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Maternal cerebellar gray matter volume is associated with daughters' psychotic experience

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Aim: A substantial portion of children and adolescents show subthreshold psychotic symptoms called psychotic experience (PE). Because PE shares its biological and environmental risk factors with psychotic spectrum disorders, parental neuroanatomical variation could reflect a heritable biological underpinning of PE that may predict an offspring's PE.

Methods: A total of 94 participants from 35 families without a diagnosis of major neuropsychiatric disorders were examined, including 14 mother–daughter, 17 mother–son, 12 father–daughter, and 16 father–son dyads. An offspring's PE was assessed with the Atypicality subscale of the Behavior Assessment System for Children – 2nd Edition, Self-Report of Personality form (BASCaty). We examined correlations between voxel-by-voxel parental gray matter volume and their offspring's BASCaty score.

Results: Maternal cerebellar gray matter volume using voxel-based morphometry was positively correlated with their daughters' BASCaty scores. The findings were significant in a more robust approach using cerebellum-specific normalization known. We did not find significant correlation between paternal gray matter volume and BASCaty scores or between offspring gray matter volumes and their BASCaty scores.

Conclusion: Expanding upon parent-of-origin effects in psychosis, maternal neuroanatomical variation was associated with daughters' PE. The nature of this sex-specific intergenerational effect is unknown, but maternally transmitted genes may relate cerebellum development to PE pathogenesis.

Keywords: *cerebellum, intergeneration, maternal, MRI, psychotic experience.*

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Subclinical psychotic symptoms that do not reach diagnostic threshold, referred to as psychotic experiences (PE), are estimated to occur in 3%–8% of the general population, predict increased risk of psychotic disorders late in life, and provide strong evidence for understanding psychosis along a continuum that varies across development.[1,2] PE symptoms include aberrant sensory perceptions (hallucinations), rigidly held but blatantly false beliefs (delusions), and abnormal thought content.[1] While for approximately 75%–90% of individuals with PE, these symptoms remit at some point across development,[1] children aged 10–12 years represent an especially high-risk group, as PE prevalence rates in this age group are as high as 20% and as many as 16%–25% of such children later convert to a psychotic disorder in adolescence or young adulthood.[3] Risk of conversion to psychotic illness has been predicted both by self-reported PE symptoms in children aged 10–12 years and through structured clinical interviews.[2,4,5] Collectively, these findings suggest that PE and clinical psychotic symptoms exist on the same continuum. Evidence from cross-sectional studies shows that PE shares environmental and genetic risk factors with clinical levels of psychosis.[2,3]

Brain morphology is a putative biological marker of both PE[4,5] and psychosis.[6,7] Patients with familial schizophrenia have been shown to have more severe symptoms than patients with sporadic schizophrenia, and their unaffected parents show more morphological changes in brain structure compared to parents of sporadic cases.[8] Therefore, it is possible that parental neuroanatomical variation predicts the severity of psychotic symptoms in offspring. This is further supported by genetic evidence of transgenerational associations of parental brain morphology and child pathology.[9] It is perhaps unsurprising that these parent-of-origin effects appear to be sexually dimorphic given that sex differences in symptomatology have been found in both psychosis (e.g., earlier onset and more severe symptoms in male compared to female patients)[10] and in PE (e.g., higher prevalence and more severe symptoms in females than in males).[11, 12] Sex differences in neuroanatomy might reflect differences in the risk for psychosis, with some studies suggesting an X-linked risk, or differences in the severity of symptoms.[9, 13–16]

The current study examines whether parental neuroanatomical variation is associated with the symptom severity of offspring PE, and whether such effects differ by sex. Based on previous findings, we hypothesized that individual differences in parental neuroanatomy would be associated with offspring PE but that such relation would show sex differences both in parents and offspring. Because we did not have any *a priori* hypothesis about parental brain regions that would show the association with the offspring's PE, we examined voxel-by-voxel correlations between maternal or paternal gray matter and their offspring's BASCaty score. We repeated the same analysis

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in sex-congruent and -incongruent dyads (mother–daughter, mother–son, father–daughter, father–son) to examine the sex-specificity of intergenerational correlations.

