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Review article

# Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods

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ABSTRACT

Variation in maternal care can lead to divergent developmental trajectories in offspring with implications for neuroendocrine function and behavioral phenotypes. Study of the long-term outcomes associated with mother–infant interactions suggests complex mechanisms linking the experience of variation in maternal care and these neurobiological consequences. Through integration of genetic, molecular, cellular, neuroanatomical, and neuroendocrine approaches, significant advances in our understanding of these complex pathways have been achieved. In this review, we will consider the impact of maternal care on male and female offspring development with a particular focus on the issues of timing and mechanism. Identifying the period of sensitivity to maternal care and the temporal dynamics of the molecular and neuroendocrine changes that are a consequence of maternal care represents a critical step in the study of mechanism.



## 1. Introduction

Parent–offspring interactions are a critical developmental cue to environmental quality and have the capacity to impact growth, survival, physiology, and behavior. In mammals, biparental care is a relatively rare occurrence and these interactions are primarily through the mother. The capacity of offspring to shift in development in response to the quality of mother–infant interactions may represent an important adaptive pathway that prepares offspring for the conditions of life (Cameron et al., 2005). Our understanding of the adaptive process and mechanisms underlying the effects of maternal care has been advanced by human longitudinal and laboratory animal studies. Overall, these studies have highlighted the impact of mother–infant interactions on multiple neuroendocrine systems, including the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–gonadal axis (HPG), and the mesolimbic dopamine (DA) system (Cameron et al., 2008; Meaney, 2001; Pena et al., 2014). Within these systems, there is evidence for long-term transcriptional activation and repression in association with postnatal maternal care, prompting analyses of the impact of mother–infant interactions on epigenetic processes (Weaver et al., 2004). Epigenetic mechanisms, such as DNA methylation, post-translational histone modifications, and microRNAs have been implicated in studies of the impact of environmental experiences including nutrition (Lillycrop et al., 2005; Heijmans et al., 2008), toxins (Anway et al., 2006; Kundakovic et al., 2013), stress (Mueller and Bale, 2008; Roth et al., 2011), and social experiences (Hollis et al., 2010; Murgatroyd et al., 2009). Variation in (Weaver et al., 2004) or deprivation of (Murgatroyd et al., 2009; Franklin et al., 2010) maternal care has been demonstrated to induce long-term epigenetic alterations, with implications for the development of neural circuits and the function of these circuits in adulthood.

Plasticity of the brain in response to the quality of mother–infant interactions during the postnatal period suggests the presence of a sensitive period for the development of these systems and their associated physiological and behavioral outcomes. The notion of critical or sensitive periods has a strong foundation within research on sensory systems (Hubel and Wiesel, 1970) and social imprinting (Hess, 1959) and suggests that there are windows of time during development in which experiences may be maximally effective in inducing neurobiological and behavioral change. However, in the case of the influence of maternal care, much of the evidence for a particular window of sensitivity is correlative and cross-fostering studies have primarily focused on dissociating the impact of genetic or prenatal *vs.* postnatal maternal care influences rather than on identifying postnatal sensitive periods. However, emerging evidence for these periods (Pena et al., 2013; Upton and Sullivan, 2010), highlights the need to integrate

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the study of the temporal dynamics of developmental change when considering the influence of maternal care. Though the long-term effects of maternal care have been relatively well described, the process of change and the intermediary molecular and neurobiological effects that may shape the developing brain have not been systematically explored.

In this review, we will highlight research approaches that have been used to study the impact of maternal care on the developing brain in male and female offspring. We will discuss three specific approaches used primarily in laboratory rodents: (1) the impact of naturally occurring variations in maternal care, (2) communal rearing, and (3) the impact of home-cage disruption. Though there are many other approaches that have been implemented (*e.g.* neonatal handling, maternal separation), the methodologies we will focus on in this review possess similarities in their effects on both the quantitative and qualitative aspects of maternal care and are currently incorporating epigenetic analyses. We will describe the literature implicating epigenetic mechanisms in the long-term impact of maternal care within these paradigms, with a particular emphasis on the timing of epigenetic changes. Finally, we will explore the notion of critical or sensitive periods in the effects of maternal care and how current and future research approaches can further our understanding of the fundamental questions of the timing and reversibility of epigenetic and neurobiological impact of maternal care.

## 2. Neurobiological and behavioral impact of variation in maternal care

Decades of research has explored the impact of maternal care on the development of offspring using a variety of observational and experimental approaches to quantify or manipulate the quality of mother–infant interactions. Historically, there has been a particular focus on the impact of disruptions to these interactions leading to the establishment of maternal separation or deprivation approaches in non-human primates (Harlow et al., 1965; Suomi et al., 1976) and rodents (Hofer, 1973; West, 1993). However, longitudinal studies in humans have implicated maternal sensitivity to offspring cues and parental warmth to early- and later-life behavioral and neurobiological outcomes (Hane et al., 2010; Narita et al., 2010). Thus, variation in care rather than deprivation of care may be an appropriate strategy for studying long-term neurodevelopmental programming. Here, we will consider three approaches in which the impact of this variation can be examined in a laboratory setting: (1) naturally occurring variations in maternal care, (2) communal rearing, and (3) home-cage disruption.

