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Association Between Genetic Risk for Type 2 Diabetes and Structural Brain Connectivity in Major Depressive Disorder

Jonathan Repple, Amelie König, Siemon C. de Lange, Nils Opel, Ronny Redlich, Susanne Meinert, Dominik Grotegerd, Marco Mauritz, Tim Hahn, Tiana Borgers, Elisabeth J. Leehr, Nils Winter, Janik Goltermann, Verena Enneking, Stella M. Fingas, Hannah Lemke, Lena Waltemate, Katharina Dohm, Maike Richter, David M.A. Mehler, Vincent Holstein, Marius Gruber, Igor Nenadic, Axel Krug, Katharina Brosch, Simon Schmitt, Frederike Stein, Tina Meller, Andreas Jansen, Olaf Steinsträter, Azmeraw T. Amare, Tilo Kircher, Bernhard T. Baune, Martijn P. van den Heuvel, and Udo Dannlowski

ABSTRACT

BACKGROUND: Major depressive disorder (MDD) and type 2 diabetes mellitus (T2D) are known to share clinical comorbidity and to have genetic overlap. Besides their shared genetics, both diseases seem to be associated with alterations in brain structural connectivity and impaired cognitive performance, but little is known about the mechanisms by which genetic risk of T2D might affect brain structure and function and if they do, how these effects could contribute to the disease course of MDD.

METHODS: This study explores the association of polygenic risk for T2D with structural brain connectome topology and cognitive performance in 434 nondiabetic patients with MDD and 539 healthy control subjects.

RESULTS: Polygenic risk score for T2D across MDD patients and healthy control subjects was found to be associated with reduced global fractional anisotropy, a marker of white matter microstructure, an effect found to be predominantly present in MDD-related fronto-temporo-parietal connections. A mediation analysis further suggests that this fractional anisotropy variation may mediate the association between polygenic risk score and cognitive performance.

CONCLUSIONS: Our findings provide preliminary evidence of a polygenic risk for T2D to be linked to brain structural connectivity and cognition in patients with MDD and healthy control subjects, even in the absence of a direct T2D diagnosis. This suggests an effect of T2D genetic risk on white matter integrity, which may mediate an association of genetic risk for diabetes and cognitive impairments.

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Major depressive disorder (MDD) and type 2 diabetes mellitus (T2D) are both disorders with a very high burden of disease in societies (1) and a high rate of co-occurrence (2,3). However, underlying mechanisms of this co-occurrence are still poorly understood.

The prevailing explanatory model of depression is multifactorial and involves an interaction of genetic predisposition and environmental influences (4,5), including preexisting T2D (6). Whereas some studies suggest MDD as a causal risk factor for a subsequent T2D development (2,7), others provide growing evidence of an increased risk for developing MDD in patients with T2D (8–10), suggesting a bidirectional relationship between conditions (11). Both MDD and T2D are indeed associated with alterations in white matter microstructure. Neuroimaging studies have shown reduced fractional anisotropy (FA), a measure acquired with diffusion tensor imaging that indicates impairment and damage of white matter microstructural connectivity (12), in several white matter pathways in patients with MDD (13–16). In parallel, white matter connectivity has also been shown to be impaired in patients with T2D, with the most pronounced effects in patients with longer illness duration (17,18).

Changes to brain structural connectivity have been associated with lower levels of cognitive performance in healthy control subjects (HCs) (19), in psychiatric patients (20), and in patients with T2D (17,21). Cognitive dysfunction is highly prevalent both in patients with diabetes, for whom dysfunction has been found especially in executive function, spatial processing, attention, and working memory (22), and in patients with MDD, for whom impairments of executive function are considered to be most pronounced (23).

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Little is known, however, about the neurobiological basis of a potential overlap in brain structure alterations and cognitive performance between the two conditions. Previous research into this overlap focused on sociodemographic factors (24) and shared biological pathways between the disorders (6,25,26). These investigated pathways included an increased activation of the immune system (27), corticotropin-releasing factor signaling, AMPK (adenosine monophosphate–activated protein kinase) signaling, cyclic AMP–mediated or G protein–coupled receptor signaling (25), a disturbed hormone stress axis (28,29), and alterations in glucose transport (6) or glucose metabolism (30). Recent meta-analyses point to the possibility of a genetic component (31,32) shared with both disorders being partly heritable. This observation is likely due to many genetic variants with small respective effect sizes contributing to the multifactorial etiology of both diseases (25,26,33,34). Polygenic risk scores (PGSs) are often used to measure the impact of a multitude of genes with small effect sizes and reflect the overall risk of an individual for a certain trait. PGS is assessed by summing the number of risk alleles weighted by the strength of its association with a trait (35). A meta-analysis revealed a genetic overlap between cardiometabolic disease risk genes, including risk genes of T2D and mood disorders, e.g., the *CACNAC1D* or *APOE* genes (25). A genome-wide association study (GWAS) identified 496 shared single nucleotide polymorphisms (SNPs) for MDD and T2D, with affected genes found to particularly code for pathways associated with immune response, cell signaling, and lipid metabolism (31).

To investigate whether the unfavorable effect of T2D on MDD is related to the genetic risk of T2D irrespective of actual disease onset, we examined effects of genetic risk for T2D in nondiabetic patients with MDD. With increasing reports on the co-occurrence of T2D and MDD, and both conditions related to patterns of white matter pathology, we hypothesize that the genetic burden of T2D is negatively associated with brain structural connectivity and cognitive performance in patients with MDD. To investigate disease specificity, we further investigated these associations in a healthy control group.