Methods

Participants

From a dataset of 51 healthy children (aged 7.5–9.8 years) and their biological parent(s) and sibling(s),[13] 35 children and their parent(s) were included in the present study based on the child having a Behavior Assessment System for Children – 2nd Edition (BASC-2)[14] score and structural magnetic resonance imaging (MRI) data, and at least one parent having structural MRI data. Because we did not include siblings of the proband, no two children shared a parent. Twenty-four children (14 boys and 10 girls) were included both in father–offspring and mother–offspring dyads. Seven children (three boys and four girls) were included only in mother–offspring dyads and four children (two boys and two girls) were included only in father–offspring dyads. As a result, there were 35 children (19 boys and 16 girls), 31 mothers, 28 fathers, and 94 participants in total. The available data provided 31 mother–offspring dyads (14 mother–daughter dyads and 17 mother–son dyads) and 28 father–offspring dyads (12 father–daughter and 16 father–son dyads; Table 1).

Participants were recruited from local newspapers, school mailings, flyers, and mothers' clubs. Participants did not have any neurological or psychiatric disorders, were not on medication, and had no contraindications to MRI. After complete description of the study to the participants, written informed consent and assent were obtained from parents and children, respectively. The Stanford University and University of California San Francisco Panel on Human Subjects in Medical Research approved the study.

Behavioral assessments

Offspring's PE was assessed using the self-report Atypicality subscale (BASCaty) of the BASC-2.[14] The BASC-2 is widely used to evaluate various behavioral and emotional problems in youth. The Atypicality subscale of the BASC-2 assesses subthreshold psychotic symptoms, such as acting confused, being out of touch with reality, saying things that makes no sense, hearing or seeing things that are not really present, or thinking that someone is watching one. The BASCaty *T*-score range is divided into five stages and a score of ≥60 is thought to mean elevated risk (Table S1). The BASCaty of the BASC-2 has high internal consistency[15] and is strongly associated with scores on the Structured Interview for Psychosis-Risk Syndromes (SIPS), a clinician-administered interview of PE that has been shown to strongly predict conversion in adolescence and young adulthood.[16–22]

Intelligence was assessed in child participants using the Woodcock–Johnson III Tests of Cognitive Abilities Brief Intellectual Ability Scale.[17] Intelligence was assessed in parents using the Shipley Institute of Living Scale (SILS).[18] SILS scores were converted to the Wechsler Adult Intelligence Scale – Revised (WAIS-R) to derive a full-scale IQ score.[19] Specifically, from the SILS, the total raw score derived from raw scores on the Vocabulary (corresponding to Verbal IQ) and Abstract Thinking (corresponding to Performance IQ) subscales were totaled and converted to an estimated WAIS-R standard score (WAIS-R est. IQ; corresponding to Full-Scale IQ) using standard conversion tables.[18,20]

Image acquisition and preprocessing

MR images were acquired using a 3T whole-body GE Signa HDxt scanner (GE Medical Systems, Milwaukee, WI, USA) with a quadrature head coil. For voxel-based morphometry (VBM), high-resolution T1 anatomical scans were obtained using a spoiled gradient recalled echo pulse sequence (160 coronal slices; repetition time, 8500 ms; echo time, 3.4 ms; inversion time, 400 ms; flip angle, 15°; number of excitations, 1; field of view, 22 cm; matrix, 256 × 256; thickness, 1.2 mm; acquisition time, 5 min 14 s).

All imaging analyses were implemented using MATLAB R2013b running on Mac OS X Mavericks. Images were first visually checked for scanner artifacts and anatomical anomalies. Preprocessing was done using DARTEL[21] for VBM in VBM8 toolbox in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The preprocessing for parents' images was done separately from that for images of children to minimize the effects of adult template biases on the offspring VBM analysis.[22] We further selected 'Modulated normalized – non-linear only,' which results in an analysis of relative differences in regional gray matter volume, corrected for individual brain size. Four gray matter masks were made by averaging all gray matter images for each target group (mother, father, daughter, son), respectively. The mask image was thresholded by the voxel value 0.3. All analysis using gray matter volume was completed with the mask.

