Environmental influences on the female epigenome and behavior

Samantha M. Keller¹ and Tania L. Roth¹,*

¹Department of Psychological and Brain Sciences, University of Delaware, Newark, DE 19716, USA

*Correspondence address: Department of Psychological and Brain Sciences, University of Delaware, 108 Wolf Hall, Newark, DE 19716, USA.
Tel.: +302-831-2787, E-mail: troth@psych.udel.edu

Abstract

Environmental factors have long-lasting effects on brain development and behavior. One way experiences are propagated is via epigenetic modifications to the genome. Environmentally driven epigenetic modifications show incredible brain region- and sex-specificity, and many brain regions affected are ones involved in maternal behavior. In rodent models, females are typically the primary caregiver and thus, any environmental factors that modulate the epigenotype of the mother could have consequences for her current and future offspring. Here, we review evidence of the susceptibility of the female epigenome to environmental factors, with a focus on brain regions involved in maternal behavior. Accordingly, implications for interventions that target the mother’s epigenome and parenting behavior are discussed.

Key words: environment; epigenetic; female; maternal circuitry; maternal behavior

Introduction

Epigenetics, a term coined by Waddington in the 1940s, is used to describe gene–environment interactions that influence phenotype [1]. Epigenetic mechanisms include DNA methylation, histone modifications, and microRNAs (miRNAs), and collectively, afford routes for environmental factors to alter gene activity. DNA methylation refers to the addition of methyl groups onto cytosine residues of a DNA strand. This commonly occurs at dinucleotide cytosine–guanine (CpG) sites, though methylation can also occur at non-CG dinucleotides [2–4]. DNA methylation is catalyzed by a group of enzymes called DNA methyltransferases (DNMTs), of which several types exist. DNMT 1 contributes to the maintenance of DNA methylation by adding methyl groups to hemi-methylated DNA, while DNMT 3a and 3b are able to modulate methylation patterns via de novo methylation [5]. Typically, DNA methylation results in the suppression of gene expression; however, under some circumstances it can also enhance gene transcription [6–8].

Posttranslational histone modifications comprise acetylation, methylation, ubiquitylation, sumoylation, and phosphorylation of the N-terminal tail of histone proteins. Because DNA is wrapped around histone molecules within nucleosomes, such modifications can either make DNA more or less accessible for transcription [9–11]. For example, histone acetylation involves the addition of acetyl groups (via histone acetyltransferases) at lysine residues on the N-terminal tail of histone proteins, decreasing the affinity between the histone and DNA and thereby allowing a more permissive transcriptional state [9–11]. Histone deacetylases (HDACs) reverse this process [9–11]. Another mode of epigenetic regulation gaining increasing attention is miRNAs, which are non-coding single stranded RNAs (usually about 22 bp in length) capable of exerting gene silencing effects via degradation or destabilization of mRNA [12–15]. Some studies also indicate that certain miRNAs upregulate gene expression [16, 17].

While epigenetic modifications were once thought to be limited to embryonic development, it has since been discovered that
Overview of Rodent Maternal Behavior and Circuity

Before delving into the epigenetics literature, here we mention several maternal behaviors and neuroanatomical substrates that are discussed in various sections of the review. For a more thorough evaluation of these topics, we refer the reader to several excellent reviews (e.g. [35–38]). One of the predominant maternal behaviors observed in laboratory rodents is licking of the pup’s body, with an emphasis on the anogenital area (anogenital licking aids in waste elimination) [39, 40]. Mothers spend a significant amount of time in the nest hovering over pups, engaging in bouts of licking, and nursing [40, 41]. Retrieval of pups becomes necessary as they wander from the nest, and this maternal behavior is elicited by ultrasonic vocalizations emitted by pups [42]. Of note, nulliparous females display retrieval behavior after continuous exposure (sensitization) to pups [43, 44]. Further, dams will engage in a behavior referred to as tail chasing, in which a dam chases their tail, eventually picking it up and carrying it in her mouth [45, 46]. The specific function of tail chasing is not known, but may be related to pup retrieval as dams often engage in this behavior antepartum and outside of the nest area, carrying the tail back to the nest [45]. Finally, brain regions involved in maternal behavior include the bed nucleus of the stria terminalis (BNST) [47–49], paraventricular nucleus (PVN) [50–52], nucleus accumbens [53–55], prefrontal cortex (PFC) [56–58], medial preoptic area (MPOA) [22, 57, 59–62], amygdala [60, 63, 64], and hippocampus [65, 66]. Several of these regions and their role in regards to maternal behavior are depicted in Fig. 1.

Adulthood and Preconception Psychosocial Stress

Stressors experienced in adulthood are capable of modulating the female epigenome and behavior. In one study that implemented a chronic variable mild stress paradigm, adult female rats were found to have increased levels of the histone acetytransferase cyclic AMP response element-binding protein (CBP) in the BNST [67]. This effect was not seen in male rats [67]. These data suggest an important role of histone acetylation in response to stress exposure that could lead to sex-specific alterations in behavioral outcomes. As further evidence for this notion, in an acute restraint stress paradigm that elicited elevated corticosterone and corticotropin releasing factor (Crf) mRNA in the PVN in male but not female rats, males demonstrated elevated CBP levels and females did not [68]. In another study that employed a subchronic variable stress paradigm to produce a depression-like phenotype, female mice had increased levels of Dnmt3a within the nucleus accumbens [69]. Mice with a knockout of Dnmt3a in the nucleus accumbens showed resilience to the subchronic variable stress, providing further support for the concept that Dnmt3a overexpression might mediate stress-induced depression [69]. Taken together, these studies show that the female brain can be epigenetically modulated in key components of maternal behavior circuitry by stress exposure. Further research is needed to understand the functional significance of sex differences in these epigenomic marks induced by these stressors.

Stress incurred by a female prior to pregnancy is also capable of modulating brain and behavioral trajectories of her offspring. In adult female rats that underwent a 7-day chronic unpredictable stress regimen, corticotropin releasing factor receptor type 1 (Crf1) mRNA was upregulated in the ova and frontal cortex [70]. A separate group of females were bred 2 weeks after termination of the same stress paradigm, and their offspring were likewise found to have increased Crf1 expression in their brain in both infancy (on postnatal day 0, prior to any maternal care received) and adulthood [70]. This altered gene expression corresponded with behavioral alterations when offspring were adults, including potentiated startle responses and increased locomotor activity in the elevated plus maze [70]. Preconception-stress-exposed rats and their first-generation female offspring also showed increased corticosterone levels. In contrast, second-generation offspring showed reduced expression of Crf1 mRNA and decreased corticosterone levels [71]. These data provide evidence that a stressor encountered by an adult female can contribute to the programming of HPA-axis reactivity for several generations.

