ELSEVIER

How social experiences influence the brain

Frances A Champagne and James P Curley

Social experiences throughout life influence gene expression and behavior, however, early in development these influences have a particularly profound effect. In mammals, mother–infant interactions are the primary source of social stimulation and result in long-term changes in offspring phenotype. This has previously been demonstrated in rodents and primates, however, recent studies in rats have advanced our understanding of how these influences are achieved at a mechanistic level, through epigenetic modification, and provide a model for studying the transmission of social behavior across generations. These studies emphasize the importance of a life-history approach to the study of brain development; incorporating information about genetic background, prenatal and postnatal maternal care received, and post-weaning social interactions of an individual, in addition to the social environment experienced by previous generations.

Addresses
Sub-Department of Animal Behaviour, University of Cambridge, High Street Madingley, Cambridge, CB3 8AA, UK

Corresponding author: Champagne, Frances A (fac25@hermes.cam.ac.uk)

Current Opinion in Neurobiology 2005, **15**:704–709

This review comes from a themed issue on
Neurobiology of behaviour
Edited by Nicola S Clayton and Rene Hen

Available online 2nd November 2005

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2005.10.001

Introduction

Early in development, the parent–offspring relationship is critical for determining survival of offspring, with the quality of this relationship being the primary focus of research examining the impact of social experiences. In mammals, the mother is the principal caregiver, providing both nutritional resources and behavioral stimulation to offspring. Experimental paradigms involving manipulation of the mother–infant relationship have been used extensively to investigate the nature of the developmental impact of these interactions, however, these manipulations are often disruptive to offspring development. In many species, aspects of maternal care show a high degree of stability and these traits can be quantified and associated with more subtle behavioral and neuroendocrine outcomes in offspring [1,2]. Use of these approaches has enabled researchers to address questions about the molecular mechanisms involved in mediating the effects of early rearing experiences and incorporate studies of transgenerational effects in their studies. Thus, when considering the question 'how do social experiences influence the brain?', it is becoming clear that we must take a broad approach; examining studies using multiple paradigms, with inter-species comparisons, and using a life-history approach considering the contribution of genetic background and social experience throughout the lifespan. Here, we discuss current understanding of the role of mother–infant interactions in mediating developmental outcomes, the interaction between social environment and genetic background, and the mechanisms mediating the long-term effects of early social experiences. Recent work illustrating the impact of social experiences beyond the postpartum period and the transmission of social behavior across generations is also explored.

Maternal influence on brain development and behavior

Though considerations of mother–infant interactions are often limited to the postpartum period, in which both behavioral and nutritional aspects of care can be readily observed, events occurring before birth also have a substantial impact on brain development and behavior. Increasing levels of gestational social stress (see glossary) in guinea pigs, experimentally induced by altering the stability of group composition by interchanging females between colonies every few days, alters the behavior and neuroendocrine function of both male and female offspring [3•]. Female offspring are masculinized, displaying male-typical play and courtship behavior, and have higher levels of serum testosterone and increased adrenal tyrosine hydroxylase activity [4]. Androgen receptors (AR) in the medial preoptic area (MPOA) and arcuate nucleus (ARC) of the hypothalamus are upregulated in these females [4]. By contrast, male offspring of these socially stressed mothers are infantilized as adults, resting in body contact with others for longer and integrating courtship behavior into their play behavior [5,6]. Development of the pituitary–adrenocortical system is also delayed in these males and they have decreased adrenal tyrosine hydroxylase activity, and downregulated ARs in the MPOA and ARC [5,6]. Thus, social experiences of the mother can influence offspring development during the prenatal period with consequences for adult reproductive function. These effects are particularly relevant in species such as the guinea pig, which have a prolonged prenatal period and relatively little postpartum mother–infant interaction.

Glossary
Cross-fostered: The biological offspring of one mother are exchanged with same-age offspring of another mother, usually immediately postpartum.
Embryo transfer: Fertilized eggs are removed from their biological mother and placed into a host mother who has been hormonally primed and is capable of implanting.
Gene x environment interactions: Refers to the process in which particular genotypes might lead to different phenotypes under different environmental conditions. Likewise, it also refers to the same environment leading to different phenotypes in individuals with different genotypes.
Social stress: Induction of increased HPA activity through contact with conspecifics.

