Unraveling the Longstanding Scars of Early Neurodevelopmental Stress

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Early neurodevelopment, both in utero and in the postnatal phase, is a time when stressors can produce long-lasting changes that significantly increase the risk of mental health problems in adulthood (1). Pregnancy complications such as depression in the mother and childhood trauma can impact on neurodevelopment and increase the likelihood of psychiatric illnesses, such as major depression together with anxiety and personality disorders. Large-scale prospective studies indicate that the increased risk of these disorders following early adversity persists into old age. It is equally clear that not everyone who experiences early stressors develops psychiatric illness in adulthood and neither is there a relationship between any specific stress and a particular psychiatric disorder. If we are to ameliorate the impact of early stress, it is important that we gain an increased understanding of the manner in which such stress impacts on biological development and the psychosocial and genetic factors that help decrease the toxic effects of stress.

In this regard, two articles in this issue of *Biological Psychiatry* focus on the underlying persistent neuronal alterations in subjects who have been exposed to, albeit qualitatively different and potent, early-life stressors (2,3). Interestingly, both articles highlight an important role for the amygdala in these effects. Olsavsky *et al.* (2) provide evidence in a functional magnetic resonance imaging experiment that altered activation of the amygdala plays a role in long-term behavioral problems in maternally deprived children that had been subsequently adopted (children were aged between 6 and 15 years at the time of scanning). Behaviorally, they found that this cohort had indiscriminate friendliness, which can be defined as an uncharacteristic reduced reticence and atypical approach behaviors towards adults, including strangers, being unable to distinguish adopted mothers from strangers and that this was also demonstrable in terms of amygdala discrimination to both types of stimuli. Interestingly, there was a positive correlation between age at adoption and hence duration of maternal deprivation and extent of the amygdala discrimination and behavioral response in terms of indiscriminate friendliness.

On the other hand, Rifkin-Graboi *et al.* (3) takes a different approach, but once again, this study highlights the role of the amygdala in the long-term effects of early-life stress. They show that microstructural changes in the right amygdala (as assessed within the first 2 weeks of life) can be induced as a result of depression in the mother. The study adds further to our understanding of the toxic effect of maternal depression on the developing fetus. It is also worth noting that recent studies are pointing to a link between maternal childhood maltreatment and maternal antenatal depression (4), thus continuing the cycle of stress-induced effects across the generations with the co-occurrence of both insults significantly increasing the risk of offspring adversity.

The mechanism for both of these associations is unclear and may include genomic and environmental influences both during fetal development and postnatally. Experimental studies in animals involving gestation stress or in early life are proving invaluable in uncovering key changes in the neurodevelopment of limbic structures, including alteration in amygdala size, neuronal activity, and expression of key stress-related genes (5). Moreover, starting with the work of Levine *et al.* (6) in Stanford and Meaney *et al.* (7) in McGill, a growing body of preclinical data in both rodents and nonhuman primates has been focused on understanding the consequences of alterations in maternal care in early life to both the susceptibility and resilience to psychopathology [see (1) for review].

The Hypothalamic-Pituitary-Adrenal Axis and the Effects of Early-Life Adversity on Brain Function

The hypothalamic-pituitary-adrenal (HPA) axis is the core endocrine regulator in maintaining the homeostasis of an organism and is activated when homeostasis is threatened. Multiple disturbances at different levels of the HPA have been described in patients with major depression and patients with more severe forms of depression hypersecrete cortisol (8). Understanding how this axis is disrupted at key critical periods of brain development has been an important goal for translational research in the field.

The negative impact of maternal depression on the developing fetus is thought to be mediated by glucocorticoids (8) such as cortisol. Cortisol can, in certain circumstances, overwhelm the placental protective mechanisms. The placenta expresses 11β-hydroxysteroid dehydrogenase 2, which converts cortisol into inactive metabolites, and changes in the expression of this enzyme have been reported to be associated with maternal anxiety and thus increased fetal exposure to cortisol (9). In utero exposure to high glucocorticoid levels can result in epigenetic changes with abnormal methylation patterns in the promoter region of key genes. Indeed, prenatal socioeconomic adversity may also alter fetal response to the postnatal environment through functional epigenetic alterations in the placenta at the level of 11β-hydroxysteroid dehydrogenase 2 methylation (10).

