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Interaction of schizophrenia polygenic risk and cortisol level on pre-adolescent brain structure

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ABSTRACT

The etiology of schizophrenia is multi-factorial with early neurodevelopmental antecedents, likely to result from a complex interaction of genetic and environmental risk. However, few studies have examined how schizophrenia polygenic risk scores (PRS) are moderated by environmental factors in shaping neurodevelopmental brain structure, prior to the onset of psychotic symptoms. Here, we examined whether hair cortisol, a quantitative metric of chronic stress, moderated the association between genetic risk for schizophrenia and pre-adolescent brain structure.

This study was embedded within the Generation R Study, involving pre-adolescents of European ancestry assessed regarding schizophrenia PRS, hair cortisol, and brain imaging (n = 498 structural; n = 526 diffusion tensor imaging). Linear regression was performed to determine the association between schizophrenia PRS, hair cortisol level, and brain imaging outcomes.

Although no single measure exceeded the multiple testing threshold, nominally significant interactions were observed for total ventricle volume ($P_{interaction}$ = 0.02) and global white matter microstructure ($P_{interaction}$ = 0.01) – two of the most well replicated brain structural findings in schizophrenia.

These findings provide suggestive evidence for the joint effects of schizophrenia liability and cortisol levels on brain correlates in the pediatric general population. Given the widely replicated finding of ventricular enlargement and lower white matter integrity among schizophrenia patients, our findings generate novel hypotheses for future research on gene-environment interactions affecting the neurodevelopmental pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is a highly heritable psychiatric disorder, mediated through a complex combination of common and rare genetic variants (Sullivan et al., 2003). In addition to genetic risk, there is substantial epidemiological evidence for the effects of several environmental determinants on the risk of schizophrenia, including chronic cannabis use (Marconi et al., 2016), obstetric complications (Cannon et al., 2002), ethnic minority status (Bourque et al., 2011), urbanicity (Vassos et al., 2012) and stressful life events (Belbasis et al., 2018). Given maximum heritability estimates of ~80% based on twin heritability estimates (Hilker et al., 2018), the genetic liability of schizophrenia

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appears to be at least partially moderated by environmental determinants (van Os et al., 2010).

Polygenic risk scores (PRS) are derived as the weighted sum of risk alleles derived from genome-wide association studies (GWAS) (Wray et al., 2014). Several studies have employed schizophrenia PRS to investigate developmental manifestations of increased genetic liability for schizophrenia in the general population (Mistry et al., 2017). The schizophrenia PRS has been associated with early life emotional and behavioral problems (Jones et al., 2016), cognition (Riglin et al., 2017), and physical health problems(Stringer et al., 2014) in the general population. Increasingly, PRS for schizophrenia are employed in imaging genetics studies to assess underlying brain correlates of vulnerability to schizophrenia (Bogdan et al., 2017; Dima and Breen, 2015). Previous studies have reported associations of schizophrenia PRS with total brain volume and gyrification indices (Caseras et al., 2015; Liu et al., 2017; Terwisscha van Scheltinga et al., 2013), though several null findings have also been published (Papiol et al., 2014; Van der Auwera et al., 2015, 2017). Studies that assess how genetic risk for schizophrenia is related to variations in structural brain correlates are important, given that both gray matter and white matter microstructural correlates have been consistently observed in patients with schizophrenia (Brugger and Howes, 2017; Kelly et al., 2018; van Erp et al., 2016, 2018), and this has also been replicated in childhood-onset schizophrenia samples (Tamnes and Agartz, 2016) and first-episode psychosis patients (Fusar-Poli et al., 2014). However, no prior studies have assessed the interaction between genetic and stress-related environmental risk factors on childhood brain development, despite that schizophrenia pathophysiology is widely hypothesized to have early neurodevelopmental antecedents that are sensitive to the environmental stressors (van Os et al., 2010).

Here, in a population-based sample of ten-year-olds, an age well before the clinical onset of overt psychotic psychopathology, we used PRS as an index of genetic vulnerability to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Cortisol levels were measured through hair analysis as a naturalistic quantitative metric of chronic physiological stress. In the recent years, hair cortisol has been increasingly studied as a biological marker of chronic physiological stress. Hair cortisol indicates long-term exposure to stress and, due to the hair's natural speed of growth, one centimeter of hair represents one month of cortisol exposure (Noppe et al., 2015). In the current study, we obtained hair samples of 3 cm in length – reflecting three months of cortisol exposure. Moreover, recent studies have demonstrated that hair cortisol levels are indicative of more chronic stress exposure and exhibit high intra-subject temporal stability (Stalder et al., 2017, 2012). Our primary aim was to examine whether chronic stress, as operationally defined by hair cortisol levels, moderated the relationship between schizophrenia PRS and pre-adolescent structural brain correlates. Our hypotheses focused on brain outcomes which have most consistently been associated with the underlying neurobiology of schizophrenia – cortical and subcortical gray matter (van Erp et al., 2016, 2018), cerebroventricular volume (van Erp et al., 2016) and white matter microstructure (Kelly et al., 2018). We expected that, among children with an elevated genetic liability to schizophrenia, high cortisol levels would be associated with lower (sub-)cortical gray matter volume, larger ventricles and decreased white matter microstructure..