In altricial species, such as rats and mice, which give birth to young that are still dependent on the mother, maternal care is predominantly postnatal. Nevertheless, the prenatal maternal environment plays a crucial role in shaping the adult behavior in these species. For instance, gestational stress (both physical and social) of rat and mouse dams leads to long-term changes in offspring behavior, typically affecting hypothalamic pituitary axis (HPA) activity and cognition in a sex-specific manner [3•,7]. Moreover, it has been recently demonstrated that male mice of the C57BL/6J strain develop anxiety and emotional phenotypes equivalent to those of another inbred strain (Balb/cJ) if they have been both embryo transferred and cross-fostered (see glossary) to Balb/cJ mothers [8]. Embryo transfer (see glossary) alone or cross-fostering alone were insufficient to generate this adult phenotype. Thus, the role of maternal factors in epigenetically shaping brain development and behavior of offspring before birth must be considered, although in most mammals the majority of maternal care and infant development occurs postpartum.

Studies of the neurobiological and behavioral consequences of deprivation of maternal care during infancy in both primates and rodents highlight the role of experiences during this period in the development of stress responsivity and social behavior. In primates, this effect has been best demonstrated in Harlow's artificial rearing paradigm, in which infant rhesus monkeys are reared in complete social isolation for periods of 3–12 months [9,10]. Juveniles reared in this environment display marked deficits in play behavior, learning impairments, heightened fear-related behaviors, and behavioral inhibition. These behavioral effects are associated with a disruption of HPA activity, even among peer-reared infants deprived of maternal stimulation but not completely socially deprived [11]. Similar results are observed in artificially reared rat pups removed from their mother on day 3 postpartum and raised in complete social isolation [12,13•]. As adults, artificially reared pups are more fearful, display cognitive impairments related to attentional-shifting, and are impaired in social recognition compared with the behavior of mother-reared infants. Long periods of daily maternal separation are also associated with increased stress responsivity and cognitive deficits in offspring [14].

However, developmental consequences are not limited to such extreme experiences. Observations of bonnet and pigtail macaques indicate that juvenile offspring of mothers who display high levels of affiliative behavior, such as infant touching and cradling, are more exploratory and engage in more social contact with conspecifics [15]. Natural variations in maternal care can also be characterized in rodents, enabling a more detailed analysis of the mechanisms mediating these changes [1]. In rats, offspring born to mothers who display high levels of licking and grooming (LG) during the first week postpartum are less fearful, have an attenuated corticosterone response to stress, and increased levels of hippocampal glucocorticoid receptor (GR) expression compared with those of offspring of mothers who display low levels of LG [16,17]. Cross-fostering studies indicate that the quality of postpartum maternal care is crucial for the development of these phenotypes [18]. Thus, even variations in social interaction that exist within the normal range of behavior can produce long-term changes in offspring.

Interaction between genes and social environment

Although social experiences early in life play a major role in shaping brain development and adult behavior, individuals vary significantly in the degree to which they are affected by these influences. One explanation for this variability is that the underlying genotype makes individuals more or less susceptible to the effects of early social environments. In rodents, such gene x environment (see glossary) interactions have previously been documented; inbred strains, for instance, vary in the degree to which offspring are affected by maternal separation and neonatal handling [19,20]. Recent molecular genetics work involving the monoamine oxidase A (MAOA) and serotonin transporter genes have highlighted the importance of these interactions in primate and human behavior. In humans, adult males who were maltreated as children and who possess a low-activity form of the MAOA gene (related to the number of variable number tandem repeats in the promoter region), exhibit significantly more violence and conduct disorders than males who either carry the high-activity form and were maltreated, or who carry the low-activity form but were not maltreated [21,22]. Male rhesus monkeys with a similar low activity form of this gene demonstrate increased aggression as infants, but only if they are raised by their mothers; males raised in peer-only groups are not more aggressive [23••]. In both instances, increased aggression is observed in male individuals who have both a copy of the low activity form of the MAOA gene and were exposed to adult aggression during development. Likewise, humans carrying at least one copy of the short form of the serotonin transporter gene (fewer repeats in the promoter region) have an accentuated risk of developing depression if they experienced at least three 'stressful' life events during childhood and adolescence [24]. Rhesus monkeys carrying an

