Published in final edited form as:

Dev Neurobiol. 2012 June ; 72(6): 878–890. doi:10.1002/dneu.20968.

The Ever-Changing Brain: Cellular and Molecular Mechanisms for the Effects of Stressful Experiences

Bruce S. McEwen

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065

Abstract

The adult brain is capable of considerable structural and functional plasticity and the study of hormone actions in brain has contributed to our understanding of this important phenomenon. In particular, stress and stress-related hormones such as glucocorticoids and mineralocorticoids play a key role in the ability of acute and chronic stress to cause reversible remodeling of neuronal connections in the hippocampus, prefrontal cortex and amygdala. To produce this plasticity, these hormones act by both genomic and non-genomic mechanisms together with ongoing, experience-driven neural activity mediated by excitatory amino acid neurotransmitters, neurotrophic factors such as brain derived neurotrophic factor (BDNF), extracellular molecules such as neural cell adhesion molecule (NCAM), neuropeptides such as corticotrophin releasing factor (CRF) and endocannabinoids. The result is a dynamic brain architecture that can be modified by experience. Under this view, the role of pharmaceutical agents, such as antidepressants, is to facilitate such plasticity that must also be guided by experiences.

Introduction

Ira Black was fascinated by the processes involved in brain development, including those subserving higher cognitive function, and he recognized that neural plasticity continued to some degree throughout the life course (Black 2004). But, the current view that the adult brain has a considerable capacity for structural plasticity was not always the case, as an earlier view held that mature brain is structurally stable and that neurochemical and electrochemical processes are solely responsible for behavior and cognitive function.

This article will first note some of the key steps by which the dogma of a fixed mature brain has given way to a new view and then discuss how actions of stress hormones have contributed not only to the notion of a plastic and adaptable brain, but also to the

Bruce S. McEwen, Ph.D., The Rockefeller University, 1230 York Avenue New York, NY 10065, Tel: 212 327 8624, FAX: 212 327 8634, mcewen@rockefeller.edu, Web: <http://www.rockefeller.edu/labheads/mcewen/mcewen-lab.php>.

The Ira Black and the McEwen laboratories collaborated on two studies of hormone actions and 3 papers related to catecholamine neural development:

- Luine VN, McEwen BS, Black IB. 1977. Effect of 17 β -estradiol on hypothalamic tyrosine hydroxylase activity. *Brain Res.* 120:188-192.
- Bohn CM, McEwen BS, Luine VN, Black, IB. 1984. Development and characterization of glucocorticoid receptors in rat superior cervical ganglion. *Dev. Brain Res.* 14:211-218.
- Friedman W, Dreyfus C, McEwen BS, Black I. 1988. Presynaptic transmitters and depolarizing influences regulate development of the substantia nigra in culture. *J. Neurosci.* 8:3616-3623.
- Friedman WJ, Dreyfus CF, McEwen B, Black IB. 1988. Substance K (NKA) increases tyrosine hydroxylase mRNA in cultured substantia nigra. *Brain Res.* 427:203-205.
- Friedman W, Dreyfus C, McEwen BS, Black I. 1989. Developmental regulation of tyrosine hydroxylase in the mediobasal hypothalamus. *Dev. Brain Res.* 48:177-185.

convergence of cellular and molecular actions of steroid hormones and neurotransmitters and neuromodulators in producing this plasticity. The picture that has emerged is that of a dynamic and adaptable brain, where the capacity for structural and functional plasticity continues, albeit with some restrictions, throughout the life course.

Initial evidence for adult brain plasticity

Long regarded as a rather static and unchanging organ, except for electrophysiological responsiveness, such as long-term potentiation (Bliss & Lomo 1973), the brain has, in recent time, been recognized as capable of undergoing rewiring after brain damage (Parnavelas et al 1974) and, uninjured, also able to grow and change as seen by dendritic branching, angiogenesis and glial cell proliferation during cumulated experience (Bennett et al 1964; Greenough & Volkmar 1973). More specific physiological changes in synaptic connectivity have also been recognized in relation to hormone action in the spinal cord (Arnold & Breedlove 1985), and in environmentally directed plasticity of the adult songbird brain (DeVoogd & Nottebohm 1981). Higher brain centers, such as the hippocampus and prefrontal cortex, show ovarian hormone dependent regulation of spine synapse formation and turnover (Dumitriu et al 2010b; Woolley et al 1990).

Seasonally varying neurogenesis in restricted areas of the adult songbird brain is recognized as part of this plasticity (Nottebohm 2002). Indeed, adult neurogenesis in the adult mammalian brain was initially described (Altman & Das 1965; Kaplan & Bell 1983) and then suppressed (see (Kaplan 2001)), only to be rediscovered in the dentate gyrus of the hippocampus (Cameron & Gould 1994; Gould & McEwen 1993) in the context of studies of neuron cell death and actions of adrenal steroids and excitatory amino acids in relation to stress (Gould et al 1990; Sloviter et al 1989). Neurogenesis in the dentate gyrus has gone on to become a large research topic related to effects of stress (Gould et al 1997), exercise (van Praag et al 1999), enriched environment (Kempermann et al 1997), antidepressants (Duman et al 1997) and learning and memory (Gould et al 1999).

Rather than being isolated examples of plasticity in certain brain regions, there are clear indications that many aspects of brain function are subject to structural plasticity. This plasticity involves dendritic branching and debranching, including respiratory and motor control regions, including midbrain central gray, during exercise training (Nelson & Iwamoto 2006; Nelson et al 2005), the nucleus accumbens after repeated sodium depletion causing increased salt appetite and enhanced amphetamine self-administration (Roitman et al 2002), the nucleus accumbens, hippocampus and orbitofrontal cortex after morphine, amphetamine or cocaine administration (Crombag et al 2005; Robinson et al 2001; Robinson et al 2002) and the hippocampus during hibernation (Magarinos et al 2006; Popov & Bocharova 1992). The turnover of synaptic connections is also evident in many of these same situations and will be discussed below.

More recently, the notion of developmental critical periods as immutable windows of plasticity have come under some revision with the finding that the effects of monocular deprivation on the visual system can be reversed with the aid of fluoxetine treatment, which may act by increasing levels of a facilitator of plasticity, namely, brain derived neurotrophic factor (BDNF) and related growth factors (Vetencourt et al 2008) that were of great interest to Ira Black (Black 2004).

Where do steroid hormones fit in?

Circulating hormones have turned out to be a very effective way to probe brain structure and function and have helped to demonstrate the plasticity of the adult, as well as developing brain, not only in relation to the important events in the hypothalamus that regulate

reproductive functions and help maintain homeostasis, but also in relation to higher cognitive processes, as well as emotional regulation and decision making.

From early work on the connections between the brain and the endocrine system via the hypothalamus and the portal blood vessels that carry releasing factors from the hypothalamus to the pituitary gland (Harris 1948; Meites 1992), there came the isolation and structural identification of peptide releasing factors (Guillemin 1978; Schally et al 1973). Then the identification of cell nuclear hormone receptors in peripheral tissues (Jensen et al 1981) using tritiated steroid and iodinated thyroid hormones led to the demonstration of similar receptor mechanisms in hypothalamus and pituitary gland (Pfaff & Keiner 1973; Stumpf & Sar 1976). For this demonstration, it was necessary to use autoradiographic methods because of the discrete nature of these receptor containing cells, although more conventional cell fractionation methods were also used, along with sucrose density gradient centrifugation to demonstrate receptors with molecular sizes, like those in the peripheral tissues (Gerlach & McEwen 1972; McEwen & Plapinger 1970; Pfaff & Keiner 1973; Zigmond & McEwen 1970).

