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FKBP5 Moderates the Association between Antenatal Maternal Depressive Symptoms and Neonatal Brain Morphology

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Antenatal maternal depressive symptoms influence fetal brain development and increase the risk for depression in offspring. Such vulnerability is often moderated by the offspring's genetic variants. This study aimed to examine whether *FKBP5*, a key regulator of the hypothalamic–pituitary–adrenal (HPA) axis, moderates the association between antenatal maternal depressive symptoms and *in utero* brain development, using an Asian cohort with 161 mother–offspring dyads. Antenatal maternal depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS) during the second trimester of pregnancy. Neonatal structural brain images were acquired using magnetic resonance imaging (MRI) shortly after birth. Maternal and neonatal *FKBP5* gene was genotyped using Illumina OmniExpress arrays. A gene set-based mixed effect model for gene–environment interaction (MixGE) was used to examine interactive effects between neonatal genetic variants of *FKBP5* and antenatal maternal depressive symptoms on neonatal amygdala and hippocampal volumes, and cortical thickness. Our study revealed that genetic variants in neonatal *FKBP5* moderate the association between antenatal maternal depressive symptoms and right hippocampal volume but only show a trend for such moderation on amygdala volumes and cortical thickness. Our findings are the first to reveal that the association between maternal depressive symptoms and *in utero* neurodevelopment of specific brain regions is modified through complex genetic variation in neonatal *FKBP5*. Our results suggest that an increased risk for depression may be transmitted from mother to child during fetal life and that the effect is dependent upon neonatal *FKBP5* genotype.
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INTRODUCTION

Depression has a strong familial component. Children of mothers depressed during pregnancy show an increased risk for emotional, behavioral, and cognitive problems (Hammen and Brennan, 2003; Klein *et al*, 2001; Weissman *et al*, 2006), as well as multiple forms of psychopathology (Hammen and Brennan, 2003; Klein *et al*, 2001; Weissman *et al*, 2006) relative to the normal population. Similarly, increasing evidence suggests that fetal exposure to maternal depression influences intermediate phenotypes that are associated with vulnerability for depression (Feldman *et al*, 2009; Wichers *et al*, 2007), including alterations in brain morphology (Chen *et al*, 2010b; Peterson and Weissman, 2011). Importantly, antenatal maternal depression is associated with fetal brain development, particularly in the amygdala and hippocampus, that are implicated in the regulation of emotional states (Qiu *et al*, 2013, 2015a). These effects appear to reflect the transmission of individual differences in vulnerability for depression from mother to child.

Vulnerability for depression in children of affected mothers may be moderated by genetic variants (Baumann *et al*, 2013). The *FK506 binding protein 5* (*FKBP5*) encoded by the *FKBP5* gene located on chromosome 6 is involved in hypothalamic–pituitary–adrenal (HPA) axis regulation. *FKBP5* participates in the inhibition of glucocorticoid receptor (GR) activity, the main regulator of the HPA axis (Provencal and Binder, 2015). *FKBP5* has been identified as a molecular genetic marker associated with depression (Binder *et al*, 2004; Zobel *et al*, 2010), posttraumatic stress disorder (PTSD) (Binder *et al*, 2008; Koenen and Uddin, 2010; Xie *et al*, 2010), and stress response (Velders *et al*, 2011). Carriers of the *FKBP5* rs1360780 T allele show an increased risk for depression (Lekman *et al*, 2008). Homozygotes of the rs1360780 T allele demonstrate more depressive episodes and better response to treatment with antidepressants

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(Binder *et al*, 2004). Similarly, high risk alleles of multiple *FKBP5* single-nucleotide polymorphisms (SNPs) (rs3800373, rs9296158, rs1360780, rs7748266, and rs9470080) are associated with a decreased cortisol level and an increased risk of depressive symptoms (Velders *et al*, 2011). *FKBP5* SNPs also moderate the impact of early-life stress that is linked with risk for later-life depression (Lahti *et al*, 2016).