equivalent short form of this gene have higher HPA activity and adrenocorticotropin releasing hormone (ACTH) levels during social separation stress when peer-reared are compared with mother-reared [25–27]. Although these examples of interactions between genotypes and early environment are striking, we are only starting to fully appreciate the complex interplay between genetic backgrounds, social environments and brain development. Indeed, it is likely that such interactions will be found to be common and significant to the development of most behavioral phenotypes.

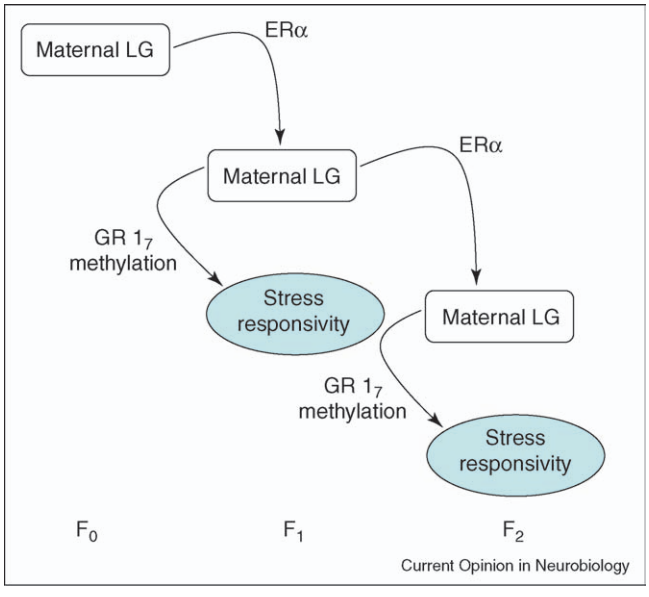
Mechanisms of social influence on development

Early rearing environments are clearly capable of exerting neurobiological changes that persist into adulthood, but only recently has the molecular mechanism mediating these long-term effects been explored. Expression of glucocorticoid receptors in the hippocampus is thought to mediate the individual differences in stress responsivity observed in offspring born to high and low LG rat dams [16,17,28]. Analysis of the regulatory regions of the glucocorticoid receptor implicates DNA methylation as a possible mechanism for phenotypic differentiation. Attachment of methyl groups to DNA blocks transcriptional factors from gaining access to the gene and, thus, expression of the gene is effectively silenced [29]. This particularly stable epigenetic modification, which is maintained after cell division, is the means by which cellular differentiation occurs during development. Investigation of the methylation status of the exon 1_7 promoter region of the glucocorticoid receptor ($GR1_7$) in hippocampal tissue taken from adult offspring born to low LG mothers indicates elevated levels of DNA methylation compared with that of adult offspring of high LG mothers, which would certainly explain the decreased level of GR expression in low LG offspring [30••]. Analysis of the developmental time course of this methylation pattern in the hippocampus indicates that just before parturition, at embryonic day 20, and immediately after birth, at day 1 postpartum, there are no differences in methylation of the GR 1_7 promoter region. However, group differences in methylation are evident by day 6 postpartum, correlated with a period of differential maternal LG, they persist post-weaning at day 21, and into adulthood at day 90. Hippocampal tissue from offspring born to low LG mothers who are then cross-fostered to high LG mothers indicates a methylation pattern corresponding to the maternal care received during the postnatal period [30••]. These epigenetic changes, thus, provide a stable mechanism whereby the effects of early social experiences can persist throughout the lifespan.

