Effects of autozygosity and schizophrenia polygenic risk on cognitive and brain developmental trajectories

Aldo Cordova-Palomera[a,*], Tobias Kaufmann[a], Francesco Bettella[a], Yunpeng Wang[a], Nhat Trung Doan[a], Dennis van der Meer[a], Dag Alnæs[a], Jaroslav Rokicki[a,b], Torgeir Moberget[a], Ida Elken Sønderby[a], Ole A. Andreassen[a], Lars T. Westlye[a,b,*]

[a] NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Norway

[b] Department of Psychology, University of Oslo, Oslo, Norway

* Corresponding authors: Aldo Cordova-Palomera, Ph.D., email: aldoc@medisin.uio.no, and Lars T. Westlye, Ph.D., email: l.t.westlye@psykologi.uio.no. Postal address: Oslo University Hospital, PoBox 4956 Nydalen, 0424 OSLO, Norway, Telephone: +47 23 02 73 50, Fax: +47 23 02 73 33.

Supported by the Research Council of Norway (204966, 249795, 223273, 213837); the South-Eastern Norway Regional Health Authority (2012-047, 2013-123, 2015-073, 2016-083); European Community's 7th Framework Programme (602450, IMAGEMEND), and Kristian Gerhard Jebsen Foundation.

Word count of abstract: 233 | Word count of text: 5254 | Number of tables: 2 | Number of figures: 3

ABSTRACT

Cognitive and brain development are determined by dynamic interactions between genes and environment across the lifespan. Aside from marker-by-marker analyses of polymorphisms, biologically meaningful features of the whole-genome (derived from the combined effect of individual markers) have been postulated to inform on human phenotypes including cognitive traits and their underlying biological substrate.

Here, estimates of inbreeding and schizophrenia genetic susceptibility calculated from genome-wide data –runs of homozygosity (ROH) and schizophrenia polygenic risk score (PGRS)– are analyzed in relation to cognitive and brain development in a general-population sample of 4,183 European-ancestry participants aged 8-22, from the Philadelphia Neurodevelopmental Cohort.

The findings suggest that a higher ROH burden and higher schizophrenia PGRS are associated with increased intelligence, both independently and in interaction (ROH×PGRS). Cognition~ROH and cognition~PGRS associations are in line with previous reports, and may respectively evidence that assortative mating influences intelligence, and that individuals with high schizophrenia genetic risk who do not transition to disease status are cognitively resilient. Additionally, ROH×PGRS significant interaction effects indicate that more inbred individuals are more likely to display higher cognitive test scores in the presence of high schizophrenia polygenic risk score.

Neuroanatomical data from a subset of 516 individuals showed that the effects of schizophrenia PGRS on cognition could be modulated by brain structure, although larger imaging datasets are needed to accurately disentangle the underlying neural mechanisms linking IQ with both inbreeding and the genetic burden for schizophrenia.

KEYWORDS

Neurodevelopment; autozygosity; polygenic risk; cognition; schizophrenia; MRI

INTRODUCTION

Cognitive abilities and neural development are determined by complex and dynamic interactions between environmental influences and the individual genetic architecture across the lifespan [1,2]. The genetically-driven temporal regulation is especially noticeable in the transition from childhood to adolescence and adulthood, and can have both immediate and lagged effects on the risk for psychiatric disorders depending on the timing of gene expression and the relevant environmental perturbations, which jointly determine the individual age of onset of the clinical phenotypes [3]. Studies on the molecular genetic architecture of cognitive and structural brain phenotypes are eliciting previous findings from quantitative genetics (i.e., heritability) [4,5]. However, a large fraction of those underlying molecular genetic mechanisms –and their relation to developmental trajectories– remains to be revealed.

The advent of easily accessible genome-wide scans has created opportunities for different types of population-based genetic analyses of human traits [6], including cognition and neuroanatomy. Aside from the conventional marker-by-marker analyses of single nucleotide polymorphisms (SNPs), accumulating evidence suggests that different global features of the genome –derived from the combined effect of SNPs, usually from high-density whole-genome data– can elucidate otherwise unexplained genetic variance linked to human phenotypes [7]. In this regard, two biologically meaningful multivariate features of the whole-genome have recently been popularized and can potentially inform on the molecular basis of neurodevelopmental trajectories: runs of homozygosity (ROHs) [8] –an estimate of inbreeding– and schizophrenia polygenic risk scores (PGRSs) [9] –a widely replicated measure of cumulative genetic burden for a (largely) neurodevelopmental disorder.

ROHs are stretches of consecutive homozygous SNPs that occur frequently in humans and can inform on population history, evolution and diversity [10,11]. They can be considered to index autozygosity: the inheritance of two chromosomal segments from a common ancestor, which would be related to inbreeding [10]. Interestingly, long ROHs display large inter-individual variation and seem to reflect the level of *recent* inbreeding [11] (mating of close relatives, in contrast to *distant* inbreeding). Across species, the occurrence of close inbreeding has classically been associated with decreased fitness and increased risk for Mendelian diseases, which is known as inbreeding depression [12]. This phenomenon is thought to be caused by increased homozygosity at loci exhibiting either partially recessive detrimental mutations or overdominance [12]. Recent reports suggest that inbreeding, as indexed by long ROHs from whole-genome data, could explain part of the variability observed across humans in a broad range of phenotypes [13,14]. Remarkably, while the ROH burden could influence multiple human traits, so far the evidence indicates mostly small effect sizes, and assortative mating (phenotypically-similar individuals mating each other) could partly explain those findings [8,14,15].

Previous research suggests that ROH could be linked to human cognitive abilities, both across the general population and discriminating healthy from abnormal cognitive function [8,13,16]. Studies on ROH

and cognition in the general population have shown mixed results, with moderate effect sizes in virtually all cases. In perhaps the largest set of cohorts assembled to date, increased ROH burden was associated with decreased cognitive ability in a meta-analysis of 26 cohorts of adults (*n* = 53,300) with diverse ancestries, assembled in an international multi-sample study [13]. Similarly, in another multi-site effort comprising 4,854 European-ancestry adult participants from nine different samples were gathered, and increased ROH was associated with a reduction in cognitive ability [16]. In contrast, in perhaps the most similar study to this one, [8] reported higher cognitive ability at age 12 with higher ROH burden in a homogeneous British sample of 2,329 European-ancestry participants from the WTCCC2 project. While the former two studies [13,16] suggest that inbreeding depression plays a role in adult intelligence, the divergent results by [8] could be explained in view of three evidences. First, assortative mating has recently been highlighted as an important factor underlying psychiatric and behavioral phenotypes [17-20], in line with specific findings showing assortative mating in relation to cognitive ability published in the late 20th century [21,22]. Secondly, similar to the age-varying pattern for the heritability of cognition [23,24], the genetic effect of ROH on cognition may be different across the lifespan. And thirdly, differences in ROH burden calculation between the report by [13] and the other two studies [8,16] may have also played a role.

Regarding schizophrenia PGRS and neurodevelopment, growing evidence indicates that the genetic architectures of schizophrenia and cognition are shared to a relatively large extent in young and middle-aged adults [25], and that the shared genetic variance between cognition and schizophrenia risk might be age-dependent [26], calling for further research on lifespan patterns. In fact, Germine et al. [27] reported that higher schizophrenia PGRS is linked to decreases in both speed of emotion identification and speed of verbal reasoning in healthy young individuals from the Philadelphia Neurodevelopmental Cohort (PNC); those effects were relatively stable across the sampled age range, starting at ~9 years old. Consistently, [28] recently found an association between schizophrenia PGRS and specific cognitive abilities in adults. While postulating that the latter findings are mediated by alterations in specific brain regions is presumably straightforward, some studies have not found an overlap between schizophrenia PGRS and subcortical phenotypes derived from magnetic resonance imaging (MRI) [29], whereas others suggest an association with cortical thickness/surface area [30]. Replication studies using independent samples and probably different brain features are thus needed.

