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Archival Report

Impact of Polygenic Risk for Schizophrenia on Cortical Structure in UK Biobank

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ABSTRACT

BACKGROUND: Schizophrenia is a neurodevelopmental disorder with many genetic variants of individually small effect contributing to phenotypic variation. Lower cortical thickness (CT), surface area, and cortical volume have been demonstrated in people with schizophrenia. Furthermore, a range of obstetric complications (e.g., lower birth weight) are consistently associated with an increased risk for schizophrenia. We investigated whether a high polygenic risk score for schizophrenia (PGRS-SCZ) is associated with CT, surface area, and cortical volume in UK Biobank, a population-based sample, and tested for interactions with birth weight.

METHODS: Data were available for 2864 participants (n_{male}/n_{female} = 1382/1482; mean age = 62.35 years, SD = 7.40). Linear mixed models were used to test for associations among PGRS-SCZ and cortical volume, surface area, and CT and between PGRS-SCZ and birth weight. Interaction effects of these variables on cortical structure were also tested.

RESULTS: We found a significant negative association between PGRS-SCZ and global CT; a higher PGRS-SCZ was associated with lower CT across the whole brain. We also report a significant negative association between PGRS-SCZ and insular lobe CT. PGRS-SCZ was not associated with birth weight and no PGRS-SCZ × birth weight interactions were found.

CONCLUSIONS: These results suggest that individual differences in CT are partly influenced by genetic variants and are most likely not due to factors downstream of disease onset. This approach may help to elucidate the genetic pathophysiology of schizophrenia. Further investigation in case-control and high-risk samples could help identify any localized effects of PGRS-SCZ, and other potential schizophrenia risk factors, on CT as symptoms develop.

Keywords: Birth weight, Cortical surface area, Cortical thickness, Cortical volume, Polygenic risk, Schizophrenia

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Schizophrenia is a heterogeneous psychiatric disorder with twin heritability estimates (h^2) of ~80% (1–3). Recent evidence suggests that the disorder is polygenic in nature (1–4), with genome-wide association studies (GWASs) identifying schizophrenia-inferring loci (3,5,6). Supporting a neurodevelopmental theory of schizophrenia, cortical decreases have been consistently associated with the disorder, are thought to predate disorder onset (7–9), and are caused by a combination of genetic and environmental factors (7,8). Limited research has explored the links between polygenic risk for schizophrenia (PGRS-SCZ) and cortical structure with consideration of other schizophrenia risk factors.

Differences in some aspects of brain structure have been consistently detected in groups of patients with schizophrenia compared with healthy control subjects (10). Recently, the field has moved toward studying cortical volume (CV), cortical thickness (CT), and surface area (SA) of the brain. These metrics are considered to have distinct developmental trajectories (11) and are heritable; h^2 ranges from 66% to 97% for CV (12) and averages around 80% for global CV (13,14), 81% for CT (15), and 89% for SA (15).

CV has been most studied in schizophrenia, with reports of lower CV in widespread areas of the brain in patients (10,16–24) and in the healthy relatives of individuals with schizophrenia as compared with control subjects (21,25–27). However, as CV is the product of CT and SA (11,15,28), studying volume alone may obscure some schizophrenia and brain structure associations (10,15). Lower CT has been evidenced in several brain regions (10,29–35) and widespread areas across the cortex (10,21,31,35–40) in those at greater genetic risk of and/or with schizophrenia. Furthermore, CT differences have been found in frontal and temporal lobes of individuals at familial high risk of schizophrenia when compared with control subjects (21,40–44) and thus may be more easily identified in those with a higher genetic risk of the disorder. SA has been less researched and with more contradictory results (24). Some studies suggest that SA is lower in patients with schizophrenia compared with control subjects both globally (45) and in specific regions (18,24,30,35,45),

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whereas others have found SA to be higher (34,46) or no different (36,47) in these groups.