Social influence throughout a lifetime: reversibility

Discussions of the impact of early environment often refer to 'programming', emphasizing the long-term effects of these experiences, and the association of epigenetic modifications with these effects certainly provides support for this notion of stability. However, plasticity exists whereby social experiences later in life can alter the course of development and, in some cases, compensate for early deprivation. In rats exposed to postnatal maternal separation, enriching the post-weaning social environment through group housing with conspecifics decreases the corticosterone response to stress and reduces behavioral indications of anxiety [31]. Cognitive deficits, as indicated by performance on a Morris water maze, of offspring who receive low levels of LG during the postnatal period can also be reversed using post-weaning social enrichment [32]. These studies also illustrate that the modulation of behavioral phenotype by the post-weaning environment does not involve the same neural mechanisms that mediate the original deficits. Social enrichment did not affect the elevated levels of corticotropin-releasing factor (CRF) in the paraventricular nucleus of the hypothalamus (PVNh) and decreased levels of hippocampal GR mRNA found in maternally separated males. Hippocampal N-methyl-D-aspartate (NMDA) receptor binding in the offspring of low LG mothers was also not altered by these post-weaning manipulations [33]. Thus, social experiences beyond the postnatal period might alter brain development via alternative, yet equally stable mechanisms.

Figure 1



Transmission of maternal care and stress responsivity across generations. Variations in maternal licking and grooming (LG) are transmitted from mother (F0) to female offspring (F1) associated with changes in expression of estrogen receptor α (ERα) in the medial preoptic area. Differential methylation of the $GR1_7$ promoter region of the glucocorticoid receptor (GR) is likewise associated with F0 LG, resulting in individual differences in stress responsivity of offspring. Variation in LG of female offspring (F1) is then transmitted to the F2 generation, as are patterns of GR methylation and stress responsivity.

Transmission of social behavior across generations

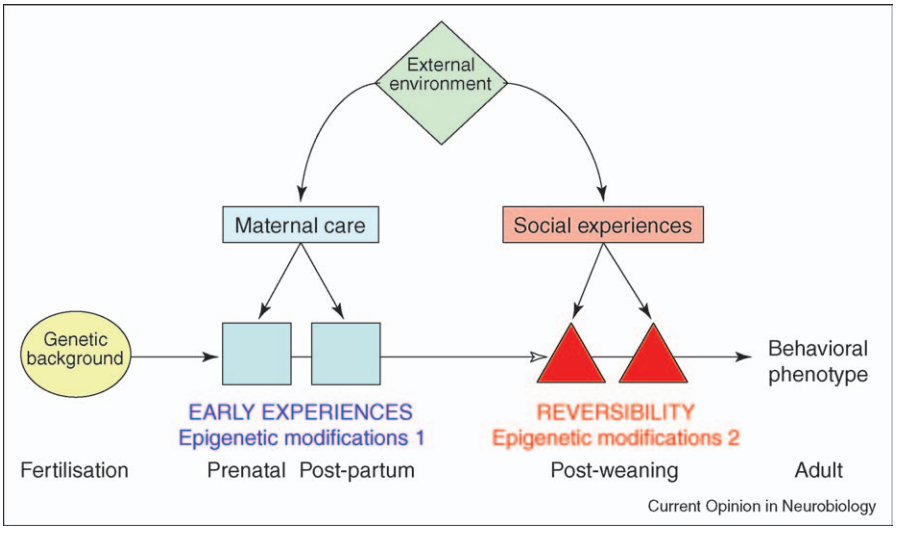
Perhaps one of the most interesting advances in our understanding of the impact of social experience on development comes from studies of transgenerational effects. In primates, frequency of contact with infants and abusive behavior are both stable maternal traits that can be transmitted from one generation to the next [2]. In rhesus macaques, primiparous females who engage in high levels of abusive behavior towards infants are also abusive to subsequent offspring [34••,35]. Females born to these mothers display high levels of abuse toward their own infants and this pattern of inheritance is observed in the biological offspring of non-abusive mothers cross-fostered to abusive females. However, females born to abusive mothers who are then cross-fostered to non-abusive mothers are not abusive toward their offspring, indicating an environmentally mediated effect.

Similar work in rats indicates that female offspring reared by mothers who are high in LG behavior are high in LG toward their own offspring, whereas female offspring reared by low LG mothers are themselves low in LG [1,18]. There is some evidence to suggest that estrogen receptor (ER) expression in the MPOA might play a role in regulating this transmission. Levels of ER α in the MPOA are elevated among high LG mothers and their female offspring compared with levels in low LG mothers and their female offspring [36]. In females, the quality of mother–infant interactions can, thus, affect reproductive behavior and, as a consequence, be passed on to subsequent generations. The implications of this transmission are that the developmental consequences of early rearing experience, such as stress responsivity and epigenetic modification of the glucocorticoid receptor, can be passed from one generation to the next (Figure 1).