2. Methods

2.1. Study population

The present study was embedded within the Generation R Study, a prospective population-based birth cohort from Rotterdam, the Netherlands. The aim of the Generation R Study is to identify genetic and environmental determinants that influence maternal and child development (Kooijman et al., 2016). For the current study, 2512 children of European descent (based on genetic ancestry; 53% of $n = 4780$ participants of European descent who were eligible for the age ten years wave) had genotype data available. Hair samples were collected in an un-selected sub-sample of the Generation R cohort at mean age six years. At mean age ten years, participants were invited for a brain magnetic resonance imaging (MRI) scan, of whom $n = 593$ consented for participation in the current study. After standardized quality control procedures, the final sample comprised 498 children for T1 and 526 for diffusion tensor imaging (DTI) analyses, respectively (Appendix Figure A.1 for a flowchart). Study protocols were approved by the Medical Ethics Committee of the Erasmus Medical Center. All participants and their parents provided assent and informed consent, respectively.

2.2. Attrition analysis

Comparisons were made between the study sample ($N = 498$) and participants who were genotyped but without hair cortisol or brain morphology data ($N = 2512$). These groups did not differ in proportion of girls (47.2% versus 49.9%, $\chi^2 = 1.07$, $df = 1$, $P = 0.30$) or in mean schizophrenia PRS ($P_t < 0.0005$; 0.01 versus -0.01, $t = -0.59$, $P = 0.56$). However, children with complete data were more likely to have mothers with higher educational levels (79.5% versus 70.5%, $\chi^2 = 14.68$, $df = 1$, $P < 0.01$).

2.3. Genotyping and quality control

Genotype quality control procedures for the Generation R Study were performed as previously described (Medina-Gomez et al., 2015). Briefly, genotype data were collected from either cord blood at birth (Illumina 610 K Quad Chip) or from whole venous blood collected during a follow-up visit (Illumina 660k Quad Chip). Variants were included if they passed sample (≥97.5%) and SNP call rates (≥90%), minor allele frequency ≥1%, and no deviation from Hardy-Weinberg disequilibrium ($P < 10^7$). Participants were screened for excess heterozygosity, sex mismatch, relatedness, and missing data. Individuals of European descent were considered those within 4 standard deviations for each of the first four genetic principal components of the HapMap Phase-II Northwestern European population.

2.3.1. Polygenic risk scoring

Genetic risk variants associated with schizophrenia were obtained from the Psychiatric Genetics Consortium case-control GWAS meta-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). SNPs were clumped according to linkage disequilibrium (LD) in order to obtain the most significant SNP per LD-block (kilobase pair window: 250, LD $r^2 < 0.1$). PRS were computed on imputed genotype data using PRSice (Euesden et al., 2015), by weighting the mean number of risk alleles against the SNP effect size. P-value thresholds (P_t) for inclusion of SNPs in the PRS varied between $P_t < 0.0005$ and $P_t < 1$. Scores were standardized to a mean of zero and standard deviation of one to facilitate interpretation.

PRS for major depressive disorder scores were derived from the most recent GWAS meta-analysis (Wray et al., 2018). If an association with the schizophrenia PRS was observed, further analyses with the major depression risk score were performed to examine specificity given the significant genetic correlations across psychiatric disorders, including schizophrenia and depression (Cross-Disorder Group of the Psychiatric et al. (2013)).

2.4. Hair cortisol

At the age six visit, children were invited with the consent of their mother to contribute a hair sample for steroid hormone assessment. Hair samples were cut from the posterior vertex using small surgical scissors, as close to the scalp as possible. Parents completed a

questionnaire regarding their child's use of hair products and corticosteroid medications. Steroids were extracted using LC-grade methanol at 25 °C for in the presence of deuterium-labeled steroids as an internal standard. Samples were centrifuged and cleaned using solid phase extraction, after which steroids were measured by liquid chromatography-tandem mass spectrometry, as previously described (Rippe et al., 2016). Concentrations of hair cortisol were log-transformed (Noppe et al., 2015; Rippe et al., 2016).

