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The Silent Epidemic of Neurodevelopmental Injuries

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Childhood maltreatment in the United States was recently recognized as a major public health problem by several influential sources including the World Health Organization and the Institute of Medicine (1,2). An extensive survey conducted by the National Incidence of Child Abuse and Neglect (NIS3) revealed that roughly 1.5 million children were abused or neglected in 1993. This number of documented cases most likely underestimates the true prevalence, given that many cases of maltreatment go unrecognized (2). Moreover, according to the three available NIS reports, the incidence of childhood maltreatment has been steadily increasing over the past 3 decades (see also NIS4 for a good summary of this issue). Although increased reporting might explain some of the data, it is unlikely to explain this alarming trend fully (3). In the absence of effective interventions, maltreated children go on to develop a host of behavioral, emotional, cognitive, and medical sequelae that are chronic and in many cases refractory to treatment (2,4–6). The relationship between early life adversity (ELA) and mental illness has now been documented with both retrospective and prospective studies (reviewed in [2]), and several reports have consistently documented that more than one-half (!) of the individuals with chronic mental illness have been physically, verbally, or sexually abused early in life (7,8). Although most clinicians and researchers will endorse the notion that ELA is associated with increased risk for chronic mental illness, few appreciate the true magnitude of this problem. Better awareness of the burden that exposure to ELA places on adult psychiatric services represents the first step necessary towards transforming current psychiatric interventions. This paradigm shift should substitute the current focus on symptom-reduction with one that focuses on prevention and incorporates a neurodevelopmental framework to diagnose and treat ELA-associated psychopathology. These interventions will require a sound biological understanding of normal neurodevelopment and how ELA interferes with this process.

The Biology

The observations that many of the symptoms associated with exposure to ELA are present early in life and persist into adulthood suggest that exposure to ELA is able to program brain development in a manner that is somewhat refractory to change later in life. How are events early in life able to modify complex behavior in adulthood, and why are these patterns so difficult to reverse in adulthood? We know little about the answers to these two questions; however, similar observations made in rodents and nonhuman primates suggest that some aspects of this phenomenon could be further understood with animal models (4).

A good example of how animal models can elucidate some of the molecular mechanisms by which ELA modifies adult behavior comes from a body of work showing that maternal care in rats is normally distributed in the population, with some dams providing almost three times

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higher levels of licking and grooming (LG) to their pups compared with others (4,9). High and Low LG dams were defined as those that are at least 1 SD above and below the mean, respectively. This paradigm establishes two non-overlapping neurodevelopmental tracks in which Low LG dams represent a form of “parental neglect,” whereas High LG dams represent a form of “active parenting.” Offspring of High LG dams are less fearful, show decreased stress reactivity, and perform better on several hippocampal-dependent tasks compared with offspring raised by Low LG dams. Several lines of evidence suggest that levels of tactile stimulation provided by the dams during the first week of life are responsible for the behavioral differences among offspring of Low and High LG dams. Similar findings with regard to the importance of tactile input in early neurodevelopment have also been documented in nonhuman primates and humans (reviewed in [4]).

How does frequency of LG during the first week of life modify stress reactivity early in life, and how does this physiological trait persist throughout life? It appears that a high frequency of LG during a specific period of brain development is necessary to remove DNA methylation from a short DNA segment (i.e., known as a promoter element) that controls expression of the glucocorticoid receptor (GR) in the hippocampus (Figure 1). In the absence of active parental tactile input, such as experienced by offspring of Low LG dams, this pattern of DNA methylation remains unchanged. In contrast, exposure to high frequency of LG resulted in removal of DNA methylation from this promoter region (10). These observations have two important implications. First, high levels of DNA methylation make this promoter less accessible to the machinery necessary to induce expression of GR, resulting in lower levels of GR in the hippocampus of Low LG offspring (Figure 1). This is important, because GR levels in the hippocampus control the rate by which stress-induced release of the stress hormone corticosterone is terminated (Figure 1) (and see [4] for more details on this issue). Because offspring of Low LG have lower levels of GR in their hippocampus, they show elevated and prolonged levels of corticosterone when stressed, compared with the more transient pattern of corticosterone release seen in offspring of High LG dams. Second, once established, this pattern of DNA methylation is highly stable and persists throughout the animal’s life. Thus, the stability of the DNA methylation at the GR promoter provides a molecular mechanism to explain how the frequency of LG early in life affects stress reactivity and why it persists later in life.

The relevance of the rodent findings to human psychopathology was recently studied with postmortem analysis comparing GR messenger RNA levels and promoter methylation in adult suicide victims with a history of ELA with suicide victims without a history of ELA. Individuals exposed to ELA showed lower levels of GR in their hippocampus—similar to results obtained in rodents—and these were associated with higher levels of DNA methylation in the same GR-promoter region described in the rat model (11). This work provides a plausible molecular model to explain previous data documenting increased stress reactivity in both humans and nonhuman primates exposed to ELA (4) and demonstrates the potential of using animal models to elucidate some of the molecular mechanisms by which ELA modifies adult behavior.