Recently, large GWASs ($n_{individuals}$ = 36,989 cases, 113,075 control subjects) have been used to derive PGRS-SCZ (3,5,6); higher scores relate to a greater risk of developing schizophrenia. PGRS-SCZ allows for the assessment of genetic liability in the general population—even among people who may never develop schizophrenia—and enables use of large-scale samples such as UK Biobank (UKB) (Stockport, Scotland; http://www.ukbiobank.ac.uk/).

A small number of studies have tested PGRS-SCZ in relation to structural brain imaging phenotypes with inconsistent results. Reus *et al.* (48) found no associations between regional subcortical volume or white matter microstructure and PGRS-SCZ using a subset of the same sample as the current study (n = 978), but they did not assess any cortical metrics. Some studies have reported higher PGRS-SCZ to be associated with a decrease in global gray and/or white matter volume (49–51) ($n_{individuals}$ range 89 to 274) with relatively small effect sizes and amount of variance explained ($\beta = -.151$, $\Delta R^2 = .023$ [change in R^2 for regional white matter volume when PGRS-SCZ is added to hierarchical regression analyses]), $R^2 = .042$ (total brain volume), while others did not find an effect (52,53) ($n_{individuals}$ range 122 to 763). Higher PGRS-SCZ has also been previously associated with lower global CT in a case-control sample, regardless of group (54) ($\eta p^2 = .116$ [left hemisphere]; .121 [right hemisphere]). Lancaster *et al.* (55) found no such association in a control sample but did report nominal regional CT effects. Owing to the limited sample sizes in these CT investigations ($n_{individuals}$ range 75 to 99), further testing is required.

Another important consideration with regard to neurodevelopmental theories of the disorder (7–9) relates to potential effects of other risk factors for schizophrenia and their interactions between schizophrenia liability and cortical structure. Several obstetric complications (OCs), for example, have been consistently identified as risk factors for schizophrenia (56–63), with some, such as birth weight (BW), considered to be influenced by both genetic and environmental components (64). Previous studies have also suggested that OCs are associated with greater cortical structure deficits in patients with schizophrenia compared with control subjects (27,63). All three of the current cortical metrics are considered to be highly susceptible to both genetic and environmental factors (65), with subtle differences in BW, in particular, previously linked to lower CV, SA (66–68), and CT (67) later in life. Moreover, evidence suggests that a genetic liability for schizophrenia can lead to higher susceptibility for experiencing OCs (69,70) and that these complications could themselves be associated with the schizophrenia-associated genes (56). Given these findings, we also tested whether PGRS-SCZ was associated with BW and if any interactions were present between the two in relation to cortical structure.

The current study tests for associations between PGRS-SCZ and cortical structure (CV, SA, and CT), in a population-based sample, with the specific hypothesis that a higher PGRS-SCZ would be associated with lower global CT. Lower global, frontal, and temporal CT in particular has been found in those at familial high risk, and global CT has been previously associated with a higher PGRS-SCZ (54). Furthermore, we predicted that these effects would interact with BW; individuals with a higher PGRS-SCZ with lower BW would have smaller CV, CT, and SA.

METHODS AND MATERIALS

Participants

Detailed participant information for UKB has been reported previously (71) (http://www.ukbiobank.ac.uk/participants/) and in Supplemental Methods. The current sample included individuals with complete genetic and cortical data for three parameters (CV, SA, and CT). Participants were excluded based on overlap in Psychiatric Genomics Consortium (PGC) prediction samples and schizophrenia status (see Derivation of Polygenic Risk Score section and Supplemental Methods). Global cortical outliers (±3 SDs) were removed for all three parameters. Thus, the current sample consisted of 2864 individuals (n_{male}/n_{female} = 1382/1482; mean age at time of scan = 62.35 years, SD = 7.40 years, range 46 to 78 years). Ethical approval for UKB was received from the research ethics committee (REC Reference No. 11/NW/0382) under application 4844. Informed consent was provided by all participants (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

