, line orientation, verbal reasoning and delayed visual memory]. Bonferroni-corrected post-hoc tests showed more severe impairments in relatives compared to controls on processing times of immediate face memory, emotion recognition, conditional elimination and verbal reasoning tests. Specificity on PCPT showed differences between relatives and controls, but not among patients and relatives or patients and controls. Schizophrenia patients showed more severe impairments on all tasks except immediate face memory, PCPT specificity and processing times of verbal reasoning and delayed visual learning compared to relatives and controls (Table 3).

Correlation of neurocognitive performance with FA of tracts showing significant heritability

Significant correlations were observed mainly for the processing times for executive functions (PCET), emotion recognition, spatial processing, and delayed face memory after controlling for age, sex, site, mother's education and diagnostic status. The processing times correlated negatively while accuracy correlated positively with FA.

Accuracy of delayed face memory positively correlated with left posterior thalamic radiation FA but not of other domains. Processing time of emotion recognition correlated negatively with the left stria terminalis, right inferior fronto-occipital fasciculus and left anterior corona radiata FA. Correlation of the processing time for executive functions with FA was more widespread across commissural and projection fibers. Delayed face memory processing time-correlated negatively with bilateral body of the corpus callosum (Table 4).

All correlations were of small effect (partial $r = 0.24$–0.28). Commissural and projection fibers with significantly heritable FA showed the highest number of correlations with more cognitive processes, especially with the processing times of executive function and emotion recognition.

Only two of the 15 tracts that did not show significant FA heritability were correlated with cognitive performance, namely the left genu of the corpus callosum ($h^2r = 0.31$) and left tapetum ($h^2r = 0.22$).

Discussion

Our study shows significant heritability of FA of all three-classes of WM pathways totaling 68% of examined tracts suggesting that FA is under strong genetic control. Genetic correlation of FA was observed in ≈40% of tracts with heritable FA suggesting

https://doi.org/10.1017/S0033291720002883 Published online by Cambridge University Press

Table 3. Diagnostic group main effect on FA of white matter tracts and neurocognitive outcome measures

	Schizophrenia (SZ)	Relatives	Healthy controls (HC)	Diagnostic group		SZ *v.* relatives		SZ *v.* HC		HC *v.* relatives	
	FA (Mean ± S.D.)	FA (Mean ± S.D.)	FA (Mean ± S.D.)	*F* (2, 413)	*P*	*P*	Effect size (Cohen's *d*)	*p*	Effect size (Cohen's *d*)	*P*	Effect size (Cohen's *d*)
L. Post Corona Radiata	0.45 ± 0.033	0.44 ± 0.032	0.44 ± 0.028	3.26	**0.039**	0.08	**0.31**	**0.03**	**0.33**	1.00	0
L. Stria Terminalis	0.40 ± 0.033	0.42 ± 0.032	0.42 ± 0.028	4.32	**0.014**	**0.01**	**0.62**	**0.05**	**0.65**	0.83	0
R. Stria Terminalis	0.37 ± 0.035	0.40 ± 0.032	0.40 ± 0.031	3.66	**0.026**	**0.04**	**0.89**	**0.02**	**0.91**	1.00	0
L. Fornix	0.27 ± 0.111	0.39 ± 0.114	0.40 ± 0.112	4.94	**0.008**	**0.007**	**1.07**	**0.03**	**1.16**	0.77	0.09
R. Fornix	0.32 ± 0.097	0.42 ± 0.103	0.42 ± 0.088	5.28	**0.005**	**0.005**	**1.00**	**0.02**	**1.08**	1.00	0
L. Body of Corpus callosum	0.51 ± 0.082	0.56 ± 0.048	0.56 ± 0.041	9.34	**<0.001**	**<0.001**	**0.74**	**0.001**	**0.77**	0.39	0
R. Body of Corpus Callosum	0.50 ± 0.081	0.55 ± 0.048	0.55 ± 0.042	7.20	**0.001**	**0.001**	**0.75**	**0.01**	**0.77**	0.27	0
	Outcome measure[a] (Mean ± S.D.)	Outcome measure[a] (Mean ± S.D.)	Outcome measure[a] (Mean ± S.D.)								
Face Memory (Processing time in ms)	2313.23 ± 482.49	2135.55 ± 643.74	1914.46 ± 578.95	4.67	**0.01**	1.0	0.31	0.54	0.75	**0.01**	0.36
Delayed Face Memory (Processing time in ms)	2576.23 ± 1316.49	1877.98 ± 653.24	1733.77 ± 503.13	8.39	**<0.001**	**0.004**	0.67	**<0.001**	0.85	0.21	0.25
Word Memory (Processing time in ms)	2538.89 ± 1219.97	1718.23 ± 432.86	1567.29 ± 504.25	16.06	**<0.001**	**<0.001**	0.90	**<0.001**	1.04	0.11	0.32
Delayed Word Memory (Processing time in ms)	2278.50 ± 1257.12	1650.89 ± 424.74	1519.76 ± 435.40	10.79	**<0.001**	**0.001**	0.67	**<0.001**	0.81	0.10	0.30
Emotion Recognition (Processing time in ms)	3299.00 ± 1018.42	2432.87 ± 658.38	2225.22 ± 565.67	13.65	**<0.001**	**<0.001**	1.01	**<0.001**	1.30	**0.02**	0.34
Letter N-Back Test (Accuracy)	24.00 ± 3.61	27.56 ± 2.62	27.63 ± 3.05	7.34	**0.001**	**0.001**	−1.13	**0.001**	−1.09	1.0	−0.02
Penn Continuous Performance Test (Specificity)	0.92 ± 0.08	0.94 ± 0.07	0.95 ± 0.05	4.83	**0.009**	0.44	−0.27	0.055	−0.45	**0.05**	−0.16
Penn Conditional Elimination Test (Perseverative errors)	22.92 ± 11.81	11.77 ± 10.90	10.09 ± 9.36	6.25	**0.002**	**0.005**	0.98	**0.001**	1.20	1.0	0.17
Penn Conditional Elimination Test (Processing time in ms)	3868.30 ± 1392.41	2431.55 ± 1491.12	2072.64 ± 985.52	10.01	**<0.001**	**0.005**	1.00	**<0.001**	1.49	**0.04**	0.28
Penn Line Orientation Test (Processing time in ms)	15962.08 ± 9577.37	10270.09 ± 3515.72	9855.08 ± 3213.90	12.14	**<0.001**	**<0.001**	0.79	**<0.001**	0.85	1.0	0.12
Penn Verbal Reasoning Test (Accuracy)	3.38 ± 2.14	4.99 ± 1.80	5.37 ± 1.69	8.12	**<0.001**	**0.002**	−0.81	**<0.001**	−1.03	0.56	−0.22
Penn Verbal Reasoning Test (Processing time in ms)	9750.42 ± 2938.24	8778.60 ± 3604.88	7418.05 ± 2563.16	8.72	**<0.001**	1.00	0.30	0.14	0.85	**<0.001**	0.44
Del Vis Obj Learning Test (Processing time in ms)	1984.35 ± 607.49	1612.35 ± 541.65	1481.37 ± 394.77	4.70	**0.01**	0.18	0.65	**0.025**	0.98	0.15	0.28