What about behavior? Before the demonstration of nuclear estrogen and androgen receptors in hypothalamus, some suggested that sex hormones acted indirectly to activate sex behavior (Young 1961). Yet, the demonstration of binding sites and receptors for estrogens in hypothalamus led to studies using hormone implants, as well as sophisticated neuroanatomical and neurophysiologic methods that demonstrated that sex hormones facilitate sex behavior via receptors in the hypothalamus (Davis et al 1979; Pfaff 1980). Furthermore, effects of stress and glucocorticoids were apparent on mood in the clinical domain (Sachar et al 1970) and on aging of the brain (Landfield et al 1978) not long after the discovery of hippocampal adrenal steroid receptors (Gerlach & McEwen 1972; McEwen et al 1968).

But tritiated steroid hormone cell nuclear uptake and retention was not all confined to the hypothalamus, although, in the case of sex hormones, the major concentration of such receptors is in the hypothalamus and amygdala (Pfaff & Keiner 1973). The big surprise was the discovery of cell nuclear receptor sites for glucocorticoids in the hippocampus, not only of rodents, but also monkeys with extension to other species (Gerlach & McEwen 1972; Gerlach et al 1976; McEwen et al 1968). This unexpected finding is a major part of our story to be elaborated below because it directed us to brain functions above the hypothalamus and, in particular, to the function of the hippocampus, a brain region important for memory and other aspects of behavioral regulation (Eichenbaum & Otto 1992).

And, as it turned out, a further serendipitous finding of estrogen receptors in the hippocampus (Loy et al 1988) also represented a turning point that led to a focus on the hippocampus and, in turn, led to the realization that not all steroid hormone actions occur via cell nuclear receptors, but rather operate via receptors in other parts of the cell via a variety of signaling pathways (Akama & McEwen 2003; McEwen & Milner 2007; Milner et al 2001; Yuen et al 2010). This is now recognized to be the case for all classes of steroid hormones (Edwards 2005), including Vitamin D (Huhtakangas et al 2004), aldosterone (Wehling et al 1992), androgens (Tabori et al 2005), as well as estrogens (McEwen & Milner 2007), progestins (Waters et al 2008) and glucocorticoids (see below). We shall illustrate this by the story of glucocorticoids, stress and the hippocampus.

Glucocorticoids, stress and the hippocampus

The hippocampus was the first higher brain center that was recognized as a target of adrenal steroids (McEwen, Weiss, and Schwartz, 1968), and it has figured prominently in our understanding of how stress impacts neural architecture and behavior. Figure 1. The

hippocampus expresses both Type I mineralocorticoid, MR and Type II glucocorticoid, GR receptors, and these receptors mediate a biphasic response to adrenal steroids in the CA1 region, although only facilitation in the dentate gyrus (Joels 2006), which, nevertheless, shows a diminished excitability in the absence of adrenal steroids (Margineanu et al 1994). Other brain regions, such as the paraventricular nucleus, lacking in MR but having GR, show a monophasic negative response to increasing glucocorticoid level (Joels 2006). Adrenal steroids exert biphasic effects on excitability of hippocampal neurons in terms of long-term potentiation and primed burst potentiation (Diamond et al 1992; Pavlides et al 1994; 1995a; Pavlides et al 1995b) and show parallel biphasic effects upon memory (Okuda et al 2004; Pugh et al 1997).

A form of structural plasticity is the remodeling of dendrites in the hippocampus, as well as in the amygdala and prefrontal cortex (McEwen & Gianaros 2010). In hippocampus, chronic restraint stress CRS, daily for 21 days, causes retraction and simplification of dendrites in the CA3 region of the hippocampus (McEwen 1999; Sousa et al 2000). Such dendritic reorganization is found in both dominant and subordinate rats undergoing adaptation to psychosocial stress in the visible burrow system and it is independent of adrenal size (McKittrick et al 2000). It also occurs in psychosocial stress in intruder tree shrews in a resident - intruder paradigm, with a time course of 28 days (Magarinos et al 1996), a procedure that does not cause a loss of pyramidal neurons in the hippocampus (Vollmann-Honsdorf et al 1997).

The mossy fiber input to the CA3 region in the stratum lucidum appears to drive the dendritic remodeling leading to the retraction of the apical dendrites above this input (McEwen 1999). See Figure 2. Moreover, the thorny excrescences giant spines, upon which the mossy fiber terminals form their synapses, show stress-induced modifications (Stewart et al 2005). And the number of active synaptic zones between thorny excrescences and mossy fiber terminals is rapidly modulated during hibernation and recovery from the hibernating state (Magarinos et al 2006). The thorny excrescences are not the only spines affected by CRS. Dendritic spines also show remodeling, with increased spine density reported after chronic restraint stress on apical dendrites of CA3 neurons (Sunanda Rao & Raju 1995) and decreased spine density reported for CA1 pyramidal neurons (Magarinos et al 2011).

Exploration of the underlying mechanism for this remodeling of dendrites and synapses reveals that it is not adrenal size or presumed amount of physiological stress per se that determines dendritic remodeling, but a complex set of other factors that modulate neuronal structure (McEwen 1999). Indeed, after repeated stress, dendritic remodeling is reversible (Conrad et al 1999), and in species of mammals that hibernate, dendritic remodeling is a reversible process and occurs within hours of the onset of hibernation in European hamsters and ground squirrels, and it is also reversible within hours of wakening of the animals from torpor (Arendt et al 2003; Magarinos et al 2006; Popov & Bocharova 1992). Along with data on post-translational modification of cytoskeletal proteins, this implies that reorganization of the cytoskeleton is taking place rapidly and reversibly (Arendt et al 2003) and that changes in dendrite length and branching are not “damage” but a form of structural plasticity.

Cellular and molecular mechanisms involving steroids contribute to structural remodeling. Specifically, adrenal steroids are important mediators of remodeling of hippocampal neurons during repeated stress, and exogenous adrenal steroids can also cause remodeling in the absence of an external stressor (Magarinos et al 1999; Sousa et al 2000). The role of adrenal steroids in the hippocampus involves many interactions with neurochemical systems including serotonin, endogenous opioids, calcium currents, GABA-benzodiazepine receptors and excitatory amino acids (McEwen 1999; McEwen & Chattarji 2004). Central to all of

these interactions is the role of excitatory amino acids, such as glutamate. Excitatory amino acids released by the mossy fiber pathway play a key role in the remodeling of the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play an important role (McEwen 1999). See Figure 3.

Among the consequences of restraint stress is the elevation of extracellular glutamate levels, leading to induction of glial glutamate transporters, as well as increased activation of the nuclear transcription factor, phosphoCREB (Wood et al 2004). Moreover, 21d of CRS leads to depletion of clear vesicles from mossy fiber terminals and increased expression of presynaptic proteins involved in vesicle release (Grillo et al 2005; Magarinos et al 1997). Taken together with the fact that vesicles which remain in the mossy fiber terminal are near active synaptic zones and that there are more mitochondria in the terminals of stressed rats, this suggests that CRS increases the release of glutamate (Magarinos et al 1997).