Conclusions

Social experiences provide cues to the overall quality of a given environment and the status of an individual within that environment. When there is stability in environmental conditions over time, these experiences enable an individual to predict and possibly be adapted to future conditions, increasing reproductive success and survival [37]. This evolutionary perspective provides an explanation for the developmental impact of social experiences and a framework for understanding what particular aspects of brain and behavior might be the target of regulation by this feature of an individual's environment. The influence of early environment on stress responsivity and social behavior can be interpreted within this context. Disruptions occurring during the prenatal or postnatal period that alter mother–infant interactions might indicate a highly variable environment. Heightened stress responsivity would enable an individual to respond more rapidly to environmental change and increase likelihood of survival. By altering social behavior, these adaptive behavioral responses to stress can then be passed on to subsequent generations.

Figure 2



The development of behavioral phenotypes. Adult behavior is a product of the dynamic interplay between genes and social environment. Offspring develop differentially according to both maternal care (including nutritional, hormonal and behavioral cues) during gestation and lactation, and social experiences (predominantly behavioral cues) post-weaning. Recent evidence suggests that these induced changes are associated with epigenetic modifications of the genome. The relative impact of these experiences might be modified by underlying genetic background, with individuals being differentially susceptible to their influence. Finally, social experiences during these periods can have disruptive, neutral or adaptive effects on development. In adaptive terms, the maternal care received during development might be regulated by, and indicative of, the external physical and social environment. Thus, through epigenetic modifications offspring might be better prepared for adult life, whereas in changing external environments, social experience post-weaning offers opportunities to modify and perhaps reverse development via alternative epigenetic mechanisms.

Perhaps a crucial aspect of social experiences that is common to humans, primates and rodents is tactile stimulation. Deprivation of contact or decreased frequency of contact, whether in the form of holding an infant or licking and grooming a pup, directs development along a path involving heightened stress responsivity and decreased social behavior. In artificial rearing paradigms, provision of licking-like tactile stimulation to rat pups reduces behavioral indices of anxiety and improves social learning [12]. Licking and grooming behavior in rats is associated with epigenetic changes that are thought to mediate these behavioral phenotypes; however, we do not yet know whether this mechanism is relevant to other species or whether these mechanisms can be generalized to other forms of social interaction. In humans and primates, social learning is crucial to behavioral development and to the transmission of traits from mother to offspring. Does this transmission involve epigenetic changes? Recent studies of learning and memory would suggest that these processes do involve epigenetic changes, producing long-term effects on hippocampal plasticity [38,39•]. Studies of the role of epigenetic modifications in the context of social behavior would, thus, provide a better understanding of the mechanisms involved in both mediating the effects of early environment and transmitting these effects to future generations.

The interplay between genetic background and environment has clear implications for the developing brain and hence adult behavior (Figure 2). Recent evidence suggests that social experiences in infancy literally build upon this genetic background through epigenetic modification; however, the relevance of this mechanism to social influence at other periods in development is not known. Investigations of the molecular mechanisms mediating the influence of the social environment from the prenatal period through to adulthood are necessary to further our understanding of gene x environment interactions and the role of these experiences in creating stable phenotypes.

Acknowledgements

FA Champagne is funded by a fellowship from the Canadian Institutes of Health Research (CIHR) and JP Curley is supported by the Cambridge-Leverhulme Initiative in Post-Genomics Research. The authors would like to thank W Swaney for providing a critical review of this manuscript.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Champagne F, Francis D, Mar A, Meaney M: **Variations in maternal care in the rat as a mediating influence for the effects of environment on development**. *Physiol Behav* 2003, **79**:359-371.

2. Fairbanks L: **Individual differences in maternal style of old world monkeys**. *Adv Study Behav* 1996, **25**:579-611.