p values in bold font denote Bonferroni-corrected statistical significance.

[a]Indicates that the outcome measures for cognitive domains in the respective cells. Briefly, **processing time (in ms)** was significant for immediate and delayed face memory, immediate and delayed word memory, emotion recognition, Penn Conditional Elimination Test, Penn Line Orientation Test, Penn Verbal Reasoning Test and delayed Visual Object Learning Test. **Accuracy** was significant for the Letter N-back Test and Penn Verbal Reasoning Test. **Specificity** was used for the Penn Continuous Performance Test and **number of Perseverative Errors** was significant for the Penn Conditional Elimination Test.

Table 4. Correlation of FA of white matter tracts with neurocognitive performance controlling for age, sex, site and mother's highest education

Fiber type	Fiber tracts	Statistic & Bonferroni *p*	D Face Mem Resp Time	ER Resp Time	PCET Resp Time	PLOT Resp Time	D Face Mem Accuracy
Association fibers	L. Stria terminalis	Partial *r*	–	−0.247	–	–	–
		Bonferroni *p*	–	0.022	–	–	–
	R. Inferior Fronto-occipital fasciculus[a]	Partial *r*	–	−0.246	–	–	–
		Bonferroni *p*	–	0.036	–	–	–
Commissural fibers	L. Body of corpus callosum	Partial *r*	−0.28	–	–	–	–
		Bonferroni *p*	0.002	–	–	–	–
	R. Body of corpus callosum	Partial *r*	−0.262	–	−0.245	−0.240	–
		Bonferroni *p*	0.007	–	0.026	0.039	–
	R. Splenium of Corpus Callosum	Partial *r*	–	–	−0.261	–	–
		Bonferroni *p*	–	–	0.008	–	–
Projection fibers	L. Anterior Corona Radiata	Partial *r*	–	−0.262	−0.273	–	–
		Bonferroni *p*	–	0.007	0.003	–	–
	R. Anterior Corona Radiata	Partial *r*	–	–	−0.248	–	–
		Bonferroni *p*	–	–	0.021	–	–
	R Posterior Thalamic Radiation	Partial *r*	–	–	−0.257	–	–
		Bonferroni p	–	–	0.011	–	–
	R. Retrolenticular limb Internal Capsule	Partial *r*	–	–	−0.252	–	–
		Bonferroni *p*	–	–	0.015	–	–
	L. Posterior Thalamic Radiation[a]	Partial *r*	–	–	–	–	0.256
		Bonferroni *p*	–	–	–	–	0.016

[a]Heritability of these tracts did not survive the Bonferroni correction for multiple comparisons.

that similar sets of genes may contribute to FA heritability. Diagnostic-group main effect on FA was observed only in tracts with significantly heritable FA but not in tracts without heritable FA. Only 1/5th of tracts with heritable FA showed diagnostic-group effect suggesting that heritability of FA alone may not be sufficient for FA differences across diagnostic groups. Further, observed neurocognitive impairments among relatives and patients correlated mainly with tracts with heritable FA but not with tracts without heritable FA. These findings suggest that heritability is an important determinant of white matter impairments and their impact on neurocognitive performance among the diagnostic groups.

