Social, Psychological, and Physiological Reactions to Stress

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Abstract

Emerging research examines biological processes not as primary causes of social outcomes but rather as mechanisms that themselves depend on social environments. In particular, environments that produce toxic stress help shape brain development and brain and body function throughout the lifespan. Early life stress, in particular, has serious consequences for life-long health and affects cognitive performance, emotional intelligence, and self-regulation. Because the brain is plastic, social as well as individual behavioral interventions can alter some of these developmental paths, modifying brain function and individual life trajectories—but with increasing difficulty as children become adolescents and adults. Now reflecting the new era of "epigenetics" and a life course perspective, this new view of stress, the brain, and social environments highlights the importance of the social, psychological, and biological sciences working together to elucidate underlying mechanisms both to expand knowledge and help promote a better society.

INTRODUCTION

Emerging trends in our multidisciplinary understanding of the effects of stress on health, behavior, and individual life trajectories have developed in the context of long traditions of foundational research in sociology, anthropology, and psychology and changing understandings of biology and the brain. Biology has progressed through the DNA revolution, which early on suggested to many in the social sciences and in the public that biologists viewed genetic endowment as "destiny." Moreover, the brain was long regarded as separate from the rest of the body and stable in its architecture laid down before birth. The connections between biology and the social sciences were limited at best.

Yet the pioneering work of Hebb focused on the changing connections among nerve cells in the brain in the formation of memories, and later research by Bennett, Krech, Diamond, and Rosenzweig described the

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growth of the cerebral cortex induced in animals by an enriched environment. Such research began to raise awareness of the dynamic nature of the adult as well as the developing brain in response to experiences. Now biology has entered the era of "epigenetics" ("above the genome," referring to the new science of the seamless interaction between genes and the environment and the underlying mechanisms that link them), which is unraveling the complexities of the regulation of genetic traits by the environment and has pointed to the enormous range of possible outcomes of environmental/experiential influences on the brain. This work has opened new possibilities for understanding how stress-producing social environments and behaviors and biological mechanisms responding to those environments interact to shape brain and body function and life trajectories. Now is the time when the social and biological sciences can build on one another's insights to deepen our understanding of patterned human behavior as well as individual variations (A and B. After most paragraphs, one or more letters will refer the reader to bibliographic sections organized broadly by topic at the end of the article).

CUTTING-EDGE RESEARCH, CONCEPTS, AND THEORY

A central challenge at present is to connect social science research to emerging findings in biology and neuroscience in order to understand how socially produced adversities get "under the skin" and what social factors buffer and protect against adverse biological effects. Social structures and relationships influence biology in at least four different ways, especially in the early years of life. *First*, social environments can create adversities—extreme poverty, physical abuse, and unsafe and chaotic neighborhoods—that lead to toxic stress and allostatic overload (the negative physiological cost to the body when the active adaptation to stressors—"allostasis"—is overused or dysregulated). These in turn shape brain structure and function and promote a variety of diseases (http://onlinelibrary.wiley.com/doi/10.1111/nyas.2010.1186.issue-1/issuetoc). *Second*, secure and warm relationships with caregivers can protect against some of the biological consequences of adversity. *Third*, social interventions—well-designed preschooling, home visiting, and classroom programming—can take advantage of the brain's plasticity either by preventing adverse changes or, when such changes have taken place, can promote reprogramming of those parts of the brain that have been disrupted by adversity and toxic stress. *Fourth*, social relationships as well as social conditions have epigenetic effects related to stress responsiveness that we are just coming to understand. A new synthesis of biology, behavior, and the social environment is made possible by emerging concepts of toxic stress, allostasis/allostatic overload,

and plasticity of the brain as the central organ of stress and adaptation, all in the context of epigenetics (C, D, E—see references, which are grouped by topic).

Toxic Stress and Allostatic Load/Overload

We now understand that the brain and body are connected in a network of reciprocal interactions via the autonomic, neuroendocrine, metabolic, and immune systems that regulate each other. What happens in the brain alters the activity of these systems and affects multiple body systems concurrently. These systems, in turn, send signals—both neural and biochemical—back to the brain. Normal stress responses exemplify the operation of these interacting systems and the allostatic responses that maintain balance among them. Normally, response to an acute stressor involves a rapid turning on of adrenalin secretion followed by cortisol secretion, leading to altered immune response, improved memory, and energy replenishment as well as more efficient cardiovascular function. When the stressor is over, the adrenalin and cortisol responses are efficiently shut off. However, when the stress–response system remains turned on in response to chronic stressors in the environment, this network of body systems becomes dysregulated. Toxic stress refers to this condition and the underlying biology can be understood in terms of allostasis and allostatic load/overload (D).