2.5. Image acquisition

Brain imaging was performed using a 3-T GE MR750w scanner with an 8-channel head coil, as previously described (White et al., 2018). Every child was invited to participate in a mock scanning session prior to the actual brain MRI scan to familiarize them with the scanning procedure. After a localizer, structural T1 was the first sequence, followed by the DTI scan. For structural T1 analyses, global metrics of volume were extracted. T1-weighted images were processed using the FreeSurfer analysis suite, version 6.0 (Fischl et al., 2004), a widely used reliable software for brain morphometry processing (Han et al., 2006; Reuter et al., 2012). Diffusion tensor imaging scanning pre-processing was conducted using the FMRIB Software Library (FSL), version 5.0.9 (Jenkinson et al., 2012). Probabilistic white matter fiber tractography was conducted on DTI images and scalar metrics (i.e. fractional anisotropy [FA], mean diffusivity [MD], axial diffusivity [AD] and radial diffusivity [RD]) were computed. Global DTI metrics were computed based on 12 well-studied white matter fiber bundles. More detail on neuroimaging acquisition and quality control is available in the Appendix.

2.6. Covariates

Age and sex were obtained from study records. Four ancestral principal components were used as covariates to correct for remaining population structure. Hair color, hair product use, and corticosteroid medication use were assessed through parental report.

2.7. Statistical analyses

All analyses were conducted using R statistical software. First, we examined main effects associations of the schizophrenia PRS with global brain correlates using linear regression. The outcomes on which we performed our analyses included cortical and subcortical gray matter volume, ventricle volume and global FA and MD. Total brain volume and white mater volume were assessed in secondary analyses. Therefore, in total we examined seven different brain outcomes in the current study. To address our main aim, whether hair cortisol levels moderated the relationship between schizophrenia PRS and brain correlates, linear regression with interaction was conducted to test deviation from additivity. The main effects of cortisol and PRS remained included in the model. All analyses were adjusted for covariates as described above. Subcortical gray matter volume and ventricular volumes were assessed as a fraction of intracranial volume to obtain estimates relative to head size. Total brain volume, cortical gray matter volume, and white matter volume were not assessed as a fraction of intracranial volume due to high correlations with the latter ($r = 0.93$, $r = 0.87$, and $r = 0.89$, respectively). Analyses involving schizophrenia PRS were conducted separately for each P-value threshold. For clarity of presentation, results are shown for schizophrenia risk score $P_t < 0.0005$ as this threshold has shown the strongest associations in previous work from our group (Serdarevic et al., 2018) and in the current analyses. Results from the other *P*-value thresholds are shown in the Appendix A false discovery rate (FDR) correction was applied to adjust for multiple testing. This was based on the total number of statistical tests across polygenic scores, cortisol level, *P*-value thresholds and all brain outcomes, resulting in a stringent multiple testing correction.

Significant associations were visually explored in scatter plots. For simplicity of visualization, hair cortisol level was categorized into two levels. Interaction graphs were visualized using the *ggplot2* package, and its extension *jtools* was employed to create Johnson-Neyman plots for visualization of confidence intervals of difference between cortisol levels. Johnson-Neyman plots and intervals indicate the values of the moderator (hair cortisol) for which the slope of the predictor (PRS) on the outcome (brain) will be statistically significant. Significant observations with the schizophrenia PRS were repeated with the major depression PRS. Finally, we assessed the relationship between schizophrenia PRS and hair cortisol level, given that an association between these variables (i.e., gene-environment correlation) would affect the estimation of gene-environment interaction models.

Table 1
Sample characteristics.

	N	Total population (N = 498)
Child characteristics		
Age at MRI, mean (SD)	498 (0% missing)	9.91 (0.40)
Sex, girls	498 (0% missing)	47.2
Hair color	498 (0% missing)	
Red		4.8
Blond		84.7
Brown		10.4
Black		0.0
Hair cortisol concentration (pg/mg), median (IQR)	498 (0% missing)	1.31 (2.21)
Hair product use on day of hair collection	498 (0% missing)	20.7
Corticoid medication use in past 3 months	498 (0% missing)	9.2
Inhalation		2.6
Intranasal		0.6
Cutaneous		5.4
Oral		0.4
Unknown		0.2
Maternal characteristics		
Educational level	478 (4.0% missing)	
High		79.5
Medium		20.5
Low		0.0

Note: numbers represent percentages until stated otherwise.

3. Results

3.1. Sample characteristics

Among the children who used corticosteroids in the 3 months prior to hair sample collection (Table 1, $n = 46$, 9.2%), the predominant routes of administration were cutaneous application ($n = 27$, 5.4%).

3.2. Main effects associations

No associations were observed between schizophrenia PRS and cortical gray matter volume, subcortical gray matter volume, global FA or global MD (Table 2). Schizophrenia PRS was associated with lower ventricular volume ($P_t < 0.0005$: β = -0.13, 95% CI -0.21;-0.04, $P = 0.01$), but this not survive FDR-correction for multiple testing ($P_{FDR\text{-}adjusted} = 0.30$). Hair cortisol level was not associated with any of the global gray or white matter measures examined. Neither schizophrenia PRS nor hair cortisol were associated with any of the secondary outcome measures (Appendix Tables A.1-A.7).