Extracellular molecules also play a role in remodeling. Neural cell adhesion molecule NCAM and its polysialated-NCAM, PSA-NCAM, as well as L1, are expressed in the dentate gyrus and CA3 region. The expression of NCAM, L1, and PSA-NCAM are regulated by CRS (Sandi 2004). Tissue plasminogen activator tPA is an extracellular protease and signaling molecule that is released with neural activity and is required for chronic stress-induced loss of spines and NMDA receptor subunits on CA1 neurons (Pawlak et al 2005).

Within the neuronal cytoskeleton, the remodeling of hippocampal neurons by CRS and hibernation alters the acetylation of microtubule subunits that is consistent with a more stable cytoskeleton (Bianchi et al 2003) and alters microtubule associated proteins, including a soluble form of tau that undergoes phosphorylation that is increased in hibernation and reversed when hibernation is terminated (Arendt et al 2003). Another cytoskeletal molecule is called M6a, a transmembrane glycoprotein belonging to the PLP family (Alfonso et al 2005a). Although the PLP family is the most abundant protein of CNS myelin, M6a is a neuronal protein, and its knock-down by siRNA results in decreased filopodial number and decreased synaptophysin expression, whereas overexpression of M6a has the opposite effect (Alfonso et al 2005a). Repeated stress decreases M6a expression in both rodents and tree shrews; this effect was prevented by the antidepressant, tianeptine, by preventing stress-induced remodeling of dendrites in the CA3 region of the hippocampus (Alfonso et al 2005b). Chronic psychosocial stress in the tree shrew also down-regulated a number of other gene transcripts associated with neurotrophic effects and cytoskeletal plasticity, including nerve growth factor, NGF (Alfonso et al 2004).

Corticotrophin releasing factor, CRF, is a key mediator of many aspects related to stress (Koob 1999). CRF in the paraventricular nucleus regulates ACTH release from the anterior pituitary gland, whereas CRF in the central amygdala is involved in control of behavioral and autonomic responses to stress, including the release of tPA that is an essential part of stress-induced anxiety and structural plasticity in the medial amygdala (Matys et al 2004). CRF in the hippocampus is expressed in a subset of GABA neurons, namely, Cajal-Retzius cells in the developing hippocampus, and early life stress produces a delayed effect that reduces cognitive function and the number of CA3 neurons, as well as decreased branching of hippocampal pyramidal neurons (Brunson et al 2001; Brunson et al 2005). Indeed CRF inhibits dendritic branching in hippocampal cultures in vitro (Chen et al 2004; Fenoglio et al 2006).

Dendritic branching and length are impacted by neurotrophic factors. BDNF is particularly interesting because it appears to be a facilitator of plasticity directed by other cellular signals, as suggested originally by work in vitro (Horch & Katz 2002; Horch et al 1999).

BDNF haploinsufficient (+/-) mice show a less branched dendritic tree and do not show a further reduction of CA3 dendrite length with chronic stress, whereas wild-type mice show reduced dendritic branching after chronic stress (Magarinos et al 2011). See Figure 4. At the same time, overexpression of BDNF prevents stress-induced reductions of dendritic branching in the CA3 hippocampus and results in antidepressant-like effects in a Porsolt forced-swim task (Govindarajan et al 2006). However, there is contradictory information thus far concerning whether CRS reduces BDNF mRNA levels in hippocampus (Smith & Cizza 1996), but see (Isgor et al 2004; Kuroda & McEwen 1998). These conflicting reports may reflect the balance of two opposing forces, namely, that stress triggers increased BDNF synthesis to replace depletion of BDNF caused by stress (Marmigere et al 2003). BDNF and corticosteroids appear to oppose each other – with BDNF reversing reduced excitability in hippocampal neurons induced by stress levels of corticosterone (Hansson et al 2006). At the same time, glucocorticoids appear to activate trkB signaling in a ligand-independent manner that has neuroprotective implications (Jeanneteau et al 2008), although this effect is transient and appears to accommodate to chronic glucocorticoid exposure (Numakawa et al 2009). The authors of this study propose that TrkB-GR interaction plays a critical role in the BDNF-stimulated PLC- γ pathway, which is required for glutamate release, and the decrease in trkB-GR interaction caused by chronic exposure to glucocorticoids results in the suppression of BDNF-mediated neurotransmitter release via a glutamate transporter (Numakawa et al 2009).

Finally, adrenal steroids have non-genomic as well as genomic mechanisms of action. Non-genomic actions involve membrane associated mineralocorticoid and glucocorticoid receptors (Prager & Johnson 2009). These actions rapid induction of endocannabinoid production (Hill et al 2010; Tasker et al 2006), rapid stimulation of glutamate release (Karst et al 2005; Venero & Borrell 1999) and biphasic effects on mitochondrial calcium buffering via translocation of GR to mitochondria (Du et al 2009). These actions occur throughout the nervous system (Prager & Johnson 2009).

Extension of stress effects to amygdala and prefrontal cortex

Besides the hippocampus, the amygdala and prefrontal cortex are targets of stress and display structural plasticity after both acute and chronic stress. Neurons in the basolateral amygdala (BLA) expand dendrites after chronic immobilization stress and increase spine density (Vyas et al 2002), whereas neurons in medial amygdala show reduced spine density after chronic stress (Bennur et al 2007). The latter changes are dependent on tissue plasminogen activator released by corticotrophin releasing factor (Matys et al 2004), based on a tPA-ko mouse, whereas stress effects in BLA are not (Bennur et al 2007). These stress-induced changes are also accompanied by increases in anxiety-like behavior (Pawlak et al 2003; Vyas et al 2002) and suggest that stress causes a reorganization and dysfunction of circuits within the amygdala.

Concurrently, with changes in the amygdala, neurons in the medial prefrontal cortex show reversible dendritic shrinkage after chronic stress (Radley et al 2005; Radley et al 2004), with spine loss (Radley et al 2008), that can be blocked by blocking NMDA receptors (Martin & Wellman 2011), similar to stress-induced atrophy of neurons in the CA3 hippocampus (see above). This chronic stress-induced atrophy is associated with deficits in executive function and cognitive flexibility (Dias-Ferreira et al 2009; Liston et al 2006), and the stressors that cause this to happen also include circadian disruption (Karatsoreos et al 2011). While medial prefrontal cortical neurons atrophy with chronic stress, neurons in the orbitofrontal cortex show hypertrophy (Liston et al 2006) similar to what happens in the basolateral amygdala (Vyas et al 2002). The functional significance of this remains to be investigated, but it may well have to do with enhanced anxiety and vigilance that

accompanies exposure to chronic stress. It should also be noted that amygdala volume is reported to decrease in anxiety-disorder subjects in relation to successful anxiety reduction using cognitive-behavioral therapy (CBT) (Holzel et al 2010). Conversely, longitudinal increases in medial prefrontal cortex volume have been reported after CBT in chronic fatigue patients (de Lange et al 2008).

What is the potential of plasticity in the adult brain?

