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Bruce McEwen led the way toward a modern understanding of the interactions among hormones, the brain, and behavior. From his discovery of stress hormone receptors in the brain more than 30 years ago to his more recent studies on the structural and functional brain changes induced by hormones and stress, his work has broadened the scope and altered the definition of neuroendocrinology. His multilevel approach to questions, ranging from the molecule to human behavior, has enhanced the impact of his work and stimulated research in fields as disparate as molecular biology and public policy. He has inspired numerous young scientists to be creative and independent thinkers.

Bruce Sherman McEwen

The Path That Led Me to Neuroscience

When I think of where I am now, I often think of the people who guided me and the serendipitous events that determined my career path. I was born in 1938 in Ft. Collins, Colo., where my dad was an English instructor at what is now Colorado State University. Both my parents grew up in the Chicago area and were among the first of their respective families to go to college—in fact, they met at Park College in Missouri. My dad's career path as a journalist in San Francisco was diverted by the Great Depression, and he then went on for a PhD in English literature at the University of Michigan and a professorial career there in Ann Arbor, where I grew up. My mother, Esther, studied French and had a passion for art history but, as was the case for many women of that time, her self-defined job was raising my brother, Craig, and me for which we are both grateful! My dad, George, a self-described "frustrated physicist," introduced Craig and me to crystal radios and other aspects of the world of popular science. He planted the seeds that led me to neuroscience and Craig to sociology and both of us to Oberlin. I sometimes call myself a "molecular sociologist" but I shall return to that later.

After public elementary school in Ann Arbor, I was fortunate to go to junior and senior high school at University High School in Ann Arbor—at that time a practice teaching school for the University of Michigan. Class sizes were small and teachers were excellent; my science teacher, Lawrence Conray, led me, and quite a few classmates, to an interest in the physical sciences. In fact, four of us from the same class went on to Oberlin College and majored in chemistry! In my freshman year at Oberlin, I took a typical class load for possible pre-meds—calculus, general chemistry, German, and English composition. As a sophomore, I needed a break from that so I took a psychology course with Celeste McCollough, a young visual system psychophysiologist ("The McCollough Effect"), who planted the seeds that led me ultimately to behavioral neuroscience. McCollough inspired others, such as Bob Wurtz and Larry Squire, also Oberlin graduates, to careers in what has become the field of neuroscience. I also was inspired at that time by another young professor, Norman Craig, to pursue a major in chemistry. I have seen Norm on campus during recent visits to Oberlin and know he is still going strong!

Summer jobs played a major role in shaping my career path. After several summers as a clerk in a local drug store, including duties as a soda jerk and

as a delivery boy (using the owner's car), I got a job as a hospital orderly at the University Hospital, spending one summer in the recovery room and the next summer divided between surgery and the children's ward. Because I was on a path toward medical school, the final summer between my junior and senior years at Oberlin was spent as a research student in the University of Michigan's physiology department and the laboratory of Irving Fritz, a researcher on lipid metabolism. This led to my coauthoring my first paper, which appeared in *Science* in 1959 (Fritz and McEwen, 1959), on the role of carnitine in facilitating fatty acid oxidation by mitochondria. Irv Fritz, who went on to chair the Banting and Best Department of Medical Research at the University of Toronto, persuaded me to apply to graduate school—not medical school—and suggested the Rockefeller University in New York. I was fortunate to gain admission to "The Rock" and I sometimes think that one of the reasons that, then president Detlev Bronk admitted me was that he had a good friend named McEwen who was president of Hamilton College in upstate New York. (Detlev Bronk was a descendent of the old Dutch family that once had a farm in that part of New York City now known as The Bronx.)

At Rockefeller, my mind was opened to the multiple possibilities within science and to the philosophy that there were no barriers to what one might accomplish. Because of my experience with Irving Fritz, I was fascinated by oxidative metabolism and oxidative phosphorylation by mitochondria, and I joined the laboratory of Alfred Mirsky and Vincent Allfrey, to study the question of how the cell nucleus obtains the adenosine triphosphate (ATP) to make ribonucleic acid (RNA). What I found in my PhD thesis research is that there is another terminal oxidase, most probably in the nuclear envelope, that is less sensitive to carbon monoxide than the cytochome c of the mitochondria (McEwen et al., 1963a,1963b, 1963c, 1964). While working in the Allfrey-Mirsky laboratory, I was imbued with Mirsky's fascination with environmental control of gene expression and the Waddington concept of epigenetics (Waddington 1942), together with Allfrey's pioneering work with Mirsky and then by Allfrey by himself on the modification of histones as the start of the current blossoming of what is now called epigenetics (Allfrey, 1977; Moberg, 2012). These have had a powerful effect on my own science, and, indeed, when I returned to Rockefeller in 1966, it was the Mirsky and Allfrey influence that led me to study steroid hormone receptors in the brain.