With this background, using an informative sample of 4,183 young participants (ages 8-22) with European-ancestry from the PNC, we pursue the following four main aims. First, the putative links between multivariate genome-wide features (ROH burden and schizophrenia PGRS, computed independently) and both intellectual abilities and a thorough set of neuroanatomical features are tested. Secondly, potential age-modulating effects on relevant outcomes of the latter analysis are tested. Thirdly, whether inbreeding modifies the effects of genome-wide schizophrenia burden on cognition and brain anatomy is evaluated by combining ROH and PGRS measures. Finally, the presence of brain anatomy differences mediating the associations between ROH/PGRS and cognition is assessed from a causal

mediation framework. Using those elements, the overall goal of this work is to outline potential neurodevelopmental pathways leading from biologically meaningful whole-genome features to neural and ultimately cognitive disruptions.

MATERIALS AND METHODS

Participants and measures. The data was retrieved from the PNC public domain resources. The PNC includes more than 9,000 individuals aged 8-22 years drawn from a larger population, enrolled through a joint collaborative effort of the Center for Applied Genomics at Children's Hospital of Philadelphia and the Brain Behavior Laboratory (University of Pennsylvania). Briefly, after visiting the Children's Hospital of Philadelphia to seek attention for different medical needs (from general health assessment to chronic conditions and life-threatening problems), those > 9,000 youth individuals accepted an invitation to participate in a research study of complex pediatric disorders. Medical history information was obtained from self-report (at the time of enrollment) and electronically from the hospital's records. The participants were randomly selected, stratified by gender, age and ethnicity; inclusion criteria involved English language proficiency and ability to complete the Computerized Neurocognitive Battery (CNB) [31]; all enrolled participants were able to provide informed consent, and parental consent was also required for subjects under age 18. All individuals underwent a psychiatric evaluation using a structured clinical interview, and the Wide Range Achievement Test (WRAT) [32] was applied. Additionally, MRI data was acquired from a subset of >1,500 individuals. Notice that in the current study, after removing participants with non-European ancestry or due to missing data for relevant variables, 4,183 individuals were included in the main analyses (ROH, PGRS and cognition), and MRI data was available for 516 of them (some subjects were removed mainly on the basis of ethnicity, as detailed in the subsections below). A more comprehensive description of the whole PNC demographics and data collection protocols is provided in previous publications [31,33,34].

Since the data was collected after the subjects visited the Children's Hospital of Philadelphia, they manifested varying severities of medical conditions. As previously described [33], the participants' status can be classified following a hierarchy of levels; in the whole dataset, they were distributed as none/minor (43.4%), mild (33.5%), moderate (22.8%) and severe (0.3%). The current study was performed using a subset of the whole PNC (4,183 participants of European-ancestry), whose distribution of medical severity scores is shown below, along with demographic and cognitive profiles (see *Results - Demographic and clinical data*). In most cases, to prevent genetic and phenotypic confounding due to medical conditions, the ensuing statistical analyses were repeated with and without the inclusion of individuals whose status had been classified as moderate and severe.

Genotyping platforms and genotype imputation. Genotyping was performed by the Center for Applied Genomics, at the Children's Hospital of Philadelphia. The DNA samples from the PNC were genotyped in different batches using the following platforms: Illumina OmniExpress (*n* = 1,657), Illumina Human-610 Quad (*n* = 3,807), Illumina HumanHap-550-v1 (*n* = 556), Illumina HumanHap-550-v3 (*n* = 1,914), Affymetrix Genome-Wide Human SNP Array 6.0 (*n* = 66) or Affymetrix Axiom (*n* = 722) (hereafter, Omni,

Quad, 550-v1, 550-v3, Affy60 and Axiom). From those datasets, only participants with European ancestry were included in the final statistical analyses, in recognition that the inclusion of subjects from other ethnicities might add genetic variability altering both ROH- and PGRS-phenotype association estimates (e.g., homozygosity might differ between ethnicities and across samples with distinct admixture levels [16] , and schizophrenia PGRS might not explain much variance in non-European samples [35]). Further details on genotype imputation can be found in Supplementary Material.

Runs of homozygosity (ROH). The sum of the total length of ROHs across chromosomes 1 to 22 was divided by the total SNP-mappable autosomal length (2.77×10^{-9} bp), to obtain an estimate of ROH burden for each individual (ROH fraction, F_{ROH}). The protocol was based on parameters widely used in previously published manuscripts [8,10,16], with slight modifications based on quality control procedures suggested elsewhere [36]. First, a set of 18 extended regions [36] of high linkage disequilibrium (LD) was removed, as well as indels and all SNPs in chromosomes X, Y and mitochondria. Similarly, participants and markers with high missing rates were excluded (--mind 0.02 --geno 0.005), and other standard SNP filtering parameters were used (MAF < 0.05; HWE < 10^{-3}). Then, to remove redundant markers, each of the filtered genotyping batches was pruned for LD using a VIF threshold of 10 (namely, $R^2 > 0.9$) with window size = 50 SNPs and window shift step = 5 SNPs. Then, F_{ROH} was calculated with PLINK's sliding-window approach (--homozyg command), with a minimum SNP length threshold and window size of 65 SNPs, 5% of missing SNPs allowed and no heterozygote SNPs accepted. The latter PLINK parameters for F_{ROH} estimation were tuned based on a report by Howrigan et al. [10]; in the same PLINK run, allelic matches within pools of overlapping ROHs were formed (--homozyg-match 0.95). While those ROH tuning parameters have been widely used, another potentially informative configuration [10] was implemented separately to evaluate reliability (LD-pruning $R^2 > 0.5$, 50-SNP window, 50-SNP minimum threshold). The outcomes were consistent across approaches; hence, the latter results are not fully reported in the main manuscript body.

Additional features were extracted from the whole-genome datasets to include as covariates in subsequent ROH analyses (see *Statistical Analyses*). First, a list of ~80,000 overlapping SNPs across genotyping arrays (Omni, Quad, 550-v1 and 550-v3) was retrieved, and the first 10 principal components from an identity-by-state matrix were estimated using those ~80,000 SNPs within each quality-controlled batch before LD pruning; moreover, percentage of missing calls (F_{miss}) and SNP-by-SNP homozygosity (F_{SNP}) were calculated for each individual.

Schizophrenia polygenic risk score (PGRS). The imputed genotypes passing quality control (see *Genotyping platforms and genotype imputation*) were used to compute schizophrenia PGRS, based on data published by the Schizophrenia Working Group of the Psychiatric Genomics Consortium [9]. Initially,

SNPs with ambiguous alleles (AT or CG), or in linkage disequilibrium with the local SNP with the smallest *p*-value were removed (the SNP with the smallest *p*-value within a 250kb window is retained, and all neighbors with a linkage disequilibrium $r^2 > 0.1$ are removed; a step known as clumping). Also, SNPs within the major histocompatibility complex region (chromosome 6, 26-33Mb) were omitted, and five hundred different PGRS values were obtained (*p*-value thresholds, $p_{threshold}$, from 0.001 to 0.5, with intervals of 0.001). The former procedures were implemented in PRSice.

As done in former studies [37-39], a specific *p*-value cutoff was chosen for the schizophrenia PGRS (out of the five hundred estimations) by tuning the fitting parameters (adjusted R^2) to maximize the explained variance of independent regression models with cognitive performance as outcome and gender, age, batch and PGRS as dependent variables.

