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Review

On the causes of early life experience effects: Evaluating the role of mom

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ABSTRACT

Early life experiences are thought to have long-lasting effects on cognitive, emotional, and social function during adulthood. Changes in neuroendocrine function, particularly the hypothalamic–pituitary–adrenal (HPA) axis, contribute to these systems-level behavioral effects. In searching for causal mechanisms underlying these early experience effects, pioneering research has demonstrated an important role for maternal care in offspring development, and this has led to two persistent ideas that permeate current research and thinking: first, environmental impact on the developing infant is mediated through maternal care behavior; second, the more care that a mother provides, the better off her offspring. While a good beginning, the reality is likely more complex. In this review, we critically examine these ideas and propose a computationally-motivated theoretical framework, and within this framework, we consider evidence supporting a hypothesis of maternal **modulation**. These findings may inform policy decisions in the context of child health and development.

1. Introduction

Few findings regarding early life experience have generated more enduring interest among researchers and the general public than the large body of rodent literature on the relation between postnatal maternal care and the development of the hypothalamic–pituitary–adrenal (HPA) axis (Meaney, 2010; Zhang and Meaney, 2010). This long-lasting interest is in part due to its implied relevance to human child development as suggested by the title of the commentary "The Importance of a Well-Groomed Child" (Sapolsky, 1997) when this line of work was first published in Science (Liu et al., 1997) and by the title of a recent New York Times Sunday Review, "Cuddle Your Kid!" (Kristof, 2012). As the human mother plays a significant role in the shaping of her child's stress response system and the development of later psychopathology (for review see Baram et al., 2012; McCrory et al., 2010), this line of animal research has been viewed as relevant to not only understanding child development (Kaffam and Meaney, 2007; Sanchez, 2006; Veenema, 2009) but also to early child development policymaking (Shonkoff and Garner, 2012). Thus, there is an urgent need to review recent conceptual progress in this line of research.

The genesis of this influential literature was the initial demonstration that early stimulation through the "handling" procedure led to both an increase in maternal licking of the pups and long-lasting differences in offspring development of the HPA axis (Liu et al., 1997). Follow-up studies showed further correlations between the naturally occurring variation in maternal licking of the pups and variations in many offspring developmental outcome measures (Meaney, 2010; Zhang and Meaney, 2010). Evidence for a causal relation between maternal licking and offspring development was strengthened by cross-fostering studies in which offspring outcome measures were found to correlate with the foster mother's licking quantity (high and low licking) but not correlate with the birth mother's licking quantity (Francis et al., 1999). This line of research has stimulated interest among human child development researchers to examine the influence of the amount of maternal contact on emotional and physiological outcomes (Sharp et al., 2012).

Two general conclusions were reached through these studies. First, the so-called "handling" effects were mediated via maternal care behavior. An implication of this conclusion is that such early stimulation itself has no effect on offspring development; and maternal care, specifically, the licking of the pups, following the

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stimulation of the pups from the "handling" manipulation is the cause of variation in offspring developmental outcomes. Second, the higher the quantity of licking, the better off the offspring will be. A practical and political implication of this conclusion may be that mothers need to more frequently engage in a specific type of maternal care behavior, for example, stroking of their babies as a presumed human analogue to the licking behavior of the rodent mother (Sharp et al., 2012).

In this review, we hope to show that the role of maternal care in shaping the physiology and behavior of her offspring is more complex than that currently assumed by the majority of the rodent studies designed to assess the contributions of maternal variables on offspring development. Specifically, we will (1) review relevant literature that led to the maternal **modulation** hypothesis; and (2) present supporting evidence for this maternal modulation hypothesis from a line of research utilizing the neonatal novelty exposure paradigm. Given these specific goals, this review will not be comprehensive but highly focused on evidence that bears direct relevance to the discrimination of the two competing hypotheses.

