

Neuroanatomical Correlates of Childhood Sexual Abuse: Identifying Biological Substrates for Environmental Effects on Clinical Phenotypes

Sexual abuse during childhood is surprisingly common, with estimates in the general population ranging from 15% to 38% (1). It is associated with significant psychiatric sequelae, including the development of major depression and posttraumatic stress disorder (PTSD). These common consequences of exposure to trauma can emerge in the aftermath of natural disasters as well as those in which humans have a hand (2). Some responses, such as suicidal behavior, are not only life-threatening but have multigenerational repercussions, as individuals who report childhood sexual abuse are at risk not only for suicidal behavior themselves but also for transmitting suicidal behavior and mood disorders to their offspring (3). The timing (4) and severity of childhood sexual abuse are also relevant to its consequences (5). Earlier age at onset of childhood sexual abuse is associated with more intent during suicide attempts (6) as well as greater severity of PTSD (7) and depressive symptoms (8). Similarly, the severity of sexual abuse during development is reportedly related to earlier-onset suicidal behavior (6), greater depression severity (9), and more pronounced symptoms among patients with borderline personality disorder (5). Interestingly, other forms of early life stress, such as childhood emotional abuse and neglect, have been found to be stronger predictors of subsequent depression in adulthood than childhood sexual or physical abuse (10).

Following the excitement generated by the gene-environment interaction literature, researchers are now exploring the biological substrates that may mediate effects of early traumatic experiences on later psychopathology. Elegant studies in animal models have identified epigenetic mechanisms through which the early environment may induce enduring effects on gene expression and, with it, behavioral phenotypes (11). Reports of environmental effects on biological alterations more proximal to clinical phenotypes are also emerging, including effects on neurocognitive, neuroendocrine, and neuroimmune function.

Structural and functional neuroimaging provide powerful tools to explore long-term effects of life experience on neurodevelopment. Most, but not all, structural MRI studies examining neuroanatomical correlates of childhood sexual abuse thus far describe volume reductions in a variety of structures. Decreased volume of the corpus callosum, the left hippocampus, the anterior cingulate, the caudate nucleus, the amygdala, and the visual cortex, as well as more general decreased cerebral volume, have all been reported in survivors of childhood sexual abuse (for reviews, see references 12 and 13).

In this issue of the *Journal*, Heim et al. (14) make use of the burgeoning structural MRI technique of measuring cortical brain thickness to understand neuroplastic responses to childhood trauma. The authors studied 51 medically healthy

women, of whom 55% (N=28) reported moderate-to-severe maltreatment, 18% (N=9) had PTSD, and 24% (N=12) had major depression. Cortical thinning was found to be present in the brain areas involved in the perception or processing of behaviors that are specific to the type of abuse experienced. For example, childhood sexual abuse was associated with cortical thinning in the genital representation field of the primary somatosensory cortex, whereas emotional abuse was associated with cortical thinning in regions linked to self-awareness and self-evaluation (15). The authors conclude that cortical adaptation to traumatic events may lead to decreases in the density of dendritic spines, leading to cortical thinning. They suggest that such changes relate to the child's sensory processing of the abusive experience, which alters cortical representation fields in a regionally specific fashion, based on the nature of the abuse itself. This finding comports with another recent work in which young adults, compared with an unexposed group, who witnessed domestic violence as children had decreased visual cortex gray matter (15), in terms of both volume and cortical thickness, regardless of whether or not they developed psychopathology. In addition, Heim et al. noted that age at onset, although not severity of childhood sexual abuse, was related to cortical thinning in the left temporal pole, the left parietal lobe, the left frontal pole, and the right frontal pole, areas associated with autobiographical memory among other functions. This, they postulate, may serve as the neuroanatomical basis for the observation that victims of childhood sexual abuse often have poor, if any, recollection of the experience and report overgeneralized memories. A question that arises from this finding is whether individuals who experience trauma at a later age, outside the window of peak vulnerability for cortical thinning, develop psychopathology through a mechanism that is distinct from the one responsible for consequences in those who experience trauma during an earlier, critical period.

What is the relevance of these neuroanatomical findings to the broader picture? If replicated, these data provide compelling evidence about the enduring structural effects on the brain as a function of early life experience that are not defined on the basis of a specific psychiatric diagnostic context. Given the nature of the environmental stressor and the difficulties in identifying victims at the time sexual abuse is occurring, it is unlikely that we will be able to develop longitudinal studies to more completely test the hypothesis. Nonetheless, this research may pave the way for the characterization of endophenotypes associated with trauma-related effects on the brain. The possible mechanisms the authors invoke to explain the neuroplasticity observed in this study may not be dependent on epigenetic effects and may suggest alternative molecular pathways underlying early life experience effects on neurodevelopment and psychopathology. Moreover, if life experience can have a role in brain restructuring during development, then appropriately timed experiential or behavioral interventions may have utility in mitigating the effects of negative environmental input or genetic deficits. Indeed, at the behavioral level, perceived social support protects against the development of adult depression among victims of childhood abuse (10). Consistent with this finding, murine studies suggest that enriched environments can mitigate the deleterious effects of low maternal licking and grooming behavior early in development (16). Of note, the

This research may pave the way for the characterization of endophenotypes associated with trauma-related effects on the brain.

question of whether the “active ingredient” of such enrichment is simply aerobic exercise (17), which is linked to hippocampal neurogenesis, has been recently raised.

