See article beginning on page 991.

The Pervasive and Persistent Neurobiological and Clinical Aftermath of Child Abuse and Neglect

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In the last 2 decades, there has been a veritable explosion of studies concerning the clinical and neurobiological consequences of early life trauma. Once an area relegated to esoteric debates on whether Freud's patients' accounts of early trauma were "real" or "fantasies," largely appearing in the psychoanalytic literature and commentaries related to Freud's vacillation on this subject,[1] child abuse and neglect are now clearly established as major risk factors for mood, anxiety, and psychotic disorders, as well as several medical disorders.[2,3] Indeed, with the exception of genetic (and perhaps epigenetic) mechanisms, child abuse and neglect, undoubtedly, are among the most significant contributors to vulnerability for the development of major psychiatric syndromes.

In this issue of *JCP*, Etain and colleagues[4] provide a seminal study on the relationship of childhood trauma to disease severity in a large cohort (almost 600) of Norwegian and French bipolar disorder patients. In brief, using one of the best validated measures of early adversity, the Childhood Trauma Questionnaire, they observed very significant effects—ie, a clear "dose-response" relationship—of childhood sexual and emotional abuse and emotional neglect on the severity and course of bipolar disorder, namely, earlier age at onset, increased suicide attempts, more rapid cycling, and an increased number of depressive episodes. For example, both emotional and sexual abuse independently predicted lower age at onset and higher number of suicide attempts, with sexual abuse a strong predictor of rapid cycling. Patients with child abuse histories developed bipolar disorders more than 4 years earlier than patients with no such histories. A similar dose-response relationship was observed between child abuse severity and number of suicide attempts. However, there was no statistically significant dose-response relationship between genders.

These findings add to the burgeoning evidence supporting a preeminent role of child abuse and neglect in the pathogenesis of serious and severe psychiatric disorders including major depression, schizophrenia, and posttraumatic stress disorder (PTSD).

In the past decade, considerable progress has been made by our group and others in elucidating the neurobiological mechanisms mediating the increased risk of mood and anxiety disorders in individuals exposed to child abuse and neglect. Space constraints preclude a comprehensive discussion, and reviews are available.[5,6] Here, we will summarize clinical studies that have sought to elucidate the biological mechanisms by which early life trauma produces these long-lasting effects on psychiatric disease morbidity. The major areas to be discussed include genetics and epigenetics, neuroendocrine systems, and inflammation, as well as structural and functional brain imaging. It is important to note that in addition to increasing risk for major psychiatric disorders, child abuse and neglect, not surprisingly, also affect treatment response. For example, in a recent meta-analysis, Nanni et al[7] reported that depressed patients with a history of child abuse or neglect exhibited a significantly reduced response to both antidepressants and psychotherapy.

The pioneering study by Caspi and colleagues[8] documented the importance of a polymorphism in the promotor region of the serotonin transporter in mediating the depressogenic effects of child abuse and neglect in the well-studied Dunedin cohort. This finding has been replicated by most (including our group[9]), but not all,[10] investigators. A multitude of studies have now documented the importance of polymorphisms of several candidate genes in mediating the depressogenic, suicidogenic, and/or anxiogenic effects of child abuse and neglect. These include studies of the corticotropin-releasing factor (CRF) type 1 receptor (*CRFR1*),[11] CRF binding protein (*CRFBP*),[12] brain-derived neurotrophic factor (*BDNF*),[13] 5-HT_3 receptor (*HTR3A*),[14] and *FKBP5*,[15] which codes for a co-chaperone protein that mediates the effects of cortisol on the glucocorticoid receptor. Single-nucleotide polymorphisms (SNPs) of each of these genes have been demonstrated in multiple studies in relatively large populations to exert significant effects in mediating the deleterious effects of early adversity. Although it has not yet been demonstrated, we would suggest that individuals with multiple vulnerability SNPs are unusually sensitive to the depressogenic and anxiogenic effects of early life trauma and that, conversely, those with few or none of these SNPs are quite likely resilient in the face of such adversity. We predict a time in the not-distant future in which personalized medicine will be realized in this domain—physicians and mental health professionals will have access to individuals' genome scans, a component of their permanent electronic medical record, and, with the advances described above, will be able to predict relative risk for mood and anxiety disorders based on the number of vulnerability and resilience SNPs present. If parents were informed immediately after a child's birth that the child would very likely be unduly sensitive to

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the effects of emotional or physical abuse or neglect, they could, for example, take precautions against bullying and be more mindful of the child's environment.

