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Polygenic Scores for Neuropsychiatric Traits and White Matter Microstructure in the Pediatric Population

Philip R. Jansen, Ryan L. Muetzel, Tinca J.C. Polderman, Vincent W. Jaddoe, Frank C. Verhulst, Aad van der Lugt, Henning Tiemeier, Danielle Posthuma, and Tonya White

ABSTRACT

BACKGROUND: Genome-wide association studies have identified numerous genetic variants that predispose to neuropsychiatric traits. Identification of mechanisms in the brain that underlie these associations is essential for understanding manifestations of genetic predisposition within the general population. Here, we investigated the association between polygenic scores (PGSs) for seven neuropsychiatric traits and white matter microstructure of the brain on diffusion tensor imaging in the pediatric population.

METHODS: Participants from the Generation R Study who had genotype and diffusion tensor imaging data available ($n = 1138$, mean age = 10.2 years, range = 8.7–12.0) were included. PGSs were calculated for five psychiatric disorders (attention-deficit/hyperactivity disorder, bipolar disorder, autism, major depressive disorder, and schizophrenia) and two cognitive traits (intelligence and educational attainment) and were tested for associations with global and tract-specific fractional anisotropy (FA) and mean diffusivity.

RESULTS: Significant positive associations with global FA were observed for the PGSs of intelligence ($\beta = .109$, $SE = .029$, $p < .001$, $\Delta R^2 = .012$) and educational attainment ($\beta = .118$, $SE = .029$, $p < .001$, $\Delta R^2 = .014$). No significant associations were observed with FA for the PGSs of psychiatric disorders. Tract-specific analysis showed that the PGSs for intelligence and educational attainment were associated with FA of several association and projection fibers of the brain.

CONCLUSIONS: Our results show that genetic predisposition for cognition-related traits, but not for psychiatric disorders, is associated with microstructural diffusion measures of white matter tracts at an early age. These results suggest a shared genetic etiology among structural connectivity, intelligence, and educational achievement.

Keywords: Children, Cognition, DTI, Polygenic scores, Psychiatric disorders, White matter

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Recent genome-wide association studies (GWASs) have improved insight into the highly complex polygenic architecture of human behavioral traits, including psychiatric disorders (1–3) and cognitive ability (4,5). The rapid discovery of genetic variants has created the need for identification of downstream mechanisms in order to understand the biological impact of genetic risk on a system level (6–8). Recent studies have used polygenic scoring analyses to estimate overall genetic risk for psychiatric disorders and test the combined effects of thousands on single nucleotide polymorphisms (SNPs) on brain imaging-derived phenotypes using magnetic resonance imaging (MRI) (9). Indeed, structural brain imaging studies in the general population have shown associations with disease-related alterations in healthy individuals carrying a high polygenic score (PGS) for psychiatric illness, including differences in gyrification patterns (10) and cortical thickness (11). Functional imaging studies have shown that polygenic risk for schizophrenia can be linked to different brain activity during tasks (12,13) and during rest (14), illustrating the complex

combined downstream effects on brain functioning. In addition, evidence of brain differences in healthy subjects at high genetic risk has also been suggested by imaging studies in high-risk individuals having a first-degree relative with a psychiatric disorder, which showed abnormalities in a variety of structural (15–17) and functional (17–19) measures of the brain. However, so far only a few studies have investigated associations of polygenic risk with white matter fibers of the brain (20,21), even though the structural connectivity of the brain is known to be related to major psychiatric disorders, including schizophrenia (22) and bipolar disorder (23,24), as well as to normal cognitive functioning (25,26), and white matter changes have been observed in healthy relatives of patients with psychiatric disorders (27,28). In addition, most prior genetic studies included only GWAS-significant SNPs ($p < 5 \times 10^{-8}$) in the PGS and do not take the contribution in genetic signal of subthreshold SNPs into account (29). Moreover, prior studies have almost exclusively focused on adolescents or adults, while deviation from normal brain

development may be present much earlier in life. Here, we investigated whether genome-wide PGSs for psychiatric traits and cognitive ability are associated with white matter microstructure on diffusion tensor imaging (DTI) of the brain in a large population-based cohort of children between 9 and 12 years of age. Insight into a possible shared genetic etiology among psychiatric disorders, cognitive ability, and white matter microstructure provides further understanding of neurobiological manifestations of genetic predisposition for psychopathology and cognition at an early age in the general population.