Imaging Procedures

UKB imaging details are described in full elsewhere (71–73) (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Briefly, structural images were acquired on a single 3T Siemens Skyra scanner (Siemens, Munich, Germany). Structural brain images were acquired in the sagittal plane using a T1-weighted magnetization prepared rapid acquisition gradient-echo sequence (1 × 1 × 1 mm resolution). Further information on the imaging protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367) and acquisition parameters (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) are documented online. Brain scans were processed locally in Edinburgh, using FreeSurfer (version 5.3; http://surfer.nmr.mgh.harvard.edu/), on a server cluster at Centre for Cognitive Ageing and Cognitive Epidemiology (http://www.ccace.ed.ac.uk/).

Magnetic Resonance Imaging Analysis

T1-weighted volumes from the first UKB imaging release were used to derive cortical measures of CT (mm), SA (mm^2), and CV (mm^3). Parcellation was conducted using the Desikan-Killiany neuroanatomical atlas (74), generating 34 bilateral cortical parcels, attributed to eight lobar structures, each with CV, SA, and mean CT measures (74). Eleven parcels were combined into four larger regions as was done previously (75,76), resulting in 27 bilateral regions of interest in total (see Supplemental Methods). The x, y, and z coordinates of the center of the brain mask within the scanner were fitted as covariates for the current analyses to account for varying head positions in the scanner (see Supplemental Methods).

Magnetic Resonance Imaging Quality Control Procedures

Quality checks of T1-weighted images were initially carried out by UKB (Brain Imaging Documentation V1.1, http://www.ukbiobank.ac.uk) (72) with further local quality control (QC)

procedures [see (76), http://enigma.ini.usc.edu/protocols/imaging-protocols/, and Supplemental Methods].

Genotyping and Imputation Processing

Procedures for genotyping, imputation, and QC for UKB have been reported previously (77–79). Briefly, 488,377 blood samples were assayed using two different genotyping arrays: Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (Applied Biosystems and Affymetrix, divisions of Thermo Fisher Scientific, Waltham, MA) (77) and Applied Biosystems UKB Axiom Array (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf); see Supplemental Methods.

Genetic QC was performed using the approach described by Howard *et al.* (79). First, participants were excluded based on shared genetic relatedness up to the third degree using kinship coefficients (>0.044) identified using the KING toolset (80), as was done previously (79,81). To maximize the sample, we subsequently added back in one member from each group of related individuals, using a genomic relationship matrix, and selected only those with a relatedness of less than 0.025 with any other individual. Individuals were also excluded based on a combination of both self-reported ethnicity and a principal component (PC) analysis (see Supplemental Methods) that revealed individuals with similar ancestral backgrounds. Final QC exclusion criteria included variant missingness per individual (>2%), sex mismatch, variant call rate (<98%), Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$), minor allele frequency < 0.01, and an imputation quality < 0.1, resulting in 331,374 individuals and 7,730,951 variants.

Derivation of Polygenic Risk Score

PGRS-SCZ were constructed using PLINK (version 1.9; https://www.cog-genomics.org/plink/1.9/) (82) to calculate the sum of all alleles that are associated with schizophrenia, across many genetic loci, and weighting these alleles by their effect sizes. These effect sizes have been previously estimated (PGC-SCZ, https://www.med.unc.edu/pgc/pgc-workgroups) in GWASs (36,989 cases, 113,075 control subjects) (5). Individual identifiers were not available for PGC-SCZ within this sample; thus, in an attempt to reduce the likelihood of any potential overlap between PGC-SCZ and the current sample, individuals from the PGC Major Depressive Disorder working group prediction sample (83) were excluded (n = 92). For the same reason, UKB individuals who reported a diagnosis of schizophrenia were also excluded (n = 812) (see Supplemental Figure S1). Schizophrenia status was determined from two separate variables within UKB: ICD-10 diagnosis (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=41202; F20–F29: Schizophrenia, schizotypal, and delusional disorders) and noncancer illness (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002). The former is a summary of the distinct diagnoses given from episodes in hospital; the latter was coded by a trained nurse based on the description of a noncancer illness given by the participant.