Heritability of FA of several tracts among relatives of multiplex schizophrenia families and correlation of FA with cognitive performance is consistent with prior studies on psychiatrically healthy twins showing higher heritability of many tracts reported in this study (Bertisch *et al.* 2010; Kochunov *et al.* 2015, 2016; Lee *et al.* 2015; Shen *et al.* 2016). Except for one study that examined a smaller sample of relatives of multiplex schizophrenia families (Bertisch *et al.*, 2010), others have examined twins, old order Amish and elderly populations. We previously reported smaller corpus callosum among familial high-risk subjects suggesting reduced inter-hemispheric axonal fibers (Francis *et al.*, 2011) that may partly contribute to reduced FA noted in this study examining whole-tract FA heritability that may better represent the integrity of entire pathways and its correlation with cognitive performance related to schizophrenia risk in a larger sample of multigenerational relatives of multiplex schizophrenia families.

Heritability varied from 0.28 to 0.70, suggesting that the FA of different tracts are variably impacted by environmental factors. Further, heritable FA was observed primarily in the white matter within the limbic circuitry, corpus callosum, long association fibers and projection fibers. Our prior study on the same sample noted heritability of volume and shape of the subcortical and limbic regions (Roalf *et al.*, 2015). Some WM tracts with heritable FA observed in this study connect these regions. Heritability of multiple projection fibers that are conventionally called 'motor fibers' merits discussion. Reduced FA in corticospinal tract in schizophrenia (Mamah, Ji, Rutlin, & Shimony, 2019), and association of FA of projection fibers (e.g. corona radiata, internal capsule) with positive symptoms (Caprihan *et al.*, 2015), social cognition (Fujino *et al.*, 2014) and cognitive performance (Spalletta, Piras, Piras, Caltagirone, & Orfei, 2014) suggests that classifying them as 'motor fibers' is too narrow, and should be included in investigating 'disconnection' in schizophrenia. The intricate relationship between motor system and neurocognition is also proposed (Abboud, Noronha, & Diwadkar, 2017).

Pleiotropy analysis showed that ≈40% of the tracts with heritable FA were genetically correlated. Among the tracts that showed significant genetic correlations of FA, corpus callosum was genetically correlated with FA of more tracts. Five of the seven tracts that showed genetic correlation also showed diagnosis main effects suggesting a common set of genes may be associated with schizophrenia risk and connectional integrity. This is consistent with findings from discordant twin pairs showing association of WM volume with genetic risk while gray matter was

https://doi.org/10.1017/S0033291720002883 Published online by Cambridge University Press

related to disease-related factors (Hulshoff Pol *et al*., 2006) and environmental factors (van Haren *et al*., 2012). This is consistent with our observation of phenotypic correlation of FA of 2/3rd of tracts without genetic correlation. Thus, our data provide a systematic prediction to group sets of genes likely to impact these traits related to schizophrenia risk.

Differences in FA among schizophrenia and their relatives compared to controls have been consistently reported (Ellison-Wright & Bullmore, 2009). Our study shows that the heritability of FA of WM tracts contributed to such differences, especially the tracts with heritable FA that are more susceptible to diagnosis effects suggesting that the tracts with heritable FA more relevant for genetic risk for the illness. However, not all tracts with heritable FA showed diagnostic group-effect suggesting that the genetic control of FA may be necessary but not sufficient for diagnosis effects and importance of the contribution of disease-related factors such as illness chronicity, medications, comorbid illnesses and environmental factors. Further studies on larger samples that include specific environmental factors are necessary to address this question.