Similarly, the function and microstructure of brain regions involved in emotion are influenced by early childhood trauma in the presence of *FKBP5* risk alleles (Tozzi *et al*, 2016). Abused *FKBP5* rs1360780 TT carriers show a significant reduction in hippocampal volume compared with abused CT/CC carriers (Grabe *et al*, 2016). High GR density and *FKBP5* expression are observed in the hippocampus (Scharf *et al*, 2011). Animal research demonstrates that fetal exposure to a high level of glucocorticoids downregulates hippocampal GR expression (Levitt *et al*, 1996). This, coupled with the role of *FKBP5* as a GR inhibitor, leads to symptoms of glucocorticoid resistance. Hence, these findings suggest a possible role of *FKBP5* in moderating the influence of maternal depressive symptoms on fetal hippocampal development.

A prospective longitudinal mother–offspring cohort study (Growing Up in Singapore Towards Healthy Outcomes (GUSTO)) provided a unique opportunity to examine whether neonatal *FKBP5* genotype moderates the association between antenatal maternal depressive symptoms and *in utero* hippocampal development without compromise from postnatal confounds. Given the link between generic variants of multiple *FKBP5* SNPs and a risk of depression, a gene set-based mixed effect model for gene–environment interaction (MixGE) (Wang *et al*, 2017) was employed to test for interactive effect between neonatal genetic variants of *FKBP5* and antenatal maternal depressive symptoms on hippocampal volume. Rather than testing each SNP individually, the MixGE model takes a set of SNPs and examines not only accumulative but also heterogeneous interactive effects of these individual SNPs with antenatal maternal depressive symptoms on neonatal hippocampal volumes. The MixGE model can detect both rare genetic variants and common genetic variants with small effect sizes by accumulating their effects within the genetic set, and by greatly reducing the number of independent statistical tests, and hence a less stringent correction for multiple comparisons is required (Lee *et al*, 2014). We hypothesized that *FKBP5* genotype moderates the association between antenatal maternal depressive symptoms and neonatal hippocampal volumes. As an exploratory analysis, we also investigated whether *FKBP5* moderates the association between antenatal maternal depression and *in utero* amygdala and cortical development. This study provides, to our knowledge, the first direct analysis of the genetic and environmental interactions associated with neonatal brain morphology and evidence that *FKBP5* may represent a molecular genetic marker moderating differential sensitivity to antenatal maternal depression.

MATERIALS AND METHODS

Subjects

Mother–offspring dyads who participated in this imaging genetic study were part of the GUSTO cohort (Soh *et al*, 2012). The GUSTO cohort consisted of pregnant Asian women attending the first trimester antenatal ultrasound scan clinic at the National University Hospital (NUH) and KK Women's and Children's Hospital (KKH) in Singapore. The parents were Singapore citizens or Permanent Residents of Chinese, Malay, or Indian ethnic background. Birth outcome and pregnancy measures were obtained from hospital records. Socioeconomic status (household income) was extracted from survey questionnaires during pregnancy. Of the 184 mother–offspring dyads with neonatal neuroimaging data, those without genetic data ($n=9$), antenatal maternal depression scores ($n=10$), or demographic information ($n=3$) were removed, leaving 164 mother–offspring dyads. Among these 164 mother–offspring dyads, neonates with gestational age <34 weeks ($n=0$), birth weight <2000 g ($n=0$), and a 5 min, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score <9 ($n=3$) were removed, resulting in 161 mother–offspring dyads as the final sample for this study.

The GUSTO cohort study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the Sing Health Centralized Institutional Review Board (CIRB). Written informed consent was obtained from mothers.

Antenatal Maternal Depressive Symptoms

The Edinburgh Postnatal Depression Scale (EPDS) questionnaire (Cox *et al*, 1987) was administered to mothers at 26 weeks of pregnancy to quantify depressive symptomatology. The EPDS is a widely used 10-item self-report scale designed as a screening instrument for postnatal depression, but it is also valid for use during pregnancy. Each item of the EPDS is scored on a four-point scale (0–3), for a total score of 30. A higher total score indicates presence of more depressive symptoms. The reliability of the EPDS for our cohort assessed using Cronbach's analysis is 0.82.

