

Epigenetics: Behavioral Influences on Gene Function, Part I. Maternal Behavior Permanently Affects Adult Behavior in Offspring

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Our ability to identify both genetic and environmental mediators of emotional-behavioral disorders in children has increased dramatically in the past decade. The human genome project, completed in 2003, fostered many other advances that have allowed us to pursue important questions about how the interaction of nature (genes) and nurture (environment) can place children at risk or protect them from psychiatric illness. During this time, the *Journal* published many articles demonstrating how specific candidate genes are associated with specific disorders. In addition, a few linkage genetic studies have demonstrated how multiple genetic loci across the genome contribute genetic risk to a variety of disorders. Most recently, and perhaps most important to the field of child and adolescent psychiatry, several wonderful articles have been published in our *Journal* and elsewhere that demonstrate the interaction between specific genes and specific environments in relation to psychiatric disorders. The majority of these articles emphasized that polymorphic genes (e.g., genes with more than one nucleotide structure due to mutations of one type or another) interact differently with different environments. The gene–environment interaction findings have emphasized the importance of the interaction between genetic makeup and the environment rather than focusing on the importance of one or the other.

Accepted October 7, 2007.

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Article Plus (online only) materials for this article appear on the Journal's Web site: www.jaacap.com.

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0890-8567/08/4703-0240©2008 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/CHI.0b013e3181635e13

Certainly many future studies will focus on how specific environments can be risky for some and other specific environments protective for others based on the individual genotype. Such research will doubtless change the way we conceptualize, assess, and treat children with psychiatric illness.

A less well-known and equally elegant line of genetic inquiry is now yielding remarkable discoveries for those of us who study developmental psychopathology. Rather than aiming to determine whether a specific mutation interacts with a specific environment, the field of epigenetics aims to determine how certain environments can turn on or turn off specific genes. This line of inquiry may be best thought of as the environment–gene interaction approach.

We now know that gene function can be altered without changing the nucleotide sequence itself. These changes are called epigenetic (from the Greek *epi-*, which means “on top of” or “in addition to”). The emerging field of epigenetics pursues a novel question: how does the environment interact with DNA? This column discusses the relevance of epigenetics to one area in the field of child and adolescent psychiatry, the effect of maternal care on later development and behavior. We have focused on the work of Michael Meaney, Arie Kaffman, and colleagues (see “Additional Readings” below), who have turned the usual line of inquiry on its head. Instead of focusing on how genes can alter behavior, they have asked how specific behaviors affect genes.

When psychiatry became a rigorous field of inquiry, a debate arose as to whether genes or the environment were paramount in the development of psychopathology. The literature no longer debates this issue, as because both nature and nurture are now known to be critical modulators of normal development. How mutations (nature) can disrupt developmental processes

is well appreciated. In this first column, we focus on how the environment (nurture) can affect gene expression. This column summarizes striking findings in rodents showing that maternal behavior in the first week of life permanently influences the offsprings' response to stress in adulthood as well some of their cognitive and maternal behaviors. The altered stress response has been studied at both the behavioral and molecular levels, and molecular mechanisms by which behavior can permanently alter gene function are known or close at hand. In other words, gene expression can be turned on and off by certain maternal behaviors through the work of precise molecular mechanisms. Perhaps most surprising, these effects are transgenerational; subsequent generations inherit the same behaviors through epigenetic rather than genetic mechanisms. There are no new DNA mutations; instead, certain molecular modifications influence the expression of specific genes or sets of genes. Similar effects are evident in nonhuman and human primates. This two-part series tells the story of these behavioral and molecular events and relates them to similar scenarios in humans. We begin here with the behavioral events. Part II of this column discusses the molecular events in a subsequent issue of the *Journal*.