### 2.1. Natural variations in maternal care

Across species, there are naturally occurring variations in maternal care that predict long-term neurobiological and behavioral phenotypes in offspring. In humans, maternal sensitivity to infant cues is a normally distributed behavior, and infants that have experienced low *vs.* high maternal sensitivity exhibit increased indices of fearfulness, reduced positive joint attention, increased negative affect, increased aggression, social inhibition and greater right frontal electroencephalographic asymmetry (Hane et al., 2010; Hane and Fox, 2006). In non-human primates, high levels of postnatal over-protectiveness (high levels of approach, contact and restraint) in *Chlorocebus pygerythrus* is associated with reduced exploratory behavior in juvenile offspring (Fairbanks and McGuire, 1988) and the experience of higher rates of rejection (from mothers, fathers, and siblings) in *Callithrix geoffroyi* predicts elevated stress-induced urinary cortisol levels (Birnie et al., 2013). Individual differences in maternal behavior in rodents emerge even within the controlled conditions of the laboratory and form the basis of variation in offspring brain and behavior. In laboratory rats (*Rattus norvegicus*), observations of home-cage maternal behavior indicate that the experience of low *vs.* high licking/grooming (LG) from mothers during the postnatal period results in prolonged elevations in plasma corticosterone following stress exposure (Liu et al., 1997), reduced exploration of novel or anxiogenic environments (Caldji et al., 1998), increased fearfulness (Menard et al., 2004), and impairments in learning and memory (Liu et al., 2000) in adult male Long-Evans rat offspring. Adult female offspring of low- compared to high-LG rat dams display increased sexual behavior (Cameron et al., 2008) and reduced maternal behavior (Francis et al., 1999). It should be noted that this methodological approach does not typically assess the LG received by individual pups but rather the overall LG "style" of the dam. There is significant stability in LG behavior by dams across subsequent litters and following cross-fostering (Champagne et al., 2003), suggesting that pup characteristics likely do not account for LG status. However, there is considerable within-litter variation in the receipt of LG by pups, such that some pups receive more LG and some pups receive less LG regardless of the LG status of the dam (Pan et al., 2014; van Hasselt et al., 2012). For example, sex differences in the receipt of LG have been observed in Long-Evans rats, such that males receive higher levels of LG than females (Moore and Morelli, 1979). This variation likely contributes to within-litter variation and sex differences in phenotype and the paradoxical findings regarding the effects of between-litter *vs.* within-litter variation in LG (Pan et al., 2014; Ragan et al., 2012).

The behavioral and physiological impact of maternal LG is mediated by alterations in the function of several neural/neuroendocrine systems. In male offspring, the focus of analyses has been on gene/protein targets implicated in stress reactivity, fear responses, and cognition. The increased stress reactivity of adult male offspring of low- *vs.* high-LG Long-Evans rat dams has been attributed to changes in gene expression and protein levels with hypothalamic and hippocampal regions associated with HPA function (see Table 1). Adult male offspring reared by low-LG dams, have elevated corticotrophin releasing factor (CRF) mRNA in the paraventricular nucleus of the hypothalamus (Liu et al., 1997) and decreased protein and mRNA levels of glucocorticoid receptors (GR) within the hippocampus which may account for the increased plasma adrenocorticotrophin (ACTH) and corticosterone levels in low-LG offspring following stress exposure (Liu et al., 1997; Francis et al., 1999). Enhanced fear responses in the offspring of low-LG dams may involve altered expression of subunits within the gamma-aminobutyric acid A receptor ($GABA_AR$) in the amygdala and locus coeruleus, decreased hippocampal glutamate decarboxylase 1 (GAD1) mRNA (Zhang et al., 2010), and increased CRH protein levels within the nucleus tractus solitarius (Caldji et al., 1998, 2003). Deficits in learning/memory in the offspring of low-LG dams may be a consequence of several cellular and molecular changes in the medial prefrontal cortex (mPFC) and hippocampus, including decreased protein levels of reelin, synaptophysin, brain-derived neurotrophic factor (BDNF), and neural cell adhesion molecule (NCAM) (Liu et al., 2000; van Hasselt et al., 2012; Smit-Rigter et al., 2009), altered hippocampal expression of subunits within N-methyl-D-aspartate receptor (NMDAR) (Liu et al., 2000; Bagot et al., 2012; Bredy et al., 2004), decreased hippocampal metabotropic glutamate receptor 1 (mGluR1) mRNA (Bagot et al., 2012), decreased hippocampal dendritic complexity (Bagot et al., 2009; Champagne et al., 2008), and decreased excitatory post-synaptic potentials (EPSPs) indicating impaired long-term potentiation (LTP) (Bagot et al., 2009; Bredy et al., 2003). The impact of maternal LG on these outcomes within the hippocampus appears to vary significantly between the dorsal and ventral regions, indicating the regional-specificity of these