METHODS AND MATERIALS

Study Sample

The current study was conducted within the Generation R Study, a population-based cohort studying multifaceted aspects of child development (30). Between March 2013 and November 2015, participants were enrolled in the cohort's MRI study with the aim of studying brain development in the general population by collecting high-quality, single-scanner MRI data of the brain (31). The current study included unrelated participants of European ancestry who had good-quality MRI data available and from whom genotype data had been collected previously. The Medical Ethics Committee of the Erasmus University Medical Center approved the study protocol, and the legal representatives of the participants provided written informed consent.

Diffusion Tensor Imaging

DTI of the brain was performed on a single study-dedicated 3T MR750w Discovery MRI scanner (General Electric, Milwaukee,

WI). Twelve major white matter tracts were identified using probabilistic tractography. Diffusion characteristics within these tracts were used to quantify mean fractional anisotropy (FA) and mean diffusivity (MD). A detailed description of the imaging procedures, scan protocol, and subsequent processing of the DTI data is provided in the [Supplement](#).

Confirmatory factor analysis was applied using the lavaan R package (32) to model a single latent factor of global FA and MD, as described by Muetzel *et al.* (25). White matter tracts included in the model and standardized factor loadings on the global factor are shown in [Figure 1](#) and [Supplemental Tables S1](#) and [S2](#). The global factors were tested for association with the PGS in univariate analyses.

Genotype Data

Genotype data were collected at birth or during a visit to the research center using Illumina 610K and 660K genotype arrays (Illumina, San Diego, CA). Data collection and subsequent processing procedures have been described previously (33). Additional quality control procedures of the genotype data and genotype imputation are described in the [Supplement](#).

Polygenic Scoring

PGSs were calculated on imputed genotype data using publicly available GWAS results for five psychiatric disorders and two cognitive traits: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, bipolar disorder, major depressive disorder, schizophrenia, intelligence, and educational attainment. An overview of the discovery GWASs is provided in [Supplemental Table S3](#). Because the Generation R cohort was included in the GWAS of intelligence, the GWAS was repeated after exclusion of the Generation R cohort

Figure 1. Standardized factor loadings of white matter tracts included in the global factor of fractional anisotropy (FA). Global factors for FA were estimated using confirmatory factor analysis. White matter tracts are color coded according to subcategory. CGC, cingulum bundle; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.

(sample size after exclusion = 267,938). Generation R was not included in any of the other six GWASs. PGSs were calculated using PRSice (34), a script for calculation of PGS in PLINK (35). We calculated PGSs based on several p -value thresholds (p_T) for inclusions of SNPs in the score ($p_T < .001, .005, .01, .05, .1, .5, \text{ and } 1$). We tested multiple thresholds to find the optimal threshold that has the strongest association with the outcome. PGSs were subsequently standardized to a mean of 0 and an SD of 1 for interpretability. The number of SNPs that were included in each PGS and threshold is shown in Supplemental Table S4.

Statistical Analysis

Statistical analyses were performed using the R statistical software (36) (version 3.2.1). Association testing was performed in a hierarchical approach. First, a global factor of white matter microstructure was predicted from the confirmatory factor analysis model and regressed on the PGS. Next, in secondary analyses, we studied tract-specific associations by regressing the individual white matter tracts on the PGS p -value threshold that showed the strongest association with the global factor in the primary analysis (lowest p value). All analyses were corrected for age, sex, and four genetic principal components as covariates. False discovery rate was used to correct for multiple testing (37). Correction was applied to the total number of statistical tests for each risk score, p -value threshold, and global and tract-specific diffusion measures. A false discovery rate-corrected significance threshold was applied, and p values below .004 were considered statistically significant.