Image acquisition and pre-processing. MRI was performed for a subset of participants at the Hospital of the University of Pennsylvania, by means of a 3T Siemens TIM Trio whole-body scanner (32-channel head coil; gradient performance: 45 mT/m; maximum slew rate: 200 T/m/s). The focus of the current study is on structural brain features derived from 3D T1-weighted images obtained using a MPRAGE sequence (TR: 1.81s; TE: 3.5ms; FA: 9°; FOV: 240×180mm; 1mm slice thickness; 160 slices), whose acquisition parameters have formerly been described in more detail [34].

Data from each participant were pre-processed using the recon-all stream from Freesurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu/) [40], using automatic parcellation and segmentation protocols to obtain 68 cortical and 14 subcortical gray matter brain regions, as well as some global brain features (e.g., total intracranial volume (ICV)) [41]. Thickness and surface measurements from cortical regions were used for the ensuing analyses, along with volumetric estimates of subcortical volumes. A total of twelve relevant brain features were selected for analysis: intracranial and seven subcortical volumes used in a recent report from the ENIGMA consortium [4], along with mean cortical thickness, total cortical surface area, cerebellar cortex volume and cerebellar white matter volume. After merging with genetic and other phenotypic data of European-ancestry participants, there were 516 participants with MRI measures available. A measure of participants' age in months was extracted from the DICOM headers of the 516 MRI files, and it was used in the analyses involving brain features.

Statistical analyses. Before analysis, a few individuals were removed based on their genetic relatedness (only one participant per family was kept), as indicated by pi-hat values above 0.185 in PLINK's identity-by-descent matrix [36]. Then, following previous reports [8,10,15,16], the putative association between genomic features (either F_{ROH} or PGRS) and cognition was tested with the next linear regression model:

$$\mathrm{WRAT\_score} = \beta_0 + \beta_1(\mathrm{sex}) + \beta_2(\mathrm{age}) + \beta_3(\mathrm{age}^2) + \beta_4(\mathrm{batch}) + \beta_5(F_{\mathrm{miss}}) + \beta_6(F_{\mathrm{SNP}}) + \beta_7(C_1) + \beta_8(C_2) + \cdots + \beta_{15}(C_9) + \beta_{16}(C_{10}) + \beta_{17}(\mathrm{genomic\_feat}) + \varepsilon, \quad (1)$$

where batch represents the genotyping platform (modeled as dummy variables), C_1 to C_{10} are the 10 first principal components from an identity-by-state matrix, and $\mathrm{genomic\_feat}$ can be either F_{ROH} or schizophrenia PGRS. age^2 was calculated after scaling age (mean-centered, divided by the standard deviation). To verify that overparameterization was not an issue in model (1), and since that set of covariates is usual in ROH studies but not commonly employed for polygenic burden analysis, a simpler PGRS model was compared:

$$\mathrm{WRAT\_score} = \beta_0 + \beta_1(\mathrm{sex}) + \beta_2(\mathrm{age}) + \beta_3(\mathrm{age}^2) + \beta_4(\mathrm{batch}) + \beta_5(\mathrm{PGRS}) + \varepsilon. \quad (2)$$

Models (1) and (2) are hereafter referred to as *15-covariate* and *4-covariate*, and are compared when relevant. As shown in *Results*, the relevant outcomes of *15-covariate* and *4-covariate* models –for both cognition and brain features– were generally consistent. Moreover, for reasons explained below, the assessment of models (1) and (2) for PGRS indicated that model (1) would explain a larger fraction of the variance; it was thus adopted as the main framework for most of the tests, although the *4-covariate* model results are also discussed when relevant. Also, the associations between cerebral variables (volume, thickness, etc.) and genomic features (F_{ROH} or PGRS) were tested with similar models, and including ICV as a covariate when appropriate (e.g., subcortical volumes).

The main results were obtained using *lm* in R. To prevent artifacts due to potential abnormalities in the distributions, the tests were repeated independently using mixed-effects models via the *lme4* package [42] (with batch as random effect) and permutation-based regression *lmPerm* [43]. Since the three approaches were consistent, only the output of *lm* is shown.

Finally, the question of whether differences in brain features mediate the association between genomic features and IQ was assessed using causal mediation models. Those tests were implemented for a few relevant brain features in a last analysis stage, following standard procedures in R's *mediation* package [44]. For reproducibility, the random seed was fixed before each round of simulations.

RESULTS

Demographic and clinical data. The data shown in Table 1 and Figure 1 summarizes phenotypic information of PNC's sample subset included herein, stratified by genotyping platform. When considering all participants together, the correlations between age, age^2 and total WRAT score were either small or moderate, with the largest coefficient being for WRAT score and age (r = 0.67). Even though the PNC participants were initially recruited randomly from the set of available genotypes regardless of genotyping platform [34], the age and IQ distributions were different across batches. Those differences were small yet statistically significant (median ages: 13, 14, 15 and 16 years, $p < 3\times10^{-16}$; median IQ scores: 105 and 106, p = 0.006), which may have had an impact on the distribution of other variables such as ICV (p = 0.024 for between-batch differences) and related neuroimaging measures. Besides, the contingency table of medical status categories (none/minor, mild, moderate and severe) and genotyping platforms displayed unbalanced frequencies ($p = 10^{-10}$, Table 1). These observations, along with the differences in genetic measures discussed below, encouraged the inclusion of genotyping platform in all ensuing analyses.

---------- Table 1 ----------

---------- Figure 1 ----------

Schizophrenia PGRS and cognitive performance. As mentioned above (see *Methods*) five hundred schizophrenia PGRS values were computed (to assess the p-value threshold ($p_{threshold}$) range from 0.001 to 0.5, in steps of 0.001). The model fitting parameters of those scores with IQ as the outcome are shown in Supplementary Figure S1, using four different –although non-independent– settings: models with or without participants displaying moderate/severe medical conditions, evaluated using either 4 or 15 covariates along with the PGRS. The models were assessed based on both the overall adjusted-R^2 of the full model, and the PGRS's p-value within that model. Data on Supplementary Figure S1 provide multiple insights: first, *15-covariate* models showed higher adjusted-R^2 values than their *4-covariate* counterparts, suggesting that the principal components extracted from the identity-by-state do explain part of the phenotypic variance in cognitive performance. Second, schizophrenia PGRS display smaller p-values when including participants with medical conditions. This might be due to pleiotropic effects between schizophrenia and other diseases, along with cognitive alterations within the medically affected group, and a larger sample size (increased power) when including all participants. Third, across all models, the best fitting parameters (smallest p-values) throughout the different threshold values were observed using a $p_{threshold}$ of either 0.005 or 0.01. Of note, when using standardized WRAT scores (a measure of IQ), 0.005 was also the threshold with the smallest p-values; it was thus selected for the analyses shown next (Supplementary Figure S1 and Supplementary Figure S2). The results indicate that a higher schizophrenia PGRS is associated with higher cognitive performance across age (β = 1669, SE = 688, p = 0.015; Supplementary Figure S3). Lastly, there were no significant interactions between PGRS and

either age or age^2 on cognitive performance in the full dataset (n = 4,183; PGRS × age: β = -340.1, SE = 188, p = 0.071; PGRS × age^2: β = 69.8, SE = 55.7, p = 0.21), although there was an association with age when excluding participants with medical conditions (n = 3,036; PGRS × age: β = -438.9, SE = 210.1, p = 0.037; PGRS × age^2: β = 92.9, SE = 62.9, p = 0.139; Supplementary Figure S4). Those results were similar when using *4-covariate* models.