When I was finishing my PhD thesis, Mirsky suggested that two key areas of the future would be developmental biology and what is now called neuroscience. Perhaps because of the latent influence of Celeste McCollough, I chose neuroscience. I went to Goteborg, Sweden, to work with Holger Hyden, where I began my career in neurobiology focusing on, among other topics, isolation of highly purified brain cell nuclei and also localization in the brain of the S100 protein, a member of the calmodulin family that was

thought to be "brain specific." While in Goteborg, I learned some Swedish to complement the German I had learned at Oberlin; I fell in love with Scandinavia, and especially Sweden, where I have returned many times. By coincidence, because my high school and college friend Alan Hooper was at the University of Minnesota, I found a job there as a junior faculty member of the University of Minnesota's department of zoology, where I began to study the cockroach nervous system, in vogue at that time because of the work of Graham Hoyle and others. I also was exposed to the Swedish/Norwegian culture of Minnesota and became a fan of Garrison Keillor and the "Prairie Home Companion."

My stay in Minnesota was to be short-lived, and serendipity intervened. Alfred Mirsky came to Minnesota in March 1966 to give a review but was snowed in for a day. I spent an afternoon with him, and he discovered that I was not particularly happy there. Upon his return to New York, Mirsky arranged for me to come east to interview for a junior faculty position with Neal Miller, who was moving from Yale and needed a "biochemist" to replace David Booth (who had returned to England) for his new laboratory at Rockefeller. I got the job and moved back to Rockefeller in the summer of 1966 and so began my evolution as a "molecular sociologist."

The Rockefeller environment that I entered in 1966 was much different from the one I left in early 1964 because of the addition not only of Neal Miller but also Carl Pfaffmann (both physiological psychologists), George Miller and William Estes (cognitive psychologists), and Peter Marler and Donald Griffin (animal behaviorists). This constituted the behavioral sciences program that, for a number of years, had a field program in Africa and connections with the New York Zoological Society. Many current leaders in behavioral neuroscience received training in this program. For me, a number of younger colleagues, notably Donald Pfaff and Fernando Nottebohm, created an exciting environment where synthesis and crosstalk began between animal behavior and psychology. A common denominator was the action of hormones, primarily sex hormones (for Pfaff and Nottebohm). Because of Neal Miller's interest in and development of "behavioral medicine," the topic of stress and stress hormones was one that I addressed. Our discovery in 1968 of adrenal steroid receptors in the hippocampus opened the path to the eventual realization in the latter part of the 20th century and beginning of the new millennium that circulating hormones of the gonads, adrenal cortex, thyroid gland, and also of the metabolic system affect many—if not most—areas of the brain, including those involved in higher cognitive function (McEwen, 2007). This provides a link, at least in retrospect, to what was in 1966 called cognitive psychology and which now includes not only cognitive neuroscience but also the burgeoning field of social neuroscience. I say this because the circulating hormones are controlled in part by the social environment—and, besides the hypothalamus—they affect the areas of the brain involved in cognitive, social, and emotional processes!

My work on adrenal steroid hormone effects on the hippocampus and other limbic system brain areas attracted the attention of Eliot Stellar and his colleagues at Penn and I was drawn into a fascinating collaboration with Stellar, Alan Epstein, and their younger colleagues, Randall Sakai and Jay Schulkin, Steve Fluharty, Ralph Norgren, and Harvey Grill to study salt appetite and (in my case) the role of mineralocorticoids and glucocorticoids. Stellar (whose Morgan and Stellar *Textbook of Physiological Psychology* I had used for a course at Oberlin with McCollough) was also a member of a MacArthur Foundation Network on Health and Behavior, together with Judy Rodin at Yale and others from many universities, and he drew me into that network, where I broadened my perspective to include many aspects of translational behavioral science and behavioral medicine. The Health and Behavior Network also was the basis of the subsequent MacArthur Foundation Research Network on Socioeconomic Status (SES) and Health, where many concepts of social neuroscience and behavioral medicine, including allostatic load, helped elucidate how SES "gets under the skin" and affects the health of human populations. It was out of these networks that the notion of "allostatic load" was born and out of which began my involvement in stress effects upon the immune system and in the translational aspect of how stress affects the brain. (Both will be discussed later.) These experiences led to my coauthoring two books for a general audience: *The Hostage Brain* (1994) with Harold M. Schmeck Jr., who founded the *New York Times* science section, and *The End of Stress As We Know It* (2002), with science writer Elizabeth Norton Lasley, that is now available as an e-book and that still fills an important niche in science writing for the public.