The theme of this article is that the adult brain is considerably more malleable and resilient than previously believed and that studies of steroid hormone action have contributed to this new view. Other hormones, such as ghrelin, leptin, IGF-1 and insulin, also make contributions to brain structural and functional plasticity (for review, see (McEwen 2007)). The hippocampus has been the focus of effects of stress, but there is now recognition that other brain regions are affected, sometimes in opposite ways, as is the case in the basolateral amygdala and orbitofrontal cortex, as noted above.

Aging animals continue to respond in terms of plasticity, albeit in a more limited manner (Diamond 1978). Yet, the aging process is accompanied by a loss of plasticity, such as the reduction in dentate gyrus neurogenesis, which can, nevertheless, be reactivated by adrenalectomy (Cameron & McKay 1998) or by blocking NMDA receptors (Nacher et al 2003). In the case of estrogen actions, the aging female rat hippocampus loses the ability to show estrogen-induced spine synapse formation by 22 months (Adams et al 2002) and this is accompanied by loss of ER alpha in dendrites of CA1 pyramidal cells (Adams et al 2002), as well as reduction in the ability of estrogen treatment to increase pLIMK immunoreactivity in the CA1 region of the aging brain (Yildirim et al 2008), both of which appear to be part of the mechanism for spine synapse formation (Yuen et al 2010). Another glimpse into age related loss of plasticity in the rhesus monkey brain is the loss of thin spine synapses that accompanies impaired prefrontal cortical function (Dumitriu et al 2010a; Dumitriu et al 2010b). Estrogen treatment is able to reduce this loss of function by inducing spine formation in the aging rhesus monkey brain (Dumitriu et al 2010b), and it should be noted that the aging rhesus brains studied so far are not as old relative to lifespan as is the case in the 22 month old rat. Therefore, it cannot be ruled out that the rhesus brain will also lose the ability to respond to estradiol at even older ages. Finally, how can this be prevented? There are indications from investigations of the aging rodent brain that estrogen treatment during the aging processes prevents age-related loss of memory capacity (Gibbs 2000).

With respect to effects of stress, the medial prefrontal cortex, as noted earlier, shows the same type of stress-induced shrinkage of apical dendrites of pyramidal neurons as in the CA3 hippocampus (reviewed in (Bloss et al 2010; McEwen 2007; McEwen & Gianaros 2010). As in the hippocampus, this plasticity is driven by glucocorticoids (Cerqueira et al 2005) in concert with excitatory amino acids (Martin & Wellman 2011). With increasing age, while the effects of stress to cause dendritic shortening and debranching persist, the spontaneous recovery within 3 weeks after the cessation of chronic stress is diminished in 12 month old rats and lost in 20 month old animals (Bloss et al 2010). Moreover, there is loss of thin spines in the mPFC neurons by 12 months of age and a loss of the ability of chronic stress to cause further significant reduction of spines (Bloss et al 2011). Future studies should address the role of diet, environmental enrichment and physical activity as a means of preventing, or at least retarding, this loss of function.

Indeed, physical activity has remarkable abilities to promote plasticity and improve function in the aging brain. Regular aerobic exercise of walking up to an hour 3 days per week over 6 months improves executive function (Kramer et al 1999) and blood flow in the prefrontal and parietal cortex (Colcombe et al 2004). The same procedure not only improved

hippocampal dependent spatial memory, but also increased hippocampal volume in the same time frame (Erickson et al 2009; Erickson et al 2011).

Depression and anxiety disorders may be an example of a loss of plasticity, where changes in brain circuitry and function become “locked” in a particular state and thus need external intervention. Indeed, prolonged depression is associated with shrinkage of the hippocampus (Sheline 1996; 2003) and prefrontal cortex (Drevets et al 1997). While there appears to be no neuronal loss, there is evidence for glial cell loss and smaller neuronal cell nuclei (Rajkowska 2000; Stockmeier et al 2004), which is consistent with a shrinking of the dendritic tree described above after chronic stress. Indeed, a few studies indicate that pharmacological treatment may reverse the decreased hippocampal volume in unipolar (Vythilingam et al 2004) and bipolar (Moore et al 2000) depression. Yet, exercise is also an effective treatment for some forms of depression (Babyak et al 2000), and both antidepressant drug treatment and exercise increase neurogenesis, as well as other types of structural changes in hippocampus and other brain regions, as noted above.

Besides depression, where reduced BDNF may be a key feature of the depressive state and elevation of BDNF by diverse treatments ranging from antidepressant drugs, such as fluoxetine, to regular physical activity (Duman & Monteggia 2006), there are other potential applications, such as the recently reported ability of fluoxetine to enhance recovery from stroke (Chollet et al 2011). However, a key aspect of this new view, (Castren & Rantamaki 2010) is that the drug is opening a “window of opportunity” that may be capitalized by a positive behavioral intervention, e.g., behavioral therapy in the case of depression or the intensive therapy to promote neuroplasticity to counteract the effects of a stroke.

In this connection it is important to reiterate that successful behavioral therapy, which is tailored to individual needs, can produce volumetric changes in both prefrontal cortex in the case of chronic fatigue (de Lange et al 2008), and in amygdala, in the case of chronic anxiety (Holzel et al 2009). This implies at least 3 important lessons: i. that antidepressant drugs should not be given without such a positive intervention; ii. that there may be a limited window of opportunity, beyond which continued drug treatment may be ineffective; and iii. that negative experiences during the window may even make matters worse (Castren & Rantamaki 2010). Moreover, it should be noted that BDNF also has the ability to promote pathophysiology, as in seizures (Heinrich et al 2011).

Conclusion

Brain architecture is much more “plastic” and adaptable than previously believed and hormones from the peripheral endocrine organs play a role along with neurotransmitters and a host of endogenous molecules, including the neurotrophic factors that fascinated Ira Black. Because of this experience-hormone mediated plasticity, the efficacy of “top down” interventions, such as physical activity and also cognitive-behavioral therapy to change the brain and alter behavior, cognitive function and physical, as well as mental health, is an important result of the ability of the brain to “change itself”. The efficacy of pharmaceutical agents, such as antidepressants, must be understood in terms of synergistic value of ongoing integrated neuronal activity and behavioral therapies.

Acknowledgments

Research support for work in the author’s laboratory described in this review includes NIH Grants MH41256, NS07080 and MH58911