Finally, if sensory input in general has the potential to precipitate neuro-architectural restructuring, then observed dose effects of the environmental insults may be related to multimodal sensory input from the traumatic experience. Although it stands to reason that more severe experiences would have more profound effects on an individual, elucidation of the exact mechanism for this observation may uncover the neurophysiological basis of such a relationship.

Studies such as the one by Heim et al. bring us closer to delineating the mechanisms that lead to changes in brain morphology and function, which are so critical to developing effective behavioral and pharmacological interventions. We need to understand the role of several key elements leading to these neurobiological changes—the relative contributions of the severity, timing, and nature of a stressor in the context of genetic endowment. Equally important for future research is to study the role of resilience and its neurobiological underpinning, a sorely neglected area. The more clearly we can delineate a biological pathway from environment to psychopathology, the more likely we are to develop interventions to mitigate, cure, or even prevent what ails our patients.

References

1. Bachmann GA, Moeller TP, Benett J: Childhood sexual abuse and the consequences in adult women. *Obstet Gynecol* 1988; 71:631–642
2. North CS, Kawasaki A, Spitznagel EL, Hong BA: The course of PTSD, major depression, substance abuse, and somatization after a natural disaster. *J Nerv Ment Dis* 2004; 192:823–829
3. Brent DA, Oquendo M, Birmaher B, Greenhill L, Kolko D, Stanley B, Zelazny J, Brodsky B, Melhem N, Ellis SP, Mann JJ: Familial transmission of mood disorders: convergence and divergence with transmission of suicidal behavior. *J Am Acad Child Adolesc Psychiatry* 2004; 43:1259–1266
4. Zalsman G: Timing is critical: gene, environment, and timing interactions in genetics of suicide in children and adolescents. *Eur Psychiatry* 2010; 25:284–286
5. Silk KR, Lee S, Hill EM, Lohr NE: Borderline personality disorder symptoms and severity of sexual abuse. *Am J Psychiatry* 1995; 152:1059–1064
6. Lopez-Castroman J, Melhem N, Birmaher B, Greenhill L, Kolko D, Stanley B: Early childhood sexual abuse increases suicidal intent. *World Psychiatry* (in press)
7. Schoedl AF, Costa MC, Mari JJ, Mello MF, Tyrka AR, Carpenter LL, Price LH: The clinical correlates of reported childhood sexual abuse: an association between age at trauma onset and severity of depression and PTSD in adults. *J Child Sex Abuse* 2010; 19:156–170
8. Kaplow JB, Widom CS: Age of onset of child maltreatment predicts long-term mental health outcomes. *J Abnorm Psychol* 2007; 116:176–187
9. Sciolla A, Glover DA, Loeb TB, Zhang M, Myers HF, Wyatt GE: Childhood sexual abuse severity and disclosure as predictors of depression among adult African American and Latina women. *J Nerv Ment Dis* 2011; 199: 471–477
10. Powers A, Ressler KJ, Bradley RG: The protective role of friendship on the effects of childhood abuse and depression. *Depress Anxiety* 2009; 26:46–53
11. Caldji C, Hellstrom IC, Zhang TY, Diorio J, Meaney MJ: Environmental regulation of the neural epigenome. *FEBS Lett* 2011; 585:2049–2058
12. Hart H, Rubia K: Neuroimaging of child abuse: a critical review. *Front Hum Neurosci* 2012; 6:52
13. Pereda N, Gallardo-Pujol D: [Neurobiological consequences of child sexual abuse: a systematic review]. *Gac Sanit* 2011; 25:233–239
14. Heim CM, Mayberg HS, Mletzko T, Nemeroff CB, Pruessner JC: Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *Am J Psychiatry* 2013; 170:616–623
15. Tomoda A, Polcari A, Anderson CM, Teicher MH: Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. *PLoS ONE* 2012; 7:e52528
16. Champagne FA, Meaney MJ: Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. *Behav Neurosci* 2007; 121:1353–1363
17. Mustroph ML, Chen S, Desai SC, Cay EB, DeYoung EK, Rhodes JS: Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. *Neuroscience* 2012; 219:62–71

MARIA A. OQUENDO, M.D.
JEFFREY M. MILLER, M.D.
M. ELIZABETH SUBLETTE, M.D., PH.D.

From the Department of Neuroscience, New York State Psychiatric Institute, New York, and the Department of Psychiatry and Molecular Imaging and Neuropathology Division, Columbia University, New York. Address correspondence to Dr. Oquendo (mao4@columbia.edu). Editorial accepted for publication March 2013 (doi: 10.1176/appi.ajp.2012.13030367).

Dr. Oquendo has received royalties for use of the Columbia Suicide Severity Rating Scale; financial compensation from Pfizer for the safety evaluation of a clinical facility; grant support from Eli Lilly; unrestricted educational grants and/or lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire; and her family owns stock in Bristol-Myers Squibb. Dr. Miller has received financial compensation for evaluations in studies sponsored by Pfizer and Orexigen Therapeutics, and his family owns stock in Johnson & Johnson. Dr. Sublette has received a grant from Umicore International for nutritional supplements. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.