RESULTS

Sample Characteristics

A total of 3992 participants underwent MRI of the brain. DTI was completed in 3786 of these participants. After DTI quality control procedures, 3279 participants remained. Of these participants, 1920 individuals had genotype data available. Subsequent filtering based on European ancestry, relatedness, and genotype quality resulted in 1138 participants who were included in

the study (see flowchart in Supplemental Figure S1). The mean age of the sample was 10.2 years (range = 8.72–11.99), with a balanced distribution of sex (50.6% boys). The mean standardized PGSs for educational attainment and intelligence were slightly higher compared with the genotyped participants of European ancestry who did not participate in the MRI study (educational attainment: 0.058 vs. -0.039 , $t = 2.56$, $p = .01$; intelligence: 0.099 vs. -0.067 , $t = 4.39$, $p = 1.17 \times 10^{-5}$) (Supplemental Table S5) and were lower for ADHD (-0.055 vs. 0.036 , $t = -2.39$, $p = .02$) and depression (-0.071 vs. 0.047 , $t = -3.09$, $p = .002$). There was a moderate correlation among several PGSs (see correlation heatmap in Supplemental Figure S2), showing the largest correlation between the educational attainment and intelligence PGSs ($r^2 = .38$ –.47 between different p -value thresholds).

Associations With IQ

We tested whether the PGSs of intelligence and educational attainment were associated with nonverbal IQ, measured in a subsample of 982 participants around 6 years of age. The PGSs of intelligence and educational attainment were strongly associated with nonverbal IQ, explaining approximately 5% by the PGS of intelligence ($\beta = .222$, $SE = .032$, $p = 1.87 \times 10^{-12}$, $\Delta R^2 = .050$) (Supplemental Table S6).

Global FA/MD

Explained variance (ΔR^2) in the global factor of FA and MD by the PGS is shown in Figures 2 and 3, respectively, and full regression results are shown in Supplemental Tables S7 and S8. The PGS of intelligence showed positive associations with global FA across different p -value thresholds, with the strongest being the PGS based on a p -value threshold of $p_T < .005$ ($\beta = .109$, $SE = .029$, $p < .001$, $\Delta R^2 = .012$) (Figure 2). Similarly, we observed positive associations across all p -value thresholds for the PGS of educational attainment, explaining approximately 1.4% of the variance in global FA at the p -value threshold of $p_T < 1$ ($\beta = .118$, $SE = .029$, $p < .001$, $\Delta R^2 = .014$). We did not observe significant associations between the global factor of FA and the PGSs of the five psychiatric traits after correcting for multiple testing. In addition, none of the seven

Figure 2. Variance explained in global fractional anisotropy by polygenic scores. **(A)** Variance explained (ΔR^2) in global fractional anisotropy by the polygenic score. **(B)** Standardized regression coefficients of associations between the different polygenic scores and global fractional anisotropy for each p -value threshold corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder.

Figure 3. Variance explained in global mean diffusivity by polygenic scores. **(A)** Variance explained (ΔR^2) in the global factor of mean diffusivity by the polygenic score. **(B)** Standardized regression coefficients of the polygenic score on global mean diffusivity for each individual p -value threshold corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder.

PGSs showed associations with the global factor MD that survived multiple testing correction (Figure 3).

Tract-Specific Analysis

To test whether associations with specific white matter tracts could explain the association between the PGS and global FA, we performed univariate associations with diffusion measures FA and MD of individual white matter tracts. PGSs based on the p -value threshold that showed the strongest association with the global factor of FA and MD in the primary analysis (lowest p value) were tested for tract-specific associations. Figure 4 shows the association results between the PGS and FA and MD in each white matter tract, and a full overview of the regression results is provided in Supplemental Tables S9 and S10. Effect sizes for intelligence and educational attainment are represented visually in Figure 5.

The PGS of intelligence showed positive associations with tract-specific FA in four major white matter tracts: the right superior longitudinal fasciculus ($\beta = .125$, $SE = .029$, $p < .001$), the left inferior longitudinal fasciculus ($\beta = .087$, $SE = .029$, $p < .001$), and both the left and right corticospinal tracts (left: $\beta = .132$, $SE = .029$, $p < .001$; right: $\beta = .148$, $SE = .029$, $p < .001$). Associations between educational attainment PGS and white matter tract partially overlapped with results of intelligence PGS and showed similar positive associations with the right superior longitudinal fasciculus ($\beta = .118$, $SE = .029$, $p < .001$), and the left and right corticospinal tracts (left: $\beta = .107$, $SE = .029$, $p < .001$; right: $\beta = .092$, $SE = .029$, $p < .001$). In addition, significant associations were observed with the right inferior longitudinal fasciculus ($\beta = .105$, $SE = .029$, $p < .001$) and the forceps minor ($\beta = .088$, $SE = .029$, $p < .001$). Tract-specific FA was not associated with the psychiatric PGS. For tract-specific MD values, we observed a significant positive association between the intelligence PGS and the forceps major ($\beta = .105$, $SE = .029$, $p < .001$), whereas a negative association was observed between the ADHD PGS and MD of the forceps minor ($\beta = -.088$, $SE = .029$, $p < .001$).

