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Recognizing resilience: Learning from the effects of stress on the brain

Bruce S. McEwen*, Jason D. Gray, Carla Nasca

Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA

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ABSTRACT

As the central organ of stress and adaptation to stressors, the brain plays a pivotal role in behavioral and physiological responses that may lead to successful adaptation or to pathophysiology and mental and physical disease. In this context, resilience can be defined as "achieving a positive outcome in the face of adversity". Underlying this deceptively simple statement are several questions; first, to what extent is this ability limited to those environments that have shaped the individual or can it be more flexible; second, when in the life course does the brain develop capacity for flexibility for adapting positively to new challenges; and third, can such flexibility be instated in individuals where early life experiences have limited that capacity? Brain architecture continues to show plasticity throughout adult life and studies of gene expression and epigenetic regulation reveal a dynamic and ever-changing brain. The goal is to recognize those biological changes that underlie flexible adaptability, and to recognize gene pathways, epigenetic factors and structural changes that indicate lack of resilience leading to negative outcomes, particularly when the individual is challenged by new circumstances. Early life experiences determine individual differences in such capabilities via epigenetic pathways and laying down of brain architecture that determine the later capacity for flexible adaptation or the lack thereof. Reactivation of such plasticity in individuals lacking such resilience is a new challenge for research and practical application. Finally, sex differences in the plasticity of the brain are often overlooked and must be more fully investigated.

1. Introduction

The brain is the central organ of stress and adaptation to stressors because it perceives what is potentially threatening and determines the behavioral and physiological responses (McEwen, 1998; McEwen and Gianaros, 2011). Moreover, the brain is a target of stress and stressful experiences change its architecture, gene expression and function through internal neurobiological mechanisms in which circulating hormones play a role (Gray et al., 2013; McEwen, 2007). In healthy young adult animals, neuroanatomical changes in response to repeated stress are largely reversible (Conrad et al., 1999; Radley et al., 2005), or so it appears, based upon the restoration of dendritic length and branching and spine density. Yet there are underlying changes that can be seen at the level of gene expression and epigenetic regulation which indicate that the brain is continually changing (Gray et al., 2013; Hunter et al., 2013; McEwen, 2007; Nasca et al., 2013). Insofar as brain architecture and associated behavioral states are restored after stressful experiences in ways that appear to be healthy and functional, does this constitute "resilience"? This review examines this question in relation to new insights from the growing topic of epigenetics and gene expression by focusing on recent work on the hippocampus, amygdala and prefrontal cortex after acute and chronic stress and treatment with antidepressant agents.

2. Definitions of resilience

Resilience means to most people "achieving a positive outcome in the face of adversity". This can involve "bending and not breaking," that is, recovering from a bad experience. Or it can involve an "active resistance" to adversity through coping mechanisms that operate at the time of trauma (Karatsoreos and McEwen, 2011). But this adaptation does not, by itself, indicate flexibility in successful adaptation to new challenges over the life course. The individual traits that allow the more flexible outcomes undoubtedly depend upon a foundational capacity of that individual that is

* Corresponding author. Harold and Margaret Milliken Hatch, Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA. Tel.: +1 212 327 8624; fax: +1 212 327 8634.
E-mail address: mcewen@mail.rockefeller.edu (B.S. McEwen).
URL: http://www.rockefeller.edu/labheads/mcewen/mcewen-lab.php

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built upon experiences in the life course, particularly early in life, that promote the development of healthy brain architecture supporting cognitive flexibility that allows the brain to continue to change with ongoing experiences. A healthy brain architecture provides the basis for good self-esteem, and a locus of control for effective self-regulation, not only of behavior but also of the physiological responses to stressors that are regulated by the central and peripheral nervous systems. We shall now review how the brain and body adapt to challenges, often called "stressors".

3. How do the brain and body adapt?

3.1. Allostasis, allostatic load and health-related behaviors

The active process of responding to challenges to, and adaptive changes by, an individual is called "allostasis". This involves multiple mediators (autonomic, cortisol, immune/inflammatory, metabolic, neuromodulators within the brain) that interact non-linearly with each other and promote adaptation in the short run as long as they are turned on efficiently when needed and turned off promptly when no longer needed. Over-use (too much stress) or dysregulation among the mediators (e.g., too much or little cortisol; too much or little inflammatory cytokines) results in cumulative change that is referred to as "allostatic load and overload" (McEwen, 1998).