METHODS AND MATERIALS

Participants

The participants in this study were part of the Marburg-Münster Affective Disorders Cohort Study and were recruited from January 2015 until November 2016 at two sites (University of Marburg and University of Münster); see (36) for the quality assurance protocol and (37) for a general description. The study was approved by the ethics committees of the medical faculties. After signing an informed consent, all participants underwent extensive testing including magnetic resonance imaging (MRI), a sampling of biomaterials, neuropsychological tests, interviews for the collection of clinical course parameters, and a Structured Clinical Interview for DSM-IV, Axis I (38) by trained examiners, which served to determine the diagnosis of the participant. For exclusion criteria and a more detailed clinical description including comorbidities, medication, and clinical course parameters in the depressive sample, see the Supplement.

Genetic Methods

Genotyping in all subjects was performed using previously published protocols (39,40). The PGS for T2D was computed for each individual in our cohort (n = 434 nondiabetic patients with MDD and 539 healthy control subjects) using genotype data imputed based on the Haplotype Reference Consortium panel, and GWAS summary statistics for T2D from 26,488 cases and 83,964 healthy controls (41). This process has already been used in previous studies (42,43).

First, quality-controlled SNPs were clumped for linkage disequilibrium based on p value–informed clumping using r^2 = 0.1 within a 250-kb window to create a SNP set in linkage equilibrium using PLINK software run on Linux (plink–clumpp1 1 –clump-p2 1 –clump-r2 0.1 –clump-kb 250). Second, a PGS was computed for each individual as the sum of reference SNP alleles (genotype dosage from 0 to 2) multiplied by the effect size (β coefficient) derived from the GWAS summary statistics (44). Higher scores reflect a higher T2D risk. Furthermore, to account for heterogeneity of genetic information based on the effect size of SNP alleles, polygenic risk scores for different p value–based thresholds were included in the study. For instance, a PGS with a threshold of p = .00001 includes only those SNP alleles that had a p value lower than .00001. Accordingly, PGSs were calculated at 8 different p value thresholds: $<$ .000001, $<$ .00001, $<$ .0001, $<$ .001, $<$ .01, $<$ .1, $<$ .5, and $<$ 1. For details on how many SNPs were included at each threshold, see the Supplement. Excluded from the calculations was the major histocompatibility complex region because of its complex disequilibrium structure. To adjust for genetic heterogeneity within the sample, we used multidimensional scaling with 4 components, which resulted from the genetic population stratification analyses in PLINK.

Cognitive Performance

To measure the cognitive impairment of the subjects, we created a global parameter of cognitive performance (CP score). This approach was in line with an extensively validated and recently employed method by the Human Connectome Project (45,46) that calculated a global cognition score (47) based on a National Institute of Health Cognition Battery (48). Here, a series of neuropsychological tests were conducted in a fixed order by a trained examiner for this purpose. This battery featured 7 tests: the Digit Symbol Substitution Test for assessment of processing speed (49,50); the Trail Making Test Part A, for processing speed/working memory (51); the Letter-Number Sequencing Test for working memory (52); the d2 Test of Attention for sustained attention (53); the Verbal Learning Memory Test A for declarative short-term memory and the Verbal Learning Memory Test B for declarative long-term memory (54,55); and a difference score from Trail Making Test Part B − A for executive function (51). An individual CP score was calculated for each subject by generating a standardized value (z score) based on a Gaussian distribution for each of the 7 tests, from which the arithmetic mean was formed. Before the arithmetic mean was computed, the values of the Trail Making Test Part A and Part B − A were inverted so

that higher scores always resembled better performance. The arithmetic mean was again standardized (*z* transformation). All subsequent analyses were performed with the CP score. For significant results, post hoc tests were performed to check whether certain subdomains drove the observed association.

MRI Data Acquisition and Anatomical Connectome Reconstruction

For details on MRI data acquisition, see the Supplement. The following connectome reconstruction methods have been described in detail in a previous publication (56). For each subject, an anatomical brain network was reconstructed, consisting of 114 areas that reflect a subdivision of the FreeSurfer Desikan–Killiany atlas (57,58) and reconstructed streamlines between these areas. These white matter pathways were reconstructed using deterministic streamline tractography using the fiber assignment by continuous tracking algorithm (59). We employed a basic single-tensor diffusion tensor imaging reconstruction combined with simple deterministic fiber tracking. We chose this method rather than more advanced reconstruction methods such as probabilistic fiber tracking that allow for more complex fiber reconstructions so that we could achieve a sufficient balance between false-negative and false-positive fiber reconstructions. This balance is known to have a major impact on network analyses (60). Network connections were included when 2 nodes (i.e., brain regions) were connected by at least 3 tractography streamlines (61). Previous work suggests that results are stable irrespective of different streamline thresholds or cortical parcellation strategies (62).

For each participant, the network information was stored in a structural connectivity matrix, with rows and columns reflecting cortical brain regions, and matrix entries representing the weights of the graph edges: network edges were weighted with FA (a marker of white matter microstructure), which has previously been implicated in the pathophysiology of MDD (14). Global FA was defined as the average of all FA values across present edges.

Total Sample

Data were available for $n = 1032$ subjects who were recruited from January 2015 until February 2019. We excluded subjects with a manifest diabetes diagnosis—including diabetes type 1 ($n = 2$) and type 2 ($n = 9$). Furthermore, we excluded 48 subjects because of low connectome quality control (for details, see the Supplement). The total sample was composed of 263 MDD patients from the Marburg site and 171 MDD patients from the Münster site, which resulted in a total sample size of 434 MDD patients. For an additional exploratory analysis in HCs, we included a group of 324 HCs from the Marburg site and a group of 215 HCs from the Münster site.