ROH and cognitive performance. Descriptive values of F_{ROH} and related variables (N_{ROH}, F_{SNP}, F_{miss}) are shown in Table 1 and Figure 2. There were no significant differences in the distribution of F_{ROH} across platforms, although a statistically significant batch-specific pattern was observed in F_{miss}, F_{SNP} and N_{ROH} ($p < 3\times10^{-16}$, $p = 7\times10^{-10}$ and $p = 4\times10^{-5}$). Pairwise analysis of these variables indicated a moderate correlation between the number of ROH per individual (N_{ROH}) and SNP-by-SNP homozygosity (F_{SNP}) (r = 0.38), whereas larger coefficients were observed between F_{ROH} and F_{SNP} (r = 0.5), and between F_{ROH} and N_{ROH} (r = 0.75). The latter is shown in more detail in Supplementary Figure S5, where the F_{ROH} and N_{ROH} values are compared for the whole sample. The correlations remained virtually unchanged after removing participants with moderate/severe medical status. Those two distributions (with and without participants with relevant medical conditions) are highly overlapping, with only two out of six high-ROH burden participants (F_{ROH} > 0.025) coming from the subsets of moderate and severe medical conditions. Of note, F_{ROH} was linearly independent of the schizophrenia PGRS (full sample: r = 0.016, p = 0.293; removing participants with medical conditions: r = 0.025, p = 0.172) (Figure 2 and Supplementary Figure S5), which further justifies the analysis of their joint effects in subsequent tests.

Regarding phenotype-ROH burden association tests, the output of linear regression analysis in the whole dataset (n = 4,183) showed a positive-signed association between cognitive performance and F_{ROH} (β = 130, SE = 36.3, $p = 3.5 \times 10^{-4}$, Supplementary Figure S6). Despite the apparent bias introduced by a few subjects with very high F_{ROH} values within the *Quad* platform, the effect was noticed across the four genotyping batches (Supplementary Figure S7). The results after excluding participants with moderate/severe medical conditions (namely, keeping n = 3,036 individuals) remained statistically significant (β = 133.5, SE = 42.2, $p = 1.6 \times 10^{-3}$). An additional analysis revealed no interactions between F_{ROH} and either age or age^2 on IQ (F_{ROH} × age: β = 8.4, SE = 8.5, p = 0.325; F_{ROH} × age^2: β = -1.5, SE = 3.6, p = 0.672; Supplementary Figure S8).

---------- Figure 2 ----------

ROH × schizophrenia PGRS interaction on IQ. A statistically significant interaction effect between ROH burden and schizophrenia PGRS on cognitive performance was detected; the explained variance was moderate. Briefly, the main effects model (*15-covariate*) showed significant results for both F_{ROH} (β =

126.3, SE = 36.4, $p = 5.2 \times 10^{-4}$) and schizophrenia PGRS (β = 1,562, SE = 687.8, p = 0.023), with an adjusted-R^2 of 0.4864 for the whole regression, whereas in the multiplicative interaction model F_{ROH} × PGRS was statistically significant ($\beta = 5.98 \times 10^5$, SE = 3×10^5, p = 0.048; overall adjusted-R^2: 0.4867). As indicated, there was slight increase in the model fitting parameter (adjusted R^2 shifting from 0.024 to 0.026), with a statistically significant effect according to the ANOVA test for the interaction (F = 3.9, p = 0.048). The results were very similar within the *4-covariate* framework, with significant effects for both F_{ROH} and PGRS (F_{ROH}: β = 103.1, SE = 30.7, $p = 7.8 \times 10^{-4}$; PGRS: β = 1,658, SE = 683.9, p = 0.015; overall adjusted-R^2: 0.4861), with a significant interaction term and improved model-fitting statistics (F_{ROH} × PGRS: $\beta = 6.6 \times 10^5$, SE = 3×10^5, p = 0.029; overall adjusted-R^2: 0.4866), and statistically significant ANOVA results (F = 4.8, p = 0.029). The data in Supplementary Figure S9 indicates that individuals with a high level of inbreeding would be more sensitive to the effects of schizophrenia polygenic burden: those in the uppermost F_{ROH} quartile would have higher cognitive performance when their schizophrenia PGRS is high. In contrast, subjects with lower F_{ROH} generally display no correlation between PGRS and cognition. As evidenced in Supplementary Figure S9, despite statistically significant, the effect sizes of these interactions were not large. There were no three-way interactions with age or age^2 (F_{ROH} × PGRS × age: $\beta = -9.8 \times 10^4$, SE = 8.2×10^4, p = 0.235; F_{ROH} × PGRS × age^2: $\beta = -1.8 \times 10^3$, SE = 2.9×10^4, p = 0.951). The significance of the findings remained unchanged after removing participants based on medical status.

Brain features, ROH and schizophrenia PGRS. Descriptive values of the brain features, in relation to age, are shown in Figure 3. They are similarly displayed, in relation to cognitive performance scores (age-standardized) in Supplementary Figure S10. Table 2 displays the results of *15-covariate* models evaluating the associations either between brain features and F_{ROH} or between brain features and schizophrenia PGRS. After multiple testing adjustments, increased PGRS was significantly associated with decreased cortical surface area and increased accumbens volume. Although there was no association between PGRS and cognitive ability in the subset of participants with MRI data (n = 516), causal mediation analysis suggested a suppression effect: modifications of brain feature sizes would compensate against the direct effect of schizophrenia PGRS on cognitive ability (cortical area: Average Causal Mediation Effects (ACME) = -0.228, 95% C.I. = [-0.548, -0.003], p = 0.046, Average Direct Effect (ADE) = 0.5, 95% C.I. = [-1.037, 2.005], p = 0.52; thalamus: ACME = -0.185, 95% C.I. = [-0.453, -0.005], p = 0.039, ADE = 0.458, 95% C.I. = [-1.075, 1.958], p = 0.55). Notice that such assertion had only limited support from the mentioned data subset, since no direct effects (ADE) of PGRS were detected.

With regards F_{ROH}, there was no statistically significant association. PGRS × F_{ROH} interaction tests did not reveal any significant association on the assessed brain features.

---------- Table 2 ----------

---------- Figure 3 ----------

DISCUSSION

In this work, the potential influence of both autozygosity and cumulative genetic risk for schizophrenia on cognitive performance was evaluated in a large and harmonized cohort (*n* = 4,183) of European-ancestry participants from the general population, aged 8-22. Increased inbreeding, as indexed by a larger fraction of the genome in ROH, was associated with higher cognitive performance. Similarly, a higher genetic burden for schizophrenia was related to higher cognitive scores. Although ostensibly paradoxical, the results agree with some previous reports using related study designs [8,45,46]. Additionally, significant interaction effects indicate that more inbred individuals are more likely to display higher cognitive test scores in the presence of high schizophrenia polygenic risk score. The relatively small effect sizes indicate that the contribution of these whole-genome features to the total heritability of cognitive performance is modest.

Regarding ROH and cognition, perhaps the most similar study to this one was conducted by [8] in a demographically analogue study sample (2,329 European-ancestry participants, age 12). The ROH-calling procedures using both here and in the former report were also equivalent, and in both cases the outcomes suggest that, in young individuals, increased autozygosity is associated with higher intelligence. To interpret their findings, Power et al. [8] hypothesized that positive assortative mating in couples with better cognitive profiles could partly explain the mentioned association, although they did not confirm that observation in post-hoc analyses on data from families living in Hawaii between 1972 and 1976 [47,48]: there were no differences in the extent of assortative mating when comparing couples with higher versus lower cognitive ability. Several other reports, however, support the hypothesis of differential assortative mating patterns influencing cognitive, behavioral and psychiatric phenotypes [17-22], which is perhaps the most plausible framework to explain the findings from these two cohorts of young individuals.