Processing times of cognitive tasks more often showed diagnosis effects and correlated with FA of tracts with heritability compared to accuracy. A prior publication on this MGI sample reported significant heritability of speed of performance on abstraction and mental flexibility (PCET), attention (PCPT), face memory, spatial processing, and sensorimotor speed, and accuracy of verbal memory, face memory, spatial memory, spatial processing and emotion recognition tasks (Gur *et al*., 2007) suggesting that the genetic influence may differentially affect performance speed and accuracy. In this sample subset, we did not observe significant heritability of these domains possibly because of reduced power (online Supplemental Table 3). Other studies reported significant heritability of cognitive performance among healthy (Tuulio-Henriksson *et al*., 2002) and schizophrenia (Alfimova & Uvarova, 2003; Gur *et al*., 2007) subjects. Previous meta-analyses showed the impaired speed of processing to be a central feature of cognitive deficits in schizophrenia (Dickinson, Ramsey, & Gold, 2007; Henry & Crawford, 2005). Cognitive remediation treatments show improvements in processing speed with the largest effect sizes (Hogarty *et al*., 2004) suggesting that performance speed may be an interventional target. Thus, genetic influence on anatomical connections that regulate cognitive performance may significantly contribute to processing speed although other factors such as differences in IQ between patients and controls and antipsychotic medications may have a role (Knowles, David, & Reichenberg, 2010).

About 1/4th of tracts with heritable FA correlated with cognitive performance after multiple test corrections. Prior twin studies, also, report correlations of tracts with heritable FA with full-scale IQ, performance IQ and object assembly, specifically with FA of association and projection fibers (Chiang *et al*., 2009). We examined individual cognitive domains providing more refined correlation patterns. We reported association of radial diffusivity of forceps minor (a component of tapetum) with sustained attention among first-degree relatives of schizophrenia (Prasad, Upton, Schirda, Nimgaonkar, & Keshavan, 2015) but not decreased FA and increased radial diffusivity of the superior longitudinal fasciculus. This study with greater power supports our previous observation that the FA of superior longitudinal fasciculi, although heritable, does not correlate with cognitive performance. Further, FA of only three of the seven tracts showing diagnostic-group main effect was correlated with cognitive performance. Similarly, FA of three of the 10 tracts that correlated with cognitive performance also showed diagnostic group main effect; of these 10 tracts, FA of two tracts was not significantly heritable. These observations suggest that different sets of genes may regulate associations with disease risk and cognitive performance.

Diffusion measures of WM fibers are proposed as potential endophenotypes (Keshavan, Prasad, & Pearlson, 2007; Voineskos, 2015). Our study showed heritability of FA among relatives of multiplex schizophrenia, and diagnostic-group effect on FA between schizophrenia patients and relatives but not between controls and relatives. Thus, FA did not meet all proposed criteria for endophenotypes (Gottesman & Gould, 2003; Prasad & Keshavan, 2008). The degree of heritability of FA in this study was similar to the heritability of neurocognitive profile on the same sample (Gur *et al*., 2007) and healthy twins (Lee *et al*., 2015; Shen *et al*., 2016) but were lower than in other healthy twin studies (Chiang *et al*., 2009; Kochunov *et al*., 2015) and large family pedigree samples (Kochunov *et al*., 2016). Estimating heritability within multiplex multigenerational samples minimizes the effect of the family environment as could happen in nuclear family studies, because the degree of sharing of environmental risk may not follow a Mendelian pattern. We did not observe differences in FA between relatives and controls possibly because of the smaller sample size in our study and also because multigenerational sample consists of relatives with different degrees of relationship to the proband. Further, the degree of relationship varies depending on which affected individual is indexed as proband in multiplex families. Lower FA has been reported in unaffected first-degree relatives compared to controls more consistently (Prasad *et al*., 2015; Skudlarski *et al*., 2013) while some have reported higher FA in relatives (Boos *et al*., 2013). Replication of these findings may contribute to building 'extended endophenotypes' (Hulshoff Pol *et al*., 2004; Hulshoff Pol *et al*., 2006; Prasad & Keshavan, 2008; van Haren *et al*., 2012).

Strengths of our study are that the number of relatives is large compared with many prior studies. We have controlled for age, sex, mother's education and site that could influence the findings, and corrected for multiple testing to minimize false-positive results. Unlike other studies, we used whole tract diffusivity compared to voxel-wise differences. Some limitations include the examination of FA as the main metric instead of multiple diffusion metrics that could provide a better estimate of WM integrity (Hasan, 2006). Since this study was conducted on multiplex schizophrenia families, the generalizability of findings to sporadic schizophrenia may be limited. The number of schizophrenia subjects was smaller because enrollment of multigenerational relatives was predicated on multiplex schizophrenia subjects. A smaller sample of schizophrenia could have biased the results; however, relatively larger samples of relatives and controls were used in testing our main goal to find the differences between relatives and controls. Further, a larger sample would have improved the power of the sample to estimate the heritability of FA and FA differences between controls and relatives. Future studies should examine larger samples of multiplex family data using orthogonal diffusion measures (e.g. FA and RD) to better elucidate the association of heritability with impaired white matter integrity.