While stressful experiences can modulate the epigenome and introduce maladaptive behavioral outcomes, other types of experiences can exert adaptive influences on behavior through epigenetic mechanisms. Induction and maintenance of maternal
behavior in response to pup interaction has been proposed to result from experience-driven chromatin remodeling [72]. In a maternal sensitization paradigm, which involved repeatedly introducing virgin nulliparous female mice to pups to stimulate maternal behavior, histone acetylation was shown to be a critical mediator for this experience-induced behavioral change [43]. Administration of the HDAC inhibitor (HDAC) sodium butyrate reduced the amount of time required for a nulliparous female to display maternal care toward pups [43]. This pharmacological manipulation also increased gene expression of estrogen receptor β, CBP, and the oxytocin receptor in the MPOA [43]. Furthermore, the HDACi-induced facilitation of maternal behavior and gene expression lasted for a month after initial maternal experience [73]. Taken together, these studies provide evidence that the induction of maternal behavior has epigenetic underpinnings and that administration of certain epigenome modifying drugs can have long-term facilitatory effects on maternal responsiveness.

**Gestational Stressors**

Epigenetic mechanisms also provide routes through which gestational stressors, either psychosocial or chemical in nature, can affect offspring. For example, prenatal predator exposure is one stressor that has both epigenetic and behavioral consequences. Female adult offspring of pregnant mouse dams exposed to predator odor demonstrated an enhanced corticosterone response and an increase in anti-predator behaviors [8]. This behavioral profile corresponded with increased Cdf1 mRNA in the amygdala and decreased Brain-derived neurotrophic factor (Bdnf) mRNA and DNA methylation of Bdnf exon IV in the hippocampus [8]. Daily exposure to restraint stress during pregnancy similarly modulates the epigenetic profile and levels of epigenetic regulators in rat offspring [23]. The placenta and fetal exposure to chronic unpredictable stress during gestation demonstrated increased levels of Dnmt3a mRNA and enhanced methylation of the 11β-hydroxysteroid dehydrogenase type 2 (Hsd11b2) gene promoter [74]. These same animals also displayed reduced levels of CpG methylation within the Hsd11b2 promoter region and increased methylation at sites within exon 1 of the hypothalamus as well as enhanced Dnmt1 mRNA within the cortex [74]. Further, adult female offspring of mouse mothers exposed to chronic unpredictable stress during gestation demonstrated impaired spatial memory capabilities, higher plasma corticosterone levels, decreased levels of H3 acetylation, and increased DNMT1 protein in the hippocampus [75].

miRNAs have been gaining attention for their ability to influence gene activity, though limited work has examined miRNAs in the female brain [76]. Rat dams exposed to stress (restraint and forced swim) during pregnancy demonstrated a decrease in the incidence of tail charring, and a correlational upregulation of 147 miRNAs and downregulation of 195 miRNAs in their frontal cortex [77]. Target genes of the affected miRNAs had roles in hormonal regulation, brain pathologies, stress response, and neurotransmission [77]. While a similar profile of altered microRNA expression was found in the brains of their male offspring, future examination is required to determine if female offspring would likewise show disrupted miRNA profiles.

Chemical perturbations during gestation likewise affect female offspring [78, 79]. Bisphenol A (BPA) is an endocrine disrupting chemical gaining increasing attention for its widespread use and association with the development of diseases [80–83]. BPA is of particular concern for females due to its ability to modulate estrogen and alter epigenetic profiles [84, 85]. Female offspring exposed to BPA, either during gestation alone or during both gestation and early postnatal development grew up to spend less time performing nurturing maternal behaviors toward their own offspring, and similarly adult females administered BPA demonstrated fewer maternal behaviors toward their offspring [86–88]. BPA exposure also modulates levels of epigenetic regulators within brain regions involved in maternal behavior, which could underlie the observed deficits in maternal behavior in BPA-exposed females. Specifically, levels of DNMT1 and DNMT3a were altered within the hypothalamus and PFC of juvenile female mice prenatally exposed to BPA [88]. Gestational and early postnatal exposure of rats to endocrine disrupting chemicals including estradiol benzoate and methoxychlor resulted in elevated estrogen receptor (ERα) mRNA and increased DNA methylation in the POA [89]. In adulthood, these perinatally exposed animals also experienced the advancement of reproductive senescence [89].

While antidepressant drugs mitigate depressive-like behavior in adult animals, developmental antidepressant exposure can have deleterious effects [90, 91]. Adult rat females that were prenatally exposed to fluoxetine displayed enhanced depression-like behavior, as assessed via the forced swim test [90]. Changes in the hippocampus of these females included decreased Bdnf exon IV mRNA and increased histone 3 lysine 27 trimethylation [80]. The presence of Bdnf mRNA was negatively correlated with immobility time in the forced swim test, suggesting that the observed epigenetic profile in these animals contributed to the phenotypic outcomes associated with developmental fluoxetine exposure [90]. Taken together, data highlighted in this section illustrate that gestational perturbations certainly have influences on neurobiological and behavioral outcomes in female offspring.