References

- Adams MM, Fink SE, Shah RA, Janssen WGM, Hayashi S, et al. Estrogen and aging affect the subcellular distribution of estrogen receptor- α in the hippocampus of female rats. *J Neurosci*. 2002; 22:3608–14. [PubMed: 11978836]
- Akama KT, McEwen BS. Estrogen stimulates postsynaptic density-95 rapid protein synthesis via the Akt/protein kinase B pathway. *J Neurosci*. 2003; 23:2333–9. [PubMed: 12657692]
- Alfonso J, Fernandez ME, Cooper B, Flugge G, Frasch AC. The stress-regulated protein M6a is a key modulator for neurite outgrowth and filopodium/spine formation. *Proc Natl Acad Sci USA*. 2005a; 102:17196–201. [PubMed: 16286650]
- Alfonso J, Frasch AC, Flugge G. Chronic stress, depression and antidepressants: Effects on gene transcription in the hippocampus. *Rev Neurosci*. 2005b; 16:43–56. [PubMed: 15810653]
- Alfonso J, Pollevick GD, van der Hart MG, Flugge G, Fuchs E, Frasch ACC. Identification of genes regulated by chronic psychosocial stress and antidepressant treatment in the hippocampus. *Eur J Neurosci*. 2004; 19:659–66. [PubMed: 14984416]
- Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol*. 1965; 124:319–36. [PubMed: 5861717]
- Arendt T, Stieler J, Strijkstra AM, Hut RA, Rudiger J, et al. Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals. *J Neurosci*. 2003; 23:6972–81. [PubMed: 12904458]
- Arnold A, Breedlove S. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. *Horm Behav*. 1985; 19:469–98. [PubMed: 3910535]
- Babyak M, Blumenthal JA, Herman S, Khatry P, Doraiswamy M, et al. Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosom Med*. 2000; 62:633–8. [PubMed: 11020092]
- Bennett E, Diamond M, Krech D, Rosenzweig M. Chemical and anatomical plasticity of brain. *Science*. 1964; 146:610–9. [PubMed: 14191699]
- Bennur S, Shankaranarayana Rao BS, Pawlak R, Strickland S, McEwen BS, Chattarji S. Stress-induced spine loss in the medial amygdala is mediated by tissue-plasminogen activator. *Neuroscience*. 2007; 144:8–16. [PubMed: 17049177]
- Bianchi M, Heidbreder C, Crespi F. Cytoskeletal changes in the hippocampus following restraint stress: Role of serotonin and microtubules. *Synapse*. 2003; 49:188–94. [PubMed: 12774303]
- Black IB. Role of growth factors in the nervous system. *Ann N Y Acad Sci*. 2004; 1038:138–41. [PubMed: 15838108]
- Bliss TVP, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiology*. 1973; 232:331–56.
- Bloss EB, Janssen WG, McEwen BS, Morrison JH. Interactive effects of stress and aging on structural plasticity in the prefrontal cortex. *J Neurosci*. 2010; 30:6726–31. [PubMed: 20463234]
- Bloss EB, Janssen WG, Ohm DT, Yuk FJ, Wadsworth S, et al. Evidence for reduced experience-dependent dendritic spine plasticity in the aging prefrontal cortex. *J Neurosci*. 2011; 31:7831–9. [PubMed: 21613496]
- Brunson KL, Eghbal-Ahmadi M, Bender R, Chen Y, Baram TZ. Long-term, progressive hippocampal cell loss and dysfunction induced by early-life administration of corticotropin-releasing hormone reproduce the effects of early-life stress. *Proc Natl Acad Sci USA*. 2001; 98:8856–61. [PubMed: 11447269]
- Brunson KL, Kramar E, Lin B, Chen Y, Colgin LL, et al. Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci*. 2005; 25:9328–38. [PubMed: 16221841]
- Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience*. 1994; 61:203–9. [PubMed: 7969902]
- Cameron HA, McKay RDG. Decreased proliferation in the aged rat dentate gyrus can be reversed by removing adrenal steroids. *Abstracts Soc Neurosci*. 1998; 24:796–10. 1993.
- Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol*. 2010; 70:289–97. [PubMed: 20186711]

- Cerqueira JJ, Pego JM, Taipa R, Bessa JM, Almeida OFX, Sousa N. Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. *J Neurosci*. 2005; 25:7792–800. [PubMed: 16120780]
- Chen Y, Bender RA, Brunson KL, Pomper JK, Grigoriadis DE, et al. Modulation of dendritic differentiation by corticotropin-releasing factor in the developing hippocampus. *Proc Natl Acad Sci USA*. 2004; 101:15782–7. [PubMed: 15496472]
- Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol*. 2011; 10:123–30. [PubMed: 21216670]
- Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA*. 2004; 101:3316–21. [PubMed: 14978288]
- Conrad CD, Magarinos AM, LeDoux JE, McEwen BS. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behav Neurosci*. 1999; 113:902–13. [PubMed: 10571474]
- Crombag HS, Gorny G, Li Y, Kolb B, Robinson TE. Opposite effects of amphetamine self-administration experience on dendritic spines in the medial and orbital prefrontal cortex. *Cerebral Cortex*. 2005; 15:341–8. [PubMed: 15269111]
- Davis P, McEwen BS, Pfaff DW. Localized behavioral effects of tritiated estradiol implants in the ventromedial hypothalamus of female rats. *Endocrinology*. 1979; 104:898–903. [PubMed: 436764]
- de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, et al. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain*. 2008; 131:2172–80. [PubMed: 18587150]
- DeVoogd T, Nottebohm F. Gonadal hormones induce dendritic growth in the adult avian brain. *Science*. 1981; 214:202–4. [PubMed: 7280692]
- Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus*. 1992; 2:421–30. [PubMed: 1308198]
- Diamond MC. The aging brain: some enlightening and optimistic results. *Am Sci*. 1978; 66:66–71. [PubMed: 623401]
- Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, et al. Chronic stress causes frontostriatal reorganization and affects decision-making. *Science*. 2009; 325:621–5. [PubMed: 19644122]
- Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–7. [PubMed: 9126739]
- Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, et al. Dynamic regulation of mitochondrial function by glucocorticoids. *Proc Natl Acad Sci USA*. 2009; 106:3543–8. [PubMed: 19202080]
- Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry*. 1997; 54:597–606. [PubMed: 9236543]
- Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiat*. 2006; 59:1116–27. [PubMed: 16631126]
- Dumitriu D, Hao J, Hara Y, Kaufmann J, Janssen WG, et al. Selective changes in thin spine density and morphology in monkey prefrontal cortex correlate with aging-related cognitive impairment. *J Neurosci*. 2010a; 30:7507–15. [PubMed: 20519525]
- Dumitriu D, Rapp PR, McEwen BS, Morrison JH. Estrogen and the aging brain: an elixir for the weary cortical network. *Ann N Y Acad Sci*. 2010b; 1204:104–12. [PubMed: 20738280]
- Edwards DP. Regulation of signal transduction pathways by estrogen and progesterone. *Annu Rev Physiol*. 2005; 67:335–76. [PubMed: 15709962]
- Eichenbaum H, Otto T. The hippocampus - what does it do? *Behav Neural Biol*. 1992; 57:2–36. [PubMed: 1567331]
- Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009
- Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011; 108:3017–22. [PubMed: 21282661]