DISCUSSION

In this study, we observed positive associations between genetic predisposition for cognition-related traits and white

matter microstructure on MRI in the pediatric population, with the PGSs of intelligence and educational attainment explaining approximately 1% of the variance in global FA. Tract-specific analyses showed that these associations are driven by several association and project fibers of the brain. These results may suggest a shared genetic etiology among global white matter integrity, general cognitive functioning, and predicted later-life educational achievement.

Previous research showed that the PGS of educational attainment is associated with general intelligence but has also been associated with socioeconomic status (38) and later-life outcomes, including reproductive behavior (39) and longevity (40). To date, genetic variants related to cognitive traits have only been linked to total intracranial volume on MRI based on GWAS summary statistics using linkage disequilibrium score regression (41). Our study is the first to report significant associations between PGSs for intelligence and educational attainment and structural connectivity of the brain, emphasizing the important role of white matter microstructure in cognitive functioning. This finding is in line with previous work from our group that reported associations between nonverbal IQ and global FA (25) and specific associations with the superior longitudinal fasciculus. Our study adds to these findings that cognition and white matter microstructure are likely to share a common genetic architecture. We hypothesize that two underlying mechanisms may explain these observed associations. First, the discovery GWAS of educational attainment by Okbay *et al.* (5) reported that candidate genes near the 74 genome-wide significant variants showed elevated expression in the central nervous system. Moreover, these candidate genes were highly enriched for gene sets related to neurodevelopment such as sprouting of dendrites and synaptic plasticity. Similar gene set results were observed by Savage *et al.* (42) in the GWAS of intelligence, which highlighted that genes related to several cellular processes in neurons influence cognitive functioning. Given the associations between PGSs of intelligence and educational attainment and white matter microstructure in our study, it may be possible that similar molecular pathways and neurobiological processes lead to higher developed states of microstructural organization, which subsequently leads to a higher FA on DTI. Genetic studies of white matter integrity on DTI indeed

Figure 4. Tract-specific associations between polygenic scores and white matter tracts. Associations between polygenic scores and tract-specific fractional anisotropy and mean diffusivity are shown. Coefficients are standardized regression coefficients corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder; FDR, false discovery rate.

confirmed that genes involved in synaptic processes, such as neuronal transmission and cell adhesion, are important contributors to white matter microstructure (43). Second, given previously described associations between the educational attainment PGS of the child and parental socioeconomic status (44), gene-environment correlations with environmental factors that positively affect white matter microstructure, including prenatal factors (45), parenting strategies (46), and a healthy lifestyle (47), may amplify the observed associations. Considering that educational achievement is correlated with a broad range of environmental factors, it is possible that the educational attainment PGS captures the combined effect of a diverse array of factors that affect white matter development.

Interestingly, we did not observe associations between the schizophrenia PGS and white matter microstructure, which is surprising given extensive literature on white matter abnormalities in patients with schizophrenia (22), individuals at high genetic risk for schizophrenia as defined by family history

(48,49), and associations between the schizophrenia PGS and behavioral problems in our sample as previously reported (50). We argue that several factors may explain this negative finding. First, at the age of our study sample (mean age of 10.2 years), white matter abnormalities described in patients with schizophrenia might be not yet present, not present on a scale detectable by DTI, or present but obscured by increased variance associated with different rates of white matter maturation between individuals. Moreover, MRI modalities examining structural phenotypes and activation patterns of the brain may be more sensitive to developmental changes related to the genetic risk for schizophrenia. Previous studies in healthy individuals indeed have shown associations between schizophrenia PGS and cortical morphology on structural imaging (10,11) and activation patterns during cognitive tasks on functional MRI (13,51). Second, the PGS in this study captures genetic signal only from common variants (minor allele frequency > 0.01) of typically low individual effect sizes (52).