Magnetic Resonance Imaging (MRI) Acquisition and Analysis

Axial fast spin-echo T2-weighted MRI (repetition time (TR) = 3500 ms; echo time (TE) = 110 ms; field of view (FOV) = 256 mm × 256 mm; matrix size = 256 × 256; 50 axial slices with 2.0 mm thickness) were acquired for neonates at 5 to 14 days of age using a 1.5-Tesla GE scanner at the Department of Diagnostic and Interventional Imaging of the KK Women's and Children's Hospital. Detailed acquisition and image quality check procedures have been previously reported (Qiu *et al*, 2013; Qiu *et al*, 2015b). All brain data were acquired when neonates were in sleep after feeding. A sip of glucose was given if neonates woke up in the scanner. The scanning was restarted after neonates fell into sleep. No sedation was used and precautions were taken to reduce exposure of neonates to MRI scanner noise. A neonatologist was present during scanning. A pulse oximeter was used to monitor heart rate and oxygen saturation throughout entire

scans. All brain scans were reviewed by a neuroradiologist. To determine image motion, all axial slices of the T2-weighted MRI data were visually inspected to ensure no cross-slice motion and checkerboard patterns.

Within individual subjects, a Markov random field model (MRF) was used to automatically delineate amygdala, hippocampus, cortical gray matter, white matter, and cerebrospinal fluid (CSF) from the neonatal T2-weighted MRI data. Manual segmentation was performed on 20 brains randomly selected from our data set. The segmentation accuracy rates of the amygdala, hippocampus, cortical gray matter, and white matter of the automatic segmentation against the manual segmentation were 0.75, 0.71, 0.79, and 0.86, respectively. This has also been reported in previous publications (Qiu *et al*, 2013, 2015b; Rifkin-Graboi *et al*, 2013).

Based on the above tissue segmentation, cortical surfaces were constructed at the boundary between gray matter and CSF and at the boundary of gray matter and white matter, using a graph-based topology correction algorithm. Cortical thickness was measured as the distances between the corresponding vertices of these two cortical surfaces. We employed a large deformation diffeomorphic metric mapping (LDDMM) algorithm to align individual cortical surfaces to the Asian atlas that was generated based on the cortical anatomy of the 20 subjects with manual segmentation, and transferred the thickness values of each subject to the atlas (Bai *et al*, 2012). The cortical thickness values were smoothed using the Laplace–Beltrami basis functions on the cortical surface.

SNP Genotyping

Genomic DNA was extracted from frozen umbilical cord specimens for offspring and from blood for mothers per standard procedures. The samples were then genotyped on both Illumina OmniExpress arrays, which perform well and have better coverage than competitors in Asian populations (Jiang *et al*, 2013), and on Illumina Exome arrays, following the manufacturer's instructions by Expression Analysis. Data were processed in GenomeStudio Genotyping Module. Genotyping calls were made by the GenCall software that incorporates a clustering algorithm (GenTrain) and a calling algorithm (Bayesian model). The GenCall Score of each SNP probe and call rate of each sample were generated. The GenCall score is primarily designed as a means by which to rank and filter failed genotypes (Oliphant *et al*, 2002). Scores of <0.15 generally indicate failed genotypes and hence the genotypes with a GenCall score of <0.15 are not assigned genotypes (Oliphant *et al*, 2002). Total 30 SNPs of *FKBP5* gene (Chr 6: 35540362–35697360) were extracted on these two arrays. Among them, 2 SNPs did not pass the GenCall score and 9 SNPs were homogeneous among our subjects. The remaining 19 SNPs were extracted and used in this study as a gene set. Table 2 and Supplementary Table S1 (the Supplementary Material) list the genotype distributions of these SNPs for neonates and mothers included in this study. As the statistical model described below was designed to incorporate rare alleles, rs16879378 with minimum allele frequency (MAF) of 0.006 was also included in this study. The 19 *FKBP5* SNPs did not deviate from Hardy–Weinberg proportions after correction for multiple comparisons. No imputation was applied to the genetic data.