- Fenoglio KA, Brunson KL, Baram TZ. Hippocampal neuroplasticity induced by early-life stress: Functional and molecular aspects. *Front Neuroendocrin.* 2006; 27:180–92.
- Gerlach J, McEwen BS. Rat brain binds adrenal steroid hormone: radioautography of hippocampus with corticosterone. *Science.* 1972; 175:1133–6. [PubMed: 5060047]
- Gerlach J, McEwen BS, Pfaff DW, Moskowitz S, Ferin M, et al. Cells in regions of rhesus monkey brain and pituitary retain radioactive estradiol, corticosterone and cortisol differently. *Brain Res.* 1976; 103:603–12. [PubMed: 175885]
- Gibbs RB. Long-term treatment with estrogen and progesterone enhances acquisition of a spatial memory task by ovariectomized aged rats. *Neurobiol of Aging.* 2000; 21:107–16.
- Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. Learning enhances adult neurogenesis in the hippocampal formation. *Nature Neurosci.* 1999; 2:260–5. [PubMed: 10195219]
- Gould E, McEwen BS. Neuronal birth and death. *Current Opinion in Neurobiology.* 1993; 3:676–82. [PubMed: 8260816]
- Gould E, McEwen BS, Tanapat P, Galea LAM, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J Neurosci.* 1997; 17:2492–8. [PubMed: 9065509]
- Gould E, Woolley C, McEwen BS. Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. *Neuroscience.* 1990; 37:367–75. [PubMed: 2133348]
- Govindarajan A, Rao BSS, Nair D, Trinh M, Mawjee N, et al. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. *Proc Natl Acad Sci USA.* 2006; 103:13208–13. [PubMed: 16924103]
- Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exper Neurol.* 1973; 40:491–504. [PubMed: 4730268]
- Grillo CA, Pirola GG, Wood GE, Reznikov LR, McEwen BS, Reagan LP. Immunocytochemical analysis of synaptic proteins provides new insights into diabetes-mediated plasticity in the rat hippocampus. *Neuroscience.* 2005; 136:477–86. [PubMed: 16226381]
- Guillemin R. Peptides in the brain: the new endocrinology of the neuron. *Science.* 1978; 202:390–402. [PubMed: 212832]
- Hansson AC, Sommer WH, Metsis M, Stromberg I, Agnati LF, Fuxe K. Corticosterone actions on the hippocampal brain-derived neurotrophic factor expression are mediated by Exon IV promoter. *J Neuroendocrin.* 2006; 18:104–14.
- Harris GW. Electrical stimulation of the hypothalamus and the mechanism of neural control of the adenohypophysis. *J Physiol.* 1948; 107:418–29. [PubMed: 16991822]
- Heinrich C, Lahtinen S, Suzuki F, Anne-Marie L, Huber S, et al. Increase in BDNF-mediated TrkB signaling promotes epileptogenesis in a mouse model of mesial temporal lobe epilepsy. *Neurobiol Dis.* 2011; 42:35–47. [PubMed: 21220014]
- Hill MN, Karatsoreos IN, Hillard CJ, McEwen BS. Rapid elevations in limbic endocannabinoid content by glucocorticoid hormones in vivo. *Psychoneuroendocrinology.* 2010; 35:1333–8. [PubMed: 20399021]
- Holzel BK, Carmody J, Evans KC, Hoge EA, Dusek JA, et al. Stress reduction correlates with structural changes in the amygdala. *Soc Cogn Affect Neurosci.* 2009
- Holzel BK, Carmody J, Evans KC, Hoge EA, Dusek JA, et al. Stress reduction correlates with structural changes in the amygdala. *Soc Cogn Affect Neurosci.* 2010; 5:11–7. [PubMed: 19776221]
- Horch HW, Katz LC. BDNF release from single cells elicits local dendritic growth in nearby neurons. *Nature Neuroscience.* 2002; 5:1177–84.
- Horch HW, Kruttgen A, Portbury SD, Katz LC. Destabilization of cortical dendrites and spines by BDNF. *Neuron.* 1999; 23:353–64. [PubMed: 10399940]
- Huhtakangas JA, Olivera CJ, Bishop JE, Zanello LP, Norman AW. The vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1 α ,25(OH) $_2$ -vitamin D $_3$ in vivo and in vitro. *Mol Endocrin.* 2004; 18:2660–71.

- Isgor C, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus*. 2004; 14:636–48. [PubMed: 15301440]
- Jeanneteau F, Garabedian MJ, Chao MV. Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. *Proc Natl Acad Sci USA*. 2008; 105:4862–7. [PubMed: 18347336]
- Jensen, E.; Geoffrey, L.; Greene, L.; Closs, LED.; Nadji, M. Receptors reconsidered a 20-year perspective. In: Greep, R., editor. *Recent Progress in Hormone Research*. New York: Academic Press; 1981. p. 1-40.
- Joels M. Corticosteroid effects in the brain: U-shape it. *Trends Pharmacol Sci*. 2006; 27:244–50. [PubMed: 16584791]
- Kaplan MS. Environment complexity stimulates visual cortex neurogenesis: death of a dogma and a research career. *Trends Neurosci*. 2001; 24:617–20. [PubMed: 11576677]
- Kaplan MS, Bell DH. Neuronal proliferation in the 9-month-old rodent-radioautographic study of granule cells in the hippocampus. *Exp Brain Res*. 1983; 52:1–5. [PubMed: 6628589]
- Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci U S A*. 2011; 108:1657–62. [PubMed: 21220317]
- Karst H, Berger S, Turiault M, Tronche F, Schutz G, Joels M. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc Natl Acad Sci USA*. 2005; 102:19204–7. [PubMed: 16361444]
- Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature*. 1997; 586:493–5. [PubMed: 9087407]
- Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiat*. 1999; 46:1167–80. [PubMed: 10560023]
- Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, et al. Ageing, fitness and neurocognitive function. *Nature*. 1999; 400:418–9. [PubMed: 10440369]
- Kuroda Y, McEwen BS. Effect of chronic restraint stress and tianeptine on growth factors, GAP-43 and MAP2 mRNA expression in the rat hippocampus. *Mol Brain Res*. 1998; 59:35–9. [PubMed: 9729259]
- Landfield PW, Waymire JC, Lynch G. Hippocampal aging and adrenocorticoids: Quantitative correlations. *Science*. 1978; 202:1098–102. [PubMed: 715460]
- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, et al. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci*. 2006; 26:7870–4. [PubMed: 16870732]
- Loy R, Gerlach J, McEwen BS. Autoradiographic localization of estradiol-binding neurons in rat hippocampal formation and entorhinal cortex. *Dev Brain Res*. 1988; 39:245–51.
- Magarinos AM, Deslandes A, McEwen BS. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *Eur J Pharm*. 1999; 371:113–22.
- Magarinos AM, Li CJ, Gal Toth J, Bath KG, Jing D, et al. Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. *Hippocampus*. 2011; 21:253–64. [PubMed: 20095008]
- Magarinos AM, McEwen BS, Flugge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *J Neurosci*. 1996; 16:3534–40. [PubMed: 8627386]
- Magarinos AM, McEwen BS, Saboureau M, Pevet P. Rapid and reversible changes in intrahippocampal connectivity during the course of hibernation in European hamsters. *Proc Natl Acad Sci USA*. 2006; 103:18775–80. [PubMed: 17121986]
- Magarinos AM, Verdugo Garcia JM, McEwen BS. Chronic restraint stress alters synaptic terminal structure in hippocampus. *Proc Natl Acad Sci USA*. 1997; 94:14002–8. [PubMed: 9391142]
- Margineanu DG, Gower AJ, Gobert J, Wulfert E. Long-term adrenalectomy reduces hippocampal granule cells excitability in vivo. *Brain Res Bull*. 1994; 33:93–8. [PubMed: 8275328]

