

Stress and the Baby Brain

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Increasingly, we are coming to understand that vulnerability to neuropsychiatric morbidities such as schizophrenia, autism, depression, and anxiety disorders are likely encoded in early events of brain development. For the last few decades, we have been successful in identifying what some of these brain-based vulnerabilities look like in adults: altered brain morphology, differences in circuit function and connectivity, and changes in gene expression and function, to name only a few. These insights have been enormously helpful in our quest to better understand how brain function can go awry, but relatively less emphasis has been placed on understanding when in the trajectory of brain development these vulnerabilities are laid down. With recent advances in research, it is becoming clearer that genetic variants and environmental factors collude to influence how the brain develops and result in impaired resilience to these neuropsychiatric conditions, likely at the earliest stages of brain development.

The elegant study by Benekareddy *et al.* (1), published in this issue of *Biological Psychiatry* illustrates this growing line of inquiry that attempts to define biological mechanisms that may help shape brain development in ways that increase the vulnerability to affective and anxiety disorders later in life. Specifically, the authors studied the interplay between early life stress and how this stress changes the function of serotonin signaling through 5-hydroxytryptamine (5-HT) 2A receptors in the prefrontal cortex of rats. Previous work had underscored the critical role of cortical 5-HT2A receptor signaling in modulating anxiety-related behaviors in adult mice (2) and provided plausible evidence that serotonin may play an important role in the top-down modulation of anxiety states, a finding emerging from brain imaging studies. However, this work did not consider whether adult cortical 5-HT2A receptor signaling was influenced by early life manipulations.

Indeed, a variety of early life manipulations influence the developmental trajectory of cortical 5-HT2A receptor signaling, from maternal separation stress, maternal viral infection, to early exposure to selective serotonin reuptake inhibitors (3-6). Last year, the authors reported that maternal separation causes long-term changes in neural function, which result in an anxiety-like phenotype in adulthood (3). The authors also previously showed that early maternal separation stress results in an altered intrinsic excitability in cortical pyramidal neurons that appears to be an adult persistence of a neonatal pattern of neuronal excitability that normally disappears at the time of weaning.

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In this issue, the authors extend their findings by showing that this compromised state and increased prefrontal cortical 5-HT2A receptor function were associated with reduced plasticity in these prefrontal-cortical neurons in that they no longer possessed the ability to habituate to stressors in adulthood. This was most strikingly demonstrated by the dysregulated expression of immediate early genes associated with 5-HT2A receptor signaling in the prefrontal cortex of maternally separated rats following chronic but not acute adult stress. This exciting result goes some way toward reconciling the conflict in the literature regarding the effect of postnatal stressors on 5-HT2A expression, pointing toward a change in expression of 5-HT2A receptor-associated signaling molecules, as opposed to expression of the receptor itself, being responsible for the altered behavioral consequences in adulthood. Another key finding was that pharmacological blockade of the 5-HT2A receptor during the early postnatal period protects against the longer-term behavioral and molecular sequelae of early postnatal traumatic experience.

Their findings suggest that one mechanism by which early-life stress may be changing brain function later in life comes from excessive signaling through 5-HT2A receptors in the prefrontal cortex. Interestingly, this population of prefrontal cortical neurons is known to undergo an elaborate change in their repertoire of 5-HT receptor expression during the early preweaning period when the 5-HT2A receptors are known to exert more dominant control over the inhibitory 5-HT1A receptor coexpressed on the same cells (3,7).

Understanding the developmental origins of neuropsychiatric disorders is an endeavor still in its infancy. Studying development poses many challenges that will require new ways of thinking about neuropsychiatric disorders and perhaps new methodologies as well. Despite the difficulties in studying a moving target such as the developing brain, it may be that studies such as those highlighted here by Benekareddy *et al.* (1,3) will help inform public health initiatives that seek to promote healthy brain development and minimize negative environmental influences. It may turn out to be more effective to intervene early in life before brain vulnerabilities are established rather than treat the neuropsychiatric conditions that subsequently arise. In the end, we need ongoing research efforts at both ends of the developmental time course. The study by Benekareddy *et al.* is emblematic of how, in understanding the biology of early environmental adversity, we can begin to imagine strategies to prevent and reverse its unwanted impact on brain maturation.

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