My involvement in those networks also led to my current membership in the National Scientific Council on the Developing Child. This last membership has increased my connection to my brother Craig, a professor of sociology and fellow of the Center for the Common Good at Bowdoin College, who studies (among other projects) the social and physical environment in midcoast Maine and relates it to measures of social harmony or discord. Craig and his wife, Maggie, are involved in community organizations that promote better housing and health, including the local United Way, which is lobbying for programs that will improve child development via strengthening the family and home environment. This program is now connected to the National Scientific Council on the Developing Child and to the Peel Region near Toronto, Ontario, another locale with an interest in improving the lot of children.

I should note that, at the beginning of my Rockefeller faculty career and while the hormone-brain story was just beginning, I was involved in several other research areas that relate, at least in part, to the plasticity of the brain. In 1968, Bernice Grafstein and I published the first characterization of the rapid axonal transport of newly synthesized proteins in particulate

material in the goldfish optic nerve and followed this with papers characterizing components of that transported material (McEwen and Grafstein, 1968). Second, in the 1970s, David Quartermain and I, together with several colleagues including former student, Efrain Azmitia, published a number of papers demonstrating the reversibility—by a "reminder" procedure—of retrograde amnesia induced by protein synthesis inhibitors and electroconvulsive shock (Quartermain and McEwen, 1970; Quartermain et al., 1970; Randt et al., 1971; Azmitia et al., 1972); these findings cast doubt on the permanence of retrograde amnesia and on the "consolidation" model of passive avoidance (fear) learning but did not go any further at the time. This topic has been reactivated recently in the work on "reconsolidation" of fear conditioning that has taken it well beyond what was envisioned at the time.

Following these reminiscences about where I came from and how I got here, let me launch into some of the scientific substance and further highlight some of the many people who have been part of this along the way.

Hormones and the Brain

Circulating hormones have turned out to be a very effective way to probe brain structure and function, and they 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 homeostatic regulation but also in relation to higher cognitive processes, as well as emotional regulation and decision making. Here, I will review highlights of this story; I will do this by giving a very brief overview of the history of neuroendocrinology dating back to the work of Geoffrey Harris and to subsequent pioneers in 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).

After the portal blood supply was shown to carry blood from the hypothalamus to the anterior pituitary (Harris, 1948), heroic efforts using hypothalami from slaughterhouse animals led to the isolation and structural identification of peptide releasing factors (Schally et al., 1973; Guillemin, 1978). The feedback regulation of hypothalamic and pituitary hormones implied the existence of receptor mechanisms for gonadal, adrenal, and thyroid hormones. 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 by my colleague, Don Pfaff, as well as Walter Stumpf, of similar receptor mechanisms in hypothalamus and pituitary gland (Pfaff and Keiner, 1973; Stumpf and Sar, 1976). For this, it was necessary to use autoradiographic methods because of the discrete nature of these receptor-containing cells; although Richard Zigmond, in

his PhD thesis work, used more conventional cell fractionation methods, along with sucrose density gradient centrifugation to demonstrate receptors with molecular sizes such as those in the peripheral tissues (McEwen and Plapinger, 1970; Zigmond and McEwen, 1970; Gerlach and McEwen, 1972; Pfaff and Keiner, 1973).

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 discrete hormone implants as well as to sophisticated neuroanatomical and neurophysiologic methods that demonstrated that sex hormones facilitate sex behavior via receptors in the hypothalamus (Davis et al., 1979; Pfaff, 1980). Yet, in retrospect and even at that time, there were other behaviors and neurological states that were known to be influenced by estrogens involving brain regions besides the hypothalamus, including fine motor control, pain mechanisms, seizure activity, mood, cognitive function and neuroprotection (Bedard et al., 1977; Van Hartesveldt and Joyce, 1986; McEwen et al., 1998; McEwen and Alves, 1999).

