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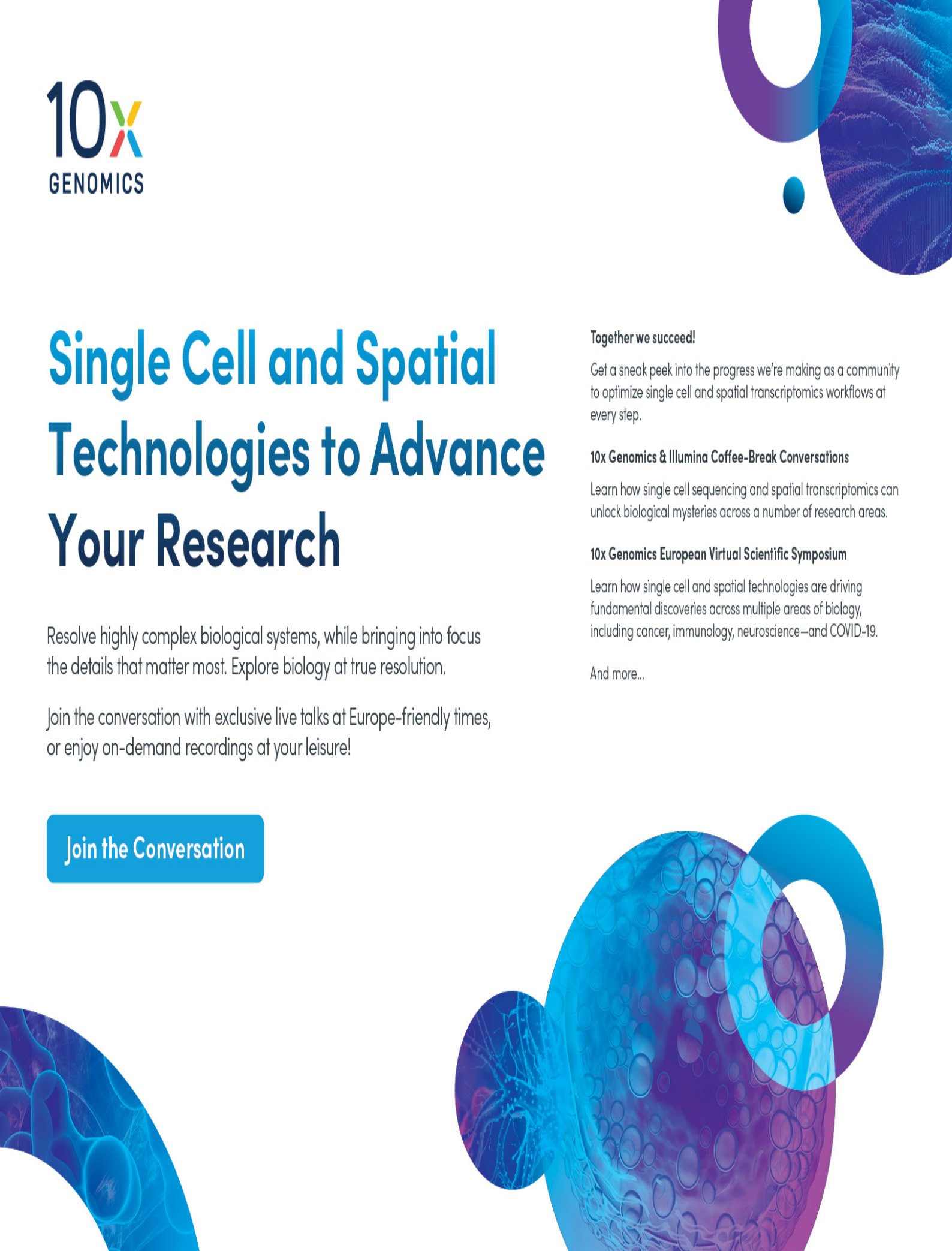

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RESEARCH ARTICLE

Sex-specific association between infant caudate volumes and a polygenic risk score for major depressive disorder

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Abstract

Polygenic risk scores for major depressive disorder (PRS-MDD) have been identified in large genome-wide association studies, and recent findings suggest that PRS-MDD might interact with environmental risk factors to shape human limbic brain development as early as in the prenatal period. Striatal structures are crucially involved in depression; however, the association of PRS-MDD with infant striatal volumes is yet unknown. In this study, 105 Finnish mother–infant dyads (44 female, 11–54 days old) were investigated to reveal how infant PRS-MDD is associated with infant dorsal striatal volumes (caudate, putamen) and whether PRS-MDD interacts with prenatal maternal depressive symptoms (Edinburgh Postnatal Depression Scale, gestational weeks 14, 24, 34) on infant striatal volumes. A robust sex-specific main effect of PRS-MDD on bilateral infant caudate volumes was observed. PRS-MDD were more positively associated with caudate volumes in boys compared to girls. No significant interaction effects of genotype PRS-MDD with the environmental risk factor "prenatal maternal depressive symptoms" (genotype-by-environment interaction) nor significant interaction effects of genotype with prenatal maternal depressive symptoms and sex (genotype-by-environment-by-sex interaction) were found for infant dorsal striatal volumes. Our study showed that a higher PRS-MDD irrespective of prenatal exposure to maternal depressive symptoms is associated with smaller bilateral caudate volumes, an indicator of greater susceptibility to major depressive disorder, in female compared to male infants. This sex-specific polygenic effect might lay the ground for the higher prevalence of depression in women compared to men.