BEHAVIORAL EFFECTS OF MATERNAL NURTURING

Newborn rat pups are pink, hairless, and sightless and have limited mobility. They are totally dependent on maternal care for their survival. Crucial maternal behaviors include nursing and retrieving pups when they stray from the nest. Other, more subtle behaviors are equally important in rodents; these include licking and grooming (LG) and crouching over the pups to nurse in a posture known as arched-back nursing (ABN; please refer to images available in the Article Plus material available on the *Journal Web* site, www.jaacap.com). LG constitute important sources of tactile stimulation in newborn rat pups. ABN is a posture that favors suckling by all pups and the ability for pups to change nipples because all nipples are exposed at once (compared with dams lying on their sides). The frequency of this maternal posture correlates with the frequency of LG. Together, the frequency of LG-ABN helps define the overall degree of nurturing by the dam and represents an important animal model for the influence of maternal behavior on adult behavior in the offspring.

The use of such animal models of maternal nurturing has become increasingly important for those studying the influences of the human family and early life experiences (particularly adversity) on mental health in adulthood. The "stress diathesis" model suggests that nervous system development is permanently influenced by adversity in early life. Adversity can take many forms in humans, such as poverty, abuse, and neglect. Recent work has shown that adversity increases the sensitivity of defensive responses during development and that, biologically, this is adaptive because it adjusts organ function to anticipated levels of environmental demands. The price, however, is an increased risk of several types of chronic illness, especially stress-related diseases (obesity, metabolic disorders, heart disease, affective disorders, and drug abuse). Two fundamental ideas underlie the stress diathesis model. First, researchers believe that environmental effects of stress can be transmitted to the developing offspring by variations in parental care. Second, this effect is part of a larger process of developmental adaptation to the environment—the effect can go either way depending on the environment into which the animals are born.

Some rat mothers naturally display relatively high levels of nurturing behaviors and others display relatively low levels. Several studies have shown that the offspring of mothers with high levels of LG-ABN (representing high levels of maternal care) are less anxious as adults. This is reflected in less circulating corticotropin (ACTH) and corticosterone in response to stress compared to the offspring of low LG-ABN mothers that are relatively less nurturing (Fig. 1). These findings are consistent with earlier work in rats showing that handling during the first postnatal week and increased tactile stimulation by stroking with a paintbrush also have lifelong effects on the animals' response to stress.

Cognitive and maternal behaviors are also different in the offspring of high versus low LG-ABN dams. Cognitive differences are related to memory; the offspring of high LG-ABN mothers do better in spatial learning and memory tasks than their counterparts, and they do better at object recognition. The mothers themselves display differences in stress reactivity; low LG-ABN mothers are more fearful than their counterparts. Accordingly, the maternal behavior of the female offspring is also affected by high versus low LG-ABN in their mothers. Offspring of low LB-ABN mothers are fearful and become low LG-ABN mothers themselves.