- Marmigere F, Givalois L, Rage F, Arancibia S, Tapia-Arancibia L. Rapid induction of BDNF expression in the hippocampus during immobilization stress challenge in adult rats. *Hippocampus*. 2003; 13:646–55. [PubMed: 12921353]
- Martin KP, Wellman CL. NMDA Receptor Blockade Alters Stress-Induced Dendritic Remodeling in Medial Prefrontal Cortex. *Cereb Cortex*. 2011
- Matys T, Pawlak R, Matys E, Pavlides C, McEwen BS, S S. Tissue plasminogen activator promotes the effects of corticotropin releasing factor on the amygdala and anxiety-like behavior. *Proc Natl Acad Sci USA*. 2004; 101:16345–50. [PubMed: 15522965]
- McEwen BS. Stress and hippocampal plasticity. *Annu Rev Neurosci*. 1999; 22:105–22. [PubMed: 10202533]
- McEwen BS. The physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev*. 2007
- McEwen BS, Chattarji S. Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine. *Eur Neuropsychopharm*. 2004; 14:S497–S502.
- McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Ann N Y Acad Sci*. 2010; 1186:190–222. [PubMed: 20201874]
- McEwen BS, Milner TA. Hippocampal formation: Shedding light on the influence of sex and stress on the brain. *Brain Res Rev*. 2007; 55:343–55. [PubMed: 17395265]
- McEwen BS, Plapinger L. Association of corticosterone-1,2 3H with macromolecules extracted from brain cell nuclei. *Nature*. 1970; 226:263–4. [PubMed: 5437515]
- McEwen BS, Weiss J, Schwartz L. Selective retention of corticosterone by limbic structures in rat brain. *Nature*. 1968; 220:911–2. [PubMed: 4301849]
- McKittrick CR, Magarinos AM, Blanchard DC, Blanchard RJ, McEwen BS, Sakai RR. Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites. *Synapse*. 2000; 36:85–94. [PubMed: 10767055]
- Meites J. Short history of neuroendocrinology and the International Society of Neuroendocrinology. *Neuroendocrinology*. 1992; 56:1–10. [PubMed: 1641067]
- Milner TA, McEwen BS, Hayashi S, Li CJ, Reagen L, Alves SE. Ultrastructural evidence that hippocampal alpha estrogen receptors are located at extranuclear sites. *J Comp Neurol*. 2001; 429:355–71. [PubMed: 11116225]
- Moore GJ, Bebehuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet*. 2000; 356:1241–2. [PubMed: 11072948]
- Nacher J, Alonso-Llosa G, Rosell DR, McEwen BS. NMDA receptor antagonist treatment increases the production of new neurons in the aged rat hippocampus. *Neurobiol Aging*. 2003; 24:273–84. [PubMed: 12498961]
- Nelson AJ, Iwamoto GA. Reversibility of exercise-induced dendritic attenuation in brain cardiorespiratory and locomotor areas following exercise detraining. *J Appl Physiol*. 2006; 101:1243–51. [PubMed: 16794024]
- Nelson AJ, Juraska JM, Musch TI, Iwamoto GA. Neuroplastic adaptations to exercise: neuronal remodeling in cardiorespiratory and locomotor areas. *J Appl Physiol*. 2005; 99:2312–22. [PubMed: 16123206]
- Nottebohm F. Why are some neurons replaced in adult brain? *J Neurosci*. 2002; 22:624–8. [PubMed: 11826090]
- Numakawa T, Kumamaru E, Adachi N, Yagasaki Y, Izumi A, Kunugi H. Glucocorticoid receptor interaction with TrkB promotes BDNF-triggered PLC-g signaling for glutamate release via a glutamate transporter. *Proc Natl Acad Sci USA*. 2009; 106:647–52. [PubMed: 19126684]
- Okuda S, Roozendaal B, McGaugh JL. Glucocorticoid effects on object recognition memory require training-associated emotional arousal. *Proc Natl Acad Sci USA*. 2004; 101:853–8. [PubMed: 14711996]
- Parnavelas J, Lynch G, Brecha N, Cotman C, Globus A. Spine loss and regrowth in hippocampus following deafferentation. *Nature*. 1974; 248:71–3. [PubMed: 4818565]
- Pavlides C, Kimura A, Magarinos AM, McEwen BS. Type I adrenal steroid receptors prolong hippocampal long-term potentiation. *NeuroReport*. 1994; 5:2673–7. [PubMed: 7696630]

- Pavlidis C, Kimura A, Magarinos AM, McEwen BS. Hippocampal homosynaptic long-term depression/depotentiation induced by adrenal steroids. *Neuroscience*. 1995a; 68:379–85. [PubMed: 7477947]
- Pavlidis C, Watanabe Y, Magarinos AM, McEwen BS. Opposing role of adrenal steroid Type I and Type II receptors in hippocampal long-term potentiation. *Neuroscience*. 1995b; 68:387–94. [PubMed: 7477948]
- Pawlak R, Magarinos AM, Melchor J, McEwen B, Strickland S. Tissue plasminogen activator in the amygdala is critical for stress-induced anxiety-like behavior. *Nature Neurosci*. 2003; 6:168–74. [PubMed: 12524546]
- Pawlak R, Rao BSS, Melchor JP, Chattarji S, McEwen B, Strickland S. Tissue plasminogen activator and plasminogen mediate stress-induced decline of neuronal and cognitive functions in the mouse hippocampus. *Proc Natl Acad Sci USA*. 2005; 102:18201–6. [PubMed: 16330749]
- Pfaff, DW. Estrogens and brain function. Springer-Verlag; 1980.
- Pfaff DW, Keiner M. Atlas of estradiol-concentrating cells in the central nervous system of the female rat. *J Comp Neurol*. 1973; 151:121–58. [PubMed: 4744471]
- Popov VI, Bocharova LS. Hibernation-induced structural changes in synaptic contacts between mossy fibres and hippocampal pyramidal neurons. *Neuroscience*. 1992; 48:53–62. [PubMed: 1584425]
- Prager EM, Johnson LR. Stress at the synapse: signal transduction mechanisms of adrenal steroids at neuronal membranes. *Sci Signal*. 2009; 2:re5. [PubMed: 19724063]
- Pugh CR, Tremblay D, Fleshner M, Rudy JW. A selective role for corticosterone in contextual-fear conditioning. *Behav Neurosci*. 1997; 111:503–11. [PubMed: 9189265]
- Radley JJ, Rocher AB, Janssen WGM, Hof PR, McEwen BS, Morrison JH. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Exper Neurol*. 2005; 196:199–203. [PubMed: 16095592]
- Radley JJ, Rocher AB, Rodriguez A, Ehlenberger DB, Dammann M, et al. Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. *J Comp Neurol*. 2008; 507:1141–50. [PubMed: 18157834]
- Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, et al. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*. 2004; 125:1–6. [PubMed: 15051139]
- Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiat*. 2000; 48:766–77. [PubMed: 11063973]
- Robinson TE, Gorny G, Mitton E, Kolb B. Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse*. 2001; 39:257–66. [PubMed: 11169774]
- Robinson TE, Gorny G, Savage VR, Kolb B. Widespread but regionally specific effects of experimenter- versus self-administered morphine on dendritic spines in the nucleus accumbens, hippocampus, and neocortex of adult rats. *Synapse*. 2002; 46:271–9. [PubMed: 12373743]
- Roitman MF, Na E, Anderson G, Jones TA, Bernstein IL. Induction of a salt appetite alters dendritic morphology in nucleus accumbens and sensitizes rats to amphetamine. *J Neurosci*. 2002; 22:RC225. [PubMed: 12040084]
- Sachar BJ, Hellman J, Fukushima DK, Gallagher TF. Cortisol production in depressive illness. *Arch Gen Psychiatry*. 1970; 23:289–98. [PubMed: 4918519]
- Sandi C. Stress, cognitive impairment and cell adhesion molecules. *Nature Rev/Neurosci*. 2004; 5:917–30.
- Schally AV, Arimura A, Kastin AJ. Hypothalamic regulatory hormones. *Science*. 1973; 179:341–50. [PubMed: 4345570]
- Sheline YI. Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity? *Mol Psychiatry*. 1996; 1:298–9. [PubMed: 9118352]
- Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiat*. 2003; 54:338–52. [PubMed: 12893109]
- Sloviter RS, Valiquette G, Abrams GM, Ronk C, Sollas AI, et al. Selective loss of hippocampal granule cells in the mature rat brain after adrenalectomy. *Science*. 1989; 243:535–8. [PubMed: 2911756]