Table 2
Main effects of schizophrenia polygenic risk score (upper panel) and hair cortisol (lower panel) on global structural volumetric and global white matter microstructural measures.

Outcome	β (95% CI)	*P*	$P_{FDR\text{-}adjusted}$
Schizophrenia polygenic risk			
Structural volumetric measures (*N* = 498)			
Cortical gray matter volume	−0.04 (-0.12;0.04)	0.32	0.62
Subcortical gray matter volume	0.02 (-0.07;0.10)	0.68	0.84
Total ventricle volume	−0.13 (-0.21;-0.04)	0.01	0.30
White matter microstructural measures (*N* = 526)			
Global fractional anisotropy (FA)	0.05 (-0.03;0.14)	0.24	0.53
Global mean diffusivity (MD)	−0.05 (-0.13;0.04)	0.29	0.58
Hair cortisol			
Structural volumetric measures (*N* = 498)			
Cortical gray matter volume	0.00 (-0.08;0.08)	0.96	0.98
Subcortical gray matter volume	0.07 (-0.02;0.16)	0.11	0.81
Total ventricle volume	−0.06 (-0.15;0.03)	0.19	0.48
White matter microstructural measures (*N* = 526)			
Global fractional anisotropy (FA)	0.04 (-0.04;0.13)	0.33	0.62
Global mean diffusivity (MD)	0.01 (-0.07;0.10)	0.73	0.85

Note: Results are shown for the P-value threshold $P_t < 0.0005$. Models were adjusted for age at MRI visit and child sex, hair color, hair product use, corticosteroid use, and 4 principal components. Subcortical gray matter volume and total ventricular volume were assessed as a fraction of intracranial volume. False discovery rate correction for multiple testing was based on the total number of statistical tests across main effects of both polygenic scores and cortisol, *P*-value thresholds and brain outcomes. Abbreviations: $P_{FDR\text{-}adjsuted}$, false-discovery rate corrected *P*-value.

3.3. Interaction effects associations

After adjustment for multiple testing, no statistically significant interaction effects were observed for any of the primary or secondary outcome measures. Nominally significant, i.e. uncorrected, estimates indicated that hair cortisol levels moderated the association between schizophrenia PRS and ventricle volume (Table 3; $P_t < 0.0005$: β = 0.10, 95% CI 0.01;0.18, *P* = 0.02), but this did not survive multiple testing correction ($P_{FDR\text{-}adjusted} = 0.30$). Effects were most pronounced at the lower end of the distribution of schizophrenia PRS (Fig. 1). The corresponding Johnson-Neyman intervals plot demonstrated that at values of (log-transformed) cortisol below 0.36, a higher schizophrenia PRS was nominally associated with a lower ventricle volume. No significant associations were observed for cortisol levels above 0.36.

Hair cortisol moderated the association between schizophrenia risk score and global MD (Appendix Table A.7, $P_t < 0.0005$: β = 0.10, 95% CI 0.02;0.19, *P* = 0.01); again this finding did not survive correction for multiple testing ($P_{FDR\text{-}adjusted} = 0.30$). Fig. 2 demonstrates nominally significant relationships at both ends of the cortisol distribution. The Neyman-Johnson plot indicates that at values of (log-transformed) hair cortisol below -0.01 and above 1.32, schizophrenia PRS was associated with global MD in a negative and a positive direction, respectively. Higher cortisol in combination with elevated polygenic risk was associated with higher global MD. Accordingly, lower cortisol in combination with higher polygenic risk was associated with lower global MD.

3.4. Follow-up analyses with global AD and RD

No main effect was observed between either PRS or hair cortisol and global AD or RD (Appendix Table A.8-A.9). A nominal interaction was observed between hair cortisol and schizophrenia PRS on both global AD ($P_t < 0.0005$: β = 0.10, 95% CI 0.02;0.18, *P* = 0.02) and global RD ($P_t < 0.0005$: β = 0.09, 95% CI 0.01;0.17, *P* = 0.04). A higher schizophrenia PRS in combination with high cortisol was associated with higher global AD (Appendix Figure A.2). This was consistent with the finding for RD, which showed a different direction reflecting the reverse correlation with other white matter parameters; a lower polygenic risk in combination with lower hair cortisol was associated with higher global RD (Appendix Figure A.3).

3.5. Sensitivity analyses with depression polygenic risk

No significant interaction effect was observed between hair cortisol level and major depressive disorder polygenic risk on brain ventricle volume or global MD (Appendix Table A.10-A.11). Post-hoc power analysis for multiple regression with total brain volume as the outcome (Soper, 2018), using the following parameters: number of predictors = 11; observed $R^2 = 0.29$; *P*-value for interaction = 0.89; sample size = 498, yielded an observed statistical power of 100%. With only hair cortisol and schizophrenia PRS included in the calculation and a resulting $R^2 = 0.01$ and *P* = 0.73, resulted in a statistical power estimation of 97%.