In summary, our study shows that heritability of FA is observed in all three-classes of WM tracts and not restricted to those proposed to be involved in cognitive processing. Further, our observations suggest that a similar set of genes may contribute to the heritability of multiple tracts and, of neurocognitive

https://doi.org/10.1017/S0033291720002883 Published online by Cambridge University Press

performance differences. Heritability estimates of our study compare well with twin studies suggesting that the estimates are not inflated. Although the diagnostic-group effect on FA was observed only in tracts with significantly heritable FA, only 20% of tracts with heritable FA showed diagnostic-group effect suggesting that heritability of FA alone may not be sufficient to contribute to diagnostic-group differences in FA. Thus, heritability is an important determinant of WM impairments among the diagnostic groups and their impact on neurocognitive performance. Further studies are needed to elucidate genetic variants and related gene expression patterns associated with these observations to understand the molecular genetic basis of pathophysiology of schizophrenia and risk for the illness. Taken together, anatomical connectional integrity, and regional volumes and shape are heritable and impact underlying cognitive processing.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002883

Acknowledgements. This work was funded through grants from the NIMH R01MH63480, R01MH105634 and 07R-1712 of the Stanley Medical Research Institute (VLN), R01MH042191 (REG), and R01MH061622 (LA), and R01MH112584 and R01MH115026 (KMP). Authors thank Ms. Sue Clifton, Ms. Joette Zarotney, Ms. Jane Sharpless and Mr. Robert Witalec for subject characterization, and Ms. Rachel Bender and Dr Ayesha Khan for image processing.

Disclosures. None of the authors has any conflict of interest applicable to this manuscript.

References

Abboud, R., Noronha, C., & Diwadkar, V. A. (2017). Motor system dysfunction in the schizophrenia diathesis: Neural systems to neurotransmitters. *European psychiatry: the Journal of the Association of European Psychiatrists*, *44*, 125–133. doi: 10.1016/j.eurpsy.2017.04.004.

Alfimova, M., & Uvarova, L. (2003). Cognitive peculiarities in relatives of schizophrenic and schizoaffective patients: Heritability and resting EEG-correlates. *International Journal of Psychophysiology*, *49*(3), 201–216. doi: 10.1016/s0167-8760(03)00133-8.

Allison, D. B., Neale, M. C., Zannolli, R., Schork, N. J., Amos, C. I., & Blangero, J. (1999). Testing the robustness of the likelihood-ratio test in a variance-component quantitative-trait loci-mapping procedure. *American Journal of Human Genetics*, *65*(2), 531–544. doi: 10.1086/302487.

Alloza, C., Cox, S. R., Duff, B., Semple, S. I., Bastin, M. E., Whalley, H. C., & Lawrie, S. M. (2016). Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia. *Psychiatry Research: Neuroimaging*, *254*, 26–33. doi: 10.1016/j.pscychresns.2016.05.008.

Almasy, L., & Blangero, J. (1998). Multipoint quantitative-trait linkage analysis in general pedigrees. *American Journal of Human Genetics*, *62*(5), 1198–1211.

Almasy, L., Gur, R. C., Haack, K., Cole, S. A., Calkins, M. E., Peralta, J. M., … Gur, R. E. (2008). A genome screen for quantitative trait loci influencing schizophrenia and neurocognitive phenotypes. *American Journal of Psychiatry*, *165*(9), 1185–1192. doi: 10.1176/appi.ajp.2008.07121869.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in biomedicine*, *15*(7–8), 435–455. doi:10.1002/nbm.782.

Beaulieu, C., & Allen, P. S. (1994). Determinants of anisotropic water diffusion in nerves. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *31*(4), 394–400. doi: 10.1002/mrm.1910310408.

Beg, M. F., Miller, M. I., Trouve, A., & Younes, L. (2005). Computing large deformation metric mappings via geodesic flows of diffeomorphisms. *International Journal of Computer Vision*, *61*(2), 139–157.

Bertisch, H., Li, D., Hoptman, M. J., & Delisi, L. E. (2010). Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, *153B*(4), 885–894. doi: 10.1002/ajmg.b.31054.

Blangero, J., Williams, J. T., & Almasy, L. (2000). Robust LOD scores for variance component-based linkage analysis. *Genetic Epidemiology*, *19*(Suppl 1), S8–14. doi: 10.1002/1098-2272(2000)19:1+<::AID-GEPI2>3.0.CO;2-Y.

Bohlken, M. M., Brouwer, R. M., Mandl, R. C., Kahn, R. S., & Hulshoff Pol, H. E. (2016). Genetic variation in schizophrenia liability is shared with intellectual ability and brain structure. *Schizophrenia Bulletin*, *42*(5), 1167–1175. doi: 10.1093/schbul/sbw034.

Bohlken, M. M., Brouwer, R. M., Mandl, R. C., Van den Heuvel, M. P., Hedman, A. M., De Hert, M., … Hulshoff Pol, H. E. (2016). Structural brain connectivity as a genetic marker for schizophrenia. *JAMA Psychiatry*, *73*(1), 11–19. doi: 10.1001/jamapsychiatry.2015.1925.