Figure 5. Visual representation of tract-specific associations between polygenic scores and white matter tracts. **(A)** Associations between the polygenic scores for intelligence and tract-weighted average fractional anisotropy. **(B)** Polygenic scores of educational attainment and tract-weighted average fractional anisotropy. Coefficients are standardized regression coefficients corrected for age, sex, and four genetic principal components. Regression results are shown in [Supplemental Tables S8 and S9](#). A, anterior; L, left; P, posterior; R, right.

White matter alterations found in patients with schizophrenia may follow from more deleterious rare variants with comparatively larger effects and higher penetrance. Compelling evidence exists that these rare mutations contribute substantially to schizophrenia risk (53,54) and commonly disrupt neurodevelopmental processes (55,56), which could potentially underlie the observed microstructural abnormalities. Third, nonparticipation among high-risk individuals compared with low-risk individuals in population-based research has been previously described (57). Subsequent underrepresentation of individuals with the highest risk of schizophrenia may further explain this null result. In addition, no associations were observed for the PGSs of four other psychiatric traits. The absence of association for these traits may be partially explained by the GWAS small sample sizes (autism, depression, and bipolar disorder), the later onset of these disorders (depression and bipolar disorder), and/or an absent relation between white matter and these psychiatric disorders.

The current study has several strengths. First, the sample is large for imaging standards, especially in pediatric populations. Second, the sample comprised a narrow age range and the study was performed in a population-based cohort, which can minimize, but certainly not remove, age-related differences in white matter development. Third, all subjects were scanned on a single, research-dedicated MRI scanner using the same software version, removing possible noise from interscanner differences or changes associated with scanner upgrades. Fourth, PGSs for multiple traits were simultaneously tested, allowing for comparisons across traits in a single study sample. Some limitations are also present. First, the associations between PGS and white matter microstructure were tested using a cross-sectional design. Prospectively collected brain-imaging data could provide evidence on whether PGSs

are associated with variation in trajectories of white matter development in children over time. Second, the current largest discovery GWASs used for calculating the PGSs of ADHD, autism, and bipolar disorder are less powered compared with other traits that were tested. As discovery sample sizes increase rapidly, we expect that PGS studies based on well-powered GWAS results will lead to more robust associations with brain imaging phenotypes. Lastly, polygenic risk scores do not provide insights into which SNPs contribute most to the observed associations with structural connectivity. Future genome-wide studies of structural connectivity in large DTI samples may further aid in estimating genetic overlap among cognitive functioning, psychiatric disorders, and structural connectivity and in identifying SNPs that are shared between these traits.

In conclusion, we report evidence that genetic predisposition for cognitive traits is associated with higher white matter microstructural integrity in children, whereas no associations were found for five major psychiatric disorders. Future studies are necessary to explore associations with longitudinal developmental trajectories of white matter microstructure over time.