Allostasis refers to the active process of responding to challenges by activating the autonomic, neuroendocrine, metabolic, and immune systems via the brain, the organ that perceives and responds to potential threats. Normally, allostatic responses lead to adaptation when they are turned on and off efficiently in response to stressful events and their conclusion. However, toxic stress leads to "allostatic load and overload" when the hormonal mediators of the stress response continue to act on the body in ways that create "wear and tear" (D).

Allostatic overload leads to pathophysiology (physiological imbalance, such as hyperglycemia or chronic inflammation leading to disease) and accelerating progression of diseases such as cardiovascular disease, diabetes, arthritis, and depression. It also affects cognitive function negatively, in part through its compromising effect on self-regulation and executive function. Self-regulation involves in part the capacity to restrain impulses, anger, and inappropriate behavior. Executive function is an aspect of self-regulation involving mobilization of short-term memory, capacity to sequence and shift tasks, and focus attention—all important to planning, thinking and solving problems. These compromised capacities in turn affect social behavior and school as well as later occupational success. Thus, the toll taken by allostatic overload is considerable (C, D).

Stressful life experiences produce toxic stress and allostatic load (http://developingchild.harvard.edu/index.php/activities/council/). Early life experiences are biologically embedded, in the sense that they can have long-lasting effects on brain function and on brain–body interactions that strongly influence life course trajectories. The Adverse Childhood Experiences (ACE) study led by Drs Vincent Fellitti and Robert Anda revealed the long-lasting consequences for physical and mental health of events early in a child's life. An ACE score derives from counts of adversities in childhood—including parental divorce, family member incarcerated, alcohol or drug abuse or depression in family, harsh language, and physical or sexual abuse. It is important to note that both mental health problems such as depression; substance abuse and antisocial behavior; and physical health disorders such as cardiovascular disease, chronic obstructive pulmonary disorder (COPD), and diabetes show a dose-dependent effect of the ACE score (G). For the brain, a child growing up over a 10-year period with a depressed mother will have an enlarged amygdala, a brain region that mediates anxiety and fear. And, in addition to ACE, which occur at all socioeconomic levels, long-term poverty adds a powerful additional stamp, impairing the development of the prefrontal cortex and of self-regulatory behavior through toxic stress, produced in part by chaotic and crowded homes and dangerous neighborhoods. Alienation and social isolation can also have devastating effects upon well-being, and both hostility and loneliness are themselves severe stressors and contribute to allostatic load (C, D G).

Importantly, supportive social relationships—especially from caregivers in early childhood—help protect against allostatic overload in the face of sustained environmental stressors (http://developingchild.harvard.edu/resources/reports_and_working_papers/foundations-of-lifelong-health/). Throughout the lifespan and particularly later in life, eudaimonic well-being (feeling connected to a deeper purpose) is associated with lower allostatic load and higher cognitive and physical function, as well as lower incidence of dementia in the elderly when compared with hedonic well-being, (feeling gratification from immediately pleasurable experiences) (E).

The Brain's Plasticity

Over the past several decades, we have become increasingly aware that the structure and function of the brain are malleable as a result of experiences in the physical and social environment, including the nature of social interactions, during development and in adult life. Building upon the work of Hebb and Bennett, Krech, Diamond, and Rosenzweig, we now understand the continuous turnover of at least some of the synaptic connections in the

brain modulated by experience and mediated, in part, by the daily fluctuations of cortisol, otherwise known as a "stress" hormone but having many other important functions. Moreover, limited development of new neurons takes place in several parts of the brain, continues throughout adult life, and can be altered both by experiences and by hormones (A).