The Challenges

A better understanding of the dotted line that connects neurodevelopment with adult brain functioning is an essential step towards developing more effective tools to diagnose and treat psychopathologies associated with ELA. Unfortunately, the biology by which neurodevelopment influences adult complex behavior is currently poorly understood in rodents and nonhuman primates. For example, many details regarding the mechanisms by which DNA methylation is removed during early development or maintained in the adult rat brain are unclear (9). It is also important to recognize that DNA methylation is likely to be only one of many “molecular tricks” by which events early in life are able to shape adult behavior. The

availability of unbiased genomic tools provides promising and powerful strategies to identify novel developmental pathways affected by ELA. The issue of sequential brain modification also needs to be studied. For example, chronic exposure to high levels of corticosterone in Low LG offspring is likely to generate secondary changes in important physiological, behavioral, and cognitive functions that are yet to be rigorously studied. Finally, preclinical and clinical work from several groups has shown that genetic makeup can modify the behavioral or physiological sequelae of ELA (4). However, the molecular mechanisms by which genes and early environment interact to modify neurodevelopment have not yet been clarified.

A recent report issued by the Neurodevelopmental Work Group sponsored by the National Advisory for Mental Health Council elegantly outlined specific areas of research that need to be expanded to bridge the gap between neurodevelopment and mental illness (for details, see the National Institute of Mental Health [NIMH] Neurodevelopment Work Group report *Transformative Neurodevelopmental Research in Mental Illness*). However, conspicuously missing from this report is the notion that child maltreatment represents a major risk factor for the development of numerous psychopathologies and therefore a particularly relevant target for intervention and study. Our current failure to recognize ELA as a major health problem in the United States is also reflected in the inadequate amount of resources we dedicate to address this issue. For example, a 2009 report from the Institute of Medicine estimated the cost related to ELA at \$247 billion annually (1), which is similar in magnitude to the estimated costs for all cancers combined. Interestingly, however, we spend only \$.05 on research related to psychopathology of ELA compared with \$2 spent on cancer research for each \$100 of their respective costs (12). Moreover, only 2% of the Division of Developmental Translational Research resources within the 2006 NIMH portfolio were allocated to study child maltreatment (see Appendix C of the Neurodevelopmental Work Group report).

Even after a significant investment in resources, progress in this area will require the development of evidence-based interventions to effectively treat exposure to ELA (4,6). Moreover, new expertise in functional neurodevelopment will need to be established at the basic science level and incorporated into a conceptual paradigm shift in the way we view the relationship between neurodevelopment and adult behavior. The lack of expertise in functional neurodevelopment is partly because laboratories that study neurodevelopment have traditionally shied away from studying complex behaviors, whereas groups studying complex behaviors know little about neurodevelopment. This division between neurodevelopment and adult brain function starts at the basic-science level, is further reinforced by the way our funding system is fragmented, and is cemented at the clinical level by the chasm we have created between child and adult psychiatry.

In summary, failure to recognize ELA as a major public-health hazard, coupled with fragmented conceptual approach, lack of expertise in functional neurodevelopment, and inadequate resources dedicated to address this issue represent four important challenges we currently face in addressing this silent epidemic. The NIMH's recent focus and increase in resource allocation to study neurodevelopment, coupled with recent advances in genomic and molecular tools available to study this problem, will likely provide new insights into the underlying biology, paving the way to psychiatric care that focuses on prevention and better interventions.

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Figure 1.

Frequency of licking and grooming (LG) programs expression of glucocorticoid receptor (GR) in the hippocampus of adult animals via stable alterations in DNA methylation of promoter elements that control GR expression. **(A)** The GR promoter is highly methylated at birth. **(B)** (Top) Exposure of pups to high frequency of LG during the first week of life (shown in light purple) leads to removal of DNA methylation from the GR promoter, leading to higher expression of the GR protein and more efficient termination of stress-induced hypothalamic-pituitary-adrenal axis (HPA) activation (i.e., decreased stress reactivity). (Bottom) Low levels of LG during the first week of life maintain the GR promoter in its methylated state, leading to poor accessibility of this promoter region to the machinery necessary to induce expression of GR. Low expression levels of the GR protein leads to less efficient termination of stress-induced HPA activation (i.e., increased stress reactivity). **(C)** The stability of the DNA methylation pattern established in **B** is responsible for maintaining the differences in GR levels and HPA reactivity between offspring of High and Low LG dams throughout life. ORF, open reading frame of the GR protein.