Because we found a significant association between maternal gray matter volume in the cerebellum and offspring's BASCaty in the whole-brain analysis level, we also normalized structural MRI data to a cerebellum-specific template using the SUIT toolbox (http://www.diedrichsenlab.org/imaging/suit.htm). SUIT provides more accurate

Table 1. Demographic background and behavioral data

	Parent			Offspring		
	Mother	Father		Daughter	Son	
n	31	28	*P*	16	19	*P*
Age (years)	41.7 ± 4.3	44.5 ± 5.6	0.04	8.4 ± 0.5	8.3 ± 0.4	0.54
WAIS-R est. IQ (FSIQ)	112.8 ± 4.8	113.3 ± 4.2	0.73			
VIQ-ss	110.5 ± 9.4	109.5 ± 8.6	0.69			
PIQ-ss	121.7 ± 5.0	124.2 ± 4.6	0.06			
WJIII-BIA Brief Intellectual Ability (FSIQ)				113.4 ± 10.4	117.8 ± 12.9	0.29
WJIII-BIA Verbal Comprehension (VIQ)				112.2 ± 7.2	118.3 ± 11.8	0.09
WJIII-BIA Concept Formation (PIQ)				116.1 ± 10.3	119.5 ± 12.5	0.4
BASC-2 Atypicality (*T*-score)				50.8 ± 9.9	50. ± 5.9	0.8

Values are given as mean ± SD except for *n*.

BASC-2, Behavior Assessment System for Children – 2nd Edition; FSIQ, Full-Scale IQ; PIQ, Performance IQ; ss, standard score; VIQ, Verbal IQ; WAIS-R, Wechsler Adult Intelligence Scale – Revised; WJIII-BIA, Woodcock–Johnson III Tests of Cognitive Abilities Brief Intellectual Ability Scale.

normalization of the cerebellum,[23] allowing a more precise identification of the cerebellar region that we found in the whole-brain analysis. Each subject's T1-weighted image was manually aligned to the anterior commissure and co-registered to the SPM8 white matter template to place the subject T1 image into approximate AC-PC alignment and to provide a starting point for the SUIT processing. Next, the cerebellum was isolated from the gray matter image. The cerebellar mask was manually edited for each subject to exclude any gray matter outside the cerebellum, using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron). Third, individual isolated cerebellar T1 images were warped to the SUIT template using DARTEL and a deformation map was created, which was used in turn to resample the gray matter segmentation maps to the SUIT space. The normalized gray matter image was modulated (Jacobian-scaled) to preserve the initial volume and total cerebellar gray matter volumes were included as covariates. All cerebellar analyses were restricted to a gray matter mask, created as described for the whole-brain gray matter mask.

Statistical significance threshold

All reported clusters were significant at a voxel height of $P < 0.001$ and cluster $P < 0.05$ corrected by family-wise error. All reported coordinates are in the Montreal Neurological Institute space.

Correlation between parental gray matter volumes and offspring's BASCaty

We examined voxel-by-voxel correlations between maternal or paternal gray matter and their offspring's BASCaty score while regressing out maternal or paternal age, respectively, as nuisance variables. Further, these analyses were repeated using parental cerebellar gray matter normalized by SUIT. We also analyzed the voxel-by-voxel correlation between an offspring's BASCaty scores and their own gray matter volume, regressing out age and sex, which were associated with brain volume, but these results are not reported as no regions showed significant correlations with BASCaty scores.

Sex-specific associations

Voxel-wise correlation analyses between parental gray matter volume and offspring BASCaty were repeated within sex-congruent and -incongruent dyads (mother–daughter, mother–son, father–daughter, father–son) to examine the sex-specificity of intergenerational correlations. Because voxels in maternal cerebellum showed a significant positive correlation with offspring's BASCaty in mother–offspring analysis combining daughters and sons, and mother–daughter analysis but not in mother–son analysis, we investigated the significance of offspring's sex. For this purpose, voxels were set in the maternal cerebellum that showed significant correlation with offspring's BASCaty as region of interest (ROI). Second, voxel values of preprocessed maternal gray matter image within ROI were extracted and averaged across all voxels within the ROI. We then performed regression analysis to examine the correlation between maternal ROI value and their offspring's BASCaty in mother–daughter dyads and mother–son dyads, respectively, regressing out maternal age. The standardized regression coefficient of ROI value for each dyad was transferred to a z-value using Fisher r-to-z transformation. As a final step, a final z-value was calculated using the formula $[(z1 - z2)/\{1/(n1 - 3) + 1/(n2 - 3)\}^{1/2}]$ where $z1$ and $z2$ were z transformed r-values of mother–daughter dyads and mother–son dyads, respectively, and $n1$ and $n2$ were number of dyads in these two dyads[24] (http://core.ecu.edu/psyc/wuenschk/docs30/CompareCorrCoeff.pdf). The significance of these new z-values was compared across sexes. Because no two children shared a mother, there were no duplicate offspring in this analysis and no partial dependency between mother–daughter and mother–son dyads. For father–offspring dyads, we did not examine the difference between the correlation of paternal brain volumes and male and female offspring's PE when correlating these (i.e., comparison between father–daughter and father–son dyads) because there were no significant correlations in father–offspring dyads. Analyses of ROI values were done using R statistics 3.1.2. (https://www.r-project.org) and the oro.nifti package (https://CRAN.R-project.org/package=oro.nifti) was used to extract ROI values from preprocessed gray matter images.