K. Kantojärvi and J. J. Tuulari have contributed equally to this study.

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KEYWORDS
brain development, Gene-environment interaction, MRI, prenatal programming, striatum

1 | INTRODUCTION

Major depressive disorder (MDD) is among the leading causes for disability, and affects women about twice as often as men (Kyu et al., 2018; Wittchen et al., 2011). MDD is partly genetically determined, showing a heritability in the range of 31 to 42% (Sullivan, Neale, & Kendler, 2000). According to the polygenic theory (first postulated for schizophrenia; Demirkan et al., 2011; Gottesman & Shields, 1967; Meyer-Lindenberg & Weinberger, 2006), the heritability of MDD is likely based on a high number of genetic variations with small effect sizes and multiple gene-by-gene and gene-by-environment interactions. Based on the polygenic theory, polygenic risk scores for MDD (PRS-MDD) have gained importance in genetic studies on MDD. Individual PRS-MDD are calculated as the sum of risk alleles of single nucleotide polymorphisms (SNPs), identified in genome-wide association studies (GWAS) of MDD or depressive symptoms, selected up to a certain significance threshold and weighted by their effect size (Ripke et al., 2013; Wray et al., 2018). There is growing evidence that PRS-MDD predict MDD risk in children and adults, as a main effect and/or in interaction with environmental factors (Peyrot et al., 2014; Taylor et al., 2019). Recent studies suggested that PRS-MDD shapes limbic brain (namely amygdalar and hippocampal) development as early as in the prenatal period, interacting with prenatal maternal depressive symptoms, an early environmental risk factor for child development (Acosta et al., 2020; Qiu et al., 2017). Evidence is mounting that psychiatric disease susceptibility can originate in early life stages (Kim, Bale, & Epperson, 2015; O'Donnell & Meaney, 2017; Rice et al., 2010), and might to some extent be mediated by altered offspring brain development (Acosta et al., 2019; Sandman, Buss, Head, & Davis, 2015; Wen et al., 2017). Thus, better knowledge of early brain development in the interplay of genetic and environmental risk factors could foster our understanding of the etiology of psychiatric disorders such as MDD. However, very few studies have addressed this topic so far (Gao et al., 2019).

An increased risk for MDD has been associated with medical diseases that affect the striatum, for instance degenerative basal ganglia disorders and striatal lesions (Drevets, Price, & Furey, 2008). The striatum, and most prominently its dorsal structures caudate and putamen, is implicated in the control of motor functions, motivation, goal-directed behavior, and its flexible adaptation to internal and external cues by reinforcement-based learning (Graybiel & Grafton, 2015; Haber, Adler, & Bergman, 2012). MDD-related alterations in striatal reactivity to emotional stimuli and reward have been reported in adults (Pizzagalli et al., 2009; Surguladze et al., 2005). A recent study proposed that parts of the caudate nucleus might even be causally involved in the generation of a subjective pessimistic state and of repetitive choices based on negative evaluations (Amemori, Amemori, Gibson, & Graybiel, 2018). Studies in adults showed that reduced caudate and putamen volumes are associated with MDD (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012; Bora, Harrison, Davey, Yücel, & Pantelis, 2012), and smaller caudate volumes predicted stronger anhedonia and overall depressive symptoms in adults (Pizzagalli et al., 2009). Striatal volumes show a high heritability (ranging between 66% and 90%; Blokland, de Zubicaray, McMahon, & Wright, 2012; Hibar et al., 2015; Kremen et al., 2010; Stein et al., 2011) and have been associated with genetic variations that play a role in early neurodevelopment (Hibar et al., 2015; Kremen et al., 2010). The striatum also displays sex differences in its neural structure and function (Wong, Cao, Dorris, & Meitzen, 2016). Striatal volumes are usually larger in healthy females than males irrespective of age (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Goldstein et al., 2001; Lenroot & Giedd, 2010; Luders, Gaser, Narr, & Toga, 2009, but see also Rijpkema et al., 2012). The striatum contains a high density of sex steroid receptors in early development, as identified in animal studies, which might convey sexually dimorphic neuronal density and synaptogenesis in early brain development (Goldstein et al., 2001). The striatal sexually dimorphic neural organization might also provide a potential mechanism for the observed sex-specific prevalence in MDD susceptibility later in development.

In sum, the dorsal striatum constitutes a set of structures crucially implicated in MDD and thus represents a relevant target for

the investigation of the developmental trajectory of MDD susceptibility. However, to date it is unknown how the prenatal developmental trajectory of striatal volumes is shaped by an interplay of genetic and environmental risk factors for MDD. With this study, we aimed at investigating the association of a PRS-MDD, as identified in a mega-analysis of several GWAS of recent European ancestry (Ripke et al., 2013), with infant striatal volumes. In more detail, we probed whether infant caudate and putamen volumes are significantly predicted by an infant PRS-MDD and its interaction with an environmental risk factor, that is, prenatal maternal depressive symptoms, in Finnish mother–infant dyads. Prenatal maternal depressive symptoms have been associated with preterm delivery and offspring behavioral and emotional problems (Gentile, 2017; Grigoriadis et al., 2013) and have been shown to interact with PRS-MDD on infant limbic (i.e., amygdalar and hippocampal) volumes (Acosta et al., 2020; Qiu et al., 2017). We assessed prenatal maternal depressive symptoms in the early and late second trimester and in the third trimester (gestational weeks 14, 24, and 34) and computed a sum score for the analyses. We further probed whether genetic main and interaction effects are sexually dimorphic.

Significance

Major depressive disorder (MDD) is among the leading causes for disability, and affects women about twice as often as men. MDD risk is influenced by genetic and environmental factors, partly as early as in the prenatal period, and might partly be mediated by altered brain development. So far, little is known about infant brain development in the interplay of genetic and environmental MDD risk factors. Our study showed that a polygenic risk score for MDD is associated with sex-specific brain structural alterations in the infant striatum, a brain structure crucially implicated in MDD in adults.

