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The Brain on Stress: Toward an Integrative Approach to Brain, Body and Behavior

Bruce S. McEwen, Ph.D.
Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY

Abstract

The discovery of stress hormone receptors in the hippocampal formation has fostered research showing that the brain, including its higher cognitive centers, is the key organ of the response to stressors, both in terms of perception of what is stressful and for its ability to determine the consequences of stress for both brain and body via the neuroendocrine, autonomic, immune and metabolic systems. These systems are, in turn, responsible for either successful adaptation or pathophysiology due to the cumulative burden of adaptation to stress and maladaptive lifestyle, known as "allostatic load". The brain, itself, is also a target of stress and stress-related hormones and it undergoes structural and functional remodeling and significant changes in gene expression that are adaptive under normal circumstances but which can lead to damage when stress is excessive. The growing recognition of the adaptive plasticity and stress vulnerability of the brain itself, beginning with the hippocampus, now includes other brain regions such as the amygdala and prefrontal cortex and fear related memories, working memory, and self-regulatory behaviors. The interactions between these brain regions during the biological embedding of experiences over the life course determines whether events in the social and physical environment will lead to successful adaptation or to maladaptation and impaired mental and physical health, with implications for understanding health disparities and the impact of early life adversity and for intervention and prevention strategies.

The Behavioral Science Program at The Rockefeller University in 1966 included as senior members Neal Miller and Carl Pfaffman, William Estes and George Miller, and Peter Marler and Donald Griffin, a who's who of physiological psychology, cognitive psychology and animal behavior, respectively. The atmosphere was exciting, as these different aspects of cutting edge behavioral science educated each other and provided a rich training ground for students, postdocs, and young faculty like myself and my current Rockefeller colleagues, Donald Pfaff and Fernando Nottebohm.

Neal Miller played a major role in defining the field of behavioral medicine through work that led to the widespread use of "biofeedback" and by calling attention to mechanisms by which the nervous system and body interact with each other. My own research on brain-body interactions, involving the neuroendocrine system, began in the Miller laboratory then and was shaped by his interest in stress, which inspired our discovery in 1968 that there are

Bruce S. McEwen, Ph.D., Alfred E. Mirsky Professor, Head, Harold and Margaret Milliken Hatch, Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Avenue, New York, NY 10065, Tel: 212 327 8624, FAX: 212 327 8634, mcewen@mail.rockefeller.edu, Web: http://www.rockefeller.edu/labheads/mcewen/mcewen-lab.php.

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stress hormone receptors in the hippocampal formation (McEwen, Weiss, & Schwartz, 1968), a brain region involved in episodic, spatial and contextual memory, and mood regulation. That stress hormones act in the hippocampus and, we now know, in other brain regions involved in cognition and affect regulation rather than only affecting the hypothalamus, has triggered a large number of studies on animal models with increasing translation to human stress-related disorders, such as depression and also changes associated with the aging process. The line of research that resulted from this has reinforced the notion that the brain is the key organ of the stress response both in terms of perception of what is stressful and for its ability to determine the consequences of stress for both brain and body.

Stress Through the Lifespan

Stress hormones progressively impair brain function, which further increases cortisol levels, which promotes further impairment. This concept, called the “glucocorticoid cascade hypothesis”, has fostered considerable research on the “weathering” of the brain and body during aging, including effects on longevity and on decline of cognitive function and was a stimulus for the allostatic load concept described below (Sapolsky, 1992; Sapolsky, Krey, & McEwen, 1986). One very productive direction of this research has been the investigation of the role of maternal care and early life stress as a determinant of stress vulnerability by Meaney, Plotsky, and others, following on the pioneering work of Levine and Denenberg on effects of “handling” of newborn rats (Levine, Haltmeyer, Kara, & Denenberg, 1967; Liu et al., 1997). This work, in turn, provides an experimental foundation for recent translational research on gene-environment interactions, now called “epigenetics”, and, in particular, for the effects of abuse and trauma in childhood on depression and antisocial behavior as well as cardiovascular disease and obesity (Caspi et al., 2002; Felitti et al., 1998). This work also shows positive effects of a nurturing environment in improving brain function and promoting a healthy body (http://developingchild.harvard.edu/index.php/activities/council/) (Shonkoff, Boyce, & McEwen, 2009).