But tritiated steroid hormone cell nuclear uptake and retention, as shown by autoradiography, was not all confined to the hypothalamus; although, in the case of sex hormones, the major concentration of such receptors is in the hypothalamic region and amygdala (Pfaff and 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 (McEwen et al., 1968; Gerlach and McEwen, 1972; Gerlach et al., 1976). This unexpected finding is a major part of the story, to be elaborated here because it directed us to brain functions above the hypothalamus and, in particular, to the function of the hippocampus—brain region important for memory and other aspects of behavioral regulation (Eichenbaum and Otto, 1992). As it turned out, a further serendipitous finding of estrogen receptors in the hippocampus (Loy et al., 1988) also represented a turning point in our 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 (Kelly and Levin, 2001; McEwen and Milner, 2007). This is now recognized to be the case for all classes of steroid hormones, including vitamin D (Huhtakangas et al., 2004), aldosterone (Wehling et al., 1992), androgens (Tabori et al., 2005), as well as estrogens, progestins, and glucocorticoids (to be discussed later in this chapter). Because of the novelty and importance of this realization for many aspects of hormone action on the central nervous system, this is where I shall continue the story, focusing on estrogens and progestins, before returning to the story of glucocorticoids and stress. But first, I shall briefly introduce the evolving concepts of plasticity in the adult brain.

Plasticity of the Adult Brain

Long regarded as a rather static and unchanging organ, except for electrophysiological responsivity—such as long-term potentiation (Bliss and Lomo, 1973)—the brain has gradually been recognized as capable of undergoing rewiring after brain damage (Parnavelas et al., 1974) and as able to grow and change as seen by dendritic branching, angiogenesis, and glial cell proliferation during cumulated experience (Bennett et al., 1964; Greenough and Volkmar, 1973). More specific physiological changes in synaptic connectivity were also recognized in relation to hormone action in the spinal cord (Arnold and Breedlove, 1985) and in environmentally directed plasticity of the adult songbird brain (DeVoogd and Nottebohm, 1981). 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 and Das, 1965; Kaplan and Bell, 1983) and then suppressed (Kaplan, 2001), only to be rediscovered in the dentate gyrus of the hippocampus (Gould and McEwen, 1993; Cameron and Gould, 1994) in the context of studies of neuron cell death and in the actions of adrenal steroids and excitatory amino acids in relation to stress. Neurogenesis in the dentate gyrus has gone on to become a huge 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).

Studies of stress and sex hormones, which will be elaborated here, have revealed extensive structural remodeling of dendrites and synaptic connections. In my laboratory, these studies were brought about by Elizabeth Gould, who introduced the Golgi technique, along with Heather Cameron, Catherine Woolley, Yoshifume Watanabe, and Ana Maria Magarinos.

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 involving dendritic branching and debranching, including respiratory and motor control regions, midbrain central gray during exercise training (Nelson et al., 2005; Nelson and Iwamoto, 2006), 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 (Robinson et al., 2001; Robinson et al., 2002; Crombag et al., 2005), and the hippocampus during hibernation (Popov and Bocharova, 1992; Magarinos et al., 2006).

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 such interventions as fluoxetine treatment during visual stimulation. Such agents may act by increasing levels or activity of

a facilitator of plasticity, such as brain derived neurotrophic factor (BDNF) and related growth factors, such as insulin-like growth factor 1 (IGF-1) (Aberg et al., 2000) and fibroblast growth factor 2 (FGF2) (Turner et al., 2011); moreover, other factors such as perineuronal nets and excitatory/inhibitory balance are also involved (Vetencourt et al., 2008; Bavelier et al., 2010). Furthermore, glucocorticoids may play an important role in such plasticity by activating Trk B receptors and by mediating spine synapse turnover (Jeanneteau et al., 2008; Liston and Gan, 2011; Spolidoro et al., 2011). The generalization of this approach is suggested by the efficacy of fluoxetine to enhance neurological signs of recovery from stroke for those doing intensive physical therapy (Chollet et al., 2011).