2 | METHODS

2.1 | Subjects

Participants were mother–infant dyads recruited from the FinnBrain Birth Cohort Study [www.finnbrain.fi] (Karlsson et al., 2018). Neuroimaging data were collected from 189 infants at the age of 1–8 weeks after birth. Inclusion criteria for neuroimaging were gestational age at birth ≥ 35 weeks and birth weight > 1,500 g. Exclusion criteria were previously diagnosed CNS anomalies or abnormal findings in a previous MRI scan. Written informed consent was obtained from all parent(s). The study was conducted according to the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:31/180/2011). Of the 189 participants, 64 were excluded due to failed MRI scanning or motion artifacts in the MR images. Of the remaining 125 infants, 19 were excluded because of missing genetic data (no GWAS performed ($N = 15$) or drop-out in quality control ($N = 4$)). One more subject was excluded due to missing maternal EPDS questionnaire data as described below. In the final sample, we included 105 infants [female: 41.9%, age after birth [days]: $M = 26.1$, $SD = 7.2$, range = 11–54, age of mothers (at term) [years]: $M = 29.7$ ($SD = 4.6$, range = 19–41)].

2.2 | Measures and procedures

2.2.1 | Maternal prenatal depressive symptoms

Maternal prenatal depressive symptoms were assessed with the Finnish version of the Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987) at three time points during pregnancy (gestational weeks (gwk) 14, 24, and 34). Missing values at each time point (at maximum three items per time point) were imputed with the mean value of the existing ones. If no EPDS questionnaire data were available for one or two of the time points, data were imputed by the MissForest method (gwk 14: $N = 2$, gwk 24: $N = 1$, gwk 34: $N = 6$; Stekhoven & Bühlmann, 2012). One mother did not provide any EPDS questionnaire data and this mother–infant dyad was therefore excluded from the analyses. In this study, the individual sum scores of all three time points were combined to form a total EPDS sum score (EPDS Sum). We observed an outlier for EPDS Sum (>3SD) and excluded it in control analyses (see 2.2.6).

2.2.2 | Other maternal and infant variables

We administered the anxiety subscale of the revised Symptom Checklist 90 (SCL-90-R; Derogatis, 1983; Holi, Sammallahti, & Aalberg, 1998) at gwk 14, 24, and 34 to control for general maternal anxiety during pregnancy. Missing values (at maximum three items per time point) were imputed with the mean value of the existing ones, and individual sum scores were computed for general anxiety (SCL Sum) during pregnancy. The following maternal variables were assessed via mothers' self-report at gwk 14 and/or 34: maternal education, maternal age, maternal prenatal medication, and prenatal alcohol, nicotine and illicit drug consumption. Obstetric data were retrieved from the Finnish Medical Birth Register of the National Institute for Health and Welfare (http://www.thl.fi) and included maternal prepregnancy body mass index (BMI), and infant birth weight (missing: $N = 1$), gestational weeks, and Apgar scores (missing: $N = 1$, Apgar = appearance, pulse, grimace, activity, and respiration). We dichotomized maternal medication use as assessed at gwk14 (selective serotonin reuptake inhibitors (SSRI) and other CNS affecting medication, thyroxine, and corticosteroids; each yes/no, missings: $N = 4$) and alcohol, nicotine and/or illicit drug exposure (yes/no, missings: $N = 8$). We further dichotomized BMI (BMI < 25, BMI >= 25, missings: $N = 2$)

given that maternal obesity has been associated with alterations in the infant brain (Pulli et al., 2019). Education was trichotomized [low: high school or vocational education (<12 years), middle: (career) college (12–15 years), high: university (+15 years)]. In the final sample, 12 infants had a record of mild asphyxia.

2.2.3 | MRI acquisition

A detailed description of the MRI acquisition protocol is provided in a previous publication by the same research team (Lehtola et al., 2019). Participants were scanned with a Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany) during natural sleep. The 40-min imaging protocol included an axial PD-T2 TSE (Dual-Echo Turbo Spin Echo) sequence (repetition time (TR): 12,070 ms, effective echo times (TE): 13ms and 102 ms) and a sagittal 3D-T1 MPRAGE (magnetization-prepared rapid acquisition gradient echo) sequence (TR: 1,900 ms, TE: 3.26 ms, inversion time: 900 ms) with whole brain coverage and isotropic voxels of 1.0 mm^3 for both sequences. All brain images were assessed for incidental findings by a pediatric neuroradiologist.

2.2.4 | Assessment of structure volumes

The volumes of the left and right caudate nuclei and putamina were assessed for each subject via label-fusion-based methods. These methods depend on achieving good registrations between the subjects and the entries in a library of templates. This is increasingly difficult to achieve the further the templates are from the subjects in terms of similarity. Thus, we constructed a template library based on the subjects in this study. We first constructed a population-specific base template and manually labeled the subcortical structures on this template (Fonov et al., 2011). We then constructed a library of warped versions of the labeled template such that the library represented the morphological variation in the sample. We then labeled the individual brains via label-fusion-based labeling methods, and calculated the volume of each structure (Lewis, Fonov, Collins, Evans, & Tohka, 2019). The details of this approach are described below.