Table 3
Interaction effect of hair cortisol levels and schizophrenia polygenic risk score on global structural volumetric and global white matter microstructural measures.

Outcome	β (95% CI)	*P*	$P_{FDR\text{-}adjusted}$
Structural volumetric measures (*N* = 498)			
Cortical gray matter volume	0.03 (-0.05;0.10)	0.52	0.76
Subcortical gray matter volume	−0.02 (-0.10;0.06)	0.62	0.81
Total ventricle volume	0.10 (0.01;0.18)	0.02	0.30
White matter microstructural measures (*N* = 526)			
Global fractional anisotropy (FA)	−0.04 (-0.12;0.05)	0.37	0.64
Global mean diffusivity (MD)	0.10 (0.02;0.19)	0.01	0.30

Note: Results are shown for the P-value threshold $P_t < 0.0005$. All models all included the main effects and the interaction term. Models were adjusted for age at MRI visit and child sex, hair color, hair product use, corticosteroid use, and 4 principal components. Subcortical gray matter volume and total ventricular volume were assessed as a fraction of intracranial volume. Abbreviations: $P_{FDR\text{-}adjsuted}$, false-discovery rate corrected *P*-value.

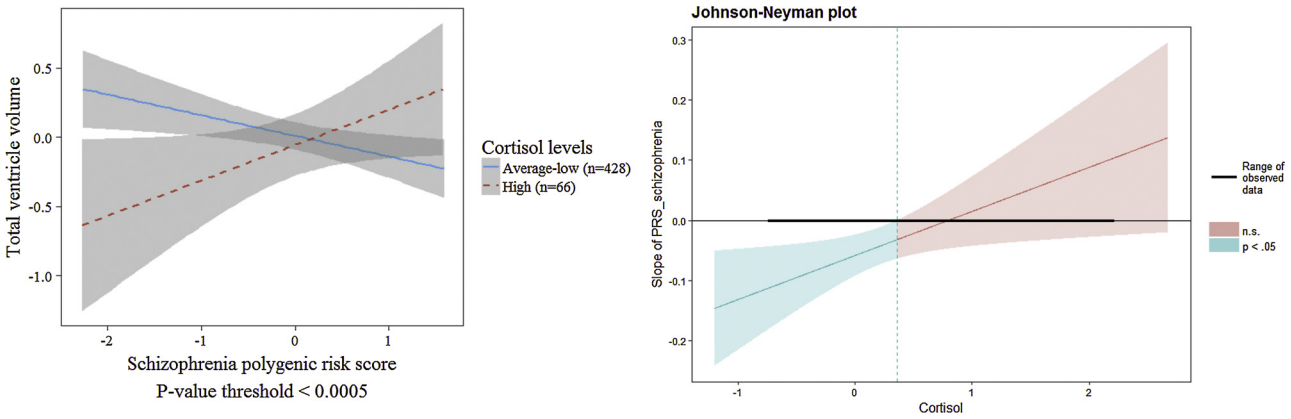

Fig. 1. Relationship between schizophrenia polygenic risk score (PRS) and total ventricular volume as a function of hair cortisol level (left) and corresponding Johnson-Neyman plot (right).
Note: For simplicity of visualization, hair cortisol level was categorized into two levels: high (n = 66), one standard deviation above the total sample mean; average-low (n = 428), one standard deviation above mean and lower. The gray-shaded areas denote 95% confidence intervals. *P*-value threshold for the schizophrenia PRS is shown at P_t < 0.0005. Both schizophrenia PRS (x-axis) and total ventricle volume (y-axis) are standardized. Total ventricle volume was taken as a fraction of total intracranial volume. The right graph shows the Johnson-Neyman plots, which indicates at values of (log-transformed) cortisol below 0.36, the slope of schizophrenia PRS is significantly different from zero, and negative (turquoise shaded area).

3.6. Association between schizophrenia vulnerability and hair cortisol

No association was observed between schizophrenia PRS and hair cortisol level (Table 4).

Table 4
Association between schizophrenia polygenic risk scores and hair cortisol level.[a.]

P-value threshold	Number of SNPs[b]	β (95% CI)	*P*
P_t < 0.0005	2 965	−0.03 (-0.12;0.06)	0.53
P_t < 0.001	4 148	−0.04 (-0.13;0.05)	0.42
P_t < 0.005	9 547	−0.02 (-0.11;0.07)	0.59
P_t < 0.01	13 916	0.01 (-0.10;0.08)	0.76
P_t < 0.05	34 947	−0.02 (-0.11;0.07)	0.70
P_t < 0.1	52 256	0.00 (-0.09;0.09)	0.96
P_t < 0.5	126 674	0.00 (-0.09;0.09)	1.00
P_t < 1.0	164 190	0.00 (-0.09;0.09)	0.97

Note: Models are adjusted for child age at hair sample collection, child sex, hair color, hair product use and 4 ancestral principal components. SNPs were clumped prior to calculation of the polygenic score. Abbreviations: P_t, *P*-value threshold; SNP, single nucleotide polymorphism.