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ARTICLE INFORMATION

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REFERENCES

- Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, *et al.* (2013): A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry* 18:497–511.
- Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50:668–681.
- Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, *et al.* (2018): Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet* 50:920–927.
- Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 50:912–919.
- Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, *et al.* (2016): Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* 533: 539–542.
- Breen G, Li Q, Roth BL, O'Donnell P, Didriksen M, Dolmetsch R, *et al.* (2016): Translating genome-wide association findings into new therapeutics for psychiatry. *Nat Neurosci* 19:1392–1396.
- Gandal MJ, Leppa V, Won H, Parikshak NN, Geschwind DH (2016): The road to precision psychiatry: Translating genetics into disease mechanisms. *Nat Neurosci* 19:1397–1407.
- Wijmenga C, Zernakova A (2018): The importance of cohort studies in the post-GWAS era. *Nat Genet* 50:322–328.
- Dima D, Breen G (2015): Polygenic risk scores in imaging genetics: Usefulness and applications. *J Psychopharmacol* 29:867–871.
- Liu B, Zhang X, Cui Y, Qin W, Tao Y, Li J, *et al.* (2017): Polygenic risk for schizophrenia influences cortical gyrification in 2 independent general populations. *Schizophr Bull* 43:673–680.
- French L, Gray C, Leonard G, Perron M, Pike GB, Richer L, *et al.* (2015): Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. *JAMA Psychiatry* 72:1002–1011.
- Miller JA, Scult MA, Conley ED, Chen Q, Weinberger DR, Hariri AR (2017): Effects of schizophrenia polygenic risk scores on brain activity and performance during working memory subprocesses in healthy young adults. *Schizophr Bull* 44:844–853.
- Lancaster TM, Ihssen N, Brindley LM, Tansey KE, Mantripragada K, O'donovan MC, *et al.* (2016): Associations between polygenic risk for schizophrenia and brain function during probabilistic learning in healthy individuals. *Hum Brain Mapp* 37:491–500.
- Wang T, Zhang X, Li A, Zhu M, Liu S, Qin W, *et al.* (2017): Polygenic risk for five psychiatric disorders and cross-disorder and disorder-specific neural connectivity in two independent populations. *Neuro-Image Clin* 14:441–449.
- McIntosh AM, Owens DC, Moorhead WJ, Whalley HC, Stanfield AC, Hall J, *et al.* (2011): Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. *Biol Psychiatry* 69:953–958.
- Lawrie SM, Whalley H, Kestelman JN, Abukmeil SS, Byrne M, Hodges A, *et al.* (1999): Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet* 353:30–33.
- Cooper D, Barker V, Radua J, Fusar-Poli P, Lawrie SM (2014): Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia. *Psychiatry Res* 221:69–77.
- Zhang R, Picchioni M, Allen P, Touloupoulou T (2016): Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies. *Schizophr Bull* 42:1068–1077.
- Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, Keefe RS, *et al.* (2015): Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. *Psychol Med* 45:97–108.
- Foley SF, Tansey KE, Caseras X, Lancaster T, Bracht T, Parker G, *et al.* (2017): Multimodal brain imaging reveals structural differences in Alzheimer's disease polygenic risk carriers: A study in healthy young adults. *Biol Psychiatry* 81:154–161.
- Reus LM, Shen X, Gibson J, Wigmore E, Ligthart L, Adams MJ, *et al.* (2017): Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. *Sci Rep* 7:42140.
- Kelly S, Jahanshad N, Zalesky A, Kochunov P, Agartz I, Alloza C, *et al.* (2017): Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA Schizophrenia DTI Working Group. *Mol Psychiatry* 23:1261–1269.
- Lin F, Weng S, Xie B, Wu G, Lei H (2011): Abnormal frontal cortex white matter connections in bipolar disorder: A DTI tractography study. *J Affect Disord* 131:299–306.
- Wise T, Radua J, Nartje G, Cleare AJ, Young AH, Arnone D (2016): Voxel-based meta-analytical evidence of structural disconnection in major depression and bipolar disorder. *Biol Psychiatry* 79:293–302.
- Muetzel RL, Mous SE, van der Ende J, Blanken LME, van der Lugt A, Jaddoe VW, *et al.* (2015): White matter integrity and cognitive performance in school-age children: A population-based neuroimaging study. *NeuroImage* 119:119–128.
- Deary IJ, Bastin ME, Pattie A, Clayden JD, Whalley LJ, Starr JM, Wardlaw JM (2006): White matter integrity and cognition in childhood and old age. *Neurology* 66:505–512.
- Sprooten E, Sussmann JE, Clugston A, Peel A, McKirdy J, Moorhead TWJ, *et al.* (2011): White matter integrity in individuals at high genetic risk of bipolar disorder. *Biol Psychiatry* 70:350–356.
- Skudlarski P, Schretlen DJ, Thaker GK, Stevens MC, Keshavan MS, Sweeney JA, *et al.* (2013): Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. *Am J Psychiatry* 170:886–898.
- International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, *et al.* (2009): Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460:748–752.
- Tiemeier H, Velders FP, Szekely E, Roza SJ, Dieleman G, Jaddoe VW, *et al.* (2012): The Generation R Study: A review of design, findings to date, and a study of the 5-HTTLPR by environmental interaction from fetal life onward. *J Am Acad Child Adolesc Psychiatry* 51:1119–1135.
- White T, Muetzel RL, El Marroun H, Blanken LME, Jansen P, Bolhuis K, *et al.* (2018): Paediatric population neuroimaging and the Generation R Study: The second wave. *Eur J Epidemiol* 33:99–125.