Results

Demographic and behavioral results

Fathers were significantly older than mothers, $t(57) = 2.12$, $P < 0.05$, but there were no sex-based differences in age in the offspring, $t(32) = 0.60$, $P = 0.54$. There were also no significant differences in Full-Scale IQ, Verbal IQ, or Performance IQ scores among parents or among offspring (Table 1). And there were no significant sex differences in offspring BASCaty scores. Three subjects' (one male and two female subjects) scores were within the low to very-low range (BASCaty ≤ 39) while three subjects' (one male and two female subjects) scores were above the average/typical range (BASCaty ≥ 60; Table 1). One child had a BASCaty score of 77, which was greater than the third quartile +1.5 × interquartile range of 70. Because this child was an outlier,[25] we repeated the analyses below without this outlier. The correlation between maternal and paternal voxel-by-voxel gray matter volume and offspring's BASCaty remained significant even after removal of this child from the analyses.

Whole-brain analyses of parental gray matter volume

Whole-brain analysis of parental gray matter revealed significant positive correlation between maternal cerebellar gray matter and offspring's BASCaty (Fig. S1, Table S1). However, no regions in paternal gray matter showed significant correlation with offspring's BASCaty. Given significant overall effects across sexes in the offspring, the above analysis was repeated in order to examine sex-specific effects in the offspring in the maternal gray matter volume only. There was a significant positive correlation in the cerebellum only among mother–daughter dyads but not mother–son dyads (Fig. S1, Table S2). The correlation between maternal cerebellar gray matter and the daughter's BASCaty remained significant even when the aforementioned outlier was excluded (Fig. S2).

Sex specificity

We performed regression analysis to examine the correlation between maternal ROI value and their offspring's BASCaty in mother–daughter dyads and mother–son dyads, respectively, regressing out maternal age. The standardized regression coefficient of ROI value was 0.78 ($P < 0.01$) for mother–daughter dyads and 0.08 ($P = 0.76$) for mother–son dyads (Fig. S3).

Z-values from the standardized correlation coefficient of the regression analysis were used to examine difference in correlation between maternal gray matter volume and daughter's PE and that of maternal gray matter volume and son's PE. Interestingly, the z-converted standardized regression coefficient in mother–daughter dyads ($z1 = 1.04$) was significantly higher than in mother–son dyads ($z2 = 0.08$, $z = -2.34$, $P = 0.01$).

Spatial localization of maternal gray matter volume effects within the cerebellum

To identify the exact location of the region of maternal cerebellar gray matter that showed significant positive correlation with their daughters' BASCaty in the whole-brain analysis, normalization was restricted to the cerebellum using SUIT. Regions of maternal cerebellar gray matter that showed significantly positive correlation with their daughters' BASCaty were distributed mainly in the cerebellar regions VIIIa and VIIIb and, to a lesser extent, in region IX (Figs 1,2, Table S2). As in the whole-brain analysis, the correlation between maternal cerebellar gray matter and their daughters' BASCaty remained significant even after the outlier was excluded (Fig. S2).

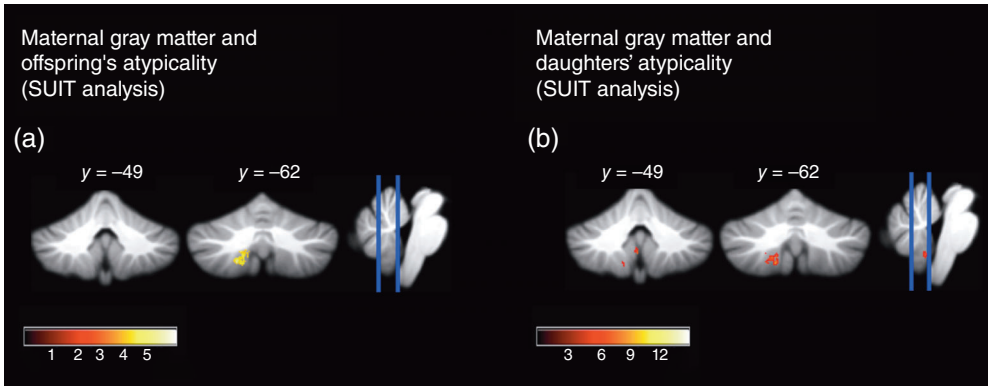

Fig.1 Maternal gray matter significantly correlated with the (a) offspring's and (b) daughters' Atypicality subscale scores for the Behavior Assessment System for Children – 2nd Edition (voxel $P < 0.001$ uncorrected, cluster $P < 0.05$ family-wise error corrected).