**Rearing Environments**

Rearing environments of rodent pups have long been recognized for their profound influence on the development of behavior, including maternal behavior [40, 92–95]. Female Long-Evans rats demonstrate a natural variability in their quality of maternal care, with some females exhibiting high levels of licking/grooming (LG), and others displaying low levels of LG [96]. This variability in maternal care is generationally transmitted, as female rats that were exposed (either born or cross-fostered) to a low-licking and grooming mother in their infancy demonstrate low levels of LG toward their own offspring [97, 98]. Work utilizing natural variations in LG maternal behavior found epigenetic modulation of the ERα gene within the MPOA of dams. Specifically, low-LG mothers showed decreased ERα gene expression within the MPOA relative to high-LG mothers [22]. This effect was transmitted to female offspring, but cross-fostering these offspring with a high-LG mother rescued ERα expression, showing that mother–infant interactions early in life are critical for MPOA development [99]. Social enrichment postweaning also enhanced LG behaviors in low-LG female offspring [100]. The variability of ERα expression and transmission of LG behaviors to offspring is mediated by DNA methylation, as low-LG caregivers demonstrate higher methylation of the ERα1b promoter [22]. The MPOA is a sexually dimorphic region critical in maternal behavior [22, 57, 59–62] and estrogen is a transcription factor with known protective effects [84]. Estrogen interacts with histone acetylation, suggesting a route for estrogen to affect expression of many genes [85, 101]. Estrogen levels also affect sexual behaviors, allowing for epigenetic alterations to have effects on mating capabilities of females [101, 102].
It is well established that the maternal behavior directed toward male versus female offspring differs, as dams spend more time licking their male pups than their female pups [39, 103, 104]. Because of the sex-specific nature of maternal care, altering the sex composition of litters changes pup-directed maternal behavior [105]. The resulting alterations in maternal behavior have lifelong effects on the brain and behavior of these offspring [106–108]. Within the Oprm1 gene promoter, which encodes for the µ-opioid receptor, it was discovered that female rats raised in female-only litters demonstrated higher levels of methylation within the hippocampus as compared with females who belonged to mixed litters (i.e. litters containing both male and female offspring) [109]. No effects on DNA methylation of Oprm1 were found within the nucleus accumbens, suggesting that this effect is brain-region specific [109]. The µ-opioid receptor is critical for mother–infant relationships, and thus, modulation of this receptor within attachment and maternal behavior circuitry could have critical implications for the maternal behavior of these offspring [110]. Another study that manipulated litter sex composition found hypermethylation of the hippocampal GR gene in adolescent female rats from female-only litters [111]. Because females receive less LG than their male counterparts, this corroborates other data with regard to lower LG behavior and enhanced DNA methylation of the GR gene in offspring [118].

Our lab and others have studied the effects of aversive rearing experiences on the Brain-derived neurotrophic factor (Bdnf) gene [Fig. 2]. The medial prefrontal cortex (mPFC) is a region critical for cognitive and memory processes and has been implicated in several neuropsychiatric disorders [112–116]. In addition, lesions to the mPFC disrupt maternal behaviors such as pup retrieval and pup licking [56, 58]. In a model of early-life maltreatment whereby rat pups are exposed to 30-min bouts of caregiver maltreatment (frequent stepping on, dropping, dragging, actively avoiding and rough handling) daily for the first postnatal week, variability in gene expression and DNA methylation can be detected in developing and adult females [117–120], and further, maltreated-females grow up to mistreat their own offspring [119].

Within the whole PFC, DNA methylation of the Bdnf gene was enhanced across the lifespan (during infant, adolescent, and adult time points) in maltreated animals, which corresponded with decreased Bdnf expression in adult females [119]. Within the mPFC, female pups subjected to maltreatment displayed a transient decrease in DNA methylation at the Reelin gene, which was no longer present in adolescence or adulthood [117]. However, these females showed decreased gene expression of Reelin in adulthood, signifying that although DNA methylation was no longer different, these developmental experiences resulted in differential expression of Reelin [117]. Adult females also displayed decreased methylation of Bdnf exon I but increased methylation of Bdnf exon IV in adulthood [117]. Gadd45b, which plays a role in DNA demethylation [121, 122], was the only epigenetic regulator significantly altered (lower mRNA levels) within the mPFC of adult females [123], thus the mechanism (or mechanisms) underlying the maltreatment-induced alterations in female gene expression and DNA methylation remains to be elucidated.

Using the same maltreatment regimen, female-specific modulations were also detected within the amygdala. The amygdala is a region involved in maternal behavior [60, 63, 64] and amygdalar pathways are particularly involved in maternal aggression [124–126]. Female rats that were maltreated in infancy displayed reduced expression of the oxytocin receptor gene in infancy and adolescence [127], a gene important for maternal behavior (i.e. higher oxytocin receptor levels are associated with more maternally responsive females) [99, 128, 129]. During adolescence, enhanced DNA methylation of the Bdnf gene [118], and decreased Bdnf gene expression and increased Neuropeptide Y (NPY) gene expression [127] were found. Contrary to adolescent gene expression, Bdnf gene expression was enhanced in females in adulthood [127] and this paralleled lower methylation levels [120]. These results further illustrate the transient and dynamic nature of epigenetic changes resulting from caregiver experiences. It is currently unclear what mechanism (or mechanisms) could underlie these changes. To further probe these effects of early-life experience and ascertain the way by which these epigenetic modifications could alter maternal behavioral outcomes, an important factor in future research will be parsing apart the nuclei within the amygdala that are functionally distinct and differentially contribute to maternal behavior [64].

Finally, restricted access to a caregiver can also have long-lasting epigenetic and behavioral consequences for female offspring [130]. In a mouse model of maternal separation, adolescent female C57BL/6J mice that experienced daily separation from their mother from postnatal days (PND) 1 through PND 14 demonstrated decreased Bdnf gene expression and enhanced GR methylation in the hippocampus [131]. Interestingly, in Balb/c mice that were exposed to this same manipulation, Bdnf expression was enhanced within the PFC and increased levels of Bdnf exon IX methylation within the hippocampus were found [131]. Altogether, data highlight the brain region-dependent nature of epigenetic modifications in females in response to different rearing environments.

### Generational Transmission of Epigenetic Modifications and Phenotypes

Quality of maternal behavior is passed from mother to female offspring [18, 22, 96, 97, 119, 128]. The transmission of LG behaviors from mother to female offspring is mediated by rearing experience, as cross-fostering offspring to high-LG mothers is
sufficient to enhance LG levels [18, 97]. In addition, LG behaviors are enhanced by social experiences post-weaning [100]. In a multigenerational stress design where three generations of rats were exposed to restraint and swim stressors, changes in antepartum behavior were found to be altered across generations [45]. Specifically, tail chasing behavior prior to parturition varied as a consequence of multiple generations of stress exposure. The first generation exposed to the stressor did not show behavioral variations, however, the second and third generations of stress-exposed females showed a reduction in tail chasing behavior, with the third generation showing the most severe decrease in tail chasing prevalence [45]. In addition to programming of antepar tum and maternal behavior, stress responsivity is likewise transmitted from parent to offspring [70, 71].