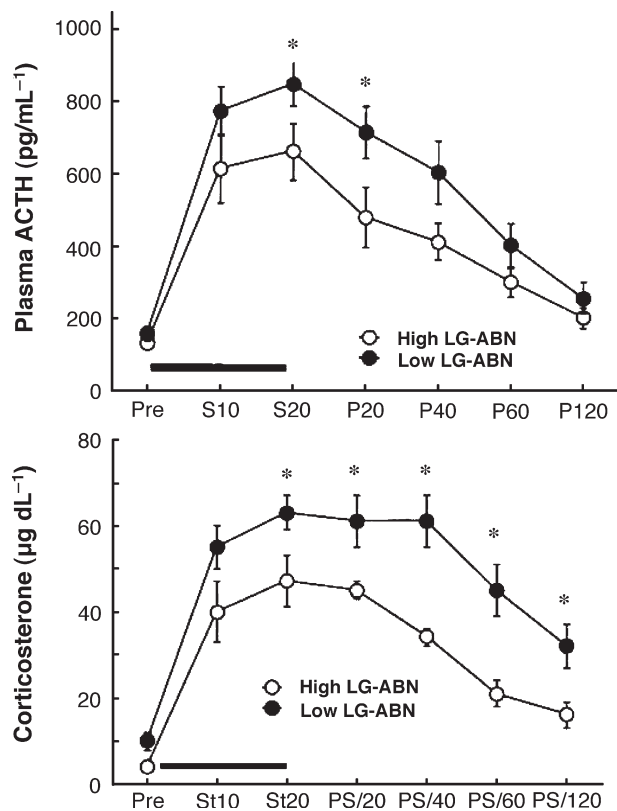


Fig. 1 The quality of maternal nurturing, in terms of tactile stimulation and nursing, affects the stress response in the offspring. Plasma corticotropin (ACTH; top) and corticosterone (bottom) responses to stress are statistically different ($p < .05$) in the offspring of high versus low licking and grooming and arched-back nursing (LG-ABN) mothers. The stress response is blunted in the offspring of high LG-ABN mothers compared with the offspring of low LG-ABN mothers. Animals ($n = 8-10$) were exposed to a 20-minute period of restraint (S10 and S20). ACTH and corticosterone levels increased in response to stress in both groups, but the offspring of more nurturing mothers (high LG-ABN) were less stressed by both measures than the offspring of less nurturing mothers (low LG-ABN). From Dong Liu et al. *Science*, 1997;277:1659. Reprinted with permission from the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

These influences on maternal behavior promote the transgenerational transmission of individual responses to stress.

It is logical to assume that these differences in the offspring of high versus low LG-ABN mothers are purely genetic, but “cross-fostering” experiments rule out this explanation. Pups born to high LG-ABN mothers who are reared by mothers with low LG-ABN are more anxious and circulate more corticosterone than their counterparts who were born to low LG-ABN mothers but reared by high LG-ABN mothers. No new genetic mutation occurred in the cross-

fostered pups; the difference in the offspring results from the environmental effects on gene expression. This is what makes the effect epigenetic rather than genetic in nature.

CRITICAL PERIOD FOR EMOTIONAL, COGNITIVE, AND SOCIAL BEHAVIOR

What is remarkable is that it only takes 1 week to establish these specific and stable behavioral phenotypes in the rodent offspring. During the first postnatal week, the frequency of tactile stimulation in the form of LG by the mother has long-term effects on adult behaviors, including the response to stress. Animals that have been handled regularly by experimenters or stroked with a paintbrush develop the same behavioral phenotype as the offspring of high LG-ABN mothers.

It is noteworthy that a parallel event is taking place during this first postnatal week; tactile stimulation involving the whiskers is necessary to ensure proper development of the primary somatosensory cortex. Anatomically defined barrel fields are present in the normal somatosensory cortex of most mammals; these are aggregates of cortical neurons representing individual whiskers. If the whiskers are experimentally removed during the first week of life, then the barrel fields fail to develop and the circuitry in the somatosensory cortex is permanently altered. Whisker removal after the first postnatal week has no such effect. This work in the somatosensory barrel fields provides some of the most striking evidence of experience-dependent cortical plasticity in mammalian cortex. This is a classic example of a “critical period” in which sensory experience has a permanent effect on cortical organization and sensory processing. Critical periods represent a specific window of time during early development when specific sensory systems are plastic. Each sensory modality has its own critical period. It is not known how these critical periods in the sensory systems relate to the work discussed here. However, the studies involving maternal behavior and the stress response are especially remarkable because they represent the first example of an experience-dependent critical period for emotional behavior. Also, the molecular events that underlie the sensory critical periods share some commonalities with those underlying the emotional critical period discussed here, as described in Part II of this column.

EFFECTS OF MATERNAL CARE IN PRIMATES

These experiments in rodents are reminiscent of the surrogate mothers devised by Harry Harlow in the late 1950s. Infant monkeys who had been removed from their mothers at birth received nourishment from surrogate mothers that were either made of wire or cloth. These animals developed abnormal cognitive, sexual, and maternal behaviors as a consequence. Remarkably, infants given access to a wire mother who provided nourishment and a cloth mother who provided no nourishment spent the majority of their time with the cloth surrogate, presumably for the tactile stimulation. These animals fared better on behavioral measures than their counterparts who had access only to the wire mothers.