Stressful experiences impair this plasticity, however, and cause reversible changes in the neural architecture of healthy brains that promote vigilance in the face of danger along with changes in gene expression reflective of cumulative experiences. When these changes persist after danger passes, the altered brain architecture can lead to anxiety and other mood disorders. Yet, regular physical activity enhances plasticity and stimulates neuron development in and increases in the volume of the hippocampus while improving memory and executive function; intense learning also changes brain architecture. In contrast, diabetes, which has increased in incidence in part as a result of poverty and early life adversity, leads to impaired brain architecture even in teenagers, along with impaired cognitive function and increased risk for Alzheimer's disease later in life. Furthermore, perceptions of inequality in adults as a result of socioeconomic differences predict health status and have correlates in aspects of brain structure and function, including impaired white matter (the "insulation" of the brain) (A, D).

As we have seen, plasticity means that early childhood experiences affect brain development. For example, language processing capacity and ability as well as emotional intelligence grow in early "serve and return" interactions between infants and caregivers (http://developingchild.harvard.edu/index.php/activities/council/). When parents coo or gesture in response to their infants or talk with their children, they are engaging in serve and return interactions that play a key role in building brain architecture. One example of serve and return involves linguistic interactions between parents and caregivers. The pioneering research of Hart and Risley and subsequent studies have shown that children from poor families are likely to hear far fewer words than their counterparts in professional families with consequences for both their vocabularies and the linguistic capacities of their brains. Ongoing research with recorders that gauge volume of linguistic interaction between parents and children suggests that helpful monitoring and feedback increases verbal interaction significantly. Serve and return interactions not only promote language and cognitive development but are a key to strong attachments with caregivers and increased capacity for self-regulation and empathy (http://developingchild.harvard.edu/index.php/activities/council/) (C).

The implications of plasticity are two-sided. On the one hand, as we have seen, adversities and toxic stress can impair brain architecture, especially

early in life. On the other hand, brain growth in response to positive interactions with caregivers builds strong brain architecture. Programs such as the Nurse Family Partnership (http://www.nursefamilypartnership.org/) intervene early on to build the positive and reduce the negative experiences of early childhood. Evidence indicates home visiting has beneficial effects by reducing childhood adversities and increasing protective relationships through support and education of parents starting even before the birth of the child. Later social interventions can also "reprogram" the brain in ways that help to overcome the effects of early adversities. Longitudinal studies of high-quality preschool programs in Michigan, North Carolina, and Illinois provide evidence that early interventions with at-risk children can have powerful long-lasting effects. For example, long-term follow-up of the Highscope Perry School's two-year preschool program for an experimental group of 3- to 4-year-olds project has shown multiple benefits, including higher rates of school completion, higher income for adults, and reduced arrests (http://www.highscope.org/Content.asp?ContentId=219). Moreover, such high-quality early childhood programs as the Abecedarian Project in North Carolina have been shown not only to have substantial benefits in reducing crime, raising earnings, and promoting education but also significantly lower prevalence of risk factors for cardiovascular and metabolic diseases in the mid-30s, especially among males. The website of the National Scientific Council on the Developing Child is a rich source of information on this topic (http://developingchild.harvard.edu/index.php/activities/council/) (E).

Genetic Variants Matter—Orchid and Dandelion Children

Recent research on children as well as studies using animal models also makes us increasingly aware that commonly occurring genetic variants (alleles) make individuals differentially responsive to their environments. The so-called "context-sensitive alleles" increase sensitivity to both positive and negative experiences. As a result, children with such alleles do better than average in functioning in positive school environments, while, in chaotic, more stressful and less nurturing environments, such context-sensitive children ("orchid children") will do worse than the so-called "dandelion children" who are far less responsive to context. It is not clear yet whether "orchid" individuals might actually do better later in life in responding to therapeutic interventions because of their context sensitivity and, possibly, their greater capacity for plasticity via epigenetic mechanisms, compared to "dandelion" individuals (B).