It is also important mentioning that two former studies have found the inverse association in samples of adult participants. First, [13] found a positive-signed association between ROH and cognition by meta-analyzing information of 53,300 participants from different cohorts and ancestries. Importantly, as the same authors showed, both F_{ROH} and N_{ROH} vary depending on ancestry, which might have induced heterogeneity in that study that is not present in the current dataset. It is worth noting that [13] included datasets (e.g., FTC_1) that are relatively similar to the present study sample (PNC) in terms of demographics, but there were no statistically significant results within those sub-cohorts. Differences in ROH-calling procedures could have also influenced this between-study discordance. Here, a validated protocol [10] of increasing popularity has been employed, which could strengthen the reliability of the findings. Another study by [16] showed, in a sample of 4,854 European-ancestry adults from nine cohorts, that increased ROH burden might be associated with higher intelligence. The main focus on adult participants in both previous studies may limit the comparability of the results, since the genetics of intelligence exhibit largely dynamic patterns over the lifetime [23,24].

Interestingly, there was a positive-signed association between schizophrenia PGRS and cognitive performance, suggesting that higher genetic burden for schizophrenia is related to better cognitive performance. This finding somehow agree with observations from two previous cohorts of healthy participants, which indicate that higher schizophrenia PGRS would be associated with decreased risk for psychosis-like experiences and schizotypy [45,46]. The findings from those two reports were interpreted by [45] in view of potential involuntary biases in sampling: samples with only *healthy* participants are not likely to include subjects with high schizophrenia PGRS and high psychosis-related phenotypes; people with high schizotypy and low resilience would seldom be part of the healthy general population, but would transition to clinical psychosis instead. Within that framework, lower genetic disease risk would protect healthy high-schizotypy individuals against transition to the clinical phenotype. A high-PGRS-low-resilience population subset would then rarely be part of a *healthy* sample, not because of an explicit sampling bias to exclude subclinical phenotypes, but rather due to psychopathological dynamics leading high-PGRS-low-resilience to the *affected/patient* groups. Of note, the current data (PNC) includes participants across a broad spectrum of phenotypes ranging from health to different diseases, and the association between higher schizophrenia PGRS and better cognition is more noticeable when removing participants with medical conditions. Namely, effect sizes for the high PGRS-better cognition association are stronger in the *healthiest* end of the phenotypic distribution, probably in concordance with an interplay between resilience and genetic schizophrenia risk as referred above.

In addition to the explanation above, the observed association between increased genetic risk for schizophrenia and higher cognitive ability might partly be due to the link between psychosis PGRS and psychological traits such as creativity [49], which might be closely related to intelligence [50]. As discussed in the literature on psychometrics, there seem to be discontinuous populations when comparing IQ and creativity: creativity would be higher in individuals above a certain IQ score [50]; analogous non-steady relationships might also be postulated when stratifying IQ by genetic risk for psychosis: perhaps only above a given schizophrenia PGRS value, individuals would transition to psychosis and display cognitive alterations.

To our knowledge, this is the first report on interactions between ROH and schizophrenia PGRS. The results indicate a small yet statistically significant effect: schizophrenia PGRS would be positively correlated with IQ particularly in individuals with a high ROH burden. In view of this and the former findings reported here, one could speculate that increases in intelligence due to assortative mating would be more noticeable in the high-PGRS-high-resilience subset of the *healthy* population. As discussed above, a high-PGRS-high-resilience profile might be much more common than high-PGRS-low-resilience in *healthy* groups, which should be considered in future studies of phenotypic continuums.

Limitations of the study include the medical conditions present in some participants, recruited from a hospital; however, as shown above, exclusion of individuals with moderate and severe medical status did not invalidate the findings. Moreover, the focus on a specific age range (8-22 years) and

ancestry group has increased specificity, but the findings might not be generalizable to populations from different demographic and genetic backgrounds. Finally, the relatively small number of participants with MRI scans (n = 516) could have limited the power of brain-genetics tests considerably.

ACKNOWLEDGEMENTS

Supported by the Research Council of Norway (204966, 249795, 223273, 213837); the South-Eastern Norway Regional Health Authority (2012-047, 2013-123, 2015-073, 2016-083); European Community's 7th Framework Programme (602450, IMAGEMEND), and Kristian Gerhard Jebsen Foundation.

AUTHOR CONTRIBUTIONS

A.C.-P. and L.T.W. conceived and designed the experiments, analyzed the data and wrote the manuscript; A.C.-P., T.K., D.A., N.T.D., T.M., and L.T.W. performed the experiments, and all authors provided substantial input to and gave approval of the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Haworth CM, Wright MJ, Luciano M *et al*: The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Mol Psychiatry* 2010; **15:** 1112-1120.

2. Schmitt JE, Neale MC, Fassassi B *et al*: The dynamic role of genetics on cortical patterning during childhood and adolescence. *Proc Natl Acad Sci U S A* 2014; **111:** 6774-6779.

3. Paus T, Keshavan M, Giedd JN: Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 2008; **9:** 947-957.

4. Hibar DP, Stein JL, Renteria ME *et al*: Common genetic variants influence human subcortical brain structures. *Nature* 2015; **520:** 224-229.

5. Plomin R, Deary IJ: Genetics and intelligence differences: five special findings. *Mol Psychiatry* 2015; **20:** 98-108.

6. McCarthy MI, Abecasis GR, Cardon LR *et al*: Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008; **9:** 356-369.

7. Ganna A, Genovese G, Howrigan DP *et al*: Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. *Nat Neurosci* 2016; **19:** 1563-1565.

8. Power RA, Nagoshi C, DeFries JC, Plomin R, Wellcome Trust Case Control C: Genome-wide estimates of inbreeding in unrelated individuals and their association with cognitive ability. *Eur J Hum Genet* 2014; **22:** 386-390.

9. Schizophrenia Working Group of the Psychiatric Genomics C: Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511:** 421-427.

10. Howrigan DP, Simonson MA, Keller MC: Detecting autozygosity through runs of homozygosity: a comparison of three autozygosity detection algorithms. *BMC Genomics* 2011; **12:** 460.

11. Kirin M, McQuillan R, Franklin CS, Campbell H, McKeigue PM, Wilson JF: Genomic runs of homozygosity record population history and consanguinity. *PLoS One* 2010; **5:** e13996.

12. Charlesworth D, Willis JH: The genetics of inbreeding depression. *Nat Rev Genet* 2009; **10:** 783-796.

13. Joshi PK, Esko T, Mattsson H *et al*: Directional dominance on stature and cognition in diverse human populations. *Nature* 2015; **523:** 459-462.

14. Verweij KJ, Abdellaoui A, Veijola J *et al*: The association of genotype-based inbreeding coefficient with a range of physical and psychological human traits. *PLoS One* 2014; **9:** e103102.

15. Johnson EC, Bjelland DW, Howrigan DP *et al*: No Reliable Association between Runs of Homozygosity and Schizophrenia in a Well-Powered Replication Study. *PLoS Genet* 2016; **12:** e1006343.

16. Howrigan DP, Simonson MA, Davies G *et al*: Genome-wide autozygosity is associated with lower general cognitive ability. *Mol Psychiatry* 2016; **21:** 837-843.

17. Nordsletten AE, Larsson H, Crowley JJ, Almqvist C, Lichtenstein P, Mataix-Cols D: Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders. *JAMA Psychiatry* 2016; **73:** 354-361.

18. Peyrot WJ, Robinson MR, Penninx BW, Wray NR: Exploring Boundaries for the Genetic Consequences of Assortative Mating for Psychiatric Traits. *JAMA Psychiatry* 2016; **73:** 1189-1195.

19. Plomin R, Krapohl E, O'Reilly PF: Assortative Mating-A Missing Piece in the Jigsaw of Psychiatric Genetics. *JAMA Psychiatry* 2016; **73:** 323-324.

20. Robinson MR, Kleinman A, Graff M *et al*: Genetic evidence of assortative mating in humans. *Nature Human Behaviour* 2017; **1:** 0016.