Statistical Analysis

The aim of this study was to examine interactive effects between genetic variants of neonatal *FKBP5* with antenatal maternal depressive symptoms on neonatal hippocampal volumes. A gene set-based mixed effect model for MixGE was employed (Wang *et al*, 2017). The software and example are available at http://www.bioeng.nus.edu.sg/cfa/imagingge netics.html. The MixGE model is in the form of

$$Y = Z\beta + \mathrm{diag}(E)G\mathbf{1}\pi + \mathrm{diag}(E)G\delta$$

where $Z = [X, E, G]$, where X consists of gestational age on the MRI visit day, neonatal total brain volume, maternal education, gender, and maternal ethnicity. Y is the hippocampal volume, E is the score of antenatal maternal depressive symptoms, and G represents a set of the 19 SNPs of neonatal *FKBP5*. The diag $(E)G$ therefore represents gene–environment interaction (G × E). $\mathbf{1}$ represents a vector of ones of length 19. The π is a fixed effect of G × E and δ is random effects of G × E. The π captures the accumulative G × E effects, whereas δ captures the heterogeneous G × E effects among all the 19 SNPs. As the genetic variants are considered as a set rather than individually, *the G × E effects of both rare genetic variants and common genetic variants with small effect sizes can be detected*, as their effects are accumulated within the genetic set. Furthermore, by greatly reducing the number of independent statistical tests, a less stringent correction for multiple comparisons is required (Lee *et al*, 2014).

The analysis using the MixGE model was repeated when considering maternal variants of *FKBP5* and its interaction with antenatal maternal depressive symptoms as additional covariates. In other words, $Z = [X, E, G, G_{\mathrm{M}}, \mathrm{diag}(E)G_{\mathrm{M}}\mathbf{1}]$, where G_{M} are the 19 SNPs of maternal *FKBP5*.

Regression analysis was also performed to examine interaction between individual neonatal *FKBP5* SNPs and antenatal maternal depressive symptoms on neonatal hippocampal volumes after partialling out the covariance of gestational age on the MRI visit day, neonatal total brain volume, maternal education, gender, and maternal ethnicity. This analysis was performed for 17 of the 19 SNPs of *FKBP5* with MAF >0.05.

The same statistical analysis was applied to amygdala volume and cortical thickness. Bonferroni correction was employed for bilateral hippocampal and amygdala volumes ($p<0.05/4=0.0125$). For cortical thickness, the p-values of the 112 200 vertices in both hemispheres were corrected via false discovery rate (FDR).

RESULTS

Table 1 lists the demographics of the 161 mother–offspring dyads in this study. Gestational age at birth ($t_{159}=-0.718$, $p=0.474$), birth weight ($t_{159}=-0.679$, $p=0.498$), gestational age on the MRI visit day ($t_{159}=-0.505$, $p=0.614$), neonatal total brain volume ($t_{159}=-0.387$, $p=0.699$), and maternal education ($t_{159}=-1.51$, $p=0.134$) did not vary as a function of antenatal maternal depressive symptoms. Difference in antenatal maternal depressive symptoms among maternal ethnic groups was marginally significant ($F_{2,158}=3.02$,

Table 1 Demographics and Brain Volumes

		Mean	SD
Gestational age at birth (weeks)		38.9	1.1
Birth weight (kg)		3.11	0.39
5 min APGAR score		9.01	0.08
Gestational age at MRI (weeks)		40.3	1.1
Antenatal maternal EPDS score		8.56	4.5
Neonatal total brain volume (cm^3)		549	47
Neonatal left hippocampal volume (mm^3)		779	107
Neonatal right hippocampal volume (mm^3)		784	111
Neonatal left amygdala volume (mm^3)		211	35
Neonatal right amygdala volume (mm^3)		187	34
		N	**%**
Maternal education	Primary	6	3.7
	Secondary	54	33.5
	GCE/Diploma	72	44.7
	Undergraduate	23	14.3
	Graduate	6	3.7
Maternal ethnicity	Chinese	73	45.3
	Malay	67	41.6
	Indian	21	13
Gender of neonates	Male	87	54
	Female	74	46
Monthly household	income <$999	4	2.4
	$1000–$1999	24	16
	$2000–$3999	60	40
	$4000–$5999	39	26
	>$6000	23	15.3
Mothers on antidepressants		0	0

