Plasticity for Affective Neurocircuitry

How the Environment Affects Gene Expression

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ABSTRACT—*We (Fox et al., 2005) recently described a gene-by-environment interaction involving child temperament and maternal social support, finding heightened behavioral inhibition in children homozygous or heterozygous for the serotonin transporter (5HTTLPR) gene short allele whose mothers reported low social support. Here, we propose a model, Plasticity for Affective Neurocircuitry, that describes the manner in which genetic disposition and environmental circumstances may interact. Children with a persistently fearful temperament (and the 5HTTLPR short allele) are more likely to experience caregiving environments in which threat is highlighted. This in turn will exacerbate an attention bias that alters critical affective neurocircuitry to threat and enhances and maintains anxious behavior in the child.*

KEYWORDS—*temperament; gene × environment interaction; attention bias to threat; parenting*

Individual differences in the stress response represent stable aspects of behavior that emerge early in life and reflect aspects of brain function. While behavioral-genetic studies implicate genes and the environment in these differences, the manner in which specific genes and environmental events shape specific aspects of brain function remains poorly specified. Recent work provides important clues, however, concerning these specific pathways. In particular, emerging findings suggest that specific genes associated with the function of the neurotransmitter serotonin (5-HT) interact with social stressors during development to shape function in a neural circuit implicated in the stress response.

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RESEARCH ON GENE × ENVIRONMENT INTERACTIONS

A series of recent research reports provides evidence for gene-by-environment (denoted gene × environment) interactions with a protein crucially involved in the effects of 5-HT on behavior. This protein regulates the fate of 5-HT released from neurons. Each of the genetically derived variants in this protein is known as an expression of a serotonin transporter protein polymorphism (5HTTLPR; Caspi et al., 2003; Kaufman et al., 2004). The 5HTTLPR gene has two major functional alleles: a long and a short, as well as another long-variant allele that behaves, functionally, like the short allele. Individuals who are homozygous have two copies of either the long or the short. Individuals who are heterozygous have one copy of each. In general, studies of gene × environment interaction with this particular gene suggest that individuals who are homozygous for the short allele of the 5HTTLPR and who are exposed to significant stress are more likely to exhibit significant maladaptive behavior than are individuals who are homozygous for the long allele and are exposed to similar levels of stress. Individuals who are heterozygous, having one copy of the long and one of the short allele, usually fall somewhere in the middle, exhibiting more maladaptive outcomes compared to individuals homozygous for the long, and somewhat fewer than individuals who are homozygous for the short allele.

For example, Caspi et al. (2003) found that individuals homozygous for the short allele of 5-HTTLPR and exposed to five or more stressful life events were more likely to experience a major depressive episode, compared to individuals homozygous for the long allele exposed to such stress. Kaufman et al. (2004) reported that children carrying the short allele who had a history of abuse were more likely to evidence depression if their caregivers reported that they themselves were under high stress. Both of these studies reported psychiatric outcomes as a result of this particular gene × environment interaction. Caspi et al. (2003) examined the probability of major depression.

Kaufman et al. (2004) reported on depressive symptoms in the subjects.

In a recent paper, we (Fox et al., 2005) reported on a similar gene × environment interaction in young children who were selected for the temperamental characteristic of behavioral inhibition. Signs of behavioral inhibition are detectable within the first months of life. For example, infants displaying high motor reactivity and negative affect when presented with novel auditory and visual stimuli are more likely to display behavioral inhibition as toddlers and preschoolers (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Behaviorally inhibited children cease their ongoing activity and withdraw to their caregiver's proximity when confronted with novel events. They are also likely to isolate themselves when confronted with unfamiliar peers or adults. This behavioral style appears early in life, is associated with physiological markers of stress, social reticence with unfamiliar peers, low self-concept in childhood, and may be a risk factor for later psychopathology (Perez-Edgar & Fox, 2005).