4. Discussion

In this population-based neuroimaging study in pre-adolescents, we examined whether hair cortisol levels moderated the relationship of schizophrenia PRS with brain structural morphology or white matter microstructure. When stringently corrected for multiple testing across polygenic risk score *P*-value thresholds for all primary and secondary neuroimaging outcome measures, no significant main or interaction associations were observed. Analyses uncorrected for multiple testing should therefore be interpreted with caution. Uncorrected associations suggested that high cortisol in combination with elevated genetic risk for schizophrenia was related to lower white matter microstructure, and that low cortisol in combination with low schizophrenia PRS was associated with larger cerebral ventricles. These associations were was

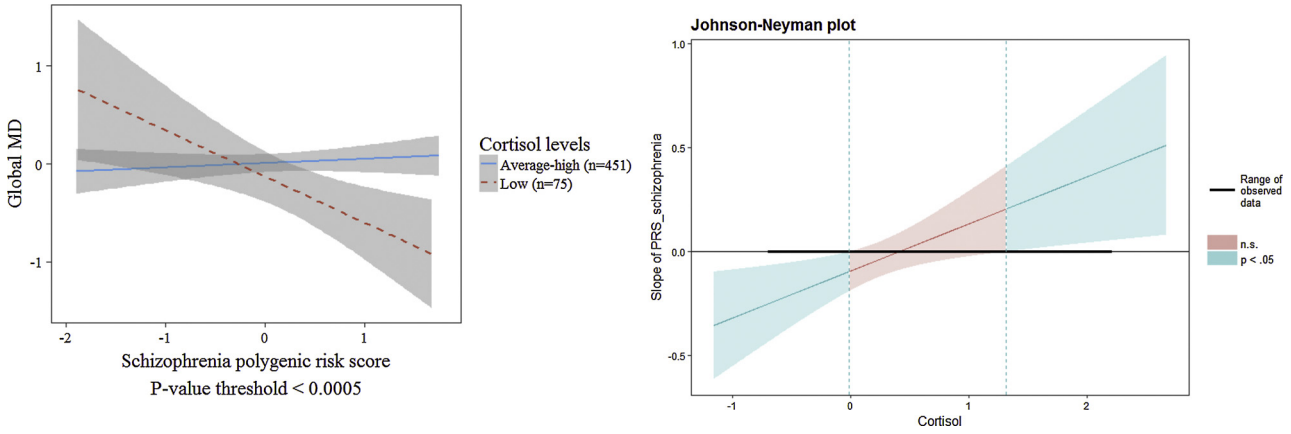

Fig. 2. Relationship between schizophrenia polygenic risk score (PRS) and global mean diffusivity as a function of hair cortisol level (left) and corresponding Johnson-Neyman plot (right).
Note: For simplicity of visualization, hair cortisol level was categorized into two levels: low (n = 75), one standard deviation below the total sample mean; average-high (n = 451), one standard deviation below the mean and higher. The gray-shaded areas denote 95% confidence intervals. *P*-value threshold for the schizophrenia PRS is shown at P_t < 0.0005. Both schizophrenia PRS (x-axis) and global mean diffusivity (y-axis) are standardized. The right graph shows the Johnson-Neyman plots, which indicates at values of (log-transformed) cortisol below -0.01 and above 1.32, the slope of schizophrenia PRS is significantly different from zero, and negative respectively positive (turquoise shaded area).

not observed for the depression PRS, possibly suggesting specificity with regard to schizophrenia genetic liability. Although our findings are suggestive, they are potentially informative in the contextualization of the genetic and environmental determinants of pre-adolescent brain structure, particularly against the background of chronic stress exposure as a moderating influence on disease-related brain pathophysiology through schizophrenia PRS.

Enlarged ventricular volume and lower white matter integrity are among the most well-established and largest effect size neurobiological findings in adult patients with schizophrenia, as confirmed by recent meta-analyses (Brugger and Howes, 2017; Kelly et al., 2018; van Erp et al., 2016). However, it has been difficult to disentangle the effects of confounding factors, most notably illness course and antipsychotic medication (Van Haren et al., 2013). Against this background, our findings in pre-adolescents without a diagnosis of a psychotic disorder provide novel hypotheses into the complex interplay of genetic and environmental determinants in influencing schizophrenia pathophysiology (Belbasis et al., 2018). We observed suggestive associations in which hair cortisol moderated the association between high polygenic risk for schizophrenia and brain structure, although these associations did not survive the correction for multiple testing. These suggestive findings might also help to explain the previous null findings arising from studies examining the brain structural correlates of schizophrenia PRS (Papiol et al., 2014; Van der Auwera et al., 2015, 2017), as the underlying effects might have been obscured by the interacting influence of environmental determinants. Accordingly, our findings highlight the importance of integrating genetic and environmental risk factors in order to better understand the pathophysiology of psychiatric illness (van Os et al., 2010). Additional environmental determinants should also be studied in the context of (polygenic) gene by environment interaction studies. For example, recent evidence has indicated that elevated schizophrenia genetic risk is associated with a higher rate of obstetric complications (Ursini et al., 2018). In this regard, prospective longitudinal neuroimaging and follow-up assessments of multiple environmental risks would provide a powerful study design for disentangling critical windows of neurodevelopment.