Another line of generational transmission comes from studies in rats using the endocrine disruptor vinclozolin, which is known to produce pregnancy abnormalities and kidney disease [132]. In addition, vinclozolin when limited to F0 exposure and then using male offspring to generate successive generations, alters expression levels of over 1000 hippocampal and 100 amygdala genes in F3 generation females, with concomitant increases in anxiety-like behavior [133]. In our own research where we found enhanced levels of DNA methylation of the Bdnf gene in the PFC and hippocampus in female rats with a history of maltreatment, we found this same change in the next generation of offspring [119]. Interestingly, cross-fostering pups of dams that experienced maltreatment in infancy was not sufficient to completely rescue DNA methylation levels [119]. This might indicate that these epigenetic marks were heritable (i.e. the associated epigenetic marks were transmitted through the germline as a result of environmental experiences). Prepar tum behavior however was different in females that had been exposed to maltreatment such that previously maltreated dams displayed more anxiety-related behaviors during the last 3 days of pregnancy [119]. Thus, it is uncertain whether the biological effects ascertained in our model were due to a compromised gestational environment (i.e. maternal state during gestation) or that the epigenetic marks were passed through the germline. Regardless of the mode of transmission in our study or others highlighted here, together data indicate that stress exposure in females has behavioral and epigenetic consequences for her offspring and grand-offspring. More research is certainly warranted in the areas of behaviorally mediated vs. germ-line-mediated inheritance.

Interventions to Alter the Female Epigenome

The inherently malleable epigenome may be a target of therapeutic or behavioral intervention, and many studies have shown this to be true (e.g. [119, 134, 135]). However, sex differences exist under basal conditions in levels of various epigenetic regulators, and these sex differences in epigenetic regulators contribute to sex differences in behavior (e.g. [29, 136]). For example, within the amygdala, mRNA levels of Dnmt3a, MeCP2 [137], and Gadd45b [138] are higher in developing females as compared with males. Sex differences are also found in baseline levels of posttranslational histone modifications and DNA methylation throughout other regions of the brain including the cortex, hypothalamus, and BNST/POA [139–141]. This suggests that experiments manipulating these molecules may see divergent effects between the sexes. In addition, levels of these regulators are dynamic and levels between the sexes differ across developmental time periods, so assessing the efficacy of administration of epigenetic regulators across the lifespan is of importance [142].

There are some data to support the notion that drugs that manipulate the epigenome can have positive effects on the female brain. For example, administration of a DNMT inhibitor in adulthood rescued aberrant PFC DNA methylation patterns resulting from exposure to caregiver maltreatment [119]. This suggests that modulating DNA methylation profiles could be utilized to normalize consequences of early-life stress, even when the intervention occurs in adulthood.Similarly, epigenetic modifications resulting from inhibition of HDACs have beneficial effects, although very few of the studies that have been conducted included female subjects. Sodium butyrate decreased depressive-like behaviors in mice, and this effect was further enhanced by co-administration with the antidepressant fluoxetine [91]. In a rat model of neonatal maternal separation, adult females exposed to separation from PND2-9 demonstrated a reduced fear-potentiated startle response, which corresponded with increased serum estradiol and decreased histone methylation in the frontal cortex [143]. Treatment with the HDACi valproic acid, but not the DNMT inhibitor 5-aza-2-deoxycytidine, prior to daily maternal separation reversed this decrease in fear-potentiated startle behavior and histone methylation [143]. As the DNMT and HDAC inhibitors employed in these studies lack target specificity (i.e. many gene loci would be presumed to be affected) and can produce off-target effects, there is a strong need to explore strategies that enable select epigenetic modifications.

Maternal diet has strong modulatory effects on the epigenome, health, and behavioral outcomes of her offspring. Supplementing maternal diet with folic acid, a methyl donor, ameliorated aberrant epigenetic profiles in mouse offspring induced by exposure to BPA [78]. Methyl donor supplementation also rescued alterations in DNA methylation and behavior resulting from exposure to high fat diet during gestation. Specifically, when a high fat diet was paired with methyl donor supplementation, the global hypomethylation typically induced by gestational exposure to high fat diet was eliminated in the PFC of female rat offspring [144]. This treatment also ameliorated the enhancement of μ-opioid receptor mRNA in the nucleus accumbens and PFC, showing dietary supplementation is capable of rescuing both global and gene-specific aberrations induced by gestational exposure to high fat diet [144]. Further, methyl donor supplementation rescued the high-fat diet preference and reduced locomotor activity observed in offspring of dams that consumed a high-fat diet during pregnancy [144]. Such epigenetic alterations could contribute to differences in processing rewarding stimuli. Because maternal behavior is a motivated behavior and pup-interactions elicit a reward response in dams [145–147], aberrant reward processing could contribute to deficient maternal behavior toward offspring. Taken together, these data highlight the ability of the maternal diet to regulate the epigenome of offspring and the therapeutic potential for dietary supplementation during the prenatal/early postnatal period.

Environmental interventions similarly rescue LG behavior in females that received low levels of LG in infancy. As previously mentioned, social enrichment post-weaning enhances levels of LG behavior in females that received low LG in infancy. This coincided with enhanced oxytocin receptor binding and exploratory behavior as measured by the open-field test [100]. This suggests that social interactions for the female beyond those occurring in infancy have behavioral and neurobiological implications, and such manipulations are capable of modulating
behavioral trajectories. Natural variation in maternal care also has implications for the development of reward systems, with adult offspring of low-LG dams exhibiting a blunted increase in the dopamine signal within the nucleus accumbens in response to licking and grooming pups. Administration of the selective dopamine re-uptake inhibitor GBR 12909 brought the dopamine signal generated by pup interactions up to that of high-LG offspring [55]. Thus, drugs that manipulate dopamine systems could have positive effects for maternal care-associated deficits in reward processing, and future studies could examine potential epigenetic underpinnings of this drug action and efficacy.