We examined the relationship between childhood behavior and two variants of the 5-HTTLPR. As noted above, this protein mediates 5-HT influences on behavior by regulating the fate of 5-HT released from neurons into the synaptic cleft, the space that separates two communicating neurons. We found that children with lower-activity variants of the 5-HTTLPR whose mothers reported experiencing low social support were more likely to display behavioral inhibition at age 7, relative to children with similar 5-HT genetics but whose mothers reported more social support. The gene × environment interaction suggested that children with high-activity forms of the gene were "protected" from manifesting inhibition, even if their mothers reported experiencing low social support. Moreover, while child 5HTTLPR strongly related to inhibition in children with low levels of social support, for children with high levels of social support, no such relationship with 5HTTLPR emerged.

These data extend the findings of previous work, reporting the interaction of environmental stress and genes in predicting behavioral outcomes. Unlike other studies, though, the Fox et al. (2005) study presents data on a sample of typically developing children with nonpsychiatric outcomes. But like the other papers it does not address the mechanisms or processes by which the environmental stressor(s) affect variations in genotype to create the particular phenotypic outcome.

NEUROBIOLOGY OF 5HTTLPR

The short and long forms of the 5HTTLPR produce proteins known as reuptake transporters. These proteins lie within the synapse, the space separating two communicating neurons, and they function to remove serotonin from the synapse after it has been released. 5-HT neurons removed from the brain and studied in the laboratory revealed that the different forms of 5-HT reuptake transporters associated with distinct genotypes act differently. This early work clearly demonstrated functional consequences of the 5HTTLPR. More recent work has begun to describe possible influences of the different polymorphisms or variations in the 5HTTLPR in the neural-system function of living primates and humans.

5-HT neurons, like neurons for other modulatory neurotransmitters, make connections with broadly distributed networks in the brain. 5-HT influences on behavior are thought to emerge through the neurotransmitter's effects on information processing. The neural architecture engaged in the service of processing dangerous stimuli has been mapped in particularly precise detail, and 5-HT is thought to modulate functioning in this circuit (Gross & Hen, 2004). The circuit encompasses the ventral prefrontal cortex (vPFC), an area involved in decision making, and the amygdala, a structure involved in the detection of salient events such as those that are novel or threatening. Both structures receive strong 5-HT innervations. Thus, the amygdala, vPFC, and connections between them constitute a neural circuit that has been labeled "vPFC–amygdala circuitry." Consistent with the laboratory evidence of its effects on serotonin reuptake, the 5HTTLPR also predicts functional aspects of this ventral prefrontal–amygdala circuitry (Pezawas et al., 2005).

One of the most important issues to resolve concerns the mapping of these 5-HT influences across development. Neuroimaging studies in humans demonstrate robust developmental influences on prefrontal–amygdala circuitry (Monk et al., 2003). Studies in animal models suggest that these influences result from developmental changes in 5-HT function (Gross & Hen, 2004). This suggests that the relationship between the 5HTTLPR and prefrontal–amygdala function is likely to change across development. Neuroimaging studies have yet to examine this issue.

Interestingly, animal models suggest that 5-HT effects on neural development emerge through interactions with the environment (Gross & Hen, 2004). Given these data, how then precisely does the action of the environment interact with the 5HTTLPR to shape brain function and behavior? In the specific case of behavioral inhibition, how does the mother's report of her social support influence the expression of her child's 5-HTT gene in a way that ultimately impacts the child's tendency to display inhibited behavior? We propose a model, called Plasticity for Affective Neurocircuitry, and suggest two possible complementary mechanisms, based upon work in the area of anxiety and our own developmental studies. The first deals with the manner in which caregivers interact with behaviorally inhibited children; the second, with the attention bias that may develop as a result of temperamental disposition, caregiver influence, or their interaction.

CAREGIVER BEHAVIOR AND SOCIAL SUPPORT

Research suggests that reported level of social support correlates with quality of caregiver behavior. Mothers who report high

levels of social support tend to be more sensitive toward their infants (Crockenberg & McCluskey, 1986) and more satisfied with their role as a parent (Thompson & Walker, 2004). Additional evidence indicates that level of social support may be particularly important for mothers of temperamentally distress-prone infants. Crockenberg and her colleagues found that the positive association between social support and maternal sensitivity was only significant for irritable infants (Crockenberg & McCluskey, 1986). Pauli-Pott, Mertesacker, and Beckmann (2004) found that maternal insensitivity was predicted by the joint effect of infant negative emotionality and low social support. Hence, social support is a factor contributing to the quality of maternal caregiving behavior, particularly for inhibited children who have a history of negative reactivity in infancy and early childhood.