Boos, H. B., Mandl, R. C., van Haren, N. E., Cahn, W., van Baal, G. C., Kahn, R. S., & Hulshoff Pol, H. E. (2013). Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings. *European Neuropharmacology*, *23*(4), 295–304. doi: 10.1016/j.euroneuro.2012.05.015.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S. J., … Pantelis, C. (2011). Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research*, *127*(1–3), 46–57. doi: 10.1016/j.schres.2010.12.020.

Caprihan, A., Jones, T., Chen, H. J., Lemke, N., Abbott, C., Qualls, C., … Bustillo, J. R. (2015). The paradoxical relationship between white matter, psychopathology and cognition in schizophrenia: A diffusion tensor and proton spectroscopic imaging study. *Neuropsychopharmacology*, *40*(9), 2248–2257. doi: 10.1038/npp.2015.72.

Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, *44*(8), 1105–1132. doi: 10.1016/j.cortex.2008.05.004.

Chiang, M. C., Barysheva, M., Shattuck, D. W., Lee, A. D., Madsen, S. K., Avedissian, C., … Thompson, P. M. (2009). Genetics of brain fiber architecture and intellectual performance. *The Journal of neuroscience: the Official Journal of the Society for Neuroscience*, *29*(7), 2212–2224. doi: 10.1523/JNEUROSCI.4184-08.2009.

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives Of General Psychiatry*, *64*(5), 532–542. doi: 10.1001/archpsyc.64.5.532.

Ellison-Wright, I., & Bullmore, E. (2009). Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research*, *108*(1–3), 3–10. doi: 10.1016/j.schres.2008.11.021.

Francis, A. N., Bhojraj, T. S., Prasad, K. M., Kulkarni, S., Montrose, D. M., Eack, S. M., & Keshavan, M. S. (2011). Abnormalities of the corpus callosum in non-psychotic high-risk offspring of schizophrenia patients. *Psychiatry Research*, *191*(1), 9–15. doi: 10.1016/j.pscychresns.2010.09.007.

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience*, *3*(2), 89–97. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7583624.

Fujino, J., Takahashi, H., Miyata, J., Sugihara, G., Kubota, M., Sasamoto, A., … Murai, T. (2014). Impaired empathic abilities and reduced white matter integrity in schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry*, *48*, 117–123. doi: 10.1016/j.pnpbp.2013.09.018.

Gottesman, I. I. (1991). *Schizophrenia genesis: The origins of madness*. New York: W. H. Freeman.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*(4), 636–645. doi: 10.1176/appi.ajp.160.4.636.

Gur, R. E., Nimgaonkar, V. L., Almasy, L., Calkins, M. E., Ragland, D., Pogue-Geile, M. F., … Gur, R. C. (2007). Neurocogntive endophenotypes in a multiplex multigenerational family study of schizophrenia. *American Journal of Psychiatry*, *164*(5), 813–819.

Hamoda, H. M., Makhlouf, A. T., Fitzsimmons, J., Rathi, Y., Makris, N., Mesholam-Gately, R. I., … Shenton, M. E. (2019). Abnormalities in thalamo-cortical connections in patients with first-episode schizophrenia: A two-tensor tractography study. *Brain Imaging Behavior*, *13*(2), 472–481. doi: 10.1007/s11682-018-9862-8.

Hasan, K. M. (2006). Diffusion tensor eigenvalues or both mean diffusivity and fractional anisotropy are required in quantitative clinical diffusion

tensor MR reports: Fractional anisotropy alone is not sufficient. *Radiology*, *239*(2), 611–612; author reply 612–613. doi:10.1148/radiol.2392051172.

Henry, J. D., & Crawford, J. R. (2005). A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. *Cognitive Neuropsychiatry*, *10*(1), 1–33. doi: 10.1080/13546800344000309.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., … Glenthoj, B. (2018). Heritability of schizophrenia and schizophrenia Spectrum based on the nationwide danish twin register. *Biological Psychiatry*, *83*(6), 492–498. doi: 10.1016/j.biopsych.2017.08.017.

Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., … Zoretich, R. (2004). Cognitive enhancement therapy for schizophrenia: Effects of a 2-year randomized trial on cognition and behavior. *Archives Of General Psychiatry*, *61*(9), 866–876. doi: 10.1001/archpsyc.61.9.866.

Hubbard, L., Tansey, K. E., Rai, D., Jones, P., Ripke, S., Chambert, K. D., … Zammit, S. (2016). Evidence of common genetic overlap between schizophrenia and cognition. *Schizophrenia Bulletin*, *42*(3), 832–842. doi: 10.1093/schbul/sbv168.

Hulshoff Pol, H. E., Brans, R. G., van Haren, N. E., Schnack, H. G., Langen, M., Baare, W. F., … Kahn, R. S. (2004). Gray and white matter volume abnormalities in monozygotic and same-gender dizygotic twins discordant for schizophrenia. *Biological Psychiatry*, *55*(2), 126–130. doi: 10.1016/s0006-3223(03)00728-5.