Construction of an unbiased population-specific template

All available, good-quality imaging data ($N = 125$) were used for template construction. Each subject's T2 was linearly registered to their T1, and their T1 was linearly registered to the MNI 152 template. The average scaling from the native MRIs to the MNI 152 template was then computed, and the inverse used to scale the MNI 152 template to the average size of the population, which served as an initial target for construction of the population-specific template, as described in Fonov et al. (2011). This iterative procedure builds a template that minimizes the mean-squared intensity difference between the template and each subject's MRI, and minimizes the magnitude of all deformations used to map the template to each subject's MRI. This method was applied to the T1 scans producing nonlinear transformations from the template space to each scan, then these transformations were used to map the T1 scans to the template space, where they were averaged to create the T1 template; these transformations were also combined with the T2 to T1 transformations to map the T2 scans into the common space where they were averaged to create the T2 template.

Labeling the template

The structures of interest, that is, the caudate nuclei and putamina, were manually labeled on the dual-contrast template. To ensure that these labels were accurate, we produced multiple variants of the template, and had each variant manually labeled.

The nonlinear transformations derived from the template construction procedure were used to cluster the subjects into 21 clusters from which 21 targets for manual segmentation of the subcortical structures were created. As the basis for clustering, the Jacobian was computed for the nonlinear transforms mapping each subject to the template. The values in the Jacobian were then extracted as a vector for each voxel within the template brain mask. These Jacobian vectors were then clustered using an equal combination of cosine similarity and Euclidean distance with Ward's clustering method (Ward, 1963), with the number of clusters chosen to be 21. Then, within each cluster, the sum-squared distance from each subject to each other subject was computed, and the subject with the minimum sum-squared distance was taken as the central-most subject of the cluster. The dual-contrast template constructed in the previous step was then warped to these 21 representative subjects, and provided for manual segmentation (the persons performing the segmentation were unaware that these were, in fact, 21 different versions of the same template). The manual segmentations were then warped back to the standard template, and each voxel was assigned a label based on the majority vote across all manual segmentations. This yielded the final labels for all structures on the standard template.

Manual segmentation

After careful consideration, we decided to create a single mask for the caudate. The work was influenced by prior publications on a similar setting (Perlaki et al., 2017). We used the sagittal plane to trace the curvature of the caudate at the midline, and we then used the coronal plane as the main segmentation plane. Furthermore, for the three-dimensional consistency of the segmentation, we checked the delineations and edited them in all three planes (axial, coronal, and sagittal). After adjusting the contrast settings, the tissue borders were the main guides for labeling, and we used a standard contrast range to assure the systematic delineation of white matter and cerebrospinal fluid boundaries. The key anatomical landmarks used for the tissue boundary detection were the lateral border of the lateral ventricles medially, the white matter forming the external capsule and adjacent areas laterally, the anterior horns of the lateral ventricles and capsula interna anteriorly, as well as the anterior commissure, and the anterior–inferior borders of putamen and pallidum.

Once the caudate segmentation was ready, we segmented the putamen (mainly in the coronal plane). The anterior border was defined close to the caudate head and otherwise the bilateral putamen was carefully traced with standard contrast settings to help systematic border delineation from the white matter while also keeping the claustrum separate from the tracings. The resolution of 0.5 mm^3 and the good contrast made the segmentation of the gray matter nuclei relatively easy.

We started with one template segmented for all structures by the primary rater NH and the senior rater JT and the segmentation was externally reviewed by JL. Then the final segmentations of the 21 subtemplates were produced with the help of research assistants and critically reviewed at all stages and corrected where appropriate (by NH and JT). The final labels were thus a consensus between the primary and the two senior raters. The base template was symmetric, and so the number of manual labeling was doubled by creating a copy that was flipped along the x-axis. The final labels were arrived at by majority agreement of both the flipped and unflipped manual segmentations of all 21 subtemplates. The final majority agreement labels were then used for the segmentation of the individual images in the subsequent automated labeling step.

Labeling the subjects

Individual MRI segmentation for each subject was done using a label-fusion-based labeling technique based on Coupé et al. (2011) and further developed by Weier, Fonov, Lavoie, Doyon, and Louis Collins (2014) and by Lewis et al. (2019). The approach uses a population-specific template library for the deep gray matter structures. The library was constructed by clustering (similar to the method described above) the deformation fields from the nonlinear transforms produced during construction of the template and using the central-most subject of each cluster to construct the entries in the template library. Thus, the template library represented the range of deformations found in the population. The clustering was done as described above, but using a dilated mask of the specific structures in order to capture the anatomical context of the nonlinear registration in that region of the brain, that is, in the region of the deep gray matter structures, with the number of clusters now chosen as the square of the natural log of the number of subjects. The representative subject for each cluster was chosen as described above, that is, the central-most subject. This was done per hemisphere to accommodate hemispheric asymmetries, and the two sets of representative subjects were merged.

To create the library entry for a cluster, the nonlinear transform for the central-most subject was used to warp the template together with the segmentation defined on it, and this pair was added to the template library. The template library was thus a set of warped copies of the template together with their correspondingly warped segmentations. Once the template library had been created, each subject in the population was nonlinearly registered to the n closest templates in the library (here, $n = 7$), and the resulting transforms were used to warp their corresponding segmentations to the subject; the final labeling was then established via patch-based label fusion. This was also done separately for each hemisphere. The volumes of each of the final labeling were then computed and scaled to the native space based on the scaling factors in the subject's linear transforms. Similarly, a brain mask was scaled to native space and used to estimate total brain volume (TBV).