An emergent body of research indicates that the quality of the mother–child relationship mitigates the relation between early and later forms of behavioral inhibition, such that some parents of behaviorally inhibited children interact with their children in a manner that appears to exacerbate or maintain their child's temperament. In our own research, we have identified a unique group of children who consistently withdraw from novelty at age 4 months and who receive insensitive maternal caregiving due to this proneness to distress. For instance, Ghera, Hane, Malesa, and Fox (2006) found that infants who responded negatively to novel stimuli at age 4 months and who were viewed by their mothers as difficult to soothe received low levels of maternal sensitivity. Hane, Fox, Henderson, and Marshall (2006) found that 9-month-old infants who showed high levels of behavioral avoidance to ominous stimuli and a corresponding pattern of right frontal electroencephalogram (EEG) asymmetry (itself a determinant of continued inhibition across early childhood; see Fox et al., 2001), received low levels of maternal sensitivity. Hane and Fox (2006) reported that infants who received low-quality maternal caregiving behavior showed more fearfulness and less sociability in the laboratory, more negative affect while interacting in the home with their mothers, and a pattern of right frontal EEG asymmetry. Taken together, this research suggests that quality of maternal caregiving behavior shapes the development of behavioral inhibition, perhaps by altering the neural systems that underlie reactivity to stress and novelty (see a review by Parent et al., 2005, for parallels in research with rodents).

ATTENTION BIAS TO THREAT

A second mechanism through which experience may affect the neural systems underlying behavioral inhibition involves the development of attention bias to threat. A variety of data using a number of different experimental paradigms suggests that individuals who self-report a high degree of anxious symptoms or who are diagnosed with a number of different anxiety disorders display an attention bias to threat. When presented with visual stimuli reflecting threat, anxious individuals are more vigilant toward these stimuli and take longer to disengage from visual attention to them (Mogg, Millar, & Bradley, 2000). In humans, as in other species, the ability to detect threatening stimuli in the environment appears to provide an important adaptive advantage for safety and survival. The neural systems that are involved in threat detection have been well described in nonhuman primates, rats, and, through the use of functional neuroimaging, in humans (Monk et al., 2006). These systems encompass prefrontal–amygdala circuitry previously tied to threat responses and 5HTTLPR in humans.

An enhanced sensitivity to threat has been suggested as an underlying mechanism in anxiety disorders (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). A recent meta-analysis (Bar-Haim, Lamy, Pergamin, Bakermans-Kraneburg, & van IJzendoorn, 2007) suggests that the distribution of attention in anxious individuals may be part of a resource-allocation system that biases the individual to pay close attention to threat. Such biases may develop over time and be the result of a person's ongoing transaction with threatening or aversive stimuli. Moreover, studies using experimental approaches, at least in adults, suggest that these attention biases are causally implicated in the genesis of anxiety following exposure to stress (MacLeod et al., 2002). From this perspective, children born with a disposition to react intensively and with negative affect to stress or novelty may go on to show different patterns of behavior, depending on the degree to which they are exposed to overzealous, intrusive maternal behavior as opposed to a more sensitive, nurturing style.

The Plasticity for Affective Neurocircuitry model that we propose suggests that early temperament influences quality of the caregiving environment and quality of the environment in turn shapes attention bias to threat and mediates the relation between early temperament and later inhibition (see Fig. 1). Rubin, Burgess, and Hastings (2002) showed that the relation between behavioral inhibition as a toddler and reticence at age 4 was significant and positive only for those children whose mothers were psychologically overcontrolling and derisive. Thus it appears that caregivers who highlight or identify negative events in their child's environment (often in an effort to control their child's behavior) may in fact be inadvertently promoting attention bias in the child. Evidence from studies of interactions between mothers and children with anxiety disorders supports this position. For example, Barrett, Rapee, and Dadds (1996) found that parental discussion of ambiguous situations was associated with increased perception of threat and the creation of avoidant plans of action in anxious children. Thus, from within the caregiving environment, children disposed to respond with negative affect to novelty or uncertainty may be further reinforced to bias their attention toward threat during the course of interactions with caregivers.

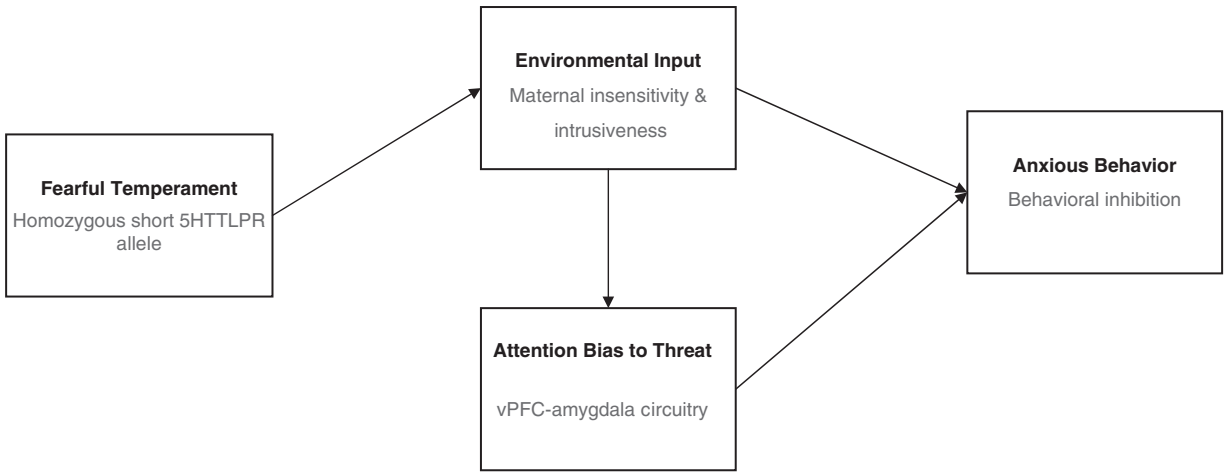

Fig. 1. Plasticity for Affective Neurocircuitry model. A child's genetically disposed fearful temperament (due to homozygosity for the short allele of the serotonin transporter, 5HTTLPR, gene) elicits and is elicited by caregiver behavior (maternal insensitivity and intrusiveness) to shape attention bias to threat and the underlying neural circuitry (in the ventral prefrontal cortex, vPFC, and amygdala) supporting this bias. Exaggerated attention bias contributes to the emergence and maintenance of anxious behaviors.

CONCLUSIONS

At the present time, there are preciously few data on the development of attention biases to evocative, threatening, or stressful stimuli. Research in this area is clearly needed in order to understand the development of these attention processes and their effects on social behavior.

Research in the area of behavioral inhibition already highlights the importance of both biological dispositions and caregiving environments in shaping the social responses of the young child. Evidence of gene × environment interactions in this group of children marks another important step toward understanding the developmental mechanisms involved in the emergence of important variations in social behavior. The next steps involve process-focused research. Studies that carefully model the development of gene × environment interactions and the factors that mitigate the relevance of such interactions to key social outcomes are warranted; such studies would elucidate the mechanisms by which the environment influences the phenotypic expression of critical genes such as the 5HTTLPR and the degree to which phenotypes change across development. Hane and Fox (in press) suggest that early environmental experiences not only change the phenotypic expression of stress reactivity, but also prime the child to respond with a similar behavioral repertoire upon encountering like environmental stressors in the future. Hence, the child who is genetically vulnerable to anxiety and who has also developed a tendency to focus on threat vis à vis interactions with his or her caregivers may develop a strong attention threat bias that maintains anxious behavior well into adulthood.

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