Hulshoff Pol, H. E., Schnack, H. G., Mandl, R. C., Brans, R. G., van Haren, N. E., Baare, W. F., … Kahn, R. S. (2006). Gray and white matter density changes in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry. *Neuroimage*, *31*(2), 482–488. doi: 10.1016/j.neuroimage.2005.12.056.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, *62*(2), 782–790. doi: 10.1016/j.neuroimage.2011.09.015.

Kanaan, R. A., Picchioni, M. M., McDonald, C., Shergill, S. S., & McGuire, P. K. (2017). White matter deficits in schizophrenia are global and don't progress with age. *Australia New Zealand Journal of Psychiatry*, *51*(10), 1020–1031. doi: 10.1177/0004867417700729.

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., … Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA schizophrenia DTI working group. *Molecular Psychiatry*, *23*(5), 1261–1269. doi: 10.1038/mp.2017.170.

Keshavan, M. S., Prasad, K. M., & Pearlson, G. (2007). Are brain structural abnormalities useful as endophenotypes in schizophrenia? *International Review of Psychiatry*, *19*(4), 397–406, doi:780490359 [pii]; 10.1080/09540260701486233.

Knochel, C., Schmied, C., Linden, D. E., Stablein, M., Prvulovic, D., de, A. d. C. L., … Oertel-Knochel, V. (2016). White matter abnormalities in the fornix are linked to cognitive performance in SZ but not in BD disorder: An exploratory analysis with DTI deterministic tractography. *Journal of Affective Disorders*, *201*, 64–78. doi: 10.1016/j.jad.2016.03.015.

Knowles, E. E., David, A. S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: Reexamining the evidence. *American Journal of Psychiatry*, *167*(7), 828–835. doi: 10.1176/appi.ajp.2010.09070937.

Kochunov, P., Fu, M., Nugent, K., Wright, S. N., Du, X., Muellerklein, F., … Hong, L. E. (2016). Heritability of complex white matter diffusion traits assessed in a population isolate. *Human Brain Mapping*, *37*(2), 525–535. doi: 10.1002/hbm.23047.

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. doi: 10.1016/j.neuroimage.2015.02.050.

Kubicki, M., Park, H., Westin, C. F., Nestor, P. G., Mulkern, R. V., Maier, S. E., … Shenton, M. E. (2005). DTI And MTR abnormalities in schizophrenia: Analysis of white matter integrity. *Neuroimage*, *26*(4), 1109–1118. doi: 10.1016/j.neuroimage.2005.03.026.

Lee, S. J., Steiner, R. J., Luo, S., Neale, M. C., Styner, M., Zhu, H., & Gilmore, J. H. (2015). Quantitative tract-based white matter heritability in twin neonates. *Neuroimage*, *111*, 123–135. doi: 10.1016/j.neuroimage.2015.02.021.

Mamah, D., Ji, A., Rutlin, J., & Shimony, J. S. (2019). White matter integrity in schizophrenia and bipolar disorder: Tract- and voxel-based analyses of diffusion data from the connectom scanner. *NeuroImage: Clinical*, *21*, 101649. doi: 10.1016/j.nicl.2018.101649.

Miller, M. I., Priebe, C. E., Qiu, A., Fischl, B., Kolasny, A., Brown, T., … Morphometry, B. (2009). Collaborative computational anatomy: An MRI morphometry study of the human brain via diffeomorphic metric mapping. *Human Brain Mapping*, *30*(7), 2132–2141. doi: 10.1002/hbm.20655.

Nurnberger, J. I., Jr., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., & …Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH genetics initiative. *Archives Of General Psychiatry*, *51*(11), 849–859; discussion 863–844. doi:10.1001/archpsyc.1994.03950110009002.

Ohtani, T., Nestor, P. G., Bouix, S., Newell, D., Melonakos, E. D., McCarley, R. W., … Kubicki, M. (2017). Exploring the neural substrates of attentional control and human intelligence: Diffusion tensor imaging of prefrontal white matter tractography in healthy cognition. *Neuroscience*, *341*, 52–60. doi: 10.1016/j.neuroscience.2016.11.002.

Prasad, K. M., Almasy, L., Gur, R. C., Gur, R. E., Pogue-Geile, M., Chowdari, K. V., … Nimgaonkar, V. L. (2010). RGS4 Polymorphisms associated with variability of cognitive performance in a family-based schizophrenia sample. *Schizophrenia Bulletin*, *36*(5), 983–990. doi: 10.1093/schbul/sbp002.

Prasad, K. M., & Keshavan, M. S. (2008). Structural cerebral variations as useful endophenotypes in schizophrenia: Do they help construct "extended endophenotypes"? *Schizophrenia Bulletin*, *34*(4), 774–790. doi: 10.1093/schbul/sbn017.