A major recent advance in the field has been epigenetics—the realization that heritable changes in gene expression associated with transcriptional modifications by methylation and demethylation occur in response to environmental changes and, in particular, to early adversity. The epigenetic changes seen in these preclinical and clinical studies pioneered by Michael Meaney and his colleagues have, for example, been shown to be associated with the increase in suicide in victims of child abuse, as demonstrated in postmortem brain studies.[16] Recently, our group demonstrated that a SNP in the *FKBP5* gene that mediates the child abuse–associated increase in PTSD is actually mechanistically regulated by just this type of demethylation.[17] Our study is the first direct demonstration in psychiatry of a SNP-epigenetics interaction with important clinical and therapeutic implications.

Other biological consequences of early trauma have been implicated in mediating the increased vulnerability of these individuals for mood and anxiety disorders. Long-lasting dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has received considerable attention, although there is no universal agreement as to the precise nature of the HPA axis alterations.[18,19] There is much evidence for hyperactivity of hypothalamic and extrahypothalamic circuits containing CRF after early life adversity in rodent, nonhuman primate, and clinical studies.[20–23] Consequent alterations in circulating adrenocorticotropic hormone and glucocorticoid concentrations have also been noted. This finding may be particularly relevant to the mixed bipolar patient with early life trauma because of the profound HPA-axis hyperactivity reported in this subpopulation.[24]

Inflammation is now known to play a preeminent role in the pathogenesis of a variety of major medical disorders including cardiovascular disease, cancer, and diabetes, and there is now evidence that it also is involved in depression, bipolar disorder, and schizophrenia. Thus, multiple studies have revealed increased inflammatory markers including C-reactive protein and interleukin-6, as well as tumor necrosis factor, in patients with depression.[25] Danese and colleagues[26] have provided groundbreaking studies unequivocally demonstrating persistent increases in inflammatory markers in adults exposed to child abuse and neglect, and these findings have been replicated by our group.[27]

Finally, the long-term neurobiological consequences of child abuse and neglect in the central nervous system have been demonstrated directly by structural and functional brain imaging studies. This area is burgeoning and can be only briefly discussed. However, it is important to note that the myriad of studies that have reported structural and functional alterations in patients with major psychiatric disorders over the last 4 decades were largely conducted without the knowledge that early life trauma could and does exert profound effects on such measures. It is impossible to determine from those early studies of patients with bipolar disorder, depression, and schizophrenia what role early life trauma played in the results obtained. What is clear is that child abuse and neglect result in structural alterations in the hippocampus, amygdala, and several cerebrocortical areas, and, moreover, the effects are in part specific to the nature of the early abuse. Thus, we recently documented reduced cortical thickness in the somatosensory cortical area for genital sensation in women with childhood sexual abuse, a finding that is congruent with their often-repeated observations of diminished libido and anorgasmia.[28] Emotional abuse was associated with structural alterations in emotional processing areas such as the anterior cingulate.[28] Functional imaging studies, largely using functional magnetic resonance imaging, by our group[29] and others[30] have revealed alterations in brain areas that mediate emotional processing to provocative stimuli. Long-lasting changes in cognitive function, including executive function, are also seen in adults victimized during childhood.[31] Coming full circle, the report by Etain et al[4] demonstrating the profound negative consequences of child abuse and neglect on the course of bipolar disorder is of considerable importance because it not only contributes to the burgeoning database on the profound impact of child abuse and neglect on adult health but also raises a fundamentally important question: Do patients with early life trauma and mood disorders represent a unique endophenotype that requires, for optimal outcome, a unique treatment approach? As we uncover the precise neurobiological consequences of child abuse and neglect, rational and novel treatment strategies can be developed.