2.2.5 | Genetic analyses

An umbilical cord blood sample was drawn from each newborn at birth. DNA samples were extracted according to standard procedures at the National Institute for Health and Welfare and genotyped with Illumina Infinium PsychArray and Illumina Infinium Global Screening Array at the Estonian Genome Centre. Quality control (QC) was performed with PLINK 1.9 (www.cog-genomics.org/plink/1.9/) (Chang et al., 2015). Markers were removed for missingness (>5%) and Hardy–Weinberg equilibrium (p-value $< 1 \times 10^{-6}$). Individuals were checked for missing genotypes (>5%), relatedness (identical by descent calculation, PI_HAT > 0.2), and population stratification (multidimensional scaling). Genotyped data were pre-phased with Eagle v2.4 (Loh et al., 2016) and imputed with Beagle v4.1 (Browning & Browning, 2016) using the population-specific SISu v2 whole-genome sequencing data as imputation reference panel.

The individual infant polygenic risk scores for major depressive disorder (PRS-MDD) were generated according to Qiu et al. (2017) and were based on a meta-analysis from the Psychiatric Genomics Consortium (discovery sample: European ancestry, 9,240 MDD cases and 9,519 controls; Ripke et al., 2013). The PRS-MDD was computed as the sum of the number of risk alleles (0, 1, and 2) across SNPs weighted by their odds ratio as reported by Ripke et al. (2013; retrieved from "https://www.med.unc.edu/pgc/results-and-downloads/downloads"). We selected the SNPs with the same threshold for linkage disequilibrium (LD) clumping as reported in Qiu et al. (2017) (r2 < 0.25 within a 500 kb window) and which survived at p-value thresholds of 0.05, 0.1, and 0.2, respectively. Additionally, we investigated a PRS-MDD with SNPs that survived a p-value threshold of $p = 0.001$. Hence, the PRS-MDD consisted of 418 (threshold $p = 0.001$), 12,878 (threshold $p = 0.05$), 23,037 (threshold $p = 0.1$), and 40,405 (threshold $p = 0.2$) selected SNPs (due to imputation the numbers of selected SNPs differ from those reported in Qiu et al. (2017), see also the Supplementary Table listing the SNPs of threshold $p = 0.001$ and threshold $p = 0.05$), and was standardized to a mean of zero for the infant MRI sample ($N = 161$).

2.2.6 | Statistical analyses

Statistical analyses were performed using R 3.4.4 (http://www.r-project.org/) (R Core Team, 2016). Statistical R packages in use were

"psych" (Revelle, 2018), "nortest" (Gross & Ligges, 2015), "ggplot2" (Wickham, 2009), and "car" (Fox & Weisberg, 2011) among others. Standard multiple linear regression analyses were performed to probe the association of bilateral caudate and putamina volumes with individual genetic (PRS-MDD) scores and their interaction with environmental risk scores (prenatal maternal depressive symptoms, measured as EPDS Sum scores) and with sex.

In total, five models were applied to each outcome measure: 1. The basic model, containing only the four control variables, namely "infant's age after birth at MRI scan time," "gestational weeks," "total brain volume," and "infant's sex" (model B). These four control variables were included into every subsequent model. 2. The main effect of PRS-MDD (model G). Scores of the four different *p*-value thresholds were analyzed separately. 3. The main effect of EPDS (model E) with individual EPDS Sum scores. 4. An additive model of genetic and environmental effects (model G+E). 5. An interaction model of genetic and environmental effects (model GxE). An analysis of variance (ANOVA) model comparison (anova function in R) was applied to determine whether each model added explanatory value over the reduced model (see Halldorsdottir et al., 2019): Model B was compared to model G, model G was compared to model G+E, and model G+E was compared to model GxE. Models that significantly differed from the reduced model were further investigated in multiple regression analyses.

Second, we investigated sex-specific associations, that is, two-way interactions between sex and the genetic scores as well as three-way interactions between genetic scores, environmental scores, and sex. In ANOVA model comparisons, we compared the model of the sex-specific (S) interaction (model GxS, model GxExS) against the model G or model GxE, respectively. Only models that significantly differed from the reduced model were further investigated. We report the estimates, their standard errors and *p*-values of significant predictors.

In sensitivity analyses of significant results, we repeated the multiple regression analyses by subsequently adding and removing each of the following control variables to/from the model in order to test if the observed results were explained by these covariates: infant birth weight, infant Apgar scores, maternal education, maternal BMI, maternal general anxiety, prenatal maternal depressive symptoms (if not included as predictor), maternal prenatal medication, and maternal prenatal alcohol, nicotine and/or illicit drug exposure. In further sensitivity analyses we excluded EPDS outliers (>3SD; $N = 1$) as well as infants with mild asphyxia at birth ($N = 12$, missings: $N = 2$, resulting sample: $N = 91$).

The significance threshold was set to $p < 0.05$. We report the 95% confidence interval (CI) of the β-values of significant predictors (confint function in R). In order to control for the error rate related to multiple comparisons, we additionally report a false-discovery-rate (FDR) correction that was used for the four outcome measures (left/right caudate, left/right putamina; p.adjust function in R). No correction for multiple comparisons was applied for the different *p*-value thresholds of PRS-MDD, which is comparable to a prior study with a similar design (Qiu et al., 2017).

3 | RESULTS

3.1 | Demographic overview

Demographic characteristics of the sample are presented in Table 1. No significant sex differences were observed for the PRS-MDD or EPDS Sum scores. Female infants exhibited significantly smaller bilateral putamina volumes than males, but also significantly smaller total brain volumes (Table 2). After controlling for total brain volumes, gestational weeks, and infant age, no significant sex differences in striatal volumes were observed (all $p > 0.25$). For the ratio of local to total brain volumes (Table 2), a trend toward larger ratios of the right caudate to total brain volumes in female compared to male infants was found ($p = 0.081$, after controlling for gestational weeks and infant age: $p = 0.093$).