Concluding Remarks

We have highlighted data demonstrating that environmental factors throughout development modify the female epigenome and create epigenetic marks within brain regions critical for maternal behavior. Epigenetic marks can be both long-lasting and dynamic (i.e. some continue to transpire over the course of the lifespan or can be modified). Future research is needed to better ascertain the effects of environmental and psychosocial perturbations on the female epigenome, as well as motherhood itself. These data are important to have in hand, as their understandings have implications for interventions for neglectful/abusive maternal care as well as for neuropsychiatric disorders such as postpartum depression, which is estimated to occur in about 15% of pregnancies and could potentially have epigenetic underpinnings [148, 149].

Funding

This study was supported by a grant from The National Institute of General Medical Sciences (1F20GM103653).

Conflict of interest statement. None declared.

References

1. Waddington CH. Organisers and Genes. Cambridge University Press, Cambridge, 1940.
2. McGowan PO, Suderman M, Sasaki A et al. Broad epigenetic signature of maternal care in the brain of adult rats. PloS One 2011;6:e14739
3. Lister R, Pelizzola M, Dowen RH et al. Human DNA methylomes at base resolution show widespread epigenomic differences. Nature 2009;462:315–22.
4. Stroud H, Do T, Du J et al. Non-CG methylation patterns shape the epigenetic landscape in Arabidopsis. Nat Struct Mol Biol 2014;21:64–72.
5. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology 2013;38:23–38.
6. Chahroum M, Jung SY, Shaw C et al. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 2008;320:1224–9.
7. Guy J, Cheval H, Selfridge J et al. The role of MeCP2 in the brain. Annu Rev Cell Dev Biol 2011;27:631–52.
8. St-Cyr S, McGowan PO. Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor. Front Behav Neurosci 2015;9:145.
9. Li B, Carey M, Workman JL. The role of chromatin during transcription. Cell 2007;128:707–19.
10. Grant PA. A tale of histone modifications. Genome Biol 2001;2:0003.1–0003.6.
11. Millar CB, Grunstein M. Genome-wide patterns of histone modifications in yeast. Nat Rev Mol Cell Biol 2006;7:657–66.
12. Adalakha YK, Saini N. Brain microRNAs and insights into biological functions and therapeutic potential of brain enriched miRNA-128. Mol Cancer 2014;13:1–18.
13. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281–97.
14. Chen K, Rajewsky N. The evolution of gene regulation by transcription factors and microRNAs. Nat Rev Genet 2007;8:93–103.
15. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004;5:522–31.
16. Valinezhad Orang A, Safaralizadeh R, Kazemzadeh-Bavili M. Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation. Int J Genom 2014;2014:15.
17. Vasudevan S. Posttranscriptional upregulation by microRNAs. RNA 2012;3:311–30.
18. Weaver IC, Cervoni N, Champagne FA et al. Epigenetic programming by maternal behavior. Nat Neurosci 2004;7:847–54.
19. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 2003;23:5293–300.
20. Skinner MK, Anway MD. Seminiferous cord formation and germ-cell programming: epigenetic transgenerational actions of endocrine disruptors. Annu Rev Genet 2005;39:181–32.
21. Levenson JM, Roth TL, Lubin FD et al. Evidence that DNA (Cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. J Biol Chem 2006;281:15763–73.
22. Champagne FA, Weaver IC, Diorio J et al. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology 2006;147:2909–15.
23. Roth TL, Sweatt JD. Epigenetic marking of the BDNF gene by early-life adverse experiences. Horm Behav 2011;59:315–20.
24. Lutz PE, Turecki G. DNA methylation and childhood maltreatment: from animal models to human studies. Neuroscience 2014;264:142–56.
25. Tamura Y, Kunugi H, Ohashi J et al. Epigenetic aberration of the human RELN gene in psychiatric disorders. Mol Psychiat 2007;12:593–600.
26. Provencal N, Binder EB. The neurobiological effects of stress as contributors to psychiatric disorders: focus on epigenetics. Curr Opin Neuropobiol 2015;30:31–7.
27. McCarthy MM, Auger AP, Bale TL et al. The epigenetics of sex differences in the brain. J Neurosci 2009;29:12815–23.
28. McCarthy MM, Nugent BM. Epigenetic contributions to hormonally-mediated sexual differentiation of the brain. J Neuroendocrinol 2013;25:1133–40.
29. Nugent BM, Wright CL, Shetty AC et al. Brain feminization requires active repression of masculinization via DNA methylation. Nat Neurosci 2015;18:690–7.
30. Ghahramani NM, Ngun TC, Chen P-Y et al. The effects of perinatal testosterone exposure on the DNA methylome of the mouse brain are late-emerging. Biol Sex Differ 2014;5:8.
31. Kessler RC, Berglund P, Demler O et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatr 2005;62:593–602.
32. Jessen HM, Auger AP. Sex differences in epigenetic mechanisms may underlie risk and resilience for mental health disorders. *Epigenetics* 2011;6:657–61.
33. Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev* 2011;35:565–72.
34. Klein SL, Schiebinger L, Stefanick ML et al. Opinion: sex inclusion in basic research drives discovery. *Proc Natl Acad Sci* 2015;112:5257–8.
35. Numan M, Woodside B. Maternity: neural mechanisms, motivational processes, and physiological adaptations. *Behav Neurosci* 2010;124:715.
36. Kristal MB. The biopsychology of maternal behavior in non-human mammals. *ILAR J* 2009;50:51–63.
37. Barrett J, Fleming AS. Annual research review: all are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. *J Child Psychol Psychiatr* 2011;52:368–97.
38. Pawluski JL, Lambert KG, Kinsley CH. Neuroplasticity in the maternal hippocampus: Relation to cognition and effects of repeated stress. *Horm Behav* 2016;77:86–97.