- Smith MA, Cizza G. Stress-induced changes in brain-derived neurotrophic factor expression are attenuated in aged Fischer 344/N rats. *Neurobiol Aging*. 1996; 17:859–64. [PubMed: 9363796]
- Sousa N, Lukoyanov NV, Madeira MD, Almeida OFX, Paula-Barbosa MM. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience*. 2000; 97:253–66. [PubMed: 10799757]
- Stewart MG, Davies HA, Sandi C, Kraev IV, Rogachevsky VV, et al. Stress suppresses and learning induces plasticity in CA3 of rat hippocampus: A three-dimensional ultrastructural study of thorny excrescences and their postsynaptic densities. *Neuroscience*. 2005; 131:43–54. [PubMed: 15680690]
- Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, et al. Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiat*. 2004; 56:640–50. [PubMed: 15522247]
- Stumpf WE, Sar M. Steroid hormone target sites in the brain: The differential distribution of estrogen, progesterone, androgen and glucocorticosteroid. *J Steroid Biochem*. 1976; 7:1163–70. [PubMed: 1025363]
- Sunanda Rao MS, Raju TR. Effect of chronic restraint stress on dendritic spines and excrescences of hippocampal CA3 pyramidal neurons - a quantitative study. *Brain Res*. 1995; 694:312–7. [PubMed: 8974660]
- Tabori NE, Stewart LS, Znamensky V, Romeo RD, Alves SE, et al. Ultrastructural evidence that androgen receptors are located at extranuclear sites in the rat hippocampal formation. *Neuroscience*. 2005; 130:151–63. [PubMed: 15561432]
- Tasker JG, Di S, Malcher-Lopes R. Minireview: Rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology*. 2006; 147:5549–56. [PubMed: 16946006]
- van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neurosci*. 1999; 2:266–70. [PubMed: 10195220]
- Venero C, Borrell J. Rapid glucocorticoid effects on excitatory amino acid levels in the hippocampus: a microdialysis study in freely moving rats. *Eur J Neurosci*. 1999; 1:2465–73. [PubMed: 10383636]
- Vetencourt JFM, Sale A, Viegi A, Baroncelli L, De Pasquale R, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science*. 2008; 320:385–8. [PubMed: 18420937]
- Vollmann-Honsdorf GK, Flugge G, Fuchs E. Chronic psychosocial stress does not affect the number of pyramidal neurons in tree shrew hippocampus. *Neurosci Letts*. 1997; 233:121–4. [PubMed: 9350847]
- Vyas A, Mitra R, Rao BSS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci*. 2002; 22:6810–8. [PubMed: 12151561]
- Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson ER, et al. Hippocampal volume, memory, and cortisol status in major depressive disorder: Effects of treatment. *Biol Psychiat*. 2004; 56:101–12. [PubMed: 15231442]
- Waters EM, Torres-Revon AT, McEwen BS, Milner TA. Extranuclear progesterone receptor immunoreactivity in the rat hippocampal formation. *J Comp Neurol*. 2008; 511:34–46. [PubMed: 18720413]
- Wehling M, Christ M, Thiesen K. Membrane receptors for aldosterone: a novel pathway for mineralocorticoid action. *Am J Physiol*. 1992; 263:E974. [PubMed: 1443130]
- Wood GE, Young LT, Reagan LP, Chen B, McEwen BS. Stress-induced structural remodeling in hippocampus: Prevention by lithium treatment. *Proc Natl Acad Sci USA*. 2004; 101:3973–8. [PubMed: 15001711]
- Woolley C, Gould E, Frankfurt M, McEwen BS. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. *J Neurosci*. 1990; 10:4035–9. [PubMed: 2269895]
- Yildirim M, Janssen WG, Tabori NE, Adams MM, Yuen GS, et al. Estrogen and aging affect synaptic distribution of phosphorylated LIM kinase (pLIMK) in CA1 region of female rat hippocampus. *Neuroscience*. 2008; 152:360–70. [PubMed: 18294775]

- Young, W. The Hormones and Mating Behavior. In: Young, W., editor. Sex and Internal Secretions. Baltimore: Williams and Wilkins; 1961. p. 1173-239.
- Yuen GS, McEwen BS, Akama KT. LIM kinase mediates estrogen action on the actin depolymerization factor Cofilin. Brain Res. 2010
- Zigmond R, McEwen BS. Selective retention of oestradiol by cell nuclei in specific brain regions of the ovariectomized rats. J Neurochem. 1970; 17:889–99. [PubMed: 5426677]

Figure 1.
Autoradiogram of ³H corticosterone uptake and retention by mineralocorticoid and glucocorticoid receptors in the hippocampus of adrenalectomized rats (Gerlach & McEwen 1972).

Figure 2.

Schematic diagram of the hippocampus showing the chronic stress-induced atrophy of apical dendrites of CA3 pyramidal neurons, which receive glutamatergic input from giant mossy fiber synapses. CA3 neurons are vulnerable to seizure-induced damage, in part because of the circuitry that subserves memory functions and receives input from the entorhinal cortex to both CA3 and dentate gyrus, between which there is extensive feed-forward and feed-back communication. Note also that the dentate gyrus is a site of neurogenesis in the adult brain. (McEwen 1999).

**Mimicked by chronic glucocorticoid treatment
Blocked by dilantin**

Prevented by....

- 1. Blocking glucocorticoid synthesis**
- 2. Blocking NMDA receptors**
- 3. Lithium**
- 4. Dilantin**
- 5. Antidepressants**
- 6. Benzodiazepine**
- 7. Deficiency or overexpression of BDNF - lack of response to chronic stress**

Figure 3.

Summary of role of excitatory amino acids, glucocorticoids and BDNF in stress-induced atrophy of apical dendrites of CA3 pyramidal neurons in hippocampus.

Figure 4.

Effect of chronic restraint stress on the number of apical and basal (upper and lower panel on left) dendritic branch points and total dendritic length (upper and lower panel on right) of CA3 pyramidal neurons from wild type and haplodeficient BDNF (BDNF6) mice. ** and * $P < 0.01$ and $P < 0.05$ respectively, compared with control wild types. One-way ANOVA, Tukey post hoc test. Bars represent means $\pm$ 1 SEM. From by permission (Magarinos et al 2011).