3.2 | No significant main effect of PRS-MDD on striatal volumes

The ANOVA model comparison analyses did not reveal significant main effects of PRS-MDD genotype on striatal volumes (right caudate: all $p > 0.34$, left caudate: all $p > 0.09$, right putamen: all $p > 0.39$, left putamen: all $p > 0.25$).

3.3 | No significant genotype-by-environment interaction effects on striatal volumes

The ANOVA model comparison analyses did not yield significant results for the genotype-by-environment interactions (model GxE; right caudate: all $p > 0.46$, left caudate: all $p > 0.19$, right putamen: all $p > 0.52$, left putamen: all $p > 0.49$).

3.4 | Sex-specific associations of infant genotype with bilateral striatal volumes

A significant genotype-by-sex interaction effect was discovered for bilateral caudate volumes: The PRS-MDD (thresholds of $p = 0.05$, $p = 0.1$, and $p = 0.2$, strongest effect for $p = 0.05$) was significantly more positively associated with right caudate volumes in boys compared to girls (PRS-MDD threshold $p = 0.05$: $\beta = 97.9 \pm 28.3$, 95% CI [41.7, 154.0], $p < 0.001$, p(FDR) = 0.003 (FDR correction for $N = 4$ tests, see methods); Figure 1). PRS-MDD (threshold of $p = 0.05$ and $p = 0.1$, stronger effect for $p = 0.05$) was also significantly more positively associated with left caudate volumes in boys compared to girls (PRS-MDD threshold $p = 0.05$: $\beta = 71.6 \pm 29.1$, 95% CI [13.9, 129.2], $p = 0.016$, p(FDR) = 0.031). The genotype-by-sex interaction effect for bilateral caudate volumes stayed significant after correction for multiple comparisons and in all sensitivity analyses for PRS-MDD (threshold $p = 0.05$). No significant results were obtained for the PRS-MDD threshold $p = 0.001$ (all $p > 0.33$).

TABLE 1 The mean scores (M) and standard deviations (*SD*) or frequencies, respectively, are listed for prenatal maternal EPDS scores and control variables, for the whole sample ($N = 105$) and for girls ($N = 44$) and boys ($N = 61$) separately (missings for infant birth weight and Apgar scores as well as for maternal BMI, prenatal medication, alcohol, nicotine and/or illicit drug consumption as described in the methods section)

Variable	Whole sample	Boys	Girls	*p*
M ± SD (range)				
Child's age (days)	26.1 ± 7.2 (11–54)	26.9 ± 7.6 (11–43)	24.9 ± 6.5 (14–54)	0.153
Gestational weeks	39.8 ± 1.1 (36.3–42.1)	39.7 ± 1.0 (37.6–41.9)	40.0 ± 1.2 (36.3–42.1)	0.208
Birth weight (g)	3,481.1 ± 418.8 (2,530–4,700)	3,536.6 ± 438.2 (2,720–4,700)	3,402.3 ± 380.8 (2,530–4,340)	0.108
Apgar, 5 min	9.0 ± 1.0 (4–10)	8.8 ± 1.1 (4–10)	9.2 ± 0.5 (8–10)	0.011*
EPDS (gwk 14)	5.51 ± 5.14 (0–25)	5.63 ± 4.99 (0–21)	5.36 ± 5.41 (0–25)	0.797
EPDS (gwk 24)	5.62 ± 5.28 (0–25)	5.99 ± 5.35 (0–23)	5.11 ± 5.22 (0–25)	0.404
EPDS (gwk 34)	5.51 ± 4.88 (0–20)	5.90 ± 5.06 (0–17)	4.98 ± 4.61 (0–20)	0.343
EPDS Sum	16.65 ± 13.74 (0.00–63.95)	17.51 ± 13.88 (0.00–57.48)	15.45 ± 13.62 (1.00–63.95)	0.451
SCL Sum	11.70 ± 12.86 (0.00–54)	12.23 ± 11.89 (0.00–41.34)	10.97 ± 14.22 (0.00–54)	0.623
Frequencies				
Prenatal alcohol, nicotine and/or illicit drug consumption (no/yes)	64/33	37/21	27/12	0.579
Prenatal maternal BMI (<25/>=25)	67/36	38/22	29/14	0.666
Prenatal medication—SSRI and other CNS affecting drugs (no/yes)	92/9	52/7	40/2	0.217
Prenatal medication—thyroxine (no/yes)	93/8	53/6	40/2	0.321
Prenatal medication—corticosteroids (no/yes)	95/6	56/3	39/3	0.666
Maternal education (low/middle/high)	31/30/42	18/16/26	13/14/16	0.768

Note: In the right column *p*-values for sex differences in the sample are listed.

Abbreviations: BMI, body mass index; CNS, central nervous system, EPDS, Edinburgh Postnatal Depression Scale; SCL, prenatal maternal general anxiety (Symptom Check List 90-R); SSRI, selective serotonin reuptake inhibitor.

*$p < 0.05$.

TABLE 2 Subcortical volumes (corrected and uncorrected for total brain volumes) are listed for the whole sample and for boys and girls separately

Volumes [mm^3] (*M ± SD*)	Whole sample	Boys ($N = 61$)	Girls ($N = 44$)	*p*
Left caudate	1,396 ± 143	1,409 ± 150	1,376 ± 132	0.244
Right caudate	1,449 ± 146	1,457 ± 139	1,438 ± 156	0.508
Left putamen	1,512 ± 146	1,543 ± 145	1,469 ± 137	0.010
Right putamen	1,500 ± 152	1,536 ± 156	1,449 ± 132	0.004
Total brain volume	621,792 ± 46,753	633,575 ± 45,810	605,455 ± 43,455	0.002
Left caudate/TBV	23 ± 2(*10^{-4})	22 ± 2(*10^{-4})	23 ± 2(*10^{-4})	0.233
Right caudate/TBV	23 ± 2(*10^{-4})	23 ± 2(*10^{-4})	24 ± 2(*10^{-4})	0.081
Left putamen/TBV	24 ± 2(*10^{-4})	24 ± 2(*10^{-4})	24 ± 2(*10^{-4})	0.779
Right putamen/TBV	24 ± 2(*10^{-4})	24 ± 2(*10^{-4})	24 ± 1(*10^{-4})	0.368

Note: In the right column *p*-values of sex differences in the sample are listed.