Discussion

In the present study, we show intergenerational association between parental neuroanatomical variation and offspring PE, which is consistent with the previous findings of parent-of-origin effects in psychotic illness.[26] In the present study, maternal cerebellar gray matter volume was positively correlated with daughters' BASCaty, but no such associations were found for mother–son or father–offspring dyads. This finding was confirmed by more robust VBM with cerebellum-specific normalization. Our study is the first to show intergenerational transmission associated with PE using parental brain morphology. These results cautiously suggest a role of sex-dependent intergenerational effects of parental neuroanatomical variation on offspring's PE.

Parent-dependent intergenerational effects are known as parent-of-origin effects.[27] In this study, we did not find any significant correlation between parental cortical regions known to be altered in psychotic illness, such as the dorsolateral prefrontal cortex, and offspring's atypicality. We found, however, an association between the maternal cerebellum and offspring's atypicality. Interestingly, several genetic variations associated with both psychosis and cerebellar development have also demonstrated parent-of-origin and sex-dependent effects. Variations in the maternal imprinting control region of the *IGF2/H19* gene have been associated with a 16% increase in cerebellar weight compared to paternally inherited alleles, suggesting a stronger maternal imprinting role in cerebellar volume in the offspring.[28] A recent twin study showed high heritability of cerebellar volume (51%) and this heritability was much higher in female (86%) than in male (42%) subjects.[29] In schizophrenia patients, previous studies have shown female-specific associations with single nucleotide polymorphism (SNP) in the reelin (*RYR2*) gene.[30,31] The *RYR2* gene encodes the development of the ryanodine receptor 3 protein, which is critically important for postnatal development of the cerebellum in mice.[32] A SNP on the *RYR2* gene is associated with schizophrenia in females only[31] and the ryanodine receptor, a Ca-release protein for caffeine- and ryanodine-sensitive Ca pools, is highly expressed in the cerebellum.[32] Interaction of these genes with sex-linked genes and/or sexual hormones is one possible mechanism of this type of gene–sex interaction.[33] In fact, testosterone has been demonstrated to decrease reelin gene expression in male European starlings, and estrogen has been shown to affect the development and function of cerebellum and contributes to sexual dimorphism in schizophrenia.[34–36] Taken together, there may be female-specific genetic pathways that are related to both cerebellar development and psychotic symptoms.

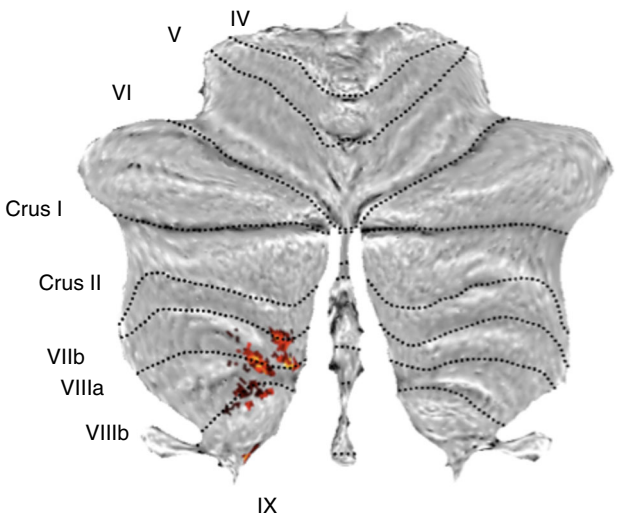

Fig.2 Flat-map of maternal cerebellar gray matter, which significantly correlated with the daughters' Atypicality subscale scores for the Behavior Assessment System for Children – 2nd Edition (voxel $P < 0.001$ uncorrected, cluster $P < 0.05$ family-wise error corrected).