To create a single nucleotide polymorphism (SNP) set in approximate linkage equilibrium, clump-based linkage disequilibrium pruning was performed with an R^2 of <.25 within a 200-kb window. For the remaining SNPs, marker weights (logarithm of the odds ratio) and p value association statistics for individual SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million autosomal SNPs) (5). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal p value thresholds of ≤ .01, .05, .1, .5, and 1, as was previously described (3). The SNP inclusion threshold was set at $p \leq .1$ for the current study, as this threshold was shown to explain the most phenotypic variance in the discovery cohort (5). There were 86,124 SNPs, available in the current sample after QC, using the $p \leq .1$ threshold (see Supplemental Methods). For results produced using the remaining SNP inclusion thresholds ($p \leq .01$, .05, .5, and 1), see Supplemental Methods. PCs were also calculated to account for population stratification (see Supplemental Methods); the first 15 PCs were used in the current analysis.

Measure of BW

Participants were asked to provide their own BW information (see Supplemental Methods). Recalled BW has been shown to have high agreement with recorded BW and was considered a valid measure for epidemiological studies (84). BWs range from 0.91 to 5.78 kg (mean = 3.40 kg, SD = 0.61 kg).

Covariate Socioeconomic Deprivation

Covariate socioeconomic deprivation (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189) was measured using the Townsend deprivation index (see Supplemental Methods) (range −6.26 to 9.16, mean = −1.98, SD = 2.68).

Standing Height

Standing height (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=50) was measured using a Seca 202 device (Seca, Hamburg, Germany) (range 143 to 196 cm, mean = 169.74 cm, SD = 9.20 cm).

Statistical Analysis

All analyses were conducted in R (version 3.2.3; R Foundation, Vienna, Austria; https://cran.r-project.org/bin/windows/base/old/3.2.3/).

Associations Between PGRS-SCZ and Cortical Structure. Linear mixed effects (LME) models (R, "nlme" package version 3.1-127) were used to determine whether PGRS-SCZ were associated with cortical structures.

LME models were first conducted in a repeated measures format, with hemisphere fitted as a random factor, as was previously reported (48,85). PGRS-SCZ × hemisphere interactions were also tested to determine whether analysis of left and right homologous structures separately was required.

For the main analyses, an LME model was tested that included age, age^2, sex, genotype array, 15 PCs, and x, y, and z coordinates of the brain mask within the scanner as fixed effects. Intracranial volume was included as a fixed effect for lobar and parcellation analyses.

Standardized regression coefficients are reported throughout. Utilizing the "p.adjust" function (R, "stats" package version 3.2.3), the false discovery rate (FDR) method, with

a rate of $p < .05$ (86), was used to correct results for multiple comparisons. Henceforth, FDR-corrected p values will be referred to as p_{FDR}.

In the first instance and in line with our main hypothesis, we tested for associations between PGRS-SCZ and global cortical structure. These PGRS-SCZ global cortical associations were FDR corrected across CV, CT, and SA at each PGRS-SCZ SNP inclusion threshold individually. Associations between PGRS-SCZ and regional cortical structures were tested for if global cortical associations were evident, first at the lobar and then at the parcellation level. Thus, for post hoc regional associations, p_{FDR} was calculated for each cortical metric individually, by correcting over all eight possible lobar structures or 27 parcellations for each PGRS-SCZ p threshold.

In the main text, we only report statistically significant associations ($p_{FDR} < .05$) between PGRS-SCZ and cortical brain structure. Furthermore, the reported results were analyzed using the SNP inclusion threshold of $p \leq .1$ as this threshold explained the most phenotypic variation in the discovery cohort ($R^2 = \sim.18$) (5). Nonsignificant associations and results for all other thresholds as can be found in Supplemental Results.