Sex Hormones, Synapses, Seizures, and Cognitive Function

In the original steroid autoradiography, a few scattered cells in the hippocampus demonstrated strong cell nuclear labeling by ^{3}H estradiol, and these have been identified as inhibitory interneurons (Loy et al., 1988; Nakamura and McEwen, 2005; Ledoux et al., 2009). In spite of the paucity of such labeled cells, there was evidence from seizure studies that the threshold for eliciting seizure activity in the hippocampus was lowest on the day of proestrus when estrogen levels are elevated (Terasawa and Timiras, 1968). Moreover, there were indications that elevated estrogens enhanced memory retention of the type involving the hippocampus (Sherwin, 1988). Using the classical Golgi method, we found that the density of spine synapses, on the principal neurons of the carbonic anhydrase 1 (CA1) region of the hippocampus, show a cyclic variation in the estrous cycle, with peak density occurring on the day of proestrus (Woolley et al., 1990), thus providing a possible structural basis for the lower seizure induction threshold. This work in our lab was led by Catherine Woolley and Nancy Weiland (Weiland, 1992; Woolley et al., 1997), and Woolley has continued this line to new heights of sophistication at Northwestern (Smejkalova and Woolley, 2010; Huang and Woolley, 2012). Because excitatory amino acids are the major neurotransmitter in these neurons and because N-methyl-D-aspartate (NMDA) receptor activity is involved not only in hippocampal memory functions but also in seizure induction, we used a competitive NMDA receptor blocker and discovered that it prevented estradiol-induced spine synapse formation. Thus, estradiol does not work alone in causing this synapse formation; the study of underlying mechanisms is revealing some remarkable new aspects not only of hormone action but also of neuronal plasticity (McEwen et al., 2012).

With Teresa Milner of Weill/Cornell Medical College and Steve Alves in my lab, the paucity of nuclear estrogen receptors in the hippocampus led to our serendipitous finding (using electron microscopic immunocytochemistry that has the resolution to see more than the cell nuclear sites) that

epitopes for the classical estrogen receptors can be localized in dendrites, synapses, mitochondria, and glial cell processes (McEwen and Milner, 2007). Concurrently, increasing recognition was being given to the so-called non-genomic actions of estrogens and their signaling pathways (Kelly and Levin, 2001). These non-nuclear sites were shown to bind 125 estradiol using steroid autoradiography at the ultrastructural level, supporting the conclusion that they are estrogen receptors (Milner et al., 2008).

As a side note, there are also androgen receptors with epitopes of the nuclear receptor that are found in the hippocampus in membrane associated locations in dendrites, spines, and glia cell processes (Tabori et al., 2005). Testosterone-induced spine synapses in the male rat hippocampus, even though estradiol does not do so, unless genetic male rats are castrated at birth or treated with aromatase blockers to prevent developmental actions of testosterone (Lewis et al., 1995; Leranth et al., 2003; MacLusky et al., 2006). However, in contrast to the estrogen receptor story, CA1 pyramidal neurons have ample expression of cell nuclear androgen receptors (Kerr et al., 1995; Tabori et al., 2005), although the functional role of these receptors is presently unclear, and like estrogens, androgens have neuroprotective effects (Pike et al., 2008).

Growing out of the recognition of the existence of non-nuclear estrogen receptors and their signaling pathways, the mechanisms implicated in estrogen-induced synapse formation and maturation have turned out to involve interactions among multiple cell types in the hippocampus, as well as multiple signaling pathways. The requirement for NMDA receptor activation is underscored by Catherine Woolley's finding that one effect of estradiol is to upregulate NMDA receptors (Woolley et al., 1997), and yet it does so via an indirect mechanism involving estrogen modulation of cholinergic activity (Daniel and Dohanich, 2001). Cholinergic modulation of inhibitory interneurons and disinhibition of their input to pyramidal neurons is likely to be involved (Murphy et al., 1998; Rudick et al., 2003).

Although it is unclear how the NMDA receptor activation participates, it may be via the altered ionic environment, in the ability of estradiol to stimulate signaling pathways within dendrites and nascent spines that lead to filapodial extension via actin polymerization (Yuen et al., 2010) and then to local protein synthesis activated by estradiol at the translational level and leading to de novo formation of postsynaptic density 95 (PSD-95), a key anchoring protein of the dendritic spine (Akama and McEwen, 2003; Znamensky et al., 2003). Signaling pathways implicated in these events include LIM kinase and cofilin phosphorylation (Yuen et al., 2010) and PI3 kinase activation (Akama and McEwen, 2003; Znamensky et al., 2003), as well as the Rac/Rho signaling system (Kramar et al., 2009).