Statistical Analysis

Statistical analyses were calculated with SPSS version 25 (IBM Corp.). For all subsequent analyses, partial correlations (as part of the general linear model) were used, all of which were corrected for age and sex. We first report on results in the whole sample (including MDD and HC groups), with all analyses corrected for group effects. In a next step, we investigate differential effects in the subgroups employing group interaction analyses. Lastly, in exploratory analyses we report on results in the MDD and HC groups separately. For all neuroimaging analyses, site was included as a covariate. Multidimensional scaling, subdivided into the 4 components (C1, C2, C3, and C4), was added when the PGS was part of the model. For all PGS analyses, we report results surviving stringent Bonferroni correction (PGS for the 8 different thresholds; $p = .05/8 = .006$). In follow-up exploratory analyses, we also report significant results on an uncorrected level, which are interpreted as potential exploratory effects.

Our main analysis strategy (Figure 1) started with the investigation of the association of PGS and global FA. To this end, partial correlations with all PGSs and global FA values were performed (see The Association Between Polygenic Risk for T2D and Brain Structural Connectivity). Next, to test for an association between PGS and cognitive performance, partial correlations were performed with all PGSs and CP scores (see The Association Between Polygenic Risk for T2D and Cognitive Performance). To investigate whether abnormalities in brain structural connectivity were also associated with cognition, a partial correlation between global FA and CP was performed (see The Association Between Cognitive Performance and Brain Structural Connectivity). To further test whether FA mediated the association of PGS and CP, we performed an exploratory mediation analysis (see Mediation Analysis; for details see the Supplement).

To study which specific connections were the most affected in the previous PGS–FA analyses (see The Association Between Polygenic Risk for T2D and Brain Structural Connectivity), we employed network-based statistics (NBS) (59) (see NBS Analyses). Detailed steps of this analysis are described in earlier work (62). We used NBS to detect the set of connections that were most strongly associated with the PGS and the FA score. The NBS identifies an effect at the cluster level by performing mass univariate testing at the edge level and controlling for familywise error. First, each edge was assigned a *p* value obtained from the negative association between FA value and PGS while correcting for group, age, sex, multidimensional scaling scores, and scanner site. Next, a set of suprathreshold connections as potential clusters was identified. We used a rather restrictive threshold of $t = 2.0$ (59) (see the Supplement for a more liberal threshold of $t = 1.5$ with more extensive results) to focus on the most strongly associated connections. Permutation testing using 5000 permutations was performed to ascribe a *p* value controlled for the familywise error to each cluster based on its size (62). Edgewise evaluation in the first step was based on a significance threshold of $p < .05$ unless noted differently, with 1-sided hypotheses. Halved *p* values are reported regarding the main hypotheses.

RESULTS

The sample consisted of 973 subjects (434 MDD patients and 539 HCs). The mean age of the sample was 34.35 years (SD 12.90; for more information see the Supplement). The PGSs were not associated with diagnosis or body mass index (Supplement). The MDD group had significantly lower average global FA and CP scores compared with the group of HCs (see the Supplement). We observed trends for a greater variance of

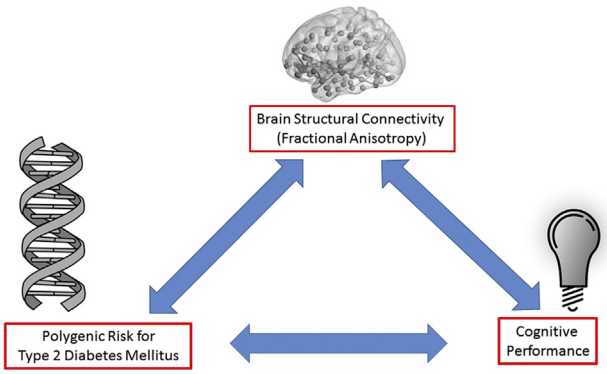

Figure 1. Analysis strategy for the association between genetic risk for type 2 diabetes mellitus (T2D) and structural brain connectivity in major depressive disorder. Our main analysis included partial correlations, which were performed with all polygenic risk scores (PGSs) and global fractional anisotropy; see The Association Between Polygenic Risk for T2D and Brain Structural Connectivity. Next, partial correlations were performed with all PGSs and the cognitive performance score (see The Association Between Polygenic Risk for T2D and Cognitive Performance). To investigate whether abnormalities in brain structural connectivity were also associated with cognition (see The Association Between Cognitive Performance and Brain Structural Connectivity), we performed partial correlation between fractional anisotropy and cognitive performance. To further test whether fractional anisotropy mediated the association of PGS and cognitive performance, we performed mediation analysis (see Mediation Analysis). All analyses were corrected for group, age, and sex. Multidimensional scaling, subdivided into the 4 components (C1, C2, C3, and C4), was added when the PGS was part of the model. For all neuroimaging analyses, site was included as a covariate.

PGSs in the MDD sample (for results and further details on group comparisons, see the Supplement).

The Association Between Polygenic Risk for T2D and Brain Structural Connectivity

Genetic load for T2D (p value based on GWAS significance threshold [p_{PGS}] = .001) was negatively correlated with global FA ($r = -0.084$, $p = .005$, Bonferroni-corrected). At an uncorrected level, we further observed a negative association between PGS and global FA for four more PGS thresholds (all $p < .05$). For more information, see Table 1, and for scatterplots for all thresholds, see the Supplement. We did not observe a group × PGS interaction on global FA with a trend-level interaction on an uncorrected level for the $p_{PGS} = .001$ ($F_1 = 2.49$, $p = .11$), driven by the negative PGS–FA association in the MDD subsample ($r = -0.141$, $p = .002$). For all interaction analyses and all results in the MDD and HC subsamples, see the Supplement.