Associations Between PGRS-SCZ and BW. Using the full sample of individuals with cortical, genotype, and BW information, excluding global cortical outliers ($n = 1659$, $n_{male}/n_{female} = 696/963$; mean age at time of scan = 60.79 years, SD = 7.41 years, range 46 to 78 years), a generalized linear model regression (R, "glm2" package version 1.1.3) was used to test for associations between PGRS-SCZ and BW. This model included all fixed effects used in the previous model, with the addition of height and socioeconomic deprivation [see (67,68)] as fixed effects. LME models, using these same fixed effects, hemisphere as a random factor, and an additional PGRS-SCZ × BW interaction, along with main effects terms, were also used to test for potential interactional effects on cortical structure.

RESULTS

Demographics

Statistical analyses were conducted to determine whether any of the demographic variables were associated with PGRS-SCZ at threshold $p \leq .1$ (see Table 1). No significant associations were found ($p > .05$).

Associations Between PGRS-SCZ and Cortical Structure

Results for PGRS-SCZ × hemisphere interactions on cortical structure can be found in Supplemental Tables S2–S4. No significant hemisphere interactions were found in the current study ($p > .05$); thus, all analyses were conducted utilizing the aforementioned repeated measure design.

Significant negative associations between PGRS-SCZ and global CT ($\beta = -.043$, $p = .012$, $R^2 = .002$) and CV ($\beta = -.033$, $p = .039$, $R^2 = .001$) were found, in that a higher PGRS-SCZ was associated with lower CT and CV across the whole brain. However, only the association with CT remained significant after multiple correction across all three metrics (CT $p_{FDR} = .036$, CV $p_{FDR} = .059$). PGRS-SCZ was also negatively associated with insular lobe CT ($\beta = -.050$, $p_{FDR} = .025$, $R^2 = .002$).

No significant associations between PGRS-SCZ and SA were found; this was true for all global, lobar, and parcellation measures (see the Supplement).

Table 1. Descriptive Statistics for Demographic Variables and Their Associations With PGRS-SCZ

	Mean or n	SD	Range	Test Statistic, p Value
Sex				$\chi^2 = 2707.8$, $p = .513$
Male	1382			
Female	1482			
Age, Years	62.35	7.40	46 to 78	$r = -.003$, $p = .863$
Birth Weight, kg	3.40	0.61	0.91 to 5.78	$r = -.044$, $p = .069$[a]
Height, cm	169.73	9.12	143 to 196	$r = -.033$, $p = .077$[a]
Townsend Deprivation Scale	−1.98	2.68	−6.26 to 9.16	$r = .017$, $p = .363$

Mean, SD, and range of all demographic variables within the current sample as well as test statistics for associations with PGRS-SCZ at the $p \leq .1$ threshold ($n = 2864$).

PGRS-SCZ, polygenic risk score for schizophrenia.

[a]$p \leq .10$.

Associations Between PGRS-SCZ and BW

There was no significant association between PGRS-SCZ and BW (see Table 2).

Effects of Interactions Between BW and PGRS-SCZ on Cortical Structure

No significant interactions between BW and PGRS-SCZ were found with respect to associations with global CV or CT. See Supplemental Tables S6 to S8 for full results.

DISCUSSION

We report an association between an increased genetic liability for developing schizophrenia and lower global CT and CV, as well as insular lobe CT. In this and previous studies (54,87), we primarily test and report corrected results using SNPs with $p \leq .1$. We also include results corrected over all three cortical metrics to illustrate the effects of more stringent control for multiple comparisons and note that the association between PGRS-SCZ and global CV was not significant after this correction. This is one of the first studies to analyze

Table 2. Results for Associations Between PGRS-SCZ and Birth Weight at All p Thresholds

PGRS Threshold	Effect Size	SD	p Value	p_{FDR}
$p \leq .01$	−.016	0.024	.513	.513
$p \leq .05$	−.037	0.024	.122	.305
$p \leq .1$	−.041	0.024	.090	.305
$p \leq .5$	−.021	0.024	.380	.513
$p \leq 1$	−.019	0.024	.423	.513

Standardized β (effect size), SD, and p values for all associations as well as false discovery rate-corrected p values (p_{FDR}) over all five PGRS single nucleotide polymorphism–inclusion thresholds ($n = 1659$).