Finally, what terminates the estradiol-induced synapse formation? Progesterone treatment after estrogen-induced synapse formation caused rapid (12h) down regulation of spine synapses; moreover, the progesterone

receptor antagonist, Ru486, blocked the naturally occurring downregulation of estradiol-induced spines in the estrous cycle (Woolley and McEwen, 1993). But where are the progestin receptors that do this? Because Ru486 is effective, it is very likely that the classical progestin receptor is the mediator as opposed to other G-protein coupled progestin receptors that are not affected by Ru486. Curiously, the classical progestin receptor is not detectable in cell nuclei within the rat hippocampus, but it is expressed in non-nuclear sites in hippocampal neurons, and virtually all of the detectable progestin receptor is estrogen inducible (Parsons et al., 1982; Waters et al., 2008). The mechanism of progesterone action on synapse down regulation presently is unknown.

It is clear that estrogen does other things, such as protecting neurons from excitotoxic damage due to seizures and stroke, as well as Alzheimer's disease (Henderson and Paganini-Hill, 1994; McCullough et al., 2003). The exact role in this process of cell nuclear estrogen receptors found on inhibitory interneurons is unclear, but one clue is the ability of estrogens to enhance neuropeptide Y (NPY) expression and release because NPY has anti-excitatory actions (Nakamura et al., 2004; Ledoux et al., 2009). Another facet of estrogen neuroprotection is its ability to regulate mitochondrial calcium sequestration, including Bcl-2 translocation (Nilsen and Brinton, 2004).

Investigation of the ability of estrogens to protect against stroke damage, as well as Alzheimer's and Parkinson's disease, has uncovered the fact that the brain is capable of locally generating estrogens from androgens and possibly also directly from cholesterol (Hojo et al., 2003); aromatization of androgen precursors is the final step, and knockout of the aromatase enzyme increases ischemic damage even beyond that found after ovariectomy of wild-type mice (McCullough et al., 2003). The brain also appears to have the capacity to locally generate the androgen, dihydrotestosterone, from as yet unknown precursors, independently of the gonads in an animal model in which mild exercise increases neurogenesis in a manner facilitated by those androgens (Okamoto et al., 2012).

Besides the hippocampus, other brain regions demonstrate estrogen-regulated spine synapse formation and turnover, including the prefrontal cortex (Hao et al., 2007) and primary sensory-motor cortex (Chen et al., 2009). Indeed, there is likely to be estrogen-regulated spine synapse turnover in other brain regions. Besides estrogen-induced spine formation, estrogens are implicated in functions in the nigrostriatal system (Xiao and Becker, 1997), brainstem (Milner et al., 2008), and cerebellum (Smith, 1989), suggesting that their effects are widespread in the central nervous system. Moreover, estrogen receptors have been demonstrated in many of these brain regions (Milner et al., 2003).

The nigrostriatal system is particularly interesting because of its role in Parkinson's disease. The Parkinson's connection arose with the observation

that high-dose estrogen treatment used in the initial contraceptive preparations exacerbated symptoms of Parkinson's disease in women (Bedard et al., 1977). This was very unexpected for those who believed in the nuclear estrogen receptor story because there are no cell nuclear estrogen receptors in the rodent striatum, and yet tiny unilateral implants of estradiol in the rodent striatum elicited unilateral rotation associated with imbalanced dopaminergic function (Van Hartesveldt and Joyce, 1986). Furthermore, estradiol regulates dopamine release from striatum in a sexually dimorphic manner (Castner et al., 1993). Now, with lower doses of estradiol, there is evidence for neuroprotection in Parkinson's disease (Leranth et al., 2000; Nakamura et al., 2004).