39. Moore CL. Maternal contributions to the development of masculine sexual behavior in laboratory rats. *Dev Psychobiol* 1994;31:347–56.
40. Stern JM. Licking, touching, and suckling: contact stimulation and maternal psychobiology in rats and women. *Ann N Y Acad Sci* 1986;474:95–107.
41. Stern JM, Lonstein JS. Neural mediation of nursing and related behaviors. *Prog Brain Res* 2001;133:263–78.
42. Brunelli SA, Shair H, Hofer MA. Hypothermic vocalizations of rats pups (Rattus norvegicus) elicit and direct maternal search behavior. *J Comp Psychol* 1994;108:298–303.
43. Stolzenberg DS, Stevens JS, Rissman EF. Experience-facilitated improvements in pup retrieval; evidence for an epigenetic effect. *Horm Behav* 2012;62:128–35.
44. Lonstein JS, Wagner CK, De Vries GJ. Comparison of the “nursing” and other parental behaviors of nulliparous and lactating female rats. *Horm Behav* 1999;36:242–51.
45. Ward ID, Zucchi FC, Robbins JC et al. Transgenerational programming of maternal behaviour by prenatal stress. *BMC Pregnancy Childbirth* 2013;13(Suppl 1):S9.
46. Gonzalez A, Lovic V, Ward GR et al. Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats. *Dev Psychobiol* 2001;38:11–32.
47. Klampfl SM, Brunton PJ, Bayerl DS et al. Hypoactivation of CRF receptors, predominantly type 2, in the medial-posterior BNST is vital for adequate maternal behavior in lactating rats. *J Neurosci* 2014;34:9665–76.
48. Bosch OJ, Pförtsch J, Beiderbeck DI et al. Maternal behaviour is associated with vasopressin release in the medial preoptic area and bed nucleus of the stria terminalis in the rat. *J Neuroendocrinol* 2010;22:420–9.
49. Numan M, Numan MJ. Projection sites of medial preoptic area and ventral bed nucleus of the stria terminalis neurons that express Fos during maternal behavior in female rats. *J Neuroendocrinol* 1997;9:369–84.
50. Giovanardi M, Padoin MJ, Cadore LP et al. Hypothalamic paraventricular nucleus modulates maternal aggression in rats: effects of ibotenic acid lesion and oxytocin antisense. *Physiol Behav* 1998;63:351–9.
51. Consiglio AR, Lucion AB. Lesion of hypothalamic paraventricular nucleus and maternal aggressive behavior in female rats. *Physiol Behav* 1996;59:591–6.
52. Insel TR, Harbaugh CR. Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. *Physiol Behav* 1989;45:1033–41.
53. Li M, Fleming AS. Differential involvement of nucleus accumbens shell and core subregions in maternal memory in postpartum female rats. *Behav Neurosci* 2003;117:426.
54. Li M, Fleming AS. The nucleus accumbens shell is critical for normal expression of pup-retrieval in postpartum female rats. *Behav Brain Res* 2003;145:99–111.
55. Champagne FA, Chretien P, Stevenson CW et al. Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *J Neurosci* 2004;24:4113–23.
56. Afonso VM, Sison M, Lovic V et al. Medial prefrontal cortex lesions in the female rat affect sexual and maternal behavior and their sequential organization. *Behav Neurosci* 2007;121:515–26.
57. Pereira M, Morrell JI. Functional mapping of the neural circuitry of rat maternal motivation: effects of site-specific transient neural inactivation. *J Neuroendocrinol* 2011;23:1020–35.
58. Febo M, Felix-Ortiz AC, Johnson TR. Inactivation of neuronal activity in the medial prefrontal cortex largely reduces pup retrieval and grouping in maternal rats. *Brain Res* 2010;1325:77–88.
59. Pedersen CA, Caldwell JD, Walker C et al. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav Neurosci* 1994;108:1163.
60. Fleming AS, Walsh C. Neuropsychology of maternal behavior in the rat: c-fos expression during mother–litter interactions. *Psychoneuroendocrinology* 1994;19:429–43.
61. Fleming AS, Miceli M, Moretto D. Lesions of the medial preoptic area prevent the facilitation of maternal behavior produced by amygdala lesions. *Physiol Behav* 1983;31:503–10.
62. Numan M, Stolzenberg DS. Medial preoptic area interactions with dopamine neural systems in the control of the onset and maintenance of maternal behavior in rats. *Front Neuroendocrinol* 2009;30:46–64.
63. Fleming AS, Vaccarino F, Luebke C. Amygdaloid inhibition of maternal behavior in the nulliparous female rat. *Physiol Behav* 1980;25:731–43.
64. Numan M, Numan MJ, English JB. Excitotoxic amino acid injections into the medial amygdala facilitate maternal behavior in virgin female rats. *Horm Behav* 1993;27:56–81.
65. Kimble DP, Rogers L, Hendrickson CW. Hippocampal lesions disrupt maternal, not sexual, behavior in the albino rat. *J Comp Physiol Psychol* 1967;63:401.
66. Pawluski JL, Galea LAM. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. *Neuroscience* 2007;149:53–67.
67. Sterrenburg L, Gaszner B, Boerriger J et al. Chronic stress induces sex-specific alterations in methylation and expression of corticotropin-releasing factor gene in the rat. *PLoS One* 2011;6:e28128.
68. Sterrenburg L, Gaszner B, Boerriger J et al. Sex-dependent and differential responses to acute restraint stress of corticotropin-releasing factor—producing neurons in the rat paraventricular nucleus, central amygdala, and bed nucleus of the stria terminalis. *J Neurosci Res* 2012;90:179–92.
69. Hodes GE, Pfau ML, Purushothaman I et al. Sex differences in nucleus accumbens transcriptome profiles associated with susceptibility versus resilience to subchronic variable stress. *J Neurosci* 2015;35:16362–76.
70. Zaidan H, Leshem M, Gaisler-Salomon I. Preriproducive stress to female rats alters corticotropin releasing factor type 1 expression in ova and behavior and brain corticotropin releasing factor type 1 expression in offspring. Biol Psychiat 2013;74:680–7.