Indeed, stress and stress hormones can have positive effects, and, along with investigating the damaging effects of chronic stress, a second direction of our research has been to elaborate the notion that the mediators of the biological and behavioral stress responses exert positive, adaptive effects in the aftermath of stress (McEwen, 1998; McEwen & Gianaros, 2011). The concepts of allostasis (active process of adaptation and maintaining homeostasis) and allostatic load (wear-and-tear produced by too much stress and a resulting unhealthy lifestyle) emphasize the protective as well as damaging effects of these mediators, which act in a non-linear manner and influence simultaneously brain and multiple body systems (McEwen & Gianaros, 2011). For example, acute stress enhances immune function and improves certain types of memory whereas chronic stress has the opposite effect; moreover, disorders such as depression, diabetes and mild cognitive impairment in aging share co-morbidities (McEwen & Gianaros, 2011).

Psychosocial Factors and Stress

Allostasis and allostatic load have helped health psychologists and other social scientists as well as epidemiologists and the fields of medicine and psychiatry to integrate the biology of

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stress with the psychosocial factors that promote stress-related disorders and pathophysiology (McEwen & Gianaros, 2010, 2011; Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010). Measurement of an allostatic load battery, developed by Teresa Seeman at UCLA, and colleagues in the MacArthur Research Network on Socioeconomic Status and Health, has provided predictive power in understanding how socioeconomic status can "get under the skin" to affect health (Seeman et al., 2010). The allostatic load battery has also provided insights into the protective role of social support on risk factors for disease. Moreover, normalization of levels of individual components of the allostatic load battery have been shown to be related to a positive outlook on life (Steptoe, Wardle, & Marmot, 2005). These results, in turn, provides encouragement for establishing a biology of resilience and positive health and for expanding the concept of allostasis to include the biology of resilience (Davidson & McEwen, 2012; Ryff & Singer, 1998).

The new view of brain body science that has been created by enormous progress in neuroscience, biomedicine and behavioral science has fostered the introduction of new measures of cumulative stress, such as telomere length and telomerase activity, which have been shown to decrease in caregivers of autistic children and in conditions such as obesity and diabetes . The new view of reciprocal influences of brain and body system has also fostered research in brain involvement in psychological concepts, such as self-esteem and locus of control, in which hippocampal volume is related to low self esteem and also to a failure to habituate to, and thereby shut off, cortisol secretion efficiently after a repeated public speaking challenge (Pruessner et al., 2005). It is the prolongation of cortisol secretion and its chronic effects on brain and body that contributes to allostatic load (McEwen, 1998).

Low self esteem and locus of control are also likely factors in explaining how subjective ratings of socioeconomic status, that is where one places oneself on a ladder of income and educational attainment, are frequently as powerful predictors of health as is objective SES (Seeman et al., 2010). Indeed, lower self-reported as well as objective SES have also been linked to systemic inflammation and reductions of brain white matter as well as increased incidence of cardiovascular disease, diabetes, depression and certain cancers (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2012; Seeman et al., 2010).

Summary

Finally, as noted, the line of research that we embarked upon under the inspiration and guidance of Neal Miller and the Rockefeller Behavioral Science Program has reinforced the notion that the brain is the key organ of the stress response for three principal reasons: 1) The brain interprets what is threatening and, therefore, stressful; 2) It determines and regulates behavioral and physiological stress responses, the latter through the autonomic, immune, neuroendocrine and metabolic systems that may result in successful adaptation or lead to allostatic load and disease; 3) And the brain is a target of stress and undergoes structural and functional remodeling and significant changes in gene expression that affects its function (McEwen, 2007; McEwen & Gianaros, 2011; McEwen & Morrison, 2013). This includes the "biological embedding" of experiences of adversity throughout the life course (Boyce, Sokolowski, & Robinson, 2012). Thus recognition of the stress vulnerability and plasticity of the brain, which began with investigations of the hippocampus, now includes

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the amygdala and prefrontal cortex and other brain regions and involves an increasing emphasis on formation and extinction of fear related memory, attentional mechanisms, executive function, and self-regulatory behaviors (McEwen, 2007; McEwen & Gianaros, 2011). These brain changes, which are reversible in healthy individuals (McEwen, 2007) and which, therefore, do not constitute "damage" *per se*, are amenable to alteration not only by pharmaceutical agents but they are also influenced by lifestyle factors such as exercise (Erickson et al., 2011), cognitive behavioral therapies (Davidson & McEwen, 2012), social support (Seeman et al., 2010), good sleep and a prudent diet, and by policies that encourage individuals to adopt healthier lifestyles and reduce stress (McEwen, 2007; McEwen & Gianaros, 2011). A major challenge for future research and practice is to harness the capacity of the brain and body to show plasticity in situations where adversity has left its mark.

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