2. Complexity in the role of the mother and a new theoretical framework

In recent years, several lines of developmental research have brought forth complexities regarding the role of maternal care in animal models. First, certain levels of maternal stress may lead to an increase in maternal circulating corticosterone (CORT), which in turn can produce effects similar to those induced by early stimulation, as demonstrated via experiments in which CORT was added to the mother's drinking water and presumably passed to her offspring via her milk (Catalani et al., 2011). This line of research clearly points to an additional source of early life experience from the mother that contributes to the HPA development of the offspring. Second, in experiments using non-human primates, in absence of differences in maternal care behaviors, intermittent stress of infant monkeys results in differences in HPA function that are similar to those produced by the "handling" treatment and to those associated with high versus low licking dams (Parker et al., 2006). These findings indicate that activation of the offspring's HPA axis early in life contributes to the programming of later HPA function. Third, in research that manipulates maternal stress levels via the imposition of a variable foraging condition, it was found that higher quantity of maternal licking did not produce differences in HPA function of their offspring (Macrì et al., 2011) demonstrating that higher quantity of maternal licking does not necessarily correlate with adaptive changes in offspring HPA function. Finally, maternal presence or contact with her pups facilitates the recovery of the offspring's stress response (Moriceau and Sullivan, 2006; Stanton and Levine, 1988, 1990; Stanton et al., 1987), thus setting the context for the modulation of the offspring's HPA function.

These pioneering lines of research demonstrate that the role of the mother is multi-dimensional, including not only the behavior of the mother, but the mother's own HPA function. Furthermore, the mother is only one source of the developing infant's environment and non-maternal aspects of the infant's environment, particularly, change in this environment, represent another salient source of inputs to the developing HPA axis. Finally, maternal characteristics, whether behavioral or physiological, can interact with other environmental changes to jointly modify the offspring's HPA axis. These have led us to develop a computationally-motivated conceptual framework for understanding early life experience effects on the development of HPA function.

This framework has the following components: (1) change in the environment, including both maternal and non-maternal aspects, is the driving force that activates components of the HPA axis; (2) key parameters of the HPA regulatory system are modifiable cumulatively by past experience; these parameters are related to the setting of the basal and peak circulating CORT levels and rates of initial rise and later recovery of a CORT response to environmental input; (3) through a process of learning, the same environmental input, or stressor, can lead to different HPA responses over time with relatively novel stimuli being more effective at activating the HPA axis and relatively familiar stimuli being less or not effective at all; and (4) the mother's behavior prior to and after her infant's experience of a stressor can change the key parameters of her infant's regulatory system thus changing the effective experience of a given stressor by the infant. Furthermore, the mother's circulating CORT and her own CORT surges in response to her own environment can also change these parameters via CORT levels transferred through her milk, thus also changing the effective experience of a given stressor by her infant.

Within this framework, the HPA axis is viewed as a dynamic system consisting of multiple interacting variables, environmental novelty (or salient change) and various maternal characteristics. In such a dynamic system, no single variable can be the exclusive cause for changes in HPA function (Thelen and Smith, 1994). The task of understanding the mechanisms that underlie the effects of early life experiences on the HPA axis is not to isolate the influence of one variable while ruling out all other variables. Instead, the task is to define and describe the dynamic interactions among the multitude of equally important maternal and non-maternal variables.

Moreover, in consideration of multiple maternal characteristics, it is important to recognize that maternal individual differences in her care-related behaviors are likely to be paralleled by individual differences in her stress physiology. Both are potential modulators of any environmental influence on the offspring. Even within the larger category of maternal care behavior, multiple types of maternal behaviors exist (e.g., anogenital and body licking of the pups, supine and arched-back nursing) and a mother may distribute her time differently across these different behavioral types (Moore, 1992; Stern, 1997). Within each type of behavior, a mother can further differ in average quantity and in the variability of the behavior over time.

In the following sections, evidence from our laboratories gathered under the guidance of the above theoretical framework and utilizing the neonatal novelty exposure paradigm will be presented in support of a broader view of maternal contribution to early experience effects.

3. Programming Infant HPA axis by Novelty

The neonatal novelty exposure paradigm is a split-litter design that consists of exposing rat pups from a given litter to a relatively novel non-home cage for 3 min/day for the first 3 weeks of life (Novel group) while the control pups from the same litter remain in the home cage (Home group) (Tang, 2001; Tang et al., 2006, 2012b). This neonatal novelty exposure paradigm is specifically designed to isolate environmental novelty, a salient component from the "neonatal handling" or "postnatal handling" paradigm (Denenberg, 1964; Levine, 1957, 1960) because novelty is known to activate the HPA axis (Dallman, 2000; Denenberg et al., 1967). This focus on novelty is motivated by a simple assumption that in order to shape or program the HPA axis, something has to be done to first activate at least some parts of the HPA axis.

This notion directly challenges an assumption implied by the maternal mediation hypothesis that a mother's highly familiar care-giving behavior, such as licking, can somehow serve to activate the HPA axis, thereby subsequently shaping HPA function. The maternal mediation hypothesis lacks a clearly articulated logical connection between the presumed cause, the licking, and the effect, some changes in HPA axis. Without such a clearly stated