The Association Between Polygenic Risk for T2D and Cognitive Performance

PGS showed no association with cognitive performance. No group × PGS interaction analysis survived Bonferroni correction (Table 1). On an uncorrected level, we found a group × PGS interaction at four different thresholds, all driven by a negative association of PGS and cognition in the MDD group (for more details and for scatterplots of all PGS–CP associations, see the Supplement). Post hoc exploratory tests for all separate cognitive subdomains in the MDD group suggested that the Digit Symbol Substitution Test showed the strongest effect sizes at $p_{PGS} = .0001$ ($r = -0.109$, $p = .013$), $p_{PGS} = 0.1$ ($r = -0.096$, $p = .025$) and $p_{PGS} = 1.0$ ($r = -0.109$, $p = .013$). For tests with all cognitive subdomains, see the Supplement.

The Association Between Cognitive Performance and Brain Structural Connectivity

A significant positive association was observed between CP and global FA ($r = 0.077$, $p = .005$). Interaction analyses further revealed a trend toward a group × FA interaction ($F_{1,950} = 2.90$, $p = .09$), on CP, driven by a stronger positive correlation in the MDD group (MDD: $r = 0.122$, $p = .006$; HC: $r = 0.022$, $p = .305$).

Mediation Analysis

Mediation analyses showed a full mediation effect of FA on $p_{PGS} = .001$ and CP [indirect effect: coefficient = −3.86,

Table 1. Association of Polygenic Risk[a] for Type 2 Diabetes With Fractional Anisotropy and Cognitive Performance

	p_{PGS} = .000001	p_{PGS} = .00001	p_{PGS} = .0001	p_{PGS} = .001	p_{PGS} = .01	p_{PGS} = .1	p_{PGS} = .5	p_{PGS} = 1.0
Fractional Anisotropy[b]								
Correlation coefficient	−0.074	−0.056	−0.076	−0.084	−0.036	−0.032	−0.050	−0.060
p Value	.012[c]	.042[c]	.009[c]	.005[d]	.132	.164	.063	.033[c]
Cognitive Performance[e]								
Correlation coefficient	−0.031	−0.027	−0.014	0.010	0.024	−0.019	−0.021	−0.018
p Value	.174	.200	.335	.374	.234	.279	.260	.286

p_{PGS}, p value based on genome-wide association study significance threshold for polygenic risk score for type 2 diabetes.

[a]To account for heterogeneity of genetic information based on the effect size of single nucleotide polymorphism alleles, polygenic risk scores for different p value–based thresholds were included in the study.

[b]Partial correlation coefficient of polygenic risk score and fractional anisotropy corrected for group, age, sex, site, and multidimensional scaling 1–4. All partial correlations are 1-tailed. All degrees of freedom = 946.

[c]$p < .05$.

[d]$p < .006$, reflecting Bonferroni correction.

[e]Partial correlation coefficient of polygenic risk score and cognitive performance corrected for age, sex, and multidimensional scaling 1–4. All partial correlations are 1-tailed. All degrees of freedom = 946.

SE = 2.17, 95% CI = −8.75 to −0.29, and no direct effect (63); for more details, see the Supplement].

NBS Analyses

NBS analysis showed a negative association of FA and p_{PGS} = .001 in a subnetwork consisting of 74 edges (see Figure 2 and the Supplement) at a familywise error–corrected significance level of $p_{FWE} < .001$ (t threshold 2.0). This subnetwork comprised connections from widespread brain regions including frontal, temporal, parietal, insular, and cingulate nodes, with a posterior point of center. For results with a t threshold of 1.5, see the Supplement.

DISCUSSION

Our study shows preliminary evidence for polygenic risk for T2D to play a role in shaping the microstructural integrity of white matter networks, with a higher genetic risk for T2D related to lower integrity of key brain networks, an effect that may further mediate an association of polygenic risk for T2D and cognitive performance, in particular in patients with MDD.

The association of metabolic disorders and MDD has been investigated extensively. Yet, the link of T2D as a risk factor for subsequent MDD has been investigated mostly in terms of socioeconomic factors (24) and the effects of altered glucose metabolism on brain structure or function (30,46,64). Only recently has the notion been established that genetic predisposition for metabolic disorders and psychiatric disorders may overlap. Our results now indeed suggest that even without a clinically manifest diagnosis of T2D, a higher polygenic risk for diabetes may be related to lower white matter integrity and compromised cognitive abilities, in particular in patients with MDD. This finding suggests a potential shared biological genetic mechanism at the brain level that goes beyond indirect effects of genetic load on brain structure via the adverse effects of increased blood glucose levels and altered insulin resistance that are known to be implicated in brain abnormalities (30). We found no association between T2D-PGS and body mass index as a potential confounding factor, which supports an interpretation of a more direct link between genetic risk for T2D and altered brain structure. The view that diabetes-related genes may impact brain structure and function is supported by previous GWAS analyses that implicate shared genes in T2D and MDD (31). These shared genes were found to particularly play a role in immune response, lipid metabolism, and cell signaling (31). As these pathways have been implicated in white matter structural connectivity (65–68), it is possible that a genetic risk for T2D confers the observed impairments of brain structural connectivity in our MDD sample. This in turn might contribute to cognitive deficits, which are also unfavorable from a clinical perspective, as cognitive deficits and brain structural alterations have been associated with poorer clinical outcome in patients with MDD (69,70). We note, however, that PGS analyses prevent conclusions about specific genes, because PGSs reflect the overall degree of impairments in these different genetic pathways.