71. Zaidan H, Gaisler-Salomon I. Preriproducive stress in adolescent female rats affects behavior and corticosterone levels in second-generation offspring. Psychoneuroendocrinology 2015;58:120–9.

72. Stolzenberg DS, Champagne FA. Hormonal and non-hormonal bases of maternal behavior: the role of experience and epigenetic mechanisms. Horm Behav 2016;77:204–10.

73. Stolzenberg DS, Stevens JS, Rissman EF. Histone deacetylase inhibition induces long-lasting changes in maternal behavior and gene expression in female mice. Endocrinology 2014;155:3674–83.

74. Pena CJ, Monk C, Champagne FA. Epigenetic effects of prenatal stress on 11 beta-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PLoS One 2012;7:e39791.

75. Benoit JD, Racić F, Frick KM. Prenatal stress induces spatial memory deficits and epigenetic changes in the hippocampus indicative of heterochromatin formation and reduced gene expression. Behav Brain Res 2015;281:1–8.

76. Ma DK, Marchetto MC, Guo JU et al. Epigenetic choreographers of neurogenesis in the adult mammalian brain. Nat Neurosci 2010;13:1338–44.

77. Zucchi FC, Yao Y, Ward ID et al. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One 2013;8:e65967.

78. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci 2007;104:13056–61.

79. Panagiotidou E, Zerva S, Mitsiou DJ et al. Perinatal exposure to low-dose bisphenol A affects the neuroendocrine stress response in rats. J Endocrinol 2014;220:207–18.

80. Calafat AM, Ye X, Wong L-Y et al. Exposure of the US population to Bisphenol A and 4-tertiary-Octylphenol: 2003–2004. Environ Health Perspect 2007;115:177–86.

81. Midoro-Horiuti T, Tiwari R, Watson CS et al. Maternal bisphenol A exposure promotes the development of experimental asthma in mouse pups. Environ Health Perspect 2010;118:273.

82. Melzer D, Rice NE, Lewis C et al. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. PLoS One 2010;5:e8673.

83. Richter CA, Birnbaum LS, Farabbolini F et al. In vivo effects of bisphenol A in laboratory rodent studies. Reprod Toxicol 2007;24:199–224.

84. Lee SJ, McEwen BS. Neurotrophic and neuroprotective actions of estrogens and their therapeutic implications. Annu Rev Pharmacol Toxicol 2001;41:569–91.

85. Kim MY, Hsiao SJ, Kraus WL. A role for coactivators and histone acetylation in estrogen receptor α-mediated transcription initiation. EMBO J 2001;20:6084–94.

86. Palanza PL, Howdeshell KL, Parmigiani S et al. Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. Environ Health Perspect 2002;110(Suppl 3):415.

87. Della Seta D, Minder I, Dessié-Fulgheri F et al. Bisphenol-A exposure during pregnancy and lactation affects maternal behavior in rats. Brain Res Bull 2005;65:255–60.

88. Kundakovic M, Gudsnuk K, Franks B et al. Sex-specific epigenetic disruption and behavioral changes following low-dose bisphenol A exposure. Proc Natl Acad Sci U S A 2013;110:9956–61.

89. Gore AC, Walker DM, Zama AM et al. Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. Mol Endocrinol 2011;25:2157–68.

90. Boule F, Pawluski JL, Homberg JR et al. Developmental fluoxetine exposure increases behavioral despair and alters epigenetic regulation of the hippocampal BDNF gene in adult female offspring. Horm Behav 2016;80:47–57.

91. Schroeder FA, Lin CL, Crunio WE et al. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol Psychiatry 2007;62:55–64.

92. Stanton ME, Levine S. Inhibition of infant glucocorticoid stress response: Specific role of maternal cues. Dev Psychobiol 1990;23:411–26.

93. Brunelli SA, Shindledcker RD, Hofer MA. Early experience and maternal behavior in rats. Dev Psychobiol 1989;22:295–314.

94. Moretto D, Paclik L, Fleming A. The effects of early rearing environments on maternal behavior in adult female rats. Dev Psychobiol 1986;19:581–91.

95. Plotsky PM, Meany MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain Res Mol Brain Res 1993;18:195–200.

96. Liu D, Diorio J, Tannenbaum B et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 1997;277:1659–62.

97. Francis DD, Diorio J, Liu D et al. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286:1155–8.

98. Champagne FA. Epigenetic mechanisms and the transgenerational effects of maternal care. Front Neuroendocrinol 2008;29:386–97.

99. Champagne FA, Weaver IC, Diorio JS et al. Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area. Endocrinology 2003;144:4720–4.

100. Champagne FA, Meaney MJ. Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. Behav Neurosci 2007;121:1353.

101. Gagnidze K, Weil ZM, Faustino LC et al. Early histone modifications in the ventromedial hypothalamus and preoptic area following oestriadiol administration. J Neuroendocrinol 2013;25:939–55.

102. Pfaff DW. Features of a hormone-driven defined neural circuit for a mammalian behavior. Principles illustrated, neuroendocrine syllogisms, and multiplicative steroid effects. Annu Rev Neurosci 1992;15:313–47.

103. Moore CL, Chadwick-Dias AM. Behavioral responses of infant rats to maternal licking: variations with age and sex. Dev Psychobiol 1986;19:427–38.

104. Alleva E, Caprioli A, Laviola G. Litter gender composition affects maternal behavior of the primiparous mouse dam (Mus musculus). J Comp Physiol 1989;103:83–7.

105. Alleva E, Caprioli A, Laviola G. Postnatal social environment affects morphine analgesia in male mice. Physiol Behav 1986;36:779–81.