3. • Kaiser S, Sachser N: **The effects of prenatal social stress on behaviour: mechanisms and function**. *Neurosci Biobehav Rev* 2005, **29**:283-294.
This is an excellent review article comprehensively surveying the effects of social stress during pregnancy on offspring development across mammals. The authors describe these behavioural effects, the neuroendocrine pathways mediating them and discuss whether they are pathological or adaptive in nature.

4. Kaiser S, Kruijver FPM, Swaab DF, Sachser N: **Early social stress in female guinea pigs induces a masculinization of adult behavior and corresponding changes in brain and neuroendocrine function**. *Behav Brain Res* 2003, **144**:199-210.

5. Kaiser S, Kruijver FPM, Straub RH, Sachser N, Swaab DF: **Early social stress in male guinea-pigs changes social behaviour, and autonomic and neuroendocrine function**. *J Neuroendocrinol* 2003, **15**:761-769.

6. Kaiser S, Sachser N: **Social stress during pregnancy and lactation affects in guinea pigs the male offsprings' endocrine status and infantilizes their behaviour**. *Psychoneuroendocrinology* 2001, **26**:503-519.

7. Welberg LA, Seckl JR: **Prenatal stress, glucocorticoids and the programming of the brain**. *J Neuroendocrinol* 2001, **13**:113-128.

8. Francis D, Szegda K, Campbell G, Martin W, Insel T: **Epigenetic sources of behavioral differences in mice**. *Nat Neurosci* 2003, **6**:445-446.

9. Harlow H, Dodsworth R, Harlow M: **Total social isolation in monkeys**. *Proc Natl Acad Sci USA* 1965, **54**:90-97.

10. Harlow H, Suomi S: **Social recovery by isolation-reared monkeys**. *Proc Natl Acad Sci USA* 1971, **68**:1534-1538.

11. Capitanio J, Mendoza S, Mason W, Manninger N: **Rearing environment and hypothalamic-pituitary-adrenal regulation in young rhesus monkeys (Macaca mulatta)**. *Dev Psychobiol* 2005, **46**:318-330.

12. Gonzalez A, Lovic V, Ward G, Wainwright P, Fleming A: **Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats**. *Dev Psychobiol* 2001, **38**:11-32.

13. • Lovic V, Fleming A: **Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional set shifting task - reversal of effects with maternal-like licking stimulation**. *Behav Brain Res* 2004, **148**:209-219.
Using an artificial rearing paradigm with rat pups, the authors illustrate the cognitive deficits that occur under conditions of complete maternal deprivation and the role that manual tactile stimulation, using a paintbrush, can have in restoring normal functioning.

14. Lehmann J, Pryce C, Bettschen D, Feldon J: **The maternal separation paradigm and adult emotionality and cognition in male and female Wistar rats**. *Pharmacol Biochem Behav* 1999, **64**:705-715.

15. Weaver A, Richardson R, Worlein J, De Waal F, Laudenslager M: **Response to social challenge in young bonnet (Macaca radiata) and pigtail (Macaca nemestrina) macaques is related to early maternal experiences**. *Am J Primatol* 2004, **62**:243-259.

16. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky P, Meaney M: **Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat**. *Proc Natl Acad Sci USA* 1998, **95**:5335-5340.

17. Liu D, Dioro J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky P, Meaney M: **Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress**. *Science* 1997, **277**:1659-1662.

18. Francis D, Dioro J, Liu D, Meaney M: **Nongenomic transmission across generations of maternal behavior and stress responses in the rat**. *Science* 1999, **286**:1155-1158.

19. Zaharia MD, Kulczycki J, Shanks N, Meaney MJ, Anisman H: **The effects of early postnatal stimulation on Morris water-maze acquisition in adult mice: genetic and maternal factors**. *Psychopharmacology (Berl)* 1996, **128**:227-239.

20. Hennessy MB, Li J, Lowe EL, Levine S: **Maternal behavior, pup vocalizations, and pup temperature changes following handling in mice of 2 inbred strains**. *Dev Psychobiol* 1980, **13**:573-584.

21. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R: **Role of genotype in the cycle of violence in maltreated children**. *Science* 2002, **297**:851-854.

22. Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, Riley B: **Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder**. *Arch Gen Psychiatry* 2004, **61**:738-744.