We note that we observed these results in a sample including patients with MDD as well as HCs and that group interaction analyses did not yield significant results. Therefore, our data do not directly provide evidence for a disease-specific effect. Exploratory analyses in both subgroups separately do, however, suggest that the observed associations were mostly driven by the MDD group and that the MDD group showed stronger effects for the PGS–FA, PGS–CP, and CP–FA associations. This result could be due to several factors. First, Levene tests revealed significantly larger variance in the CP scores for the MDD sample, which might suggest that the observed effects might be driven by disease-related variance in cognitive performance. Second, unaccounted environmental influences that contributed to the disease onset (71) or disease-related processes (62) could also influence white

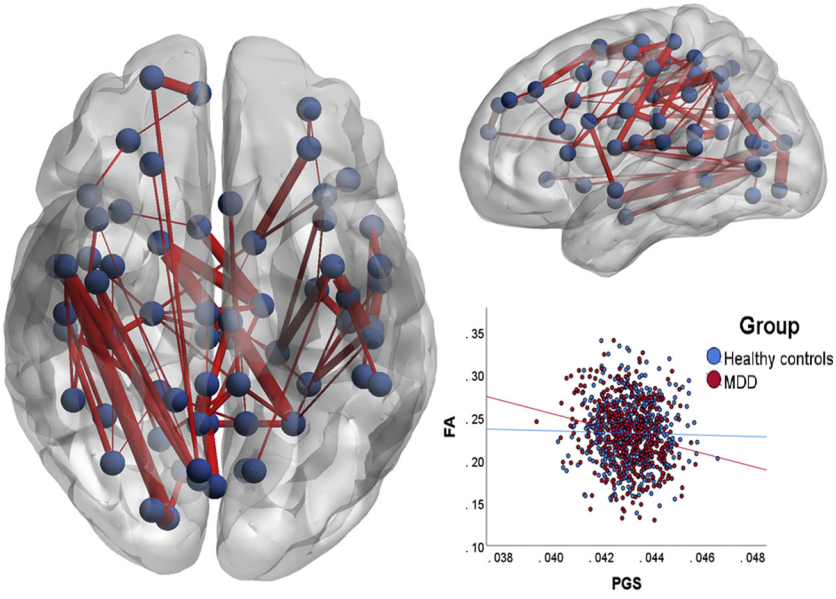

Figure 2. Subnetwork with a negative correlation between fractional anisotropy (FA) and p value based on genome-wide association study significance threshold (p_{PGS}) = .001. Edges (red) and nodes (blue) that show a negative association of polygenic risk for type 2 diabetes mellitus (threshold p = .001) and FA within the entire sample, including major depressive disorder (MDD) patients and healthy control subjects. Results show a subnetwork based on a network-based statistics analysis with a p value (familywise error–corrected) of $p < .001$ and a suprathreshold t value of t = 2.0. Images were created using the BrainNet Viewer software (76). Left panel: axial view. Right top panel: sagittal view. Right bottom panel: scatterplot depicting the association of mean FA (extracted from the significant cluster) and polygenic risk score (PGS).

matter microstructure and cognition or the association of PGS on these dimensions. Here, future longitudinal studies could shed light on the question of when and how these genetic variations start to affect brain structure and cognitive deficits and identify which environmental factors play a role in eliciting these effects. As the interaction analyses did not clearly point to an MDD-specific effect, future studies with larger sample sizes and including other psychiatric disorders should elucidate whether the observed effects are significantly more pronounced in patients with MDD compared with healthy control subjects and individuals with other psychiatric disorders.

A second important note is that previous studies have predominantly reported on PGS at one specific p threshold, based either on thresholds used in previous work (72,73) or on highest explained variance (74). In contrast, we opted to report results on the whole bandwidth of p thresholds (from p = .000001 to p = 1), which results in a more comprehensive picture, but it also raises the issue of multiple testing. It is noteworthy that while most reported effects are rather small, the PGS–FA association survives even stringent Bonferroni correction. In contrast, no single PGS–cognition association survives Bonferroni correction, but the uncorrected associations provide directions that could be further tested in future studies with more power. Additionally, mediation analysis suggests a full mediation of FA on the PGS–cognition association at the Bonferroni-corrected p_{PGS} = .001.

Although our study describes a large group of MDD patients and HCs, it is currently a single-cohort study, with no other multimodal dataset of similar size containing MRI, genetic, and extensive cognitive data available to us. This limits our possibilities for performing a direct validation of our findings. Furthermore, the study is cross-sectional in nature and therefore inherently limited in finding direct causal links. Longitudinal studies are required that investigate the link between polygenic risk for T2D and brain structure, cognitive performance, emotion processing alterations (75), and possibly poorer clinical outcome in patients with MDD. A mediation analysis nevertheless suggests a potential causal link of PGS and cognition, which might be driven by the negative effect of PGS on structural brain connectivity. Future longitudinal studies would help to deepen our understanding of this potential causal link and rule out alternative explanations. For instance, we assessed a detailed medical history and, based on this, excluded patients with manifest T2D. Future research should further include formal diagnostic testing including the measurement of blood metabolic markers (e.g., hemoglobin A1c, fasting blood glucose levels, insulin sensitivity), which would allow for testing for effects of a continuous spectrum of altered glucose metabolism, prediabetes, and manifest T2D (46). All these data are missing from the current study. Our results should be placed in light of these limitations and can thus be best interpreted as potentially first, preliminary evidence for an effect of T2D PGS on brain structure, with future studies needed to more directly test our proposed hypothesis.