Table 2 Genotype Distributions of *FKBP5* SNPs in Children

	A	a	N_{AA}	N_{Aa}	N_{aa}	MAF	P_{HWP}
rs10807151	A	G	91	64	6	0.236	0.194
rs3800373	A	C	76	72	13	0.304	0.476
rs7757037	A	G	49	89	23	0.419	0.086
rs9296158	G	A	73	74	14	0.317	0.433
rs3777747	G	A	49	88	24	0.422	0.127
rs6926133	C	A	89	64	8	0.248	0.413
rs9380524	C	A	81	63	17	0.301	0.371
rs16879378	A	C	159	2	0	0.006	0.937
rs1475774	G	A	151	10	0	0.031	0.684
rs4713904	A	G	78	70	13	0.298	0.622
rs9470080	G	A	70	73	18	0.339	0.875
rs9380526	A	G	69	74	18	0.342	0.782
rs10456432	A	G	139	19	3	0.078	0.026
rs9380529	G	A	57	81	23	0.394	0.500
rs9394314	A	G	80	71	10	0.283	0.266
rs2766533	G	A	61	80	20	0.373	0.426
rs12200498	G	A	131	29	1	0.096	0.656
rs2817032	A	G	77	70	14	0.304	0.734
rs7751693	G	A	140	21	0	0.065	0.376

The second and third columns list the nucleotides of the major (A) and minor (a) alleles respectively. The fourth, fifth, and sixth columns show the number of subjects with major allele homozygotes (N_{AA}), heterozygotes (N_{Aa}), and minor allele homozygotes (N_{aa}), respectively. The seventh column shows minor allele frequency (MAF). The eighth column shows *p*-values suggesting that the 19 *FKBP5* SNPs did not deviate from Hardy–Weinberg proportions after correction for multiple comparisons.

$p = 0.052$). Monthly household income was highly correlated with antenatal maternal depressive symptoms ($\rho = -0.277$, $p < 0.001$), maternal education ($\rho = 0.520$, $p < 0.001$), and significantly differed among maternal ethnic groups ($F_{2, 147} = 5.43$, $p = 0.005$). To avoid collinearity, the following analysis did not include monthly household income as covariate. Maternal education was chosen over monthly household income as it is a much more stable indicator of social economic status.

Table 2 and Supplementary Table S1 (the Supplementary Material) list the distributions of individual *FKBP5* SNPs in the children and mothers. Antenatal maternal depressive symptoms were not associated with the neonatal ($p = 0.729$) or maternal ($p = 0.855$) *FKBP5* genotype. Gestational age at birth ($p = 0.190$), birth weight ($p = 0.984$), and neonatal total brain volume ($p = 0.368$) were not associated with neonatal *FKBP5* genotype.

The MixGE model revealed a significant interaction of neonatal *FKBP5* and antenatal maternal depressive symptoms on the right ($p = 5.68 \times 10^{-4}$) but not on the left hippocampal volume ($p = 0.095$) after partialling out the covariance of gestational age on the MRI visit day, neonatal total brain volume, maternal education, gender, and maternal ethnicity. After additionally controlling for maternal *FKBP5*, the neonatal *FKBP5* interaction with maternal depressive symptoms showed a marginally significant effect on the left hippocampal volume ($p = 0.018$) and a statistically significant effect on the right hippocampal volume ($p = 0.002$). Further traditional regression analysis revealed that 7 out of 17 *FKBP5* SNPs with MAF >0.05 showed statistically significant individual interactive effects with antenatal maternal depressive symptoms on the right hippocampal volume after Bonferroni correction for multiple comparisons ($p < 0.05/17 = 0.00294$; uncorrected *p*-values in Supplementary Table S2 in the Supplementary Material). We noticed that the genotyping arrays used in this study did not cover a popular SNP, rs1360780, mentioned in the Introduction. Nevertheless, rs3800373 genotyped in this study is in the same haplotype block as rs1360780 (Szczepankiewicz *et al*, 2014). The analysis for individual *FKBP5* SNPs showed a significant interaction between rs3800373 and antenatal maternal depressive symptoms on right hippocampal volume after Bonferroni correction for multiple comparisons (see Supplementary Table S2 in the Supplementary Material). A similar finding would be expected for rs1360780.