32. Rosseel Y (2012): lavaan: An R package for structural equation modeling and more: Version 0.5-12 (BETA). *J Stat Softw* 48:1–36.
33. Medina-Gomez C, Felix JF, Estrada K, Peters MJ, Herrera L, Kruihof CJ, *et al.* (2015): Challenges in conducting genome-wide association studies in highly admixed multi-ethnic populations: The Generation R Study. *Eur J Epidemiol* 30:317–330.
34. Euesden J, Lewis CM, O'Reilly PF (2014): PRSice: Polygenic risk score software. *Bioinformatics* 31:1466–1468.
35. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, *et al.* (2007): PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 81:559–575.
36. R Core Team (2013): R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.
37. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 57:289–300.
38. Selzam S, Krapohl E, von Stumm S, O'Reilly PF, Rimfeld K, Kovas Y, *et al.* (2017): Predicting educational achievement from DNA. *Mol Psychiatry* 22:267–272.
39. Barban N, Jansen R, De Vlaming R, Vaes A, Mandemakers JJ, Tropf FC, *et al.* (2016): Genome-wide analysis identifies 12 loci influencing human reproductive behavior. *Nat Genet* 48:1462–1472.
40. Marioni RE, Ritchie SJ, Joshi PK, Hagenaars SP, Okbay A, Fischer K, *et al.* (2016): Genetic variants linked to education predict longevity. *Proc Natl Acad Sci U S A* 113:13366–13371.
41. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh P-R, *et al.* (2015): An atlas of genetic correlations across human diseases and traits. *Nat Genet* 47:1236–1241.
42. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 50:912–919.
43. Lopez LM, Bastin ME, Maniega SM, Penke L, Davies G, Christoforou A, *et al.* (2012): A genome-wide search for genetic influences and biological pathways related to the brain's white matter integrity. *Neurobiol Aging* 33:1847.e1–1847.e14.
44. Krapohl E, Plomin R (2016): Genetic link between family socioeconomic status and children's educational achievement estimated from genome-wide SNPs. *Mol Psychiatry* 21:437–443.
45. Taylor PA, Jacobson SW, van der Kouwe A, Molteni CD, Chen G, Wintermark P, *et al.* (2015): A DTI-based tractography study of effects on brain structure associated with prenatal alcohol exposure in newborns. *Hum Brain Mapp* 36:170–186.
46. Puetz VB, Parker D, Kohn N, Dahmen B, Verma R, Konrad K (2017): Altered brain network integrity after childhood maltreatment: A structural connectomic DTI-study. *Hum Brain Mapp* 38:855–868.
47. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, *et al.* (2014): Aerobic fitness is associated with greater white matter integrity in children. *Front Hum Neurosci* 8:584.
48. Hoptman MJ, Nierenberg J, Bertisch HC, Catalano D, Ardekani BA, Branch CA, DeLisi LE (2008): A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. *Schizophr Res* 106:115–124.
49. Maniega SM, Lymer GKS, Bastin ME, Marjoram D, Job DE, Moorhead TWJ, *et al.* (2008): A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. *Schizophr Res* 106:132–139.
50. Jansen PR, Polderman TJ, Bolhuis K, Ende J, Jaddoe VW, Verhulst FC, *et al.* (2018): Polygenic scores for schizophrenia and educational attainment are associated with behavioural problems in early childhood in the general population. *J Child Psychol Psychiatry* 59:39–47.
51. Whalley HC, Hall L, Romaniuk L, Macdonald A, Lawrie SM, Sussmann JE, McIntosh AM (2015): Impact of cross-disorder polygenic risk on frontal brain activation with specific effect of schizophrenia risk. *Schizophr Res* 161:484–489.
52. Wray NR, Lee SH, Mehta D, Vinkhuyzen AAE, Dudbridge F, Middeldorp CM (2014): Research review: Polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry* 55:1068–1087.
53. Gratten J (2016): Rare variants are common in schizophrenia. *Nat Neurosci* 19:1426–1428.
54. Gibson G (2012): Rare and common variants: Twenty arguments. *Nat Rev Genet* 13:135–145.
55. Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, *et al.* (2014): A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 506:185–190.
56. Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, *et al.* (2008): Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320:539–543.
57. Martin J, Tilling K, Hubbard L, Stergiakouli E, Thapar A, Davey Smith G, *et al.* (2016): Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. *Am J Epidemiol* 183:1149–1158.