Conclusions

We observed a relationship between genetic risk for T2D and impaired structural connectivity and cognitive performance in MDD patients in the absence of T2D. These findings suggest an effect of T2D genetic risk on brain structure and function. PGS analysis for T2D could support early identification of individuals with MDD who have a more severe disease trajectory characterized by impaired brain structural connectivity and cognitive performance. Future studies can help to further disentangle the exact role of specific genes and pathways of both disorders on brain connectivity and cognition.

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ARTICLE INFORMATION

From the Department of Psychiatry (JR, AK, NO, RR, SM, DG, MM, TH, TB, EJL, NW, JG, VE, SMF, HL, LW, KD, MR, DMAM, VH, MG, BTB, UD), University of Muenster, Muenster; Institute of Psychology (RR), University of Halle, Halle; Department of Psychiatry and Psychotherapy (IN, AK, KB, SS, FS, TM, AJ, OS, TK), University of Marburg, Marburg; and Department of Psychiatry and Psychotherapy (AK), University of Bonn, Bonn, Germany; Department of Complex Trait Genetics (SCdL, MPvdH), Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam Neuroscience; and Department of Child Psychiatry (MPvdH), Amsterdam University Medical Center, Amsterdam Neuroscience, Amsterdam, The Netherlands; South Australian Health and Medical Research Institute (ATA), Adelaide; Discipline of Psychiatry (ATA), School of Medicine, University of Adelaide, Adelaide, South Australia; Department of Psychiatry (BTB), Melbourne Medical School, The University of Melbourne, Melbourne; and The Florey Institute of Neuroscience and Mental Health (BTB), The University of Melbourne, Melbourne, Victoria, Australia.

JR and AK contributed equally to this work as joint first authors.

MPvdH and UD contributed equally to this work as joint senior authors.

Address correspondence to Jonathan Repple, M.D., at jonathan.repple@ukmuenster.de.

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REFERENCES

1. Murray CJL, Lopez A, editors. (1996). The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability From Disease, Injures and Risk Factors in 1990 and Projected to 2020. Geneva, Switzerland: World Health Organization.
2. Mezuk B, Eaton WW, Albrecht S, Golden SH (2008): Depression and type 2 diabetes over the lifespan: A meta-analysis. Diabetes Care 31:2383–2390.
3. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2001): The prevalence of comorbid depression in adults with diabetes: A meta-analysis. Diabetes Care 24:1069–1078.
4. Kendler KS, Aggen SH, Neale MC (2013): Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. JAMA Psychiatry 70:599–607.
5. Kendler KS, Gatz M, Gardner CO, Pedersen NL (2006): Personality and major depression: A Swedish longitudinal, population-based twin study. Arch Gen Psychiatry 63:1113–1120.
6. Musselman DL, Betan E, Larsen H, Phillips LS (2003): Relationship of depression to diabetes types 1 and 2:Epidemiology, biology, and treatment. Biological Psychiatry 54:317–329.
7. Brown LC, Majumdar SR, Newman SC, Johnson JA (2005): History of depression increases risk of type 2 diabetes in younger adults. Diabetes Care 28:1063–1067.
8. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K (2006): The prevalence of co-morbid depression in adults with Type 2 diabetes: A systematic review and meta-analysis. Diabet Med 23:1165–1173.
9. Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, Pouwer F (2010): Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. Diabetologia 53:2480–2486.
10. Rotella F, Mannucci E (2013): Diabetes mellitus as a risk factor for depression: A meta-analysis of longitudinal studies. Diabetes Res Clin Pract 99:98–104.
11. Pan A, Lucas M, Sun Q, Van Dam RM, Franco OH, Manson JAE, *et al.* (2010): Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med 170:1884–1891.
12. Thomason ME, Thompson PM (2011): Diffusion imaging, white matter, and psychopathology. Annu Rev Clin Psychol 7:63–85.
13. Repple J, Meinert S, Grotegerd D, Kugel H, Redlich R, Dohm K, *et al.* (2017): A voxel-based diffusion tensor imaging study in unipolar and bipolar depression. Bipolar Disord 19:23–31.
14. Wise T, Radua J, Nortje G, Cleare AJ, Young AH, Arnone D (2016): Voxel-based meta-analytical evidence of structural disconnectivity in major depression and bipolar disorder. Biol Psychiatry 79:293–302.
15. Repple J, Zaremba D, Meinert S, Grotegerd D, Redlich R, Förster K, *et al.* (2019): Time heals all wounds? A 2-year longitudinal diffusion tensor imaging study in major depressive disorder. J Psychiatry Neurosci 44:407–413.
16. Yang X-H, Wang Y, Wang D-F, Tian K, Cheung EFC, Xie G-R, Chan RCK (2017): White matter microstructural abnormalities and their association with anticipatory anhedonia in depression. Psychiatry Res Neuroimaging 264:29–34.
17. Reijmer YD, Brundel M, De Bresser J, Kappelle LJ, Leemans A, Biessels GJ (2013): Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: A diffusion tensor imaging study. Diabetes Care 36:137–144.
18. Hsu JL, Chen YL, Leu JG, Jaw FS, Lee CH, Tsai YF, *et al.* (2012): Microstructural white matter abnormalities in type 2 diabetes mellitus: A diffusion tensor imaging study. Neuroimage 59:1098–1105.
19. Opel N, Martin S, Meinert S, Redlich R, Enneking V, Richter M, *et al.* (2019): White matter microstructure mediates the association between physical fitness and cognition in healthy, young adults. Sci Rep 9:12885.
20. Kochunov P, Coyle TRR, Rowland LMM, Jahanshad N, Thompson PMM, Kelly S, *et al.* (2017): Association of white matter with core cognitive deficits in patients with schizophrenia. JAMA Psychiatry 74:958–966.
21. Reijmer YD, Leemans A, Brundel M, Kappelle LJ, Biessels GJ (2013): Disruption of the cerebral white matter network is related to slowing of information processing speed in patients with type 2 diabetes. Diabetes 62:2112–2115.
22. Zhang J, Wang Y, Wang J, Zhou X, Shu N, Wang Y, Zhang Z (2014): White matter integrity disruptions associated with cognitive impairments in type 2 diabetic patients. Diabetes 63:3596–3605.
23. Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lönnqvist J (2008): A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord 106:1–27.
24. Kaholokula JK, Haynes SN, Grandinetti A, Chang HK (2003): Biological, psychosocial, and sociodemographic variables associated with depressive symptoms in persons with type 2 diabetes. J Behav Med 26:435–458.
25. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT (2017): The genetic overlap between mood disorders and cardiometabolic diseases: A systematic review of genome wide and candidate gene studies. Transl Psychiatry 7:e1007.
26. Haljas K, Amare AT, Alizadeh BZ, Hsu YH, Mosley T, Newman A, *et al.* (2018): Bivariate genome-wide association study of depressive symptoms with type 2 diabetes and quantitative glycemic traits. Psychosom Med 80:242–251.
27. Stuart MJ, Baune BT (2012): Depression and type 2 diabetes: Inflammatory mechanisms of a psychoneuroendocrine co-morbidity. Neurosci Biobehav Rev 36:658–676.
28. Kupfer DJ, Frank E, Phillips ML (2012): Major depressive disorder: New clinical, neurobiological, and treatment perspectives. Lancet 379:1045–1055.
29. Laake JPS, Stahl D, Amiel SA, Petrak F, Sherwood RA, Pickup JC, Ismail K (2014): The association between depressive symptoms and systemic inflammation in people with type 2 diabetes: Findings from the South London diabetes study. Diabetes Care 37:2186–2192.
30. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ (2015): Glucose regulation, cognition, and brain MRI in type 2 diabetes: A systematic review. Lancet Diabetes Endocrinol 3:75–89.
31. Ji HF, Zhuang QS, Shen L (2016): Genetic overlap between type 2 diabetes and major depressive disorder identified by bioinformatics analysis. Oncotarget 7:17410–17414.