In the *post hoc* analysis, a genetic risk score was calculated for individual neonates by summing the number of minor alleles across all 19 *FKBP5* SNPs. Figure 1 illustrates a scatter plot of antenatal maternal depressive symptoms and right hippocampal volume in neonates with low and high genetic risk groups. Neonates with the genetic risk score lower than or equal to its median showed a positive association between antenatal maternal depressive symptoms and the right hippocampal volume after partialling out the covariance of gestational age on the MRI visit day, neonatal total brain

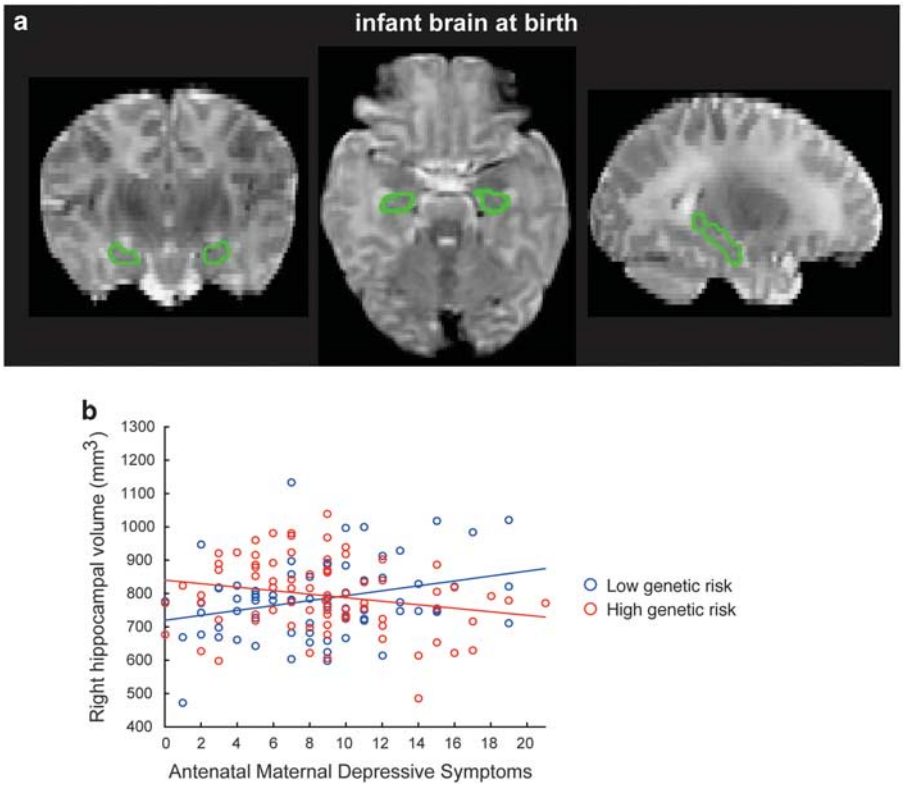

Figure 1 Hippocampus of neonatal brain. (a) Hippocampus on T2-weighted MRI. (b) Scatter plot for the relationship between right hippocampal volume and antenatal maternal depressive symptoms in neonates with a low *FKBP5* genetic risk (blue) and a high *FKBP5* genetic risk (red).

volume, maternal education, gender, and maternal ethnicity ($t_{80} = 3.03$, $p = 0.003$). In contrast, neonates with the genetic risk score greater than its median showed a negative association between antenatal maternal depressive symptoms and the right hippocampal volume after partialling out the covariance of gestational age on the MRI visit day, neonatal total brain volume, maternal education, gender, and maternal ethnicity ($t_{77} = -2.00$, $p = 0.049$).

Similarly, our study revealed no significant interaction between *FKBP5* and antenatal maternal depressive symptoms on bilateral amygdala volumes (left amygdala: $p = 0.029$; right amygdala: $p = 0.060$) and cortical thickness (corrected $p > 0.05$).