21. Mascie-Taylor CG: Spouse similarity for IQ and personality and convergence. *Behav Genet* 1989; **19:** 223-227.

22. Vandenburg SG: Assortative mating, or who marries whom? *Behav Genet* 1972; **2:** 127-157.

23. Deary IJ, Yang J, Davies G *et al*: Genetic contributions to stability and change in intelligence from childhood to old age. *Nature* 2012; **482:** 212-215.

24. Trzaskowski M, Yang J, Visscher PM, Plomin R: DNA evidence for strong genetic stability and increasing heritability of intelligence from age 7 to 12. *Mol Psychiatry* 2014; **19:** 380-384.

25. Lencz T, Knowles E, Davies G *et al*: Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Mol Psychiatry* 2014; **19:** 168-174.

26. Hill WD, Davies G, Liewald DC, McIntosh AM, Deary IJ, Grp CCW: Age-Dependent Pleiotropy Between General Cognitive Function and Major Psychiatric Disorders. *Biol Psychiat* 2016; **80:** 266-273.

27. Germine L, Robinson EB, Smoller JW *et al*: Association between polygenic risk for schizophrenia, neurocognition and social cognition across development. *Transl Psychiat* 2016; **6**.

28. Shafee R, Nanda P, Padmanabhan JL *et al*: Higher genetic risk of schizophrenia is associated with lower cognitive performance in healthy individuals. *bioRxiv* 2017**:** 103622.

29. Franke B, Stein JL, Ripke S *et al*: Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof of concept. *Nat Neurosci* 2016; **19:** 420-431.

30. Lee PH, Baker JT, Holmes AJ *et al*: Partitioning heritability analysis reveals a shared genetic basis of brain anatomy and schizophrenia. *Mol Psychiatry* 2016; **21:** 1680-1689.

31. Gur RC, Richard J, Calkins ME *et al*: Age group and sex differences in performance on a computerized neurocognitive battery in children age 8-21. *Neuropsychology* 2012; **26:** 251-265.

32. Wilkinson GS, Robertson GJ, Psychological Assessment Resources Inc.: *WRAT 4 : wide range achievement test ; professional manual*, 4th edn. Lutz, FL: Psychological Assessment Resources, Inc., 2006.

33. Robinson EB, Kirby A, Ruparel K *et al*: The genetic architecture of pediatric cognitive abilities in the Philadelphia Neurodevelopmental Cohort. *Mol Psychiatry* 2015; **20:** 454-458.

34. Satterthwaite TD, Elliott MA, Ruparel K *et al*: Neuroimaging of the Philadelphia neurodevelopmental cohort. *Neuroimage* 2014; **86:** 544-553.

35. Vassos E, Di Forti M, Coleman J *et al*: An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis. *Biol Psychiatry* 2017; **81:** 470-477.

36. Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT: Data quality control in genetic case-control association studies. *Nat Protoc* 2010; **5:** 1564-1573.

37. Kapoor M, Chou YL, Edenberg HJ *et al*: Genome-wide polygenic scores for age at onset of alcohol dependence and association with alcohol-related measures. *Transl Psychiat* 2016; **6**.

38. Maciejewski DF, Renteria ME, Abdellaoui A *et al*: The Association of Genetic Predisposition to Depressive Symptoms with Non-suicidal and Suicidal Self-Injuries. *Behavior Genetics* 2017; **47:** 3-10.

39. Tesli M, Espeseth T, Bettella F *et al*: Polygenic risk score and the psychosis continuum model. *Acta Psychiatr Scand* 2014; **130:** 311-317.

40. Fischl B, Dale AM: Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000; **97:** 11050-11055.

41. Desikan RS, Segonne F, Fischl B *et al*: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; **31:** 968-980.

42. Bates D, Machler M, Bolker BM, Walker SC: Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software* 2015; **67:** 1-48.

43. Wheeler B: lmPerm: Permutation tests for linear models, 2010.

44. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K: mediation: R Package for Causal Mediation Analysis. *2014* 2014; **59:** 38.

45. Barrantes-Vidal N, Grant P, Kwapil TR: The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophr Bull* 2015; **41 Suppl 2:** S408-416.

46. Zammit S, Hamshere M, Dwyer S *et al*: A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophr Bull* 2014; **40:** 1254-1262.

47. Nagoshi CT, Johnson RC, Defries JC, Wilson JR, Vandenberg SG: Group-Differences and 1st Principal-Component Loadings in the Hawaii Family Study of Cognition - a Test of the Generality of Spearmans Hypothesis. *Pers Indiv Differ* 1984; **5:** 751-753.

48. Wilson JR, Defries JC, Mcclearn GE, Vandenberg SG, Johnson RC, Rashad MN: Cognitive-Abilities - Use of Family Data as a Control to Assess Sex and Age-Differences in 2 Ethnic Groups. *Int J Aging Hum Dev* 1975; **6:** 261-276.

49. Power RA, Steinberg S, Bjornsdottir G *et al*: Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. *Nat Neurosci* 2015; **18:** 953-955.

50. Jauk E, Benedek M, Dunst B, Neubauer AC: The relationship between intelligence and creativity: New support for the threshold hypothesis by means of empirical breakpoint detection. *Intelligence* 2013; **41:** 212-221.

	Subjects (*n*)		Medical status	Age at CNB[a] (years)		Raw WRAT score		Standardized WRAT score (IQ, standard units)		Intracranial volume (10^6 mm^3)[b]		PGRS[c]		F_{SNP}		F_{miss}		N_{ROH}		F_{ROH}	
	male/female		*0 / 1 / 2 / 3 / 4*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*	*Median*	*Range*
Omni	573/590		207 / 321 / 342 / 213 / 78	13	8 – 21	54	18 – 70	106	64 – 145	1.609	1.218 – 1.988	-3.935×10^{-3}	-4.397×10^{-3} – -3.509×10^{-3}	0.6×10^{-3}	-0.017 – 0.039	0.5×10^{-3}	0.1×10^{-3} – 5×10^{-3}	3	0 – 19	1.652×10^{-3}	0 – 41×10^{-3}
Quad	886/896		264 / 529 / 496 / 368 / 112	14	8 – 21	55	16 – 70	105	55 – 145	1.603	1.095 – 1.98	-3.926×10^{-3}	-4.45×10^{-3} – -3.386×10^{-3}	0.001	-0.023 – 0.133	93×10^{-6}	12×10^{-6} – 0.01	3	0 – 40	1.603×10^{-3}	0 – 127×10^{-3}
550-v1	148/154		30 / 56 / 105 / 81 / 30	16	8 – 22	57	24 – 69	106	71 – 145	1.55	1.253 – 1.893	-3.962×10^{-3}	-4.363×10^{-3} – -3.463×10^{-3}	-0.9×10^{-3}	-0.019 – 0.012	0.1×10^{-3}	0.02×10^{-3} – 8.9×10^{-3}	2	0 – 12	1.331×10^{-3}	0 – 12×10^{-3}
550-v3	462/474		103 / 220 / 337 / 216 / 49	15	8 – 21	55	11 – 70	105	55 – 145	1.573	1.179 – 1.849	-3.952×10^{-3}	-4.427×10^{-3} – -3.422×10^{-3}	0.7×10^{-3}	-0.018 – 0.052	0.2×10^{-3}	0.01×10^{-3} – 12.8×10^{-3}	3	0 – 21	1.438×10^{-3}	0 – 49×10^{-3}
Between-group comparisons (test statistics)[d]																					
	X^2	*p*	X^2	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
	0.094	0.993	72.804	10^{-10}	30.922	$<3\times10^{-16}$	7.091	9.5×10^{-5}	4.106	0.006	2.292	0.077	7.238	8×10^{-5}	15.315	7×10^{-10}	74.885	$<3\times10^{-16}$	7.63	4×10^{-5}	1.659	0.174