32. Kan C, Pedersen NL, Christensen K, Bornstein SR, Licinio J, MacCabe JH, *et al.* (2016): Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. Mol Psychiatry 21:903–909.
33. Herder C, Roden M (2011): Genetics of type 2 diabetes: Pathophysiologic and clinical relevance. Eur J Clin Invest 41:679–692.
34. Demirkan A, Penninx BWJH, Hek K, Wray NR, Amin N, Aulchenko YS, *et al.* (2011): Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Mol Psychiatry 16:773–783.
35. Euesden J, Lewis CM, O'Reilly PF (2015): PRSice: Polygenic Risk Score software. Bioinformatics 31:1466–1468.
36. Vogelbacher C, Möbius TWD, Sommer J, Schuster V, Dannlowski U, Kircher T, *et al.* (2018): The Marburg-Münster Affective Disorders Cohort Study (MACS): A quality assurance protocol for MR neuroimaging data. Neuroimage 172:450–460.
37. Kircher T, Wöhr M, Nenadic I, Schwarting R, Schratt G, Alferink J, *et al.* (2019): Neurobiology of the major psychoses: a translational perspective on brain structure and function—the FOR2107 consortium. Eur Arch Psychiatry Clin Neurosci 269:949–962.
38. Wittchen H-U, Zaudig M, Fydrich T (1997): Strukturiertes Klinisches Interview für DSM-IV (SKID I und SKID II). Göttingen, Germany: Hogrefe.
39. Dannlowski U, Grabe HJ, Wittfeld K, Klaus J, Konrad C, Grotegerd D, *et al.* (2014): Multimodal imaging of a tescalcin (TESC)-regulating polymorphism (rs7294919)-specific effects on hippocampal gray matter structure. Mol Psychiatry 20:398–404.
40. Opel N, Redlich R, Kaehler C, Grotegerd D, Dohm K, Heindel W, *et al.* (2017): Prefrontal gray matter volume mediates genetic risks for obesity. Mol Psychiatry 22:703–710.
41. Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, *et al.* (2014): Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 46:234–244.
42. Leehr EJ, Opel N, Werner J, Redlich R, Repple J, Grotegerd D, *et al.* (2019): Evidence for a sex-specific contribution of polygenic load for anorexia nervosa to body weight and prefrontal brain structure in nonclinical individuals. Neuropsychopharmacology 44:2212–2219.
43. Opel N, Amare AT, Redlich R, Repple J, Kaehler C, Grotegerd D, *et al.* (2020): Cortical surface area alterations shaped by genetic load for neuroticism. Mol Psychiatry 25:3422–3431.
44. Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Heilbronner U, *et al.* (2018): Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: A genome-wide association study. JAMA Psychiatry 75:65–74.
45. Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K (2013): The WU-Minn Human Connectome Project: An overview. Neuroimage 80:62–79.
46. Repple J, Karliczek G, Meinert S, Förster K, Grotegerd D, Goltermann J, *et al.* (2019): Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults [published correction appears in Mol Psychiatry 2020 Mar 13]. Mol Psychiatry 507186.
47. Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, *et al.* (2014): Reliability and validity of composite scores from the NIH toolbox cognition battery in adults. J Int Neuropsychol Soc 20:588–598.
48. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, *et al.* (2013): Cognition assessment using the NIH Toolbox. Neurology 80:S49–S53.
49. Wechsler D (1997): WAIS-III Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation.
50. Jaeger J (2018): Digit Symbol Substitution Test: The case for sensitivity over specificity in neuropsychological testing. J Clin Psychopharmacol 38:513–519.
51. Reitan RM (1986): Trail Making Test: Manual for Administration and Scoring. Tempe, AZ: Reitan Neuropsychology Laboratory.
52. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR (1997): Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry 54:159–165.
53. Brickenkamp R, Schmidt-Atzert L, Liepmann D (2010): Test D2-Revision: Aufmerksamkeits- und Konzentrationstest. Göttingen, Germany: Hogrefe.
54. Helmstaedter C, Lendt M, Lux S (2001): VLMT—Verbaler Lern- und Merkfähigkeitstest. Göttingen, Germany: Hogrefe.