DISCUSSION

Antenatal maternal depressive symptoms influence fetal neurodevelopment (Field *et al*, 2010). This study revealed that genetic variants in neonatal *FKBP5* moderate the association of antenatal maternal depressive symptoms and neonatal right hippocampal morphology but show only marginal significance for the amygdala and cortical morphology. This effect was characterized by allelic variation in the neonatal *FKBP5* gene and many of the neonatal *FKBP5* SNPs (Supplementary Table S2 in the Supplementary Material). Our results suggest that the association between maternal depressive symptoms and *in utero* neurodevelopment of specific brain regions is modified through complex genetic variation in offspring *FKBP5*. Such genetic moderation was because of neonatal and not maternal genotype. Thus, the *FKBP5* moderation may explain, in part, the variation in neonatal phenotypic outcomes associated with antenatal maternal depressive symptoms. This conclusion is consistent with a wealth of studies showing that *FKBP5* genotype moderates the impact of childhood adversity on neural development and function, as well as on mental health outcomes (Binder *et al*, 2008; Grabe *et al*, 2016; Tozzi *et al*, 2016; Xie *et al*, 2010).

FKBP5 genotype is associated with individual differences in hippocampal morphology and activation in response to threat (Fani *et al*, 2014; Holz *et al*, 2015). *FKBP5* is highly expressed in the hippocampus (Scharf *et al*, 2011) that is strongly implicated in depression (Bremner *et al*, 2000; Campbell *et al*, 2004; Chen *et al*, 2010b; Sheline *et al*, 1996; Videbech and Ravnkilde, 2004) as well as with the vulnerability for depression in adolescents (Chen *et al*, 2010a). Stress reactivity predicts the risk for depression, and fMRI studies reveal that hippocampal activation, particularly in the right hemisphere (Pruessner *et al*, 2008), predicts individual differences in HPA response to stress (Pruessner *et al*, 2008). Our findings thus suggest a role for *FKBP5* genotype in shaping fetal hippocampal development and subsequent differences in stress reactivity under conditions in increased antenatal maternal depressive symptoms. Such effects may underlie the observed increase in negative emotionality and stress reactivity that is apparent in the infant offspring of depressed mothers (Feldman *et al*, 2009).

Our study suggested that neonates with both risk factors (environmental and genetic) had a smaller right hippocampal volume than those with only the genetic risk factor. This

is in line with the study in patients with major depression (Frodl *et al*, 2010). On the other hand, our study also suggested that neonates with only the environmental risk factor could have a larger hippocampal volume than those without any environmental or genetic risk factor. This may seem surprising. However, our study was based on a general population rather on a clinical sample. Antenatal maternal depressive symptoms were relatively mild among the mothers in this study. Sapolsky (2015) suggested that effects of stress could follow an inverted-U shape, where mild stress could be beneficial.

The strengths of this study include a unique opportunity to examine interactive effects of genetic variation and antenatal maternal depressive symptoms on neural development in neonate independent of postnatal influences, such as postnatal parenting and postnatal maternal mood (Chen *et al*, 2010b; Field *et al*, 2004; Fleming *et al*, 1988; Peterson and Weissman, 2011). Second, the study of the *FKBP5* gene set is considered highly advantageous as the MixGE model incorporates the correlational nature of the underlying genetic variants. However, there were several limitations in this study. Antenatal maternal depressive symptoms were only assessed at one time point during pregnancy to minimize subject burden. The cohort was recruited during pregnancy, which resulted in the lack of maternal information before pregnancy. Though additional measurements may have allowed for a better understanding of specificity in timing, it is important to note that the second and third trimesters during pregnancy are critical periods when neural migration and synaptogenesis of the fetal brain rapidly develop. Moreover, our sample size for a genetic study is considered relatively moderate. This is mainly because of challenges in imaging neonates that is also the uniqueness of this study. Finally, our study did not consider linkage disequilibrium among the FKBP5 SNPs in the MixGE model that could result in the inflated statistical finding because of large haplotype blocks among these SNPs. Nevertheless, our study additionally performed regression analysis on the individual FKBP5 SNPs, independent of linkage disequilibrium among these SNPs, as complementary information to confirm our findings from the MixGE model.

In conclusion, these findings are the first to reveal that antenatal maternal depressive symptoms interact with genetic variants of neonatal *FKBP5*, resulting in alteration in the hippocampal morphology of neonates. Our results suggest that an increased risk for depression may be transmitted from mother to child during fetal life and that the effect is dependent upon neonatal *FKBP5* genotype.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)