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REFERENCES

1. Freud S. The aetiology of hysteria. In: Strachey J, ed. *The Complete Psychological Works of Sigmund Freud*. London, UK: Hogarth Press; 1971.
2. Green JG, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the National Comorbidity Survey Replication, 1: associations with first onset of *DSM-IV* disorders. *Arch Gen Psychiatry*. 2010;67(2):113–123.
3. Brent DA, Silverstein M. Shedding light on the long shadow of childhood adversity. *JAMA*. 2013;309(17):1777–1778.
4. Etain B, Aas M, Andreassen OA, et al. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. *J Clin Psychiatry*. 2013; 74(10):991–998.
5. Heim C, Shugart M, Craighead WE, et al. Neurobiological and psychiatric

consequences of child abuse and neglect. *Dev Psychobiol*. 2010;52(7):671–690.
6. Neigh GN, Gillespie CF, Nemeroff CB. The neurobiological toll of child abuse and neglect. *Trauma Violence Abuse*. 2009;10(4):389–410.
7. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry*. 2012;169(2):141–151.
8. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386–389.
9. Ressler K, Bradley B, Mercer K, et al. Polymorphisms in *CRHR1* and the serotonin transporter loci: gene × gene × environment interactions on depressive symptoms. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B(3):812–824.
10. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23):2462–2471.
11. Bradley RG, Binder EB, Epstein MP, et al. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Arch Gen Psychiatry*. 2008;65(2):190–200.
12. Binder EB, Owens MJ, Liu W, et al. Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. *Arch Gen Psychiatry*. 2010;67(4):369–379.
13. Gatt JM, Nemeroff CB, Dobson-Stone C, et al. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry*. 2009;14(7):681–695.
14. Gatt JM, Nemeroff CB, Schofield PR, et al. Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. *Biol Psychiatry*. 2010;68(9):818–824.
15. Binder EB, Bradley RG, Liu W, et al. Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. 2008;299(11):1291–1305.
16. Labonte B, Yerko V, Gross J, et al. Differential glucocorticoid receptor exon 1_B, 1_C, and 1_H expression and methylation in suicide completers with a history of childhood abuse. *Biol Psychiatry*. 2012;72(1):41–48.
17. Klengel T, Mehta D, Anacker C, et al. Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. *Nat Neurosci*. 2013;16(1):33–41.
18. Ouellet-Morin I, Odgers CL, Danese A, et al. Blunted cortisol responses to stress signal social and behavioral problems among maltreated/bullied 12-year-old children. *Biol Psychiatry*. 2011;70(11):1016–1023.
19. Roy A, Hodgkinson CA, Deluca V, et al. Two HPA axis genes, *CRHBP* and *FKBP5*, interact with childhood trauma to increase the risk for suicidal behavior. *J Psychiatr Res*. 2012;46(1):72–79.
20. Plotsky PM, Thrivikraman KV, Nemeroff CB, et al. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. *Neuropsychopharmacology*. 2005;30(12):2192–2204.
21. Coplan JD, Andrews MW, Rosenblum LA, et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci U S A*. 1996;93(4):1619–1623.
22. Carpenter LL, Tyrka AR, McDougle CJ, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depression patients and healthy control subjects. *Neuropsychopharmacol*. 2004;29(4):777–784.
23. Gillespie CF, Nemeroff CB. Corticotropin-releasing factor and the psychobiology of early life stress. *Curr Dir Psychol Sci*. 2007;16(2):85–89.
24. Evans DL, Nemeroff CB. The dexamethasone suppression test in mixed bipolar disorder. *Am J Psychiatry*. 1983;140(5):615–617.
25. Currier MB, Nemeroff CB. Inflammation and mood disorders: proinflammatory cytokines and the pathogenesis of depression. *AntiInflamm Antiallergy Agents Med Chem*. 2010;9:212–220.
26. Danese A, Pariante CM, Caspi A, et al. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci U S A*. 2007;104(4):1319–1324.
27. Pace TWW, Mletzko TC, Alagbe O, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry*. 2006;163(9):1630–1633.
28. Heim CM, Mayberg HS, Mletzko T, et al. Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *Am J Psychiatry*. 2013;170(6):616–623.
29. Cisler JM, James GA, Tripathi S, et al. Differential functional connectivity within an emotion regulation neural network among individuals resilient and susceptible to the depressogenic effects of early life stress. *Psychol Med*. 2013;43(3):507–518.
30. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. 2012;71(4):286–293.
31. Gould F, Clarke J, Heim C, et al. The effects of child abuse and neglect on cognitive functioning in adulthood. *J Psychiatr Res*. 2012;46(4):500–506.