Finally, aging is known to lead to loss of cognitive acuity, and loss of estrogens after natural or surgical menopause is reported to impair certain aspects of memory, as well as other neurological functions (Halbreich et al., 1995; Sherwin, 2003; Sherwin and Henry, 2008). What happens to estrogen-induced synapse formation? In the female rat, where it is possible to look at animals near the end of their lifespan, there is a loss of the ability of estradiol to induce spine synapses in the hippocampus, along with a loss of the memory-enhancing effects of estradiol (Dumitriu et al., 2010a; Dumitriu et al., 2010b). Recent evidence suggests that this is due, at least in part, to the consequences of long-term estrogen deprivation. Mechanistically, the loss of estrogen effects on spine synapse formation may be explained by an age-related loss of estrogen receptors in dendrites and spines, as well as a loss of the ability of estradiol to stimulate LIM kinase phosphorylation that may be related to actin polymerization and filapodial outgrowth, as described earlier. Further insights into the effects of age come from the rhesus monkey, where estrogen-induced spine synapse formation is detected in the hippocampus and prefrontal cortex (Dumitriu et al., 2010a; Dumitriu et al., 2010b). In these studies by Morrison and colleagues, post-menopausal rhesus monkeys responded to estradiol as far as spine synapse formation, but there is also an age-related and estrogen-independent loss of synapses that can be compensated as far as cognitive function by estrogen treatment. Of great interest is that estrogen shifts the distribution of spine head diameter toward smaller size in both the young and the aged animals. However, aging dramatically reduced the representation of spines with small heads and long necks (Dumitriu et al., 2010a; Dumitriu et al., 2010b). This age-related selective loss of small spines and the partial recovery with estrogen treatment fits in nicely with a developing framework in neurobiology of the essential role that small spines play in learning and memory. Kasai and Harris have recently suggested that thin spines are "learning" spines while big, mushroom-type spines represent "memory" traces (Kasai et al., 2003; Bourne and Harris, 2008). Could age-related loss of cognitive function be related to stress and stress hormone actions? Now we return to the hippocampus and the story of stress and glucocorticoid actions.

Stress, Adrenal Steroids, and the Hippocampus

After the initial discovery of adrenal steroid uptake and retention in the rodent and monkey hippocampus, there were six discoveries that set the agenda for future investigations. The first discovery was the recognition that two classical receptor types, Type 1 or mineralocorticoid receptors (MR) and Type 2 or glucocorticoid receptors (GR), account for the uptake and cell nuclear retention of tritiated corticosterone in the rat and tritiated cortisol in the monkey (Gerlach and McEwen, 1972; Gerlach et al., 1976; Reul and DeKloet, 1985). These receptors coexist in hippocampal neurons of Ammon's horn and the dentate gyrus, with GR being more scarce in CA3 and MR being more uniform across Ammon's horn and dentate gyrus (Herman et al., 1989; Sanchez et al., 2000). The MR and GR represent a two-level recognition system for circulating adrenal steroids, with the MR having higher affinity and giving rise to enhanced excitation of hippocampal neurons and the GR having lower affinity and occupancy as glucocorticoid levels rise to the diurnal peak and after stress, with the result that excitation is impaired. In other words, there are inverted U-shaped dose response curves (Diamond et al., 1992; Joels, 2006).

The second discovery was that glucocorticoids exacerbate excitotoxic damage from ischemia and seizures and do so at the higher glucocorticoid levels and through the GR (Sapolsky and Pulsinelli, 1985; Sapolsky, 1992). Along with studies of the aging brain, this led Robert Sapolsky, who did his dissertation in my laboratory, to propose the "glucocorticoid cascade hypothesis" of stress and aging, in which stressful experiences accelerate the aging process and lead, among other consequences, to impaired hippocampal-dependent cognitive function (Sapolsky et al., 1986). Recent evidence suggests that overactivity of excitatory amino acid transmission in the CA3 region of the hippocampus may play a key role (Koh et al., 2010).

The third discovery was that repeated stress causes neurons, particularly those of the CA3 region (but we will see that neurons in the prefrontal cortex and amygdala also change), to shrink their apical dendrites by a mechanism involving not only glucocorticoids but also excitatory amino acid neurotransmission because the shrinkage of dendrites was preventable by an NMDA receptor blocker, as well as a glucocorticoid synthesis blocker, and by drugs such as Dilantin and lithium that stabilize excitatory neuronal activity (Watanabe et al., 1992). In contrast to the damaging actions related to stroke and head trauma, these changes in plasticity are reversible within several weeks of the termination of stress and are reminiscent of the reversible shrinkage and expansion of dendrites in the CA3 region of the hippocampus during hibernation and recovery from torpor in European hamsters and ground squirrels (Popov et al., 1992; Conrad et al., 1999; Magarinos et al., 2006). Mechanistically, besides excitatory amino acids and glucocorticoids (Magarinos and McEwen, 1995), BDNF and tissue plasminogen activator

are recognized as modulators of stress-induced remodeling of dendrites and synapses in the hippocampus (Pawlak et al., 2005; Magarinos et al., 2011), as well as in amygdala (see following).