Epigenetics

Emerging knowledge of epigenetics further reveals the power of social environments, experiences, and behavior to shape and reshape biology. "Epigenetics" refers to the seamless and continuous interaction between environmental and experiential factors and the genetic constitution of an individual. Epigenetic mechanisms operate via folding and unfolding of the DNA double helix to repress or expose genes and involving modifications of DNA by methylation of the cytosine base as well as through the operation of so-called "non-coding" RNAs that modify how the primary RNA messages are processed and encoded into proteins. These mechanisms operate throughout the life course and offer opportunities to change brain and body function at any age, although making such changes becomes harder after the critical or sensitive developmental periods have past. Epigenetics emphasizes plasticity and malleability, which can be observed at many different levels and not only at the level of gene regulation. For example, environmentally regulated changes can occur in neural architecture, involving limited neurogenesis and also the turnover of synaptic connections and shrinkage and expansion of neuronal dendritic trees. Yet, ultimately everything that happens to the cells of our body influences the expression of our genetic code, and the modern science of "epigenetics" has started to uncover multiple mechanisms that provide many permutations and combinations with many possible outcomes. Particularly noteworthy is the fact that genetically identical individuals can become different owing to epigenetic effects of nonshared experiences (B).

Recent research by Meaney demonstrates the powerful effects that social relationships can have on gene expression related to the experience of stress. This research shows that the extent to which rat mothers lick and groom their nursing pups affects whether or not at least the expression of one of the pup's genes is modified. When this epigenetic change takes place as a result of intense licking and grooming, the pups will be better able to limit their reactions to high-stress situations. This epigenetic change (with no alteration in the DNA) then is later passed on by the pup to its offspring. Emerging evidence from Chen, Miller, and colleagues about parallel epigenetic changes in human infants resulting from adversities suggests that they affect genes that react to stress in ways affecting blood pressure and heart rate. Over the life course, the result is a body with greater sensitivity to stress and inflammation (B).

SUMMARY

Recent research and theorizing focus on biological stress processes in the brain and body, in continuous interaction with social as well as physical environments and their effects on the health and life chances of individuals and

throughout the life course. As a result, biological stress mechanisms can reinforce broad social patterns of inequality—for example, increasing the chances that poor children will be poor as adults and the likelihood that illnesses such as depression, obesity, diabetes, and cardiovascular disease will occur more frequently among the poor and working class. On the other hand, the plasticity of the brain and responsiveness of the body to the environment open up opportunities through evidence-based interventions such as home visiting, high-quality preschool education, and changes in social supports for parents to prevent or overcome early disadvantages and build the foundations for productive and satisfying lives. The research also implies that reducing the sources of toxic stress by interventions such as lowering poverty, supporting neighborhood development, and providing affordable, high-quality child care can affect developing brains and provide long-term dividends in health and well-being.

KEY ISSUES FOR FUTURE RESEARCH

This emerging view of closely interlinked biology, behavior, and social structures and relationships has many implications for both research and interventions. As a result, it is vital that there be both research collaborations across disciplines and organized attention to communicating research results to policy makers. The research issues include the following:

- Research to find ways to open "windows of plasticity" so that behavioral and social interventions can promote beneficial change even after early adversity has occurred. We know that regular physical activity is one way to do this, but research could open other ways to open those windows (F).
- Research to refine our understanding of which social and environmental conditions produce toxic stress and under what conditions. Current research examines a wide array of adversities—environmental, interpersonal, social structural—but without either an organizing theory or systematic evidence using consistent variables to indicate which adversities created by poverty matter most for toxic stress.
- Enhance understanding of protective factors and the social structures and resources that support them. We know that warm, supportive relationships and strong parent–child bonding protect against toxic stressors. But we know far less well how and why the availability of such relationships varies across families and groups and what social interventions might be most effective in building those relationships and at what ages they can be effective.

- Research to elaborate our understanding of the epigenetic basis of context sensitivity and the ways that they influence the responses of infants and children to their social environments. This research is in its early stages. We need to know not only the early developmental implications of context sensitivity and insensitivity but also their potential contributions to efforts to "reprogram" the plastic brain through later school programs or therapeutic interventions.
- Reorienting research on health, social and cognitive ability, social mobility, and schooling to recognize the entire life course—especially including early childhood. We are beginning to recognize the importance of experiences over the entire life course (the "life course development model" by Halfon and colleagues) in the emerging era of "epigenetics" and brain plasticity and brain–body reciprocal interactions. In the domain of health, this has led to what is now called "integrative medicine" to prevent as well as treat disorders in an era when health care costs are increasing and people are living longer (B).
- Systematic evaluation research on interventions to reduce toxic stress or to overcome its effects on brain and body. In order to arrange our society in order to realize human potential, research is needed to assess interventions such as high quality child care, parent education, income supports on children's development, and their subsequent trajectories. This research ideally should involve scholars of many disciplines in order to gauge the nature and implementation of the interventions, their impact on brain and body development, and school behavior and performance, among other variables.
- Research to assess macro-level social interventions. Which macrolevel interventions, if any (such as widely available publicly supported child care, universal family leave, income supports) reduce childhood adversity and toxic stress and improve developmental outcomes? Comparative international research or studies comparing localities or states with differing social policies can help answer these questions. At the societal level, the most important top-down interventions are the policies of government and the private sector that not only improve education but also allow people to make choices that improve their chances for a healthy life. For example, the Acheson report of the British Government in 1998 recognized that no public policy of virtually any kind should be enacted without considering the implications for the health of all citizens. In addition, private sectors policies that encourage healthy lifestyle practices among their employees are likely to gain reduced health insurance costs and possibly a more loyal workforce (E).