106. Cirulli F, Adriani W, Laviola G. Sexual segregation in infant mice: behavioural and neuroendocrine responses to d-
amphetamine administration. Psychopharmacology 1997;134:140–52.
108. Laviola G, Terranova M. The developmental psychobiology of behavioural plasticity in mice: the role of social experiences in the family unit. Neurosci Biobehav Rev 1998;23:197–213.
109. Hao Y, Huang W, Nielsen DA et al. Litter gender composition and sex affect maternal behavior and DNA methylation levels of the oprim1 gene in rat offspring. Front Psychiatr 2011;2:21.
110. Nelson E, Panksepp J. Brain substrates of infant-mother attachment: contributions of opioids, oxytocin, and norepinephrine. Neurosci Biobehav Rev 1998;22:437–52.
111. Kosten TA, Huang W, Nielsen DA. Sex and litter effects on anxiety and DNA methylation levels of stress and neurotrophin genes in adolescent rats. Dev Psychobiol 2014;56:392–406.
112. Chai XJ, Whitfield-Gabrieli S, Shinn AK et al. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 2011;36:2009–17.
113. Broadbelt K, Byne W, Jones LB. Evidence for a decrease in basilar dendrites of pyramidal cells in schizophrenic medial prefrontal cortex. Schizophrenia Res 2002;58:75–81.
114. Joel D, Weiner I, Feldon J. Electrolytic lesions of the medial prefrontal cortex in rats disrupt performance on an analog of the Wisconsin Card Sorting Test, but do not disrupt latent inhibition: implications for animal models of schizophrenia. Behav Brain Res 1997;85:187–201.
115. Vertes RP. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. Neuroscience 2006;142:1–20.
116. Ridderinkhof KR, Ullsperger M, Crone EA et al. The role of the medial frontal cortex in cognitive control. Science 2004;306:443–7.
117. Blaze J, Scheuing L, Roth TL. Differential methylation of genes in the medial prefrontal cortex of developing and adult rats following exposure to maltreatment or nurturing care during infancy. Dev Neurosci 2013;35:306–16.
118. Doherty TS, Forster A, Roth TL. Global and gene-specific DNA methylation alterations in the adolescent amygdala and hippocampus in an animal model of caregiver maltreatment. Behav Brain Res 2016;298:55–61.
119. Roth TL, Lubin FD, Funk AJ et al. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatr 2009;65:760–9.
120. Roth TL, Matt S, Chen K, et al. Bdnf DNA methylation modifications in the hippocampus and amygdala of male and female rats exposed to different caregiving environments outside the homecage. Dev Psychobiol 2014;56:1755–63.
121. Ma DK, Guo JU, Ming GL et al. DNA excision repair proteins and Gadd45 as molecular players for active DNA demethylation. Cell Cycle 2009;8:1526–31.
122. Ma DK, Jang MH, Guo JU et al. Neuronal activity-induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. Science 2009;323:1074–7.
123. Blaze J, Roth TL. Exposure to caregiver maltreatment alters expression levels of epigenetic regulators in the medial prefrontal cortex. Int J Dev Neurosci 2013;31:804–10.
124. Lubin DA, Elliott JC, Black MC et al. An oxytocin antagonist infused into the central nucleus of the amygdala increases maternal aggressive behavior. Behav Neurosci 2003;117:195–201.
125. Sheehan T, Paul M, Amaral E et al. Evidence that the medial amygdala projects to the anterior/ventromedial hypothalamic nuclei to inhibit maternal behavior in rats. Neuroscience 2001;106:341–56.
126. Ferriera CF, Foote KB, Meltser HM et al. Oxytocin in the amygdala facilitates maternal aggression. Ann N Y Acad Sci 1992;652:456–7.
127. Hill KT, Warren M, Roth TL. The influence of infant-caregiver experiences on amygdala Bdnf, OXTR, and NPY expression in developing and adult male and female rats. Behav Brain Res 2014;272:175–80.
128. Francis DD, Champagne FA, Meaney MJ. Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. J Neuroendocrinol 2000;12:1145–8.
129. Champagne FA, Diorio J, Sharma S et al. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proc Natl Acad Sci 2001;98:12736–41.
130. Kalinichev M, Easterling KW, Plotksy PM et al. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long-Evans rats. Pharmacol Biochem Behav 2002;73:131–40.
131. Kundakovic M, Lim S, Gudsnuk K et al. Sex-specific and strain-dependent effects of early life adversity on behavioral and epigenetic outcomes. Front Psychiatri 2013;4:78.
132. Nilsson E, Anway MD, Stanfield J et al. Transgenerational epigenetic effects of the endocrine disruptor vinclozolin on pregnancies and female adult onset disease. Reproduction 2008;135:713–21.
133. Skinner M, Anway MD, Savenkova MI et al. Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. PLoS One 2008;3:e3745.
134. Weaver IC, Champagne FA, Brown SE et al. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J Neurosci 2005;25:11045–54.
135. Syzuf M. Epigenetics, DNA methylation, and chromatin modifying drugs. Annu Rev Pharmacol Toxicol 2009;49:243–63.
136. Auger AP, Jessen HM, Edelmann MN. Epigenetic organization of brain sex differences and juvenile social play behavior. horm Behav 2011;59:358–63.
137. Kolodkin MH, Auger AP. Sex difference in the expression of DNA methyltransferase 3a in the rat amygdala during development. J Neuroendocrinol 2011;23:577–83.
138. Kigar S, Chang L, Hayne MR et al. Sex differences in Gadd45b expression and methylation in the developing rodent amygdala. Brain Res 2016;1642:461–6.
139. Schwarz JM, Nugent BM, McCarthy MM. Developmental and hormone-induced epigenetic changes to estrogen and progestosterone receptor genes in brain are dynamic across the life span. Endocrinology 2010;151:4871–81.
140. Shen EY, Ahern TH, Cheung J et al. Epigenetics and sex differences in the brain: a genome-wide comparison of histone-3 lysine-4 trimethylation (H3K4me3) in male and female mice. Exp Neurol 2015;268:21–9.
141. Tsai H-W, Grant PA, Rissman EF. Sex differences in histone modifications in the neonatal mouse brain. Epigenetics 2009;4:47–53.
142. Kurian JR, Forbes-Lorman RM, Auger AP. Sex difference in mc2p2 expression during a critical period of rat brain development. Epigenetics 2007;2:173–8.
143. Kao G-S, Cheng L-Y, Chen L-H et al. Neonatal isolation decreases cued fear conditioning and frontal cortical histone 3
lysine 9 methylation in adult female rats. *Eur J Pharmacol* 2012;697:65–72.

144. Carlin J, George R, Reyes TM. Methyl donor supplementation blocks the adverse effects of maternal high fat diet on offspring physiology. *PLoS One* 2013;8:e63549.

145. Ferris CF, Kulkarni P, Sullivan JM et al. Pup suckling is more rewarding than cocaine: evidence from functional magnetic resonance imaging and three-dimensional computational analysis. *J Neurosci* 2005;25:149–156.

146. Gaffori O, Le Moal M. Disruption of maternal behavior and appearance of cannibalism after ventral mesencephalic tegmentum lesions. *Physiol Behav* 1979;23:317–23.

147. Hansen S, Harthon C, Wallin E et al. Mesotelencephalic dopamine system and reproductive behavior in the female rat: effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. *Behav Neurosci* 1991;105:588.

148. O’Hara MW, McCabe JE. Postpartum depression: current status and future directions. *Annu Rev Clin Psychol* 2013;9:379–407.

149. Kaminsky Z, Payne J. Seeing the future: epigenetic biomarkers of postpartum depression. *Neuropsychopharmacology* 2014;39:234.

150. Dulac C, O’Connell LA, Wu Z. Neural control of maternal and paternal behaviors. *Science* 2014;345:765–70.