PGRS-SCZ, polygenic risk score for schizophrenia.

associations for CV, CT, and SA measures within a single large, population-based sample, and to examine the association between these parameters and PGRS-SCZ. These results suggest that lower CT, commonly reported in patients with schizophrenia, may be driven by a genetic liability for schizophrenia and is most likely not due to factors downstream of disease onset [e.g., medication use (88)]. No significant associations were found for SA.

Previous study of associations between PGRS-SCZ and brain volume have been inconsistent. Lee *et al.* (89) found intracranial volume to be significantly linked with enrichment of schizophrenia-associated genetic variants, but they could not determine the direction of these effects. Another study, utilizing a PGRS-SCZ created from the first PGC-SCZ GWAS (90), found an association between decreased total brain volume and higher PGRS-SCZ (49), but attempts to replicate these results, with the most recent PGC-SCZ GWAS findings (5), have so far been unsuccessful (52,53). However, the sample sizes used within these studies are relatively small ($n_{individuals}$ range 122 to 763). This is especially pertinent when considering that despite the current sample's being much larger ($n_{individuals}$ = 2864) than the samples of these previous studies, our CV result did not survive FDR corrections for multiple comparisons over all three cortical metrics. Thus, further testing in even larger population-based samples is desirable.

The global CT association is consistent with previous familial high-risk studies for schizophrenia, which also found thinning in widespread areas of the cortex both longitudinally (42,44,47) and cross-sectionally (21,40,41,43). A genetic enrichment study also found several CT parcels to be associated with schizophrenia risk variants (89). Furthermore, a case-control study found that a higher PGRS-SCZ was associated with lower global CT in both the schizophrenia-only analysis and in the whole sample (54). Specific links between reduced insular CT and genetic risk for schizophrenia have been less commonly reported, although reductions in this region, among others, have been found in patients with schizophrenia compared with control subjects and individuals at high genetic risk of the disorder (41). Additionally, the insula is a region commonly reported to be involved in schizophrenia symptomatology [e.g., auditory hallucinations (91)].

That no PGRS-SCZ associations were found for SA is not entirely surprising. Evidence of SA abnormalities associated with schizophrenia has been inconsistent (24) and has been described as a "weak intermediate phenotype" for schizophrenia (20). However, evidence does suggest that this phenotype is highly heritable (15) and is associated with some deficits in the healthy relatives of patients with schizophrenia (21). A general limitation of PGRS, at present, is that the amount of phenotypic variation that they explain is far smaller than the heritability of the phenotype (48,92); thus, it may be that the predictive power of PGRS-SCZ in combination with the current sample size is not large enough to detect an effect with SA.

No association was found between PGRS-SCZ and BW, nor were there interaction effects between these two factors within global CT. As previous studies have found lower BW to be associated with lower CV (66–68), thinning and thickening across the cortex (67,93), an increased risk of schizophrenia (60–62), and several independent SNPs (94,95), we expected to find links among these factors. However, the current findings suggest that genetic variants for schizophrenia and BW could have independent effects on CT. Further investigation is needed to determine this.

Strengths and Limitations

The main limitation of the current study and PGRS-SCZ studies in general is that, at present, the variance of schizophrenia explained by PGRS is relatively small [around 2%–3% (3)] and that larger sample sizes could significantly increase the power of this method (96). Despite this study's being the largest imaging PGRS study to date, with 2864 individuals (48,49,52,53), it is still relatively small compared with other PGRS studies [e.g., (97–99)]. Furthermore, a post hoc analysis (see Supplemental Results) suggests that the current study was underpowered (5%–41%) for some analyses, highlighting the need for even larger imaging samples. Current calculations suggest that a sample of at least ~21,500 is required to reliably detect some effects of current PGRS-SCZ on cortical structure. Given UKB's goal of acquiring 100,000 scans by 2022 (https://imaging.ukbiobank.ac.uk/), we should be able to improve our sample size in the near future. This sample size, coupled with larger discovery GWASs, will allow for detection of smaller effects (48,100,101) and may eventually allow PGRS to be used in the development of personalized medicine (100); however, further research would be necessary.