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Bruce S. McEwen obtained his PhD in Cell Biology in 1964 from the Rockefeller University. He is a member of the US National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He served as President of the Society for Neuroscience in 1997–1998. As a neuroscientist and neuroendocrinologist, McEwen studies environmentally regulated, variable gene expression in the brain, mediated by circulating steroid hormones and endogenous neurotransmitters in relation to brain sexual differentiation and the actions of sex and stress hormones on the adult brain, in particular related to structural and functional plasticity via epigenetic mechanisms. His laboratory discovered adrenal steroid receptors in the hippocampus in 1968. His laboratory combines molecular, anatomical, pharmacological, physiological, and behavioral methodologies and relates their findings to human clinical information. His current research focuses on stress effects on amygdala and prefrontal cortex, as well as the hippocampus, and his laboratory also investigates sex hormone effects and sex differences in these brain regions involved in cognitive function and mood regulation. He served on the MacArthur Foundation Research Network on Socioeconomic Status and Health, in which he has helped to reformulate concepts and measurements related to stress and stress hormones in the context of

human societies, which led to the concept of "allostatic load and overload" that describes the wear and tear on the body and brain from chronic stress and related life style behaviors that lead to dysregulation of physiological stress pathways that are normally protective. He is also a member of the National Council on the Developing Child, which focuses on biological embedding of early life experiences and promoting healthy brain development. He is the coauthor of a book with science writer, Elizabeth Lasley, for a lay audience called "The End of Stress as We Know It," published in 2002, and "The Hostage Brain" with science writer, the late Harold M. Schmeck, Jr., published in 1994, both of which are now available as eBooks.

Web: http://www.rockefeller.edu/labheads/mcewen/mcewen-lab.php

CRAIG A. McEWEN SHORT BIOGRAPHY

Craig A. McEwen is Daniel B. Fayerweather Professor of Political Economy and Sociology Emeritus at Bowdoin College where he taught from 1975 to 2012. A 1967 graduate of Oberlin College, he earned his PhD in sociology at Harvard University in 1975 after teaching 4 years at Morgan State College (now University). Over the past decade he has become deeply involved in community initiatives addressing poverty and early childhood development with the United Way of Mid Coast Maine particularly. For example, he chairs the implementation committee for a home visiting initiative that will expand those resources in the region. At Bowdoin he helped to found the Center for the Common Good and then served as Senior Faculty Fellow there for 5 years supporting student involvement in community service and community-based courses. He developed and taught a course that involved students in doing research with and for local agencies providing services to low income clients. His scholarly interests have followed this teaching and community engagement and now focus particularly on the impact of poverty on child development. His early research and writing examined community corrections in comparison in a book, *Designing Correctional Organizations for Youths*. Over the next 30 years his research and commentary focused largely on the legal profession, courts and mediation programs—small claims, community, corporate, family and general civil—and has been published widely in law reviews, social science journals and professional magazines. He is coauthor of the treatise *Mediation: Law, Policy, Practice* (with Sarah Cole, Nancy Rogers, James Coben, and Peter N. Thompson). He also coauthored with Lynn Mather and Richard Maiman an empirical study of *Divorce Lawyers at Work: Varieties of Professionalism in Practice*, and with Nancy Rogers, Robert Bordone and Frank Sander wrote *Designing Systems and Processes for Managing Disputes*. At Bowdoin he served as Dean for Academic Affairs from 1999 to 2006.

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