Abbreviation: TBV, total brain volume.

In post hoc multiple linear regression analyses, performed separately for girls and boys, right caudate volumes were positively associated with PRS-MDD in boys (PRS-MDD threshold $p = 0.05$: $\beta = 47.0 \pm 16.0$, $p = 0.005$), and negatively in girls (PRS-MDD threshold $p = 0.05$: $\beta = -52.2 \pm 25.7$, $p = 0.049$). Left caudate volumes were positively related to PRS-MDD in boys (PRS-MDD threshold $p = 0.05$: $\beta = 39.5 \pm 18.3$, $p = 0.035$), but only weakly negatively in girls (PRS-MDD threshold $p = 0.05$: $\beta = -34.9 \pm 22.8$, $p = 0.135$).

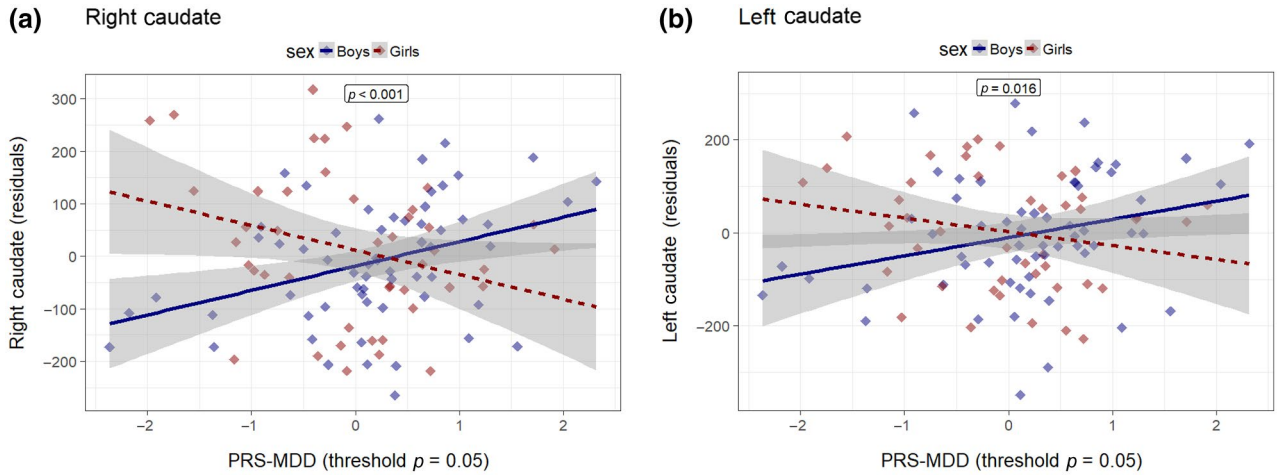

FIGURE 1 Interaction of genotype and sex on caudate volumes. The interaction between infant PRS-MDD (threshold: $p = 0.05$) and infant sex on (a) infant right caudate ($\beta = 97.9 \pm 28.3$, $p < 0.001$) and (b) infant left caudate volumes ($\beta = 71.6 \pm 29.1$, $p = 0.016$) is depicted (residuals, controlling for infant age, gestational weeks and TBV, and the regression lines and their 95% confidence intervals) [Color figure can be viewed at wileyonlinelibrary.com]

No sex-specific genotype effects were found for the putamina (right putamen: all $p > 0.33$, left putamen: all $p > 0.22$).

The analyses further indicated significant three-way interactions (GxExS) for right caudate volumes. However, in the multiple regression analyses, none of the three-way interactions were significant (all $p > 0.6$). No significant results for the model GxExS were obtained for left caudate (all $p > 0.08$) or putamina volumes (right: all $p > 0.55$; left: all $p > 0.61$).

4 | DISCUSSION

With this study, we investigated the association of an infant polygenic risk score for MDD and its interaction with prenatal maternal depressive symptoms with infant dorsal striatal volumes, and probed sexually dimorphic effects. We observed a sex-specific genetic main effect of PRS-MDD on bilateral caudate volumes. Caudate volumes were more positively associated with PRS-MDD in boys compared to girls. No significant genotype-by-environment interaction effects were observed. Moreover, no significant sex differences of infant striatal volumes were found though we observed a trend for larger "right caudate to total brain volume ratios" in female compared to male infants.

The dorsal striatum is a highly sexually dimorphic subcortical structure. During fetal and early postnatal development, the striatum contains a high density of estrogen and androgen receptors as shown in animal studies (Goldstein et al., 2001). It has been put forward that sex differences in brain structure originate during critical periods of early development driven by gonadal hormones and sex chromosome genes and might be partly irreversible (Goldstein et al., 2001; Pilgrim & Hutchison, 1994). Sex steroids influence the migration of neuroblasts into cortical layers, neuronal growth, synaptogenesis, and neuronal apoptosis, affecting neuronal number and size of brain structures (Pilgrim & Hutchison, 1994). Prenatally, the striatum of female compared to male rats displayed larger numbers of dopaminergic and GABA-immunoreactive cells (Pilgrim & Hutchison, 1994) and larger human female dorsal striatal volumes have been observed from early childhood on (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997). Our data did not show significant sex differences of infant dorsal striatal volumes, but right caudate volume ratios were larger in female compared to male infants. Thus, our results provide weak evidence that sex differences of caudate, but not putamina volumes, might start to develop prenatally. Interestingly, in adulthood, caudate nuclei show the greatest effect size for sex-specific subcortical volume differences (Goldstein et al., 2001).