Fourth, Elizabeth Gould and Heather Cameron "rediscovered" neurogenesis in the dentate gyrus of the hippocampus, a phenomenon first described in the 1960s but largely ignored (Cameron et al., 1993; Cameron and Gould, 1996). This has led to a growing body of work on factors that control neurogenesis and the underlying molecular mechanisms. What became evident right away is that stressors of various types can inhibit neurogenesis; indeed, chronic restraint stress over six weeks can actually decrease the number of dentate gyrus neurons and reduce dentate gyrus volume (Pham et al., 2003). Conversely, physical activity increases neurogenesis as does housing rodents in an "enriched environment." The role of these new neurons in hippocampal function is a matter of ongoing research. Mechanistically, the inhibition of neurogenesis is related to elevated excitatory neurotransmission via NMDA receptors, as well as elevated glucocorticoids (Cameron and Gould, 1996), and endogenous opioids and inflammatory cytokines also play a role (Koo and Duman, 2008). On the positive side, the circulating hormone IGF-1 and the endogenous neurotrophic factor BDNF appear to mediate increased neurogenesis (Aberg et al., 2000; Schmidt and Duman, 2007).

A fifth discovery was the recognition that adrenal steroids have trophic and protective effects at low doses, even if they promote damage at high levels, particularly when combined with the actions of excitatory amino acids. The inverted U-shaped dose/time response curves represent this and apply also to the biphasic effects of adrenal steroids on hippocampal-dependent memory, as well as to molecular and cellular aspects. For example, low levels of adrenal steroids protect dentate gyrus neurons from programmed cell death and also promote dendritic growth and branching of dentate gyrus granule neurons (Gould et al., 1990). Similar effects on dendritic growth and branching have been reported for the prefrontal cortex (Cerqueira et al., 2005). Low levels of adrenal steroids also have protective effects against excitotoxic cell death in neurons and appear to do this by promoting translocation of glucocorticoid receptors to mitochondria along with Bcl2, a process that exists in many cell types (Du et al., 2009a; Du et al., 2009b). Moreover, the ongoing pulsatile secretion of adrenal steroids (Stavreva et al., 2009) is associated with turnover of spine synapses in the brain (Liston and Gan, 2011) that may be responsible for the ability of glucocorticoids to activate the Trk B receptor in a ligand-independent manner (Jeanneteau et al., 2008).

The sixth discovery concerns rapid glucocorticoid actions via a membrane G protein coupled receptor, as yet unidentified, that causes endocannabinoid formation from lipid precursors (Tasker et al., 2006). Among their many effects, endocannabinoids influence the presynaptic release of glutamate and gamma-aminobutyric acid (GABA), as well as acetylcholine and noradrenaline (Hill and McEwen, 2010).

Table 1 Human Hippocampus: Reported Effects on Volume Using Magnetic Resonance Imaging

Smaller volume in
• Cushing's disease (Starkman et al., 1999)
• Diabetes (Gold et al., 2007; Yau et al., 2010)
• Depression (Sheline et al., 1996; Sheline, 2003)
• Post-traumatic stress disorder (Gurvits et al., 1996; Gilbertson et al., 2002)
• Chronic stress (Gianaros et al., 2007)
• Chronic inflammation (Marsland et al., 2008)
• Jet lag (Cho, 2001)
• Lack of exercise (Erickson et al., 2009; Erickson et al., 2011)
• Low self esteem (Pruessner et al., 2005)
Increased volume
• Learning (Draganski et al., 2006)
• Physical fitness (Erickson et al., 2009; Erickson et al., 2011)

Taken together, these findings portray a multi-faceted role for adrenal steroids in hippocampal structure and function in which these hormones operate in concert with other mediators and via direct and indirect genomic, as well as non-genomic, mechanisms involving regulation not only of mitochondrial calcium balance but also of endocannanoid production. Regarding other mediators, it is important to note that metabolic hormones such as insulin, leptin, and ghrelin, along with IGF-1, all have important effects on hippocampal structure and function (McEwen, 2007).

How do these findings in animal models apply to the human hippocampus? Structural and functional imaging has revealed a wide range of phenomena in the human hippocampus suggesting that this brain region is responding, as might be predicted, similarly to the animal model studies (see Table 1). However, the hippocampus is not the only brain region that responds to stress, as we shall now discuss.

Stress and the Amygdala

Whereas chronic restraint stress in rats and mice causes dendrites to shrink and spines to be down regulated in the hippocampus, the basolateral amygdala responds in the opposite direction with increased branching and length of dendrites and increased spine density (Vