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An Evolutionary and Developmental Perspective

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The human brain is a remarkable product of evolution. While the basic machinery of the vertebrate brain has been in place for more than 450 million years, our subspecies emerged just 100,000 to 200,000 years ago. In the struggle for life, certain traits have come to predominate. It is likely that that elements in our mental and behavioral repertoire related to successful mammalian reproduction have been the focus of intense selective pressures since the first lactating proto-mammals appeared some 300 million years ago (1). The selection of a mate, bearing of viable offspring, and the formation of parental commitments that will sustain an infant along with our neurocognitive abilities including attention, executive processing, working memory, threat detection, and response inhibition are just a few of the crucial complex, interdependent processes needed for survival and hence, species viability. It is likely that there are highly conserved, overlapping brain-based systems that are specifically activated over the course of development to achieve and sustain these processes. A thorough understanding of these “normal” processes and the multiplicity of genetic, epigenetic, and environmental factors that condition these capacities may also lead to deeper insights into our vulnerability to develop a range of psychopathological outcomes. Several of the articles in this issue touch on aspects of this story with regard to affective disorders and obsessive-compulsive disorder (OCD).

Despite our halting progress of identifying specific vulnerability genes in psychiatry, research continues to advance at a rapid pace with the sequencing of the human genome and the mapping of human haplotypes (2,3). Cost-effective genotyping technologies also now allow systematic genome-wide interrogations that depend in large measure for their success on the availability of the large sample sizes needed for genome-wide studies. Given the small sample sizes used, caution is warranted as we consider the results of the genome-wide linkage scan in 26 OCD families and the candidate gene studies reported in this issue of *Biological Psychiatry*. There will probably always be room for good hypothesis-driven candidate gene studies. However, it appears that large *N* genome-wide association studies will be the favored methodology that will drive the next big advances in our field along with studies arising from the growing appreciation of the importance of non-protein-coding transcripts and transcriptional regulation (4,5).

Although none of the studies in this issue consider the role of epigenetic changes on gene expression, both the glucocorticoid receptor (GCCR) gene and the estrogen receptor 1 (ESR1) gene are known to be susceptible to such alterations. In a landmark series of studies, Michael Meaney and his colleagues at McGill have shown that the level of expression of the GCCR gene in the hippocampus and the ESR1 gene in the medial preoptic area of the hypothalamus

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are in part dependent on the patterns of early nurturance (6,7). Although the extent to which similar mechanisms play a role in our species has yet to be determined, it seems likely that events early in development may well be among the environmental factors that influence patterns of stress response, as well as anxiety-mediated and affiliative behaviors in adulthood (8). Further, if it is true that stable epigenetic programming occurs for these two genes, it is almost certain that it will be true for many other genes, some of which are likely to influence domains such as cognitive performance or immune function, as well as some subset of vulnerability genes that can influence psychopathological outcomes (9).

The close resemblance of symptom domains seen in OCD to the normal behavior observed in new parents have led us to hypothesize that these anxious intrusive thoughts associated with threat detection and harm avoidant behaviors are related to OCD and that some forms of OCD are the result of a dysregulation of the overlapping neural circuits that are normally active during the initial phases of parental behavior (10). Consistent with this viewpoint, neuroimaging studies and neurosurgical findings have consistently implicated orbitofrontal, hippocampal and amygdala regions and their connections with the thalamus and the ventral striatum in OCD (11). When comparing the data from typical subjects in the midst of a major life transition (e.g., becoming a parent for the first time) to individuals with an impairing mental disorder, as OCD, it will be crucial to consider the role of a variety of factors that may make such comparisons inherently problematic. These include the involvement of brain circuits activated in order to compensate for or suppress unwanted cognitions and behaviors as well as the confounding effects of chronic medications and the likelihood that sustained periods of illness will likely have enduring untoward effects on aspects of brain function.

Another intriguing set of findings concerns the close interface of the hypothalamic-pituitary-adrenal (HPA) axis and the circuitry involved in affiliation and trust. Perhaps the most exciting recent work involves the interactive effects of oxytocin administration and social support on stress response (12). In this placebo-controlled, double-blind study, subjects were exposed to the Trier Social Stress Test (TSST). They were randomly assigned to receive intranasal oxytocin or placebo before the TSST. They were also randomized to either have social support from their best friend during the preparation for the TSST or not. Oxytocin administration enhanced the effect of social support on stress responsiveness. The subjects who were randomized to the combination of oxytocin and social support exhibited the lowest cortisol concentrations as well as increased calmness and decreased anxiety during the TSST. It is also of interest to note that compared with placebo; oxytocin potently reduces the activation of the amygdala in response to fear-inducing visual stimuli in a recent fMRI study (13). Oxytocin administration also leads to a substantial increase in trust as measured by an individual's willingness to accept risks arising in a computer game with anonymous individuals for actual monetary rewards (14). This effect appears to be reciprocal. Zak et al. reported that the receipt of a money transfer designed to enhance trust is associated with higher levels of circulating oxytocin (15). These results confirm data from animal research suggesting that oxytocin has anxiolytic properties and point to the biological mechanisms involved in the stress-protective effects of positive social interactions.

We can expect the number of research studies focused on the interface of the HPA axis and the circuitry of affiliation to increase (16–20). Hopefully, these studies will clarify some of the complexities surrounding risk versus resilience to psychopathology as conditioned by parental attachment style and nurturance, infant temperament, the presence of supportive non-parent caretakers, material hardships, and early emotional trauma. It is also likely that further progress in this field will lead to novel therapeutic interventions as well as a deeper understanding of individual differences in treatment response to currently available medications and behavioral therapies.

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