As the key organ of stress and adaptation, the brain directs "health-related behaviors" (caloric intake, alcohol, smoking, sleep, exercise) that contribute to or ameliorate physiological dysregulation and thereby play a key role in exacerbating or counteracting allostatic load/overload (McEwen, 2007). Brain development and healthy or unhealthy neural function determines in part whether the response to challenges or "stressors" is efficient or dysregulated. The development of self esteem and locus of control and good self regulatory behaviors are key factors that determine whether a challenge, such as going to a new place or giving a speech, will result in "positive stress", with a satisfying outcome, or have negative consequences. Tolerable stress refers to experiencing stressful major life events that will result in successful coping with minimal allostatic load due to good internal resources and external support. Toxic stress refers to the situation where there is unsuccessful coping due to lack of adequate internal capacities as well as poor external support that may also be based upon inadequate neural architecture to handle the stressors, and "allostatic overload" applies to those toxic stress situations where physiological dysregulation is likely to accelerate development of disease (McEwen and Wingfield, 2003).

3.2. Brain architecture responds to stressors

In the healthy brain, structural remodeling occurs after both acute and chronic stress. The discovery of receptors for glucocorticoids in the hippocampus has led to many investigations in animal models and translation to the human brain using modern imaging methods. The most striking findings from animal models have identified structural plasticity in the hippocampus, consisting of ongoing neurogenesis in the dentate gyrus (Cameron and Gould, 1996) and remodeling of dendrites and synapses in the major neurons of Ammon's horn (McEwen, 1999). Indeed, neurogenesis in the adult mammalian brain was initially described (Altman and Das, 1965; Kaplan and Bell, 1983) and then suppressed (Kaplan, 2001), only to be rediscovered in the dentate gyrus of the hippocampus (Cameron and Gould, 1994; Gould and McEwen, 1993) in the context of studies of neuron cell death and actions of adrenal steroids and excitatory amino acids in relation to stress. This was further developed to call attention to the generality of neurogenesis across vertebrates (Alvarez-Buylla and Lois, 1995), with recent evidence making it clear that the human hippocampus shows significant neurogenesis in adult life (Spalding et al., 2013). See also Box 1.

The mediators of brain structural plasticity include excitatory amino acids and glucocorticoids, along with a growing list of other mediators such as oxytocin, corticotrophin releasing factor, brain derived neurotrophic factor (BDNF), lipocalin-2 and tissue plasminogen activator (tPA) (McEwen, 2010). Moreover, glucocorticoid actions involve both genomic and non-genomic mechanisms that implicate mineralocorticoid, as well as glucocorticoid receptors and their translocation to mitochondria as well as cell nuclei; and, an as-yet unidentified G-protein coupled membrane receptor related to endocannabinoid production (Du et al., 2009; Hill and McEwen, 2010; Popoli et al., 2012).

Box 1
Relevance to neural architecture of the human brain

Studies of the human hippocampus have demonstrated shrinkage of the hippocampus not only in mild cognitive impairment and Alzheimer's disease (de Leon et al., 1997), but also in Type 2 diabetes (Gold et al., 2007), prolonged major depression (Sheline, 2003), Cushing's disease (Starkman et al., 1999) and post-traumatic stress disorder (PTSD) (Gurvits et al., 1996). Moreover, in non-disease conditions, such as chronic stress (Gianaros et al., 2007b), chronic inflammation (Marsland et al., 2008), lack of physical activity (Erickson et al., 2009) and jet lag (Cho, 2001), smaller hippocampal or temporal lobe volumes have been reported.

So far there is no indication as to whether these changes are due to volume reduction in dentate gyrus due to inhibited neuronal replacement or to dendritic shrinkage or glial cell loss, or a combination of all three. Autopsy studies on depression-suicide have indicated loss of glial cells and smaller neuron soma size (Stockmeier et al., 2004), which is indicative of a smaller dendritic tree.

With regard to Type 2 diabetes, it should be emphasized that the hippocampus has receptors for, and the ability to take up and respond to insulin, ghrelin, insulin-like growth factor-1 (IGF1) and leptin; and that IGF-1 mediates exercise-induced neurogenesis (McEwen, 2007). Thus, besides its response to glucocorticoids, the hippocampus is an important target of metabolic hormones that have a variety of adaptive actions in the healthy brain which is perturbed in metabolic disorders, such as diabetes (McEwen, 2007).

The implications of stress and glucocorticoid effects in the hippocampus have led to exploration of other brain regions involved in cognition, mood and behavioral self-regulation. The amygdala shows quite different responses to acute and chronic stress compared to the hippocampus. The amygdala responds to glucocorticoids in the formation of emotionally-charged memories (Roozendaal et al., 2004), and acute stress causes a delayed formation of dendritic spines in basolateral amygdala neurons and an increase of anxiety after 10 days (Mitra et al., 2005). Chronic stress of the same type that impairs dentate gyrus neurogenesis and cause dendritic shrinkage and spine loss in Ammon's horn neurons, causes expansion of dendrites in the basolateral amygdala (Vyas et al., 2002) while causing spine down-regulation in the medial amygdala (Bennur et al., 2007). The latter is dependent on tissue plasminogen activator (tPA) while the former does not (Bennur et al., 2007). See Box 2.