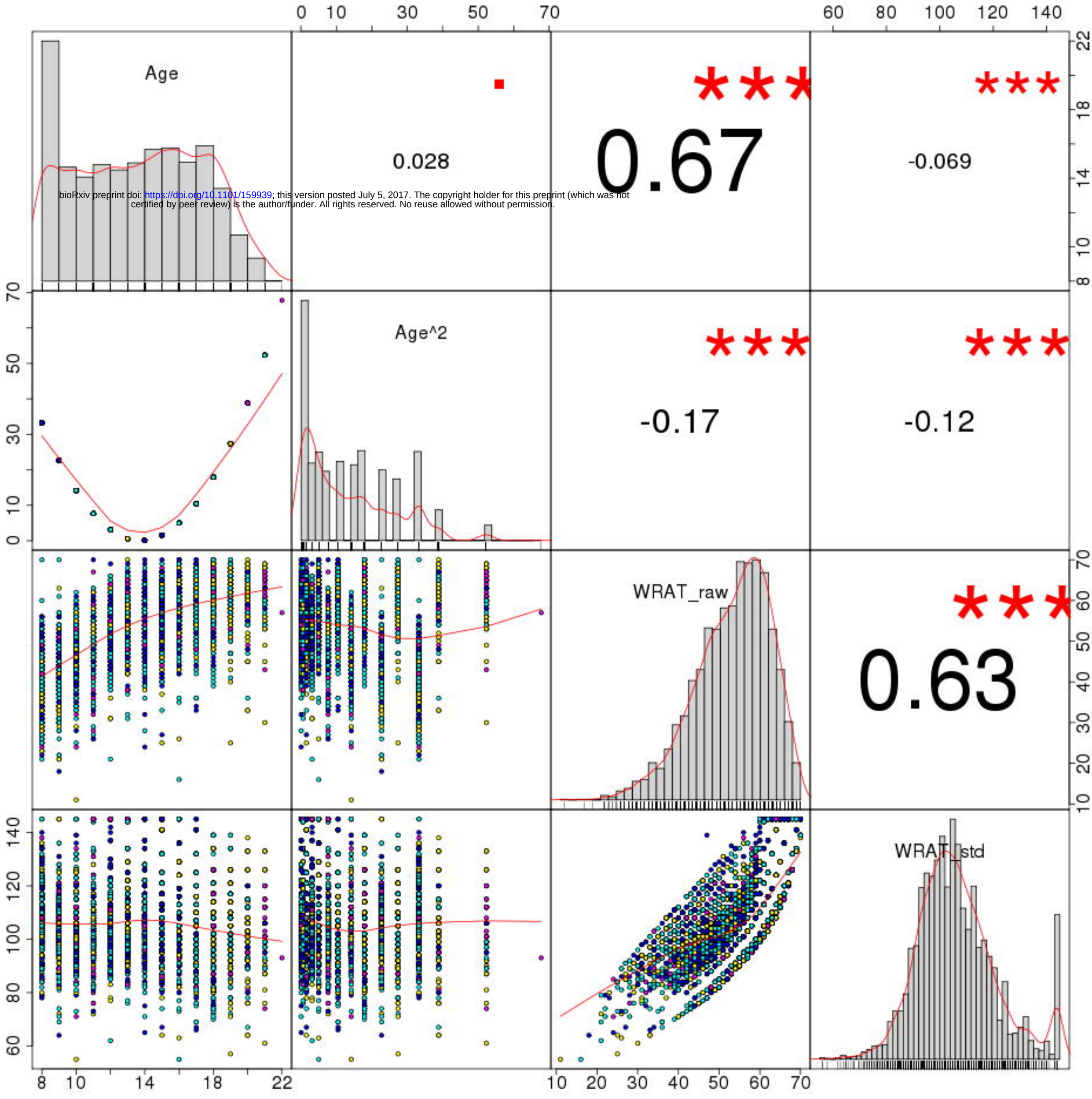
Table 1. Descriptive values of the main phenotypic and genetic variables included in the analyses

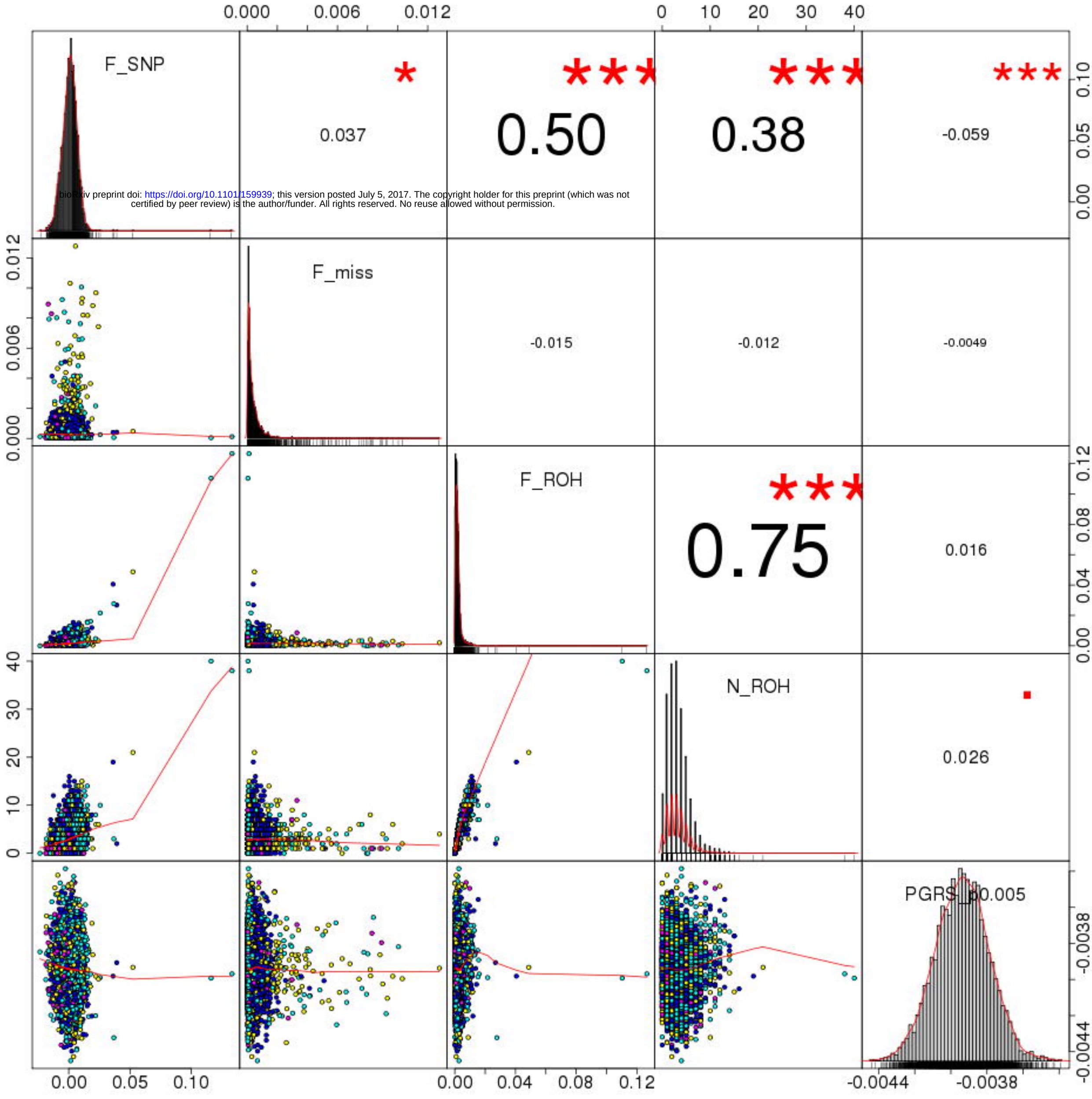
Notes: a, age at Computerized Neurocognitive Battery test date; b, values of estimated total intracranial volume were available only for a subset of participants (*n* = 385) with genetic and cognitive information included in the study (see *Materials and methods – Image acquisition and pre-processing*); c, schizophrenia PGRS at the best-fitting $p_{threshold}$ (0.005), as mentioned in the manuscript; d, between-group comparisons were performed using analysis of variance (ANOVA) tables for most of the variables displayed (continuous measures; *F* and *p* values reported), except for gender and medical status, where chi-squared tests were applied on the contingency tables.