Further evidence of a dysregulated HPA axis playing a role in the consequences of early-life stress has emerged recently from the Whitehall II occupational health study, whereby the diurnal pattern of cortisol secretion in a cohort of more than 3000 adults in whom 12% had experienced childhood maternal separation was reported (11). Two measures of cortisol secretion were examined, the cortisol awakening response and the diurnal slope in cortisol. Participants provided six samples of saliva over a working day and cortisol levels in the saliva were measured. A higher proportion of women than men reported separation from their mothers for more than 1 year in childhood. These subjects were more likely to be in the lowest socioeconomic group, from

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ethnic minority backgrounds, and not married or cohabiting, and reporting parental strictness, poor paternal warmth, and material and emotional problems in childhood. They were also far more likely to experience depressive symptoms. The findings strongly suggest that maternal separation in childhood is associated with alterations in the diurnal cortisol pattern in middle age.

Inflammatory Markers

Together with HPA axis overactivity, major depression has been shown to be associated with activation of the inflammatory response. These changes include increased numbers of peripheral leucocytes, including monocytes and neutrophils. Positive acute phase proteins, including C-reactive protein, are increased, while negative acute phase proteins such as albumin are decreased. The syndrome also correlates with an increase in proinflammatory cytokines. We have very limited knowledge regarding the impact of increased peripheral proinflammatory cytokines on the developing human fetal brain. Data from rodent studies suggest a very negative impact. By activating the HPA axis, interleukin-1 and interleukin-6 have a very obvious indirect negative impact on the fetus. Studies focused on investigating if there is a link between antenatal inflammatory exposure and amygdala structure and function are now warranted.

Stress and Amygdala Development

Data from both preclinical, especially the work of James McGaugh (12) at the University of California, Irvine, and clinical studies indicate that the amygdala is an essential brain region involved in mediating stress hormone influences on memory consolidation. Unpleasant or emotionally charged events are much more likely to be remembered than neutral events. While certain traumatic events in childhood may not be recalled, as a general rule, absent, intermittent, or poor quality maternal care is generally remembered in adulthood. Recent studies have also shown that young boys who were previously institutionalized and as a result experienced early maternal deprivation, exhibit altered amygdala–medial prefrontal cortex connectivity (13). Specifically, unlike the immature connectivity of comparison children, children with a history of early adversity evidenced mature connectivity that resembled the pattern seen in adolescents. This pattern of connectivity was mediated by cortisol, indicating that stress-induced modifications of the HPA shape amygdala–medial prefrontal cortex circuitry and support the view that structural connectivity changes at the level of the amygdala may be an ontogenetic adaptation in response to early-life stress.

One of the important aspects of both articles in this issue is the focus on the amygdala as a key structure involved in the consequences of early-life stress. Traditionally, the hippocampus has been the brain area most studied in this context to date, which in many ways makes sense, given its role in cognition, mood, and HPA axis regulation. However, it is clear that there is a more complex corticolimbic deficit induced by early-life stress and in particular involving the amygdala.

Finally, both of the studies (2,3) highlight the benefit of having large prospective studies on well-defined and phenotyped populations. Long-term studies such as The Growing Up in Singapore (2) and others, including the Bucharest Early Intervention Project led by Charles Nelson and colleagues at Harvard are invaluable in offering insight into the biological basis and temporal effects of stress susceptibility and resilience.

In conclusion, findings from both rodent and human studies provide convincing evidence that early-life stress-mediated activation of the amygdala plays a fundamental role in ensuring that emotionally significant experiences are remembered. A neurodevelopmental stress model involving the HPA axis and immune activation as a mediator of vulnerability to later affective disturbance is now gaining traction. That major changes at a structural and functional level in the amygdala play a key role in the process is now becoming clear. Finally, we are gaining an appreciation that the antenatal period is an optimum period to identify vulnerable women and to provide interventions that not only will help them and their children but may persist into further generations too.

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