A further limitation, related to the derivation of the PGRS-SCZ, is that we were unable to remove any individuals utilized in the discovery dataset for the PGC Schizophrenia Working Group that may also be included in the current UKB sample, as this information is not currently available. However, owing to the methodological efforts made to overcome this issue (e.g., exclusion of schizophrenia cases and identifications from the PGC Major Depressive Disorder group), we believe this limitation to be relatively minor as effects will be restricted to control subjects only.

Although multicenter collaborations have made larger samples more achievable, different acquisition protocols could lead to variability in image contrast and, in turn, discordance over brain segmentation between sites, necessitating the development of reliable acquisition protocols to attempt to reduce such issues (35,102). A strength of the current study is that all brain images were collected on a single scanner using the same protocol and analysis pipeline, thus bypassing multiscanner variability problems and the need to assess reliability. Furthermore, as UKB is a population-based sample and all schizophrenia cases were excluded, we are also able to test for associations while avoiding confounds such as secondary effects of illness or antipsychotic medication use (88).

Previous studies have reported that individuals at high familial risk who developed schizophrenia have significantly higher PGRS-SCZ than those at high risk who remained well and that these PGRS are positively associated with gyral folding (87). It is possible that there are different genetic associations for different brain measures than we derived for in the current study. Given that the current sample consisted of older individuals (age, 46–78 years; mean = 62.3), compared with most schizophrenia studies (49,50,52,53,103), which commonly include age ranges that more closely map to age of

disorder onset (18 to 55 years), we cannot rule out effects of aging on the current results. Further investigation in prospective case-control samples is required.

Although the inclusion of BW, a proxy for OCs and risk factor for schizophrenia that is influenced by both genetic and environmental factors (60–62,65), is a strength of the current study, we cannot rule out environmental effects on our current findings. For example, both cannabis use and developmental trauma have been linked with reductions in CT (104), and an accumulation of environmental risk factors (including migration, cannabis use, urbanicity, OCs, and adverse events) has been associated with lower temporal CT (54). Furthermore, cannabis use has been found to moderate the link between PGRS-SCZ and cortical maturation (105). Thus, environmental risk factors should be explored in further studies of potential gene-by-environment interactions on structural brain measures in schizophrenia.

Conclusions

In summary, our current finding is that lower global CT, as well as insular lobe CT, is associated with an increased genetic loading for schizophrenia. This provides further evidence that individual differences in CT are, at least partly, influenced by a genetic component. Importantly, these findings also suggest that the schizophrenia and CT associations, reported here and in previous literature, are most likely not confounded by factors downstream of disorder onset (e.g., use of medication). Furthermore, it suggests that using a PGRS approach may help to elucidate the genetic pathophysiology of the disorder; as GWASs and genomic imaging studies get larger, they could identify how more specific genetic, expression, and pathway effects impact global and/or particular brain structures, connections, and networks. Further consideration of environmental risk factors for schizophrenia will also be crucial to understanding the nature of the relationship between schizophrenia and cortical structure.

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The UKB team collected data. EN and XS analyzed the data. SML, AMM, and HCW supervised the analysis. XS, SRC, T-KC, MJA, DMH, EMW, and JG contributed reagents, materials, and/or analysis tools. EN, XS, SRC, EMW, JG, DMH, MJA, MAH, and GD aided in quality control of magnetic resonance imaging and genetic data. EN prepared the manuscript. SML, IJD, DMH, and T-KC performed additional editing. All authors commented on drafts of the article.

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ARTICLE INFORMATION

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