Our analyses did not observe any main association between schizophrenia PRS and structural brain volumes or white matter microstructure. This is largely consistent with previous studies exploring main effects of genetic risk on brain structure (Papiol et al., 2014; Van der Auwera et al., 2015, 2017), although a few studies have reported neuroimaging correlates of schizophrenia genetic risk (Fonville et al., 2018; Liu et al., 2017; Terwisscha van Scheltinga et al., 2013). Moreover, the absence of significant hair cortisol by polygenic risk interaction effects might be explained by the relatively small sample size of this study and the relatively young age of the cohort. Larger samples with more power will be needed to detect small effects in pre-adolescence. Further, the joint effects of stress hormone levels and genetic risk for schizophrenia on brain structure might only become apparent when prodromal symptoms become apparent during adolescence as opposed to earlier in childhood development prior to the symptoms onset. However, it should be noted that schizophrenia PRS has been associated with psychiatric problems in the general pediatric population from as young as 3 years of age (Jansen et al., 2018), and infant neuromotor development at 9 months of age (Serdarevic et al., 2018), suggesting that the genetic risk for schizophrenia has neurobiological manifestations from early childhood onwards. Furthermore, the schizophrenia PRS explains approximately 7% of variation in the original GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), so it can be expected that the explained variance is much lower in an unrelated sample, much younger age group and a quite different outcome measure. In addition, functional neuroimaging modalities might be more sensitive to detect subtle neurobiological changes associated with early life genetic risk for schizophrenia (Lancaster et al., 2016). More importantly, it has been noted that interaction testing with PRS might not be ideal as risk scores assume genetic additivity and some, but not all, of the SNPs in the risk score might be involved in the interaction to various degrees and, potentially, in opposing directions (i.e. some but not all variants might follow a pattern of differential susceptibility) (Peyrot et al., 2017; Zwicker et al., 2018). Another avenue for gene-environment-interaction research is to employ biologically informed multi-locus profile scores, which are composites of genetic polymorphisms from a given neural signaling pathway (Bogdan et al., 2017), and examine how these differentially associate with environmental factors (Zwicker et al., 2018).

Although no significant associations were observed after correction for multiple testing, our uncorrected suggestive findings provide novel hypotheses about schizophrenia's pathophysiology. Interestingly, and somewhat paradoxically, we found that in children with low cortisol levels, reduced schizophrenia genetic liability was associated with larger ventricles. Furthermore, the combination of low genetic risk for schizophrenia and high cortisol levels was associated with lower ventricular volume. These seemingly incongruous observations should be evaluated in the context of brain development throughout the first years of life. Although larger cerebral ventricles have been strongly associated with schizophrenia in clinical samples (Brugger and Howes, 2017), longitudinal cohort studies from the general population indicate that brain ventricles increase in size with advancing childhood development (Lenroot and Giedd, 2006), for which relative brain ventricular enlargement has also been associated with adaptive outcomes in childhood, such as fetal growth maturation (Gilmore et al., 2018; Roza et al., 2008b). Indeed, some studies have indicated that *lower* ventricular volume is associated with worse behavioral outcomes in childhood, such as temperamental difficulties (Roza et al., 2008a), and attention-deficit/hyperactivity disorder (Castellanos et al., 1996). Brain ventricles have been reported to have the highest variability of brain morphometric structures, possibly since they verge on many other brain structures (Gilmore et al., 2018). These observations contrast with findings from clinical samples of adults with schizophrenia, which have robustly implicated larger cerebral ventricles in the neurobiological pathophysiology of schizophrenia (Brugger and Howes, 2017; van Erp et al., 2016), a finding that has also been extended to samples of childhood-onset schizophrenia (Rapoport et al., 1997). Against this background, reports of increased ventricular volume in the context of neuropsychiatric conditions should therefore be interpreted with caution. Further research across distinct sampling designs and neurodevelopmental stages are needed to examine how these seemingly contradictory observations relate to the neurodevelopmental risk of schizophrenia (Murray et al., 2017).