23. •• Newman TK, Syagailo YV, Barr CS, Wendland JR, Champoux M, Graessle M, Suomi SJ, Higley JD, Lesch KP: **Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys**. *Biol Psychiatry* 2005, **57**:167-172.
Non-human primates provide an excellent model system to study gene x environment interactions, because rearing environments can be easily controlled. This paper, investigating a study group of 45 unrelated adult males, reinforces earlier findings from human studies that the low activity form of the MAOA gene is associated with increased aggression in males but subject to early rearing environment.

24. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A *et al.*: **Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene**. *Science* 2003, **301**:386-389.

25. Champoux M, Bennett A, Shannon C, Higley JD, Lesch KP, Suomi SJ: **Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates**. *Mol Psychiatry* 2002, **7**:1058-1063.

26. Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, Schwandt M, Champoux M, Lesch KP, Goldman D *et al.*: **Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques**. *Biol Psychiatry* 2004, **55**:733-738.

27. Barr CS, Newman TK, Schwandt M, Shannon C, Dvoskin RL, Lindell SG, Taubman J, Thompson B, Champoux M, Lesch KP *et al.*: **Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques**. *Proc Natl Acad Sci USA* 2004, **101**:12358-12363.

28. Liu D, Dioro J, Day J, Francis D, Meaney M: **Maternal care, hippocampal synaptogenesis and cognitive development in rats**. *Nat Neurosci* 2000, **3**:799-806.

29. Razin A: **CpG methylation, chromatin structure and gene silencing - a three-way connection**. *EMBO J* 1998, **17**:4905-4908.

30. •• Weaver I, Cervoni N, Champagne F, D'Alessio A, Sharma S, Seckl J, Dymov S, Szyf M, Meaney M: **Epigenetic programming by maternal behavior**. *Nat Neurosci* 2004, **7**:847-854.
Exploration of the influence of maternal care on DNA methylation of the GR17 promoter region indicating that low levels of maternal stimulation are associated with hypermethylation of this region preventing binding of the transcription factor NGFI-A. This is an excellent series of studies, and the first paper shows the epigenetic effects of early rearing.

31. Francis D, Dioro J, Plotsky P, Meaney M: **Environmental enrichment reverses the effects of maternal separation on stress reactivity**. *J Neurosci* 2002, **22**:7840-7843.

32. Bredy T, Humpartzoomian R, Cain D, Meaney M: **Partial reversal of the effect of maternal care on cognitive function through environmental enrichment**. *Neuroscience* 2003, **118**:571-576.

33. Bredy T, Zhang T, Grant R, Dioro J, Meaney M: **Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression**. *Eur J Neurosci* 2004, **20**:1355-1362.

34. •• Maestripieri D: **Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys**. *Proc Natl Acad Sci USA* 2005, **102**:9276-9279.
The authors combine behavioral characterization under semi-naturalistic conditions and cross-fostering in a longitudinal study of rhesus monkeys to demonstrate the transmission of abusive behavior across generations. This study provides an elegant example of how early rearing environment influences the maternal behavior of female offspring.

35. Maestripieri D, Lindell S, Ayala A, Gold P, Higley JD: **Neurobiological characteristics of rhesus macaque abusive mothers and their relation to social and maternal behavior**. *Neurosci Biobehav Rev* 2005, **29**:51-57.

36. Champagne F, Weaver I, Dioro J, Sharma S, Meaney M: **Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area**. *Endocrinology* 2003, **144**:4720-4724.

37. Gluckman PD, Hanson MA, Spencer HG, Bateson P: **Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies**. *Proc Biol Sci* 2005, **272**:671-677.

38. Levenson JM, Sweatt JD: **Epigenetic mechanisms in memory formation**. *Nat Rev Neurosci* 2005, **6**:108-118.

39. • Levenson JM, O'Riordan KJ, Brown KD, Trinh MA, Molfese DL, Sweatt JD: **Regulation of histone acetylation during memory formation in the hippocampus**. *J Biol Chem* 2004, **279**:40545-40559.
The authors provide evidence that the formation of long-term memory is mediated by epigenetic changes in the hippocampus involving histone acetylation. This work advances our understanding of the molecular basis of learning.