In our study, caudate volumes, but not putamina volumes, were also more positively associated with PRS-MDD in boys compared to girls, providing support for the notion that infant caudate volumes are modulated by sex-specific genetic mechanisms. The striatum is the main target of dopaminergic neurons (Haber et al., 2012). A pharmacological blockade of dopamine receptors in humans has been related to striatal volume reductions within hours (Tost et al., 2010). It is conceivable that sex-specific striatal volume differences might be associated with differences in the striatal dopaminergic tone. In healthy humans, a higher striatal presynaptic dopamine synthesis has been found in women compared to men (Laakso et al., 2002) paralleling larger striatal volumes in females compared to males. Rodent and primate studies revealed that striatal dopaminergic activity is modulated by gonadal hormones (Becker, 1999; Kritzer, Adler, & Bethea, 2003), but there is also evidence that neither expression nor pruning of the striatal dopaminergic receptors are dependent on gonadal hormones during adolescence (Andersen, Thompson, Krenzel, & Teicher, 2002; Neufang et al., 2009) and presumably depend on sex-specific neuronal genetic programs (Pilgrim & Hutchison, 1994). We assume that PRS-MDD might implicate genetic variations of sex-specific dopaminergic neuronal programs that affect the striatal dopaminergic tone and thereby shape striatal volumes. According to this argumentation, a higher

PRS-MDD would be associated with a reduced striatal dopaminergic tone in females, but an enhanced one in males.

Caudate volume reductions have also consistently been linked to MDD in adults (Arnone et al., 2012; Bora et al., 2012) and these volume alterations predicted higher depressive symptoms (Pizzagalli et al., 2009). Considering the putative key role of caudate nuclei in MDD (Amemori et al., 2018), our findings suggest that a higher PRS-MDD increases vulnerability for MDD in female, but not male offspring. Interestingly, in adulthood, women are more vulnerable to MDD than men (Kyu et al., 2018; Wittchen et al., 2011), and our results suggest that sex-specific striatal genetic mechanisms might be involved in this sexually dimorphic prevalence of MDD.

We did not observe an interaction of PRS-MDD with an early environmental risk factor, that is, prenatal maternal depressive symptoms, on dorsal striatal volumes. By contrast, such an interaction has been found for infant limbic volumes (i.e., amygdalar and hippocampal volumes; Acosta et al., 2020; Qiu et al., 2017). Striatal compared to limbic volumes show a higher heritability and are less influenced by unshared environmental factors (~20% vs. ~35%–50%; Blokland et al., 2012; Kremen et al., 2010). This might explain why we were less likely to detect an interaction of PRS-MDD with an environmental risk factor on striatal volumes.

4.1 | Limitations

Several limitations of our study have to be acknowledged. The sample size was moderately large, and regarded as sufficient for investigating genetic main effects in neuroimaging studies. However, we cannot rule out that the investigation of sexually dimorphic effects of the infant brain whose effect sizes are not yet known might have suffered from a lack of statistical power.

The GWAS from which the PRS-MDD have been derived did not yield genome-wide significant results, and the network of MDD-related risk genes might not yet be fully known. However, GWAS are considered as suitable for detecting MDD-related genes despite their limited statistical power (Lubke et al., 2012).

4.2 | Future directions

It would be worthwhile to investigate how the observed brain volume alterations are related to offspring emotional, cognitive, and behavioral development and how they shape future vulnerability to psychiatric diseases.

5 | CONCLUSIONS

A higher PRS-MDD, irrespective of prenatal exposure to maternal depressive symptoms, was associated with smaller bilateral caudate volumes, an indicator of higher vulnerability to MDD, in female compared to male infants. Thus, our results highlight the importance of sex-specific polygenic influences on early caudate volume development and might help to understand the sexually dimorphic prevalence of MDD. Future studies should elucidate how the observed brain volume alterations predict offspring development and sexually dimorphic susceptibility to MDD.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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CONFLICT OF INTEREST

No conflicting interests exist.

AUTHOR CONTRIBUTIONS

Conceptualization, H.K., L.K., J.T. and H.A.; *Methodology*, V.F., J.L. and H.A.; *Investigation*, S.L., N.M.S., J.T., J.S., R.P. and T.L.; *Formal Analysis*, H.A., T.P., K.K., V.F., J.L. and N.H.; *Resources*, L.K., H.K., D.C. and A.E.; *Data Curation*, H.M., J.L. and J.T.; *Project Administration*, H.K.; *Validation*, J.L.; *Writing – Original Draft*, H.A., K.K., J.S., J.L. and J.T.; *Writing – Review & Editing*: K.K., J.T., J.L., N.H., N.M.S., S.L., V.F., D.C., A.E., R.P., T.L., J.S., H.M., L.K., T.P. and H.K.; *Visualization*, H.A.; *Supervision*, H.K., J.L., J.T. and N.H.; *Funding Acquisition*, L.K., H.K., N.M.S. and J.T.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data sets for this study will not be made publicly available because of Finnish data protection legislation. Requests to access the data sets should be directed to HK (hasseka@utu.fi).

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Additional supporting information may be found online in the Supporting Information section.

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Table S1

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