55. Heubrock D (1992): Der Auditiv-Verbale Lerntest (AVLT) in der klinischen und experimentellen Neuropsychologie. Durchführung, Auswertung und Forschungsergebnisse. Zeitschrift für Differ und Diagnostische Psychol 13:161–174.
56. Collin G, van den Heuvel MP, Abramovic L, Vreeker A, de Reus MA, van Haren NEM, *et al.* (2016): Brain network analysis reveals affected connectome structure in bipolar I disorder. Hum Brain Mapp 134:122–134.
57. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Van Wedeen J, Sporns O (2008): Mapping the structural core of human cerebral cortex. PLoS Biol 6:e159.
58. Cammoun L, Gigandet X, Meskaldji D, Thiran JP, Sporns O, Do KQ, *et al.* (2012): Mapping the human connectome at multiple scales with diffusion spectrum MRI. J Neurosci Methods203 386–397.
59. Zalesky A, Fornito A, Bullmore ET (2010): Network-based statistic: Identifying differences in brain networks. Neuroimage 53:1197–1207.
60. Sarwar T, Ramamohanarao K, Zalesky A (2019): Mapping connectomes with diffusion MRI: Deterministic or probabilistic tractography? Magn Reson Med 81:1368–1384.
61. de Reus MA, van den Heuvel MP (2013): Estimating false positives and negatives in brain networks. Neuroimage 70:402–409.
62. Repple J, Mauritz M, Meinert S, de Lange SC, Grotegerd D, Opel N, *et al.* (2019): Severity of current depression and remission status are associated with structural connectome alterations in major depressive disorder. Mol Psychiatry 25:1550–1558.
63. Rucker DD, Preacher KJ, Tormala ZL, Petty RE (2011): Mediation analysis in social psychology: current practices and new recommendations. Soc Personal Psychol Compass 5:359–371.
64. Winokur A, Maislin G, Phillips JL, Amsterdam JD (1988): Insulin resistance after oral glucose tolerance testing in patients with major depression. Am J Psychiatry 145:325–330.
65. Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambrée O, de Wit H, *et al.* (2016): Inflammatory cytokines influence measures of white matter integrity in bipolar disorder. J Affect Disord 202:1–9.
66. Xiang B, Wang Q, Lei W, Li M, Li Y, Zhao L, *et al.* (2019): Genes in immune pathways associated with abnormal white matter integrity in first-episode and treatment-naïve patients with schizophrenia. Br J Psychiatry 214:281–287.
67. Wang F, Mcintosh AM, He Y, Gelernter J, Blumberg HP (2011): The association of genetic variation in CACNA1C with structure and function of a frontotemporal system. Bipolar Disord 13:696–700.
68. Dennis EL, Jahanshad N, Braskie MN, Warstadt NM, Hibar DP, Kohannim O, *et al.* (2014): Obesity gene *NEGR1* associated with white matter integrity in healthy young adults. Neuroimage 102(Pt 2):548–557.
69. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, *et al.* (2013): Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. Depress Anxiety 30:515–527.
70. Repple J, Meinert S, Bollettini I, Grotegerd D, Redlich R, Zaremba D, *et al.* (2020): Influence of electroconvulsive therapy on white matter structure in a diffusion tensor imaging study. Psychol Med 50:849–856.
71. Meinert S, Repple J, Nenadic I, Krug A, Jansen A, Grotegerd D, *et al.* (2019): Reduced fractional anisotropy in depressed patients due to childhood maltreatment rather than diagnosis. Neuropsychopharmacology 44:2065–2072.
72. Peyrot WJ, Milaneschi Y, Abdellaoui A, Sullivan PF, Hottenga JJ, Boomsma DI, Penninx BWJH (2014): Effect of polygenic risk scores on depression in childhood trauma. Br J Psychiatry 203:113–119.
73. Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, *et al.* (2017): Genetic association of major depression with a typical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry 74:1214–1225.
74. Tesli M, Espeseth T, Bettella F, Mattingsdal M, Aas M, Melle I, *et al.* (2014): Polygenic risk score and the psychosis continuum model. Acta Psychiatr Scand 130:311–317.
75. Roiser JP, Sahakian BJ (2013): Hot and cold cognition in depression. CNS Spectrums 18:139–149.
76. Xia M, Wang J, He Y (2013): BrainNet Viewer: A network visualization tool for human brain connectomics. PLoS One 8:e68910.