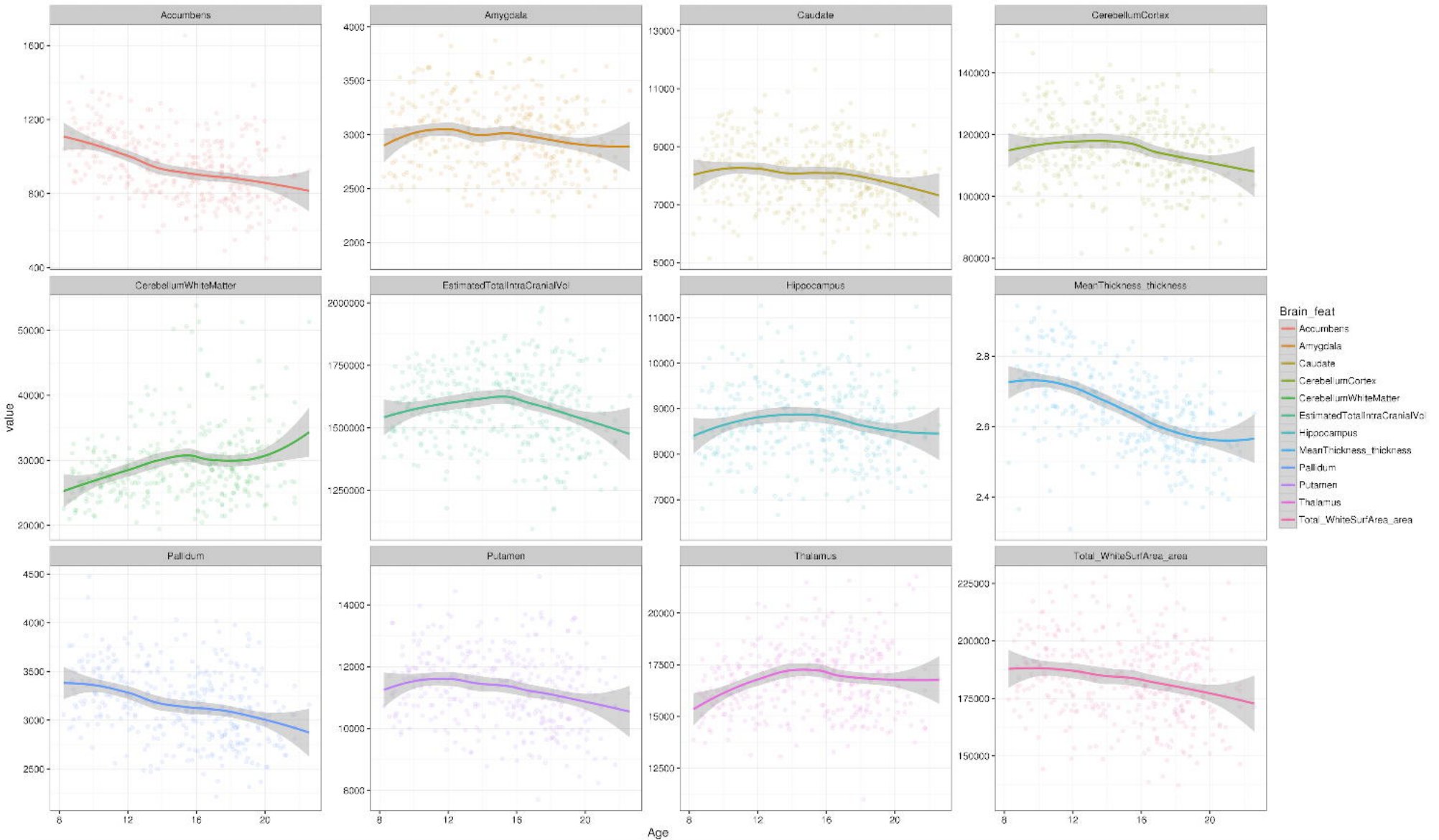
	Schizophrenia PGRS					F_{ROH}				
	Beta	**SE**	***t* value**	***p* (>|*t*|)**	**FDR-*p***	**Beta**	**SE**	***t* value**	***p* (>|*t*|)**	**FDR-*p***
Total_WhiteSurfArea_area	-9.157E+06	3.134E+06	-2.922	0.004	0.025	5.610E+04	2.654E+05	0.211	0.833	0.981
Accumbens	1.296E+05	4.495E+04	2.882	0.004	0.025	6.586E+03	3.794E+03	1.736	0.083	0.539
Amygdala	-1.584E+05	9.105E+04	-1.740	0.082	0.247	7.821E+03	7.660E+03	1.021	0.308	0.739
Caudate	-1.454E+04	2.820E+05	-0.052	0.959	0.959	-3.414E+04	2.363E+04	-1.445	0.149	0.539
Hippocampus	-3.540E+05	2.227E+05	-1.590	0.112	0.270	-2.715E+04	1.870E+04	-1.452	0.147	0.539
Pallidum	1.116E+05	9.005E+04	1.239	0.216	0.370	9.156E+02	7.572E+03	0.121	0.904	0.981
Putamen	2.800E+05	3.076E+05	0.910	0.363	0.437	1.608E+04	2.584E+04	0.622	0.534	0.916
Thalamus	-7.352E+05	3.420E+05	-2.150	0.032	0.128	-3.870E+04	2.879E+04	-1.344	0.180	0.539
CerebellumWhiteMatter	1.841E+06	1.625E+06	1.133	0.258	0.387	-3.305E+03	1.366E+05	-0.024	0.981	0.981
CerebellumCortex	-2.513E+06	3.320E+06	-0.757	0.449	0.490	-2.414E+05	2.787E+05	-0.866	0.387	0.773
MeanThickness_thickness	2.476E+01	2.727E+01	0.908	0.364	0.437	-7.676E-01	2.296E+00	-0.334	0.738	0.981
EstimatedTotalIntraCranialVol	-5.905E+07	3.999E+07	-1.477	0.140	0.281	-7.785E+05	3.372E+06	-0.231	0.817	0.981

Table 2. Association between brain features and either schizophrenia PGRS or F_{ROH}

Notes: The analyses were performed on 516 participants with both genetic and cognitive information included in the study (see *Materials and methods – Image acquisition and pre-processing*). Results correspond to the *15-covariate* model, and ICV was included as a covariate in tests of subcortical, cerebellar and cortical surface area. FDR: false discovery rate. *, significant *p*-value (less than 0.05) after FDR adjustment.






Accumbens
Amygdala
Caudate
CerebellumCortex
CerebellumWhiteMatter
EstimatedTotalIntraCranialVol
Hipocampus
MeanThickness_thickness
Pallidum
Putamen
Thalamus
Total_WhiteSurfArea_area
value
Age
Brain_feat
Accumbens
Amygdala
Caudate
CerebellumCortex
CerebellumWhiteMatter
EstimatedTotalIntraCranialVol
Hipocampus
MeanThickness_thickness
Pallidum
Putamen
Thalamus
Total_WhiteSurfArea_area