White matter microstructural integrity increases in normal childhood and adolescence (Di Martino et al., 2014), i.e. FA increases and diffusion indices (MD, AD and RD) decrease with age. Lower FA and higher diffusion metrics, in particular MD, have been observed across several brain regions in patients with schizophrenia (Kelly et al., 2018). This is consistent with our observation of increased MD in children with elevated genetic risk for schizophrenia who also had high cortisol levels, even though this association did not survive correction for multiple testing. No such moderation effect was seen for FA, which we had hypothesized given the lower FA commonly observed in persons with schizophrenia (Kelly et al., 2018). However, few studies have comprehensively examined FA in conjunction with diffusion metrics, which is important for future research to disentangle neurobiological mechanisms. When viewed from the perspective of ventricle volume and white matter microstructure, it appears that the optimal level of stress exposure varies between children as a function of their genetic risk.

Over the past several years, hair cortisol has gained increasing attention as a biological marker of chronic physiological stress, which is interesting considering the hypothalamic-pituitary-adrenal-axis involvement in schizophrenia. Consistent with prior work from our group, our current results did not identify main effect associations between hair cortisol and brain structure (Chen et al., 2016). In addition, schizophrenia PRS was not associated with hair cortisol in the current

sample, consistent with previous research demonstrating a low SNP heritability (Neumann et al., 2017), and potentially reflecting the large environmental component of hair cortisol assessments. Rather, we found suggestive evidence for hair cortisol moderating the association of schizophrenia PRS with ventricle volume and global MD. Results from an earlier twin study had already hinted that the association of salivary cortisol with brain correlates might be at least partially determined by genetic factors (Kremen et al., 2010), further supporting our finding that genetic predisposition is a potential consideration in the association between environmental stressors and brain structure.

The strengths of this study included the use of exclusively biological metrics for examining determinants of psychiatric pathophysiology, its prospective design, and the population-based sample. However, our sample was not large enough to detect small effects, potentially increasing the chances of false negatives. However, the Generation R Study is the largest pre-adolescent neuroimaging study to date, so although our analyses might be underpowered, we are working with the best data available. Large collaborative efforts will be needed to further examine how increased genetic risk for psychiatric disorders affect neurodevelopment. Relatedly, the current sample size was relatively small compared with other Generation R studies using genotype data (Serdarevic et al., 2018), which might indicate a potential selective loss to follow-up. Although non-participation in population-based cohort studies has been related to higher schizophrenia PRS (Martin et al., 2016), our attrition analyses demonstrated no group differences in PRS between participants with complete data and participants lost to follow-up. Furthermore, we did not have imaging and hair cortisol data available at both ages six and ten years to study their relative prospective relationships. However, we have previously shown an absence of a statistical interaction between hair cortisol and the time interval between hair sampling and MRI scanning (Chen et al., 2016). In addition, cortisol measures, even if performed in hair, could reflect temporary states of stress. However, hair cortisol levels exhibit high intra-subject stability (Stalder et al., 2012) and have been demonstrated to reflect chronic exposure to stress (Rippe et al., 2016; Stalder et al., 2017). And, from a neurodevelopmental perspective, whether hair cortisol at age 6 years reflects stress at age 10 years is less relevant, because the neurodevelopmental process giving rise to a change in brain structure must necessarily have occurred long before age 10 years. In addition, similar to many other genetic studies, our analyses were limited to children of European descent. Future large psychiatric GWAS efforts should prioritize genetic discovery among a wide diversity of ethnic backgrounds, and not only focus on people of European ancestry. Finally, this was an observational study, which limits inferences regarding the purported causality of our observations. Long-term follow-up of this population into adolescence will provide us with the opportunity to examine how these observations relate to the onset of prodromal symptomatology.

5. Conclusions

In summary, following stringent correction for multiple testing, we found no significant moderating effects of hair cortisol on the association between schizophrenia PRS and pre-adolescent brain structure, precluding any firm conclusions regarding the interaction between schizophrenia PRS and hair cortisol on neuroimaging outcomes in pre-adolescence. We obtained statistically suggestive evidence that hair cortisol levels moderated the relationship of schizophrenia PRS with brain ventricular volume and white matter microstructure. Such observations potentially attest to the importance of considering the interaction between genetic and environmental determinants in psychiatric disease pathophysiology.

Author contributions

KB: Conceptualization, formal analysis, writing – original draft. **HT:** Conceptualization, methodology, resources, writing – review & editing, supervision, funding acquisition. **PJ:** Software, formal analysis, writing – review & editing. **RM:** Software, writing – review & editing. **AN:** Formal analysis, writing – review & editing. **MH:** Resources, writing – review & editing, supervision. **EvdA:** Resources, validation, writing – review & editing, supervision. **EvR:** Resources, validation, writing – review & editing, supervision. **VJ:** Resources, validation, writing – review & editing, supervision. **MV:** Resources, validation, writing – review & editing, supervision. **TW** Resources, validation, writing – review & editing, supervision. **SK:** Conceptualization, methodology, resources, writing – review & editing, supervision, funding acquisition.

Conflict of interest statement

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.12.231.

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