Prasad, K. M., Upton, C. H., Schirda, C. S., Nimgaonkar, V. L., & Keshavan, M. S. (2015). White matter diffusivity and microarchitecture among schizophrenia subjects and first-degree relatives. *Schizophrenia Research*, *161*(1), 70–75. doi: 10.1016/j.schres.2014.09.045.

Roalf, D. R., Gur, R. C., Almasy, L., Richard, J., Gallagher, R. S., Prasad, K., … Gur, R. E. (2013). Neurocognitive performance stability in a multiplex multigenerational study of schizophrenia. *Schizophrenia Bulletin*, *39*(5), 1008–1017. doi: 10.1093/schbul/sbs078.

Roalf, D. R., Ruparel, K., Gur, R. E., Bilker, W., Gerraty, R., Elliott, M. A., … Gur, R. C. (2014). Neuroimaging predictors of cognitive performance across a standardized neurocognitive battery. *Neuropsychology*, *28*(2), 161–176. doi: 10.1037/neu0000011.

Roalf, D. R., Ruparel, K., Verma, R., Elliott, M. A., Gur, R. E., & Gur, R. C. (2013). White matter organization and neurocognitive performance variability in schizophrenia. *Schizophrenia Research*, *143*(1), 172–178. doi: 10.1016/j.schres.2012.10.014.

Roalf, D. R., Vandekar, S. N., Almasy, L., Ruparel, K., Satterthwaite, T. D., Elliott, M. A., … Gur, R. E. (2015). Heritability of subcortical and limbic brain volume and shape in multiplex-multigenerational families with schizophrenia. *Biological Psychiatry*, *77*(2), 137–146. doi: 10.1016/j.biopsych.2014.05.009.

Schmahmann, J. D., & Pandya, D. N. (2007). Cerebral white matter--historical evolution of facts and notions concerning the organization of the fiber pathways of the brain. *Journal of the History of the Neurosciences*, *16*(3), 237–267. doi: 10.1080/09647040500495896.

Shen, K. K., Dore, V., Rose, S., Fripp, J., McMahon, K. L., de Zubicaray, G. I., … Salvado, O. (2016). Heritability and genetic correlation between the cerebral cortex and associated white matter connections. *Human Brain Mapping*, *37*(6), 2331–2347. doi: 10.1002/hbm.23177.

Skudlarski, P., Schretlen, D. J., Thaker, G. K., Stevens, M. C., Keshavan, M. S., Sweeney, J. A., … Pearlson, G. D. (2013). Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. *American Journal of Psychiatry*, *170*(8), 886–898. doi: 10.1176/appi.ajp.2013.12111448.

Spalletta, G., Piras, F., Piras, F., Caltagirone, C., & Orfei, M. D. (2014). The structural neuroanatomy of metacognitive insight in schizophrenia and its psychopathological and neuropsychological correlates. *Human Brain Mapping*, *35*(9), 4729–4740. doi: 10.1002/hbm.22507.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives Of*

General Psychiatry, *60*(12), 1187–1192. doi: 10.1001/archpsyc.60.12.1187, 60/12/1187 [pii].

Tuulio-Henriksson, A., Haukka, J., Partonen, T., Varilo, T., Paunio, T., Ekelund, J., … Lonnqvist, J. (2002). Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, *114*(5), 483–490. doi: 10.1002/ajmg.10480.

van Haren, N. E., Rijsdijk, F., Schnack, H. G., Picchioni, M. M., Toulopoulou, T., Weisbrod, M., … Kahn, R. S. (2012). The genetic and environmental determinants of the association between brain abnormalities and schizophrenia: The schizophrenia twins and relatives consortium. *Biological Psychiatry*, *71*(10), 915–921. doi: 10.1016/j.biopsych.2012.01.010.

Vitolo, E., Tatu, M. K., Pignolo, C., Cauda, F., Costa, T., Ando, A., & Zennaro, A. (2017). White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging studies. *Psychiatry Research: Neuroimaging*, *270*, 8–21. doi: 10.1016/j.pscychresns.2017.09.014.

Voineskos, A. N. (2015). Genetic underpinnings of white matter 'connectivity': Heritability, risk, and heterogeneity in schizophrenia. *Schizophrenia Research*, *161*(1), 50–60. doi: 10.1016/j.schres.2014.03.034.

Yang, X., Cao, D., Liang, X., & Zhao, J. (2017). Schizophrenia symptomatic associations with diffusion tensor imaging measured fractional anisotropy of brain: A meta-analysis. *Neuroradiology*, *59*(7), 699–708. doi: 10.1007/s00234-017-1844-9.

Yao, L., Lui, S., Liao, Y., Du, M. Y., Hu, N., Thomas, J. A., & Gong, Q. Y. (2013). White matter deficits in first episode schizophrenia: An activation likelihood estimation meta-analysis. *Progress in Neuropsychopharmacology and Biological Psychiatry*, *45*, 100–106. doi: 10.1016/j.pnpbp.2013.04.019.