The benefits of tactile stimulation are evident in premature human infants as well. In the past, these infants had been confined to incubators without sufficient tactile stimulation. When regular sessions of massage therapy are introduced into their daily routine, these preterm infants show evidence of increased weight gain and longer periods of alertness. Moreover, premature infants who have had the benefit of just 1 hour per day of skin-to-skin contact with their mothers show improved performance on cognitive and motor tasks when tested at 6 months.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH TACTILE STIMULATION

It is difficult to imagine how the physical sensation of LG by a dam or, for that matter, handling by experimenters or being stroked with a paintbrush could permanently change the way an animal behaves throughout its lifetime. The chain of events involves several groups of neurons including those related to the hypothalamic-pituitary axis and specific molecular events (Fig. 2), which are discussed in more detail in Part II of this column. The molecular changes that make the changes permanent are an extremely important focus of this work because they provide avenues for pharmacological intervention.

Tactile stimulation, or the lack of it, promotes some important physiological responses. As mentioned earlier, rodents with lots of maternal care in the form of tactile stimulation are the least fearful, and secrete the lowest levels of ACTH and corticosterone in response to stress throughout their lives (Fig. 1). Rodents with prolonged

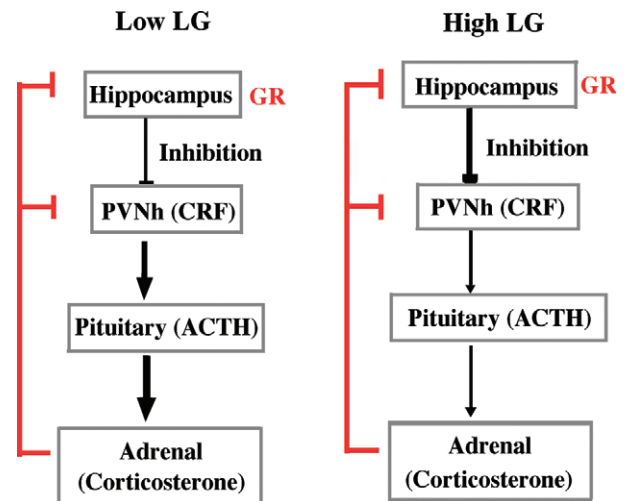


Fig. 2 The quality of maternal nurturing influences hypothalamic-pituitary-adrenal (HPA) activity in the offspring. The response of the adrenal glands is blunted (right-hand column) in animals with high licking and grooming (LG) and enhanced in animals with low LG. These effects result from changes in hippocampal neurons and their downstream effects on the pituitary and adrenal glands (discussed in Part II of this column). From Kaffman A, Meaney M, *Journal of Child Psychology and Psychiatry* 2007;48:3/4. Reprinted with permission from Blackwell Publishing.

separation from their mother, and the resulting loss of tactile stimulation during this period, secrete the highest level of corticosterone in response to stress as the result of an increased release of ACTH.

In other words, tactile stimulation reduces the activity of the hypothalamic-pituitary axis in neonates. This has the beneficial effect of protecting well-nurtured neonates from the effects of circulating glucocorticoids that would otherwise be released from the adrenal gland. Besides the effects on the stress response, this effect is related to the increased incidence in chronic disease associated with high stress childhoods. Chronically high levels of circulating corticosteroids early in life predispose human children to chronic disease. The molecular changes that mediate blunted hypothalamic-pituitary axis reactivity in animals with higher levels of tactile stimulation during the critical first week of life is the subject of the next column as is the way in which this effect is made permanent (i.e., the epigenetic effect).

These exciting findings in animal models are leading to epigenetic studies that will shed new light on human psychiatric illnesses. Classic genetic inheritance mechanisms clearly play a role in many psychopathologies such as depression, anxiety, and some types of schizophrenia.

However, these effects are likely to occur together with environmentally driven epigenetic mechanisms (i.e., the interaction of genes and the environment clearly modifies neurodevelopment). A precise understanding of the environmental contribution will provide us with the opportunity to intervene in nonpharmacological ways, such as enhancing parenting skills, to reduce psychopathology and disrupt the transmission of certain pathologies across generations.

Disclosure: The authors report no conflicts of interest.

ADDITIONAL READING

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