In the present study, only maternal cerebellar gray matter volume correlated with daughters' PE, while the daughters' own cerebellar gray matter did not show such correlation. A recent study in healthy individuals aged 12 to 65 years showed that the volume of posterior cerebellum showed an inverse-U-shaped pattern, with the peak at around 30 years old,[37] though in children the peak is around 12 years old in the inferior and 16 years old in the superior posterior lobe.[34] Taking into account these findings, the daughters' cerebellums in the current study were still in the process of maturation and subtle volume variance associated with non-clinical PE may have been masked by individual differences. Future studies should replicate the present analyses in parents and older children to investigate whether such correlations may be present in daughters' cerebellums at later stages of brain development.

Although gray matter volume reduction has repeatedly been shown in patients with schizophrenia[6] and high-risk subjects,[35] some studies have reported an increase in gray matter volume in high-risk subjects.[36] In non-clinical healthy adults, the severity of PE has been positively associated with bilateral prefrontal cortex volume.[38] Another MRI study in non-clinical 11–13-year-old children examining PE also showed that their gray matter volumes in the left temporal lobe and right orbitofrontal gyrus were increased compared to children without PE.[4] Although its etiological nature is unknown, functional compensation,[36] or abnormal synaptic pruning, has been posited as a possible explanation for these discrepant findings on gray matter volume across the psychosis spectrum.[4] Since Andreasen hypothesized the important role of the cerebellum in the pathophysiology of schizophrenia,[39] many studies have shown abnormalities in the cerebellums of patients with schizophrenia.[40,41] However, because there was no direct relation between the offspring's cerebellum and the offspring's PE, the present study is not able to posit on the relation of cerebellar volume to PE symptoms based on the current findings.

There are several important limitations to the present study that may explain the negative findings of this direct link and provide directions for future studies. First, parental PE scores were not available because the dataset had not originally been collected to examine intergenerational effects of atypicality. In our sample, only three subjects showed BASCaty higher than 60, which is below what would be expected from a normal distribution of scores (approximately 8 out of 51 children). This may be due to the relatively high IQ of subjects, as it has been shown that verbal IQ is inversely correlated with schizotypal traits,[42] a measure of PE that overlaps with items that comprise BASCatyp scores. Although it is important to study PE in non-clinical participants, given the need for interventions and treatment in non-help-seeking populations, the small sample size that leads to the low probability of the participants ultimately developing psychosis may limit the generalizability of our findings, and hence is a major limitation of our study. Second, although internal consistency and external validation have been performed for the Atypicality subscale of the BASC-2 in ages 12–20 years,[15,16] no such reports exist in younger children. More research on validating this index in this age group is warranted. Finally, because of the relatively small sample size and exploratory nature of our analysis, the current findings are preliminary. Further research with larger sample size is warranted.

In summary, consistent with theories surrounding parent-of-origin effects and genetic evidence of sex-specific effects on cerebellar development, the present study demonstrates a sex-specific intergenerational association between brain morphology and PE. Specifically, maternal cerebellar gray matter volume was significantly associated with the daughters' Atypicality scores, a self-report measure of psychotic experiences. Further intergenerational studies of cerebellar morphology, PE, and risk for psychosis may lead to a better understanding of the etiology of psychotic symptoms, as well as improved ability to provide early identification and treatment services in both clinical and non-clinical populations.

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Author contributions

R.H. and F.H. acquired the scans and other data. N.H., R.H., and F.H. analyzed the data. N.H. and T.I.M. wrote the article and R.H., I.K., and F.H. edited the article. All authors have reviewed the article and approved submission.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Maternal gray matter volume that significantly correlated with the offspring's Behavior Assessment System for Children – 2nd Edition (BASC-2) Atypicality *T*-scores in whole-brain voxel-based morphometry (VBM) analyses.

Figure S2. Maternal gray matter volume that positively correlated with the offspring's Behavior Assessment System for Children – 2nd Edition (BASC-2) Atypicality *T*-scores in whole-brain voxel-based morphometry (VBM) analyses, but without the outlier.

Figure S3. Scatter plot of region of interest value of maternal gray matter with the offspring's Behavior Assessment System for Children – 2nd Edition (BASC-2) self-report Atypicality *T*-score.

Table S1. Interpretation guide for Atypicality subscale (BASCaty) of the Behavior Assessment System for Children – 2nd Edition (BASC-2).[14]

Table S2. Montreal Neurological Institute coordinates of maternal cerebellum region, which correlated with the offspring's or daughter's atypicality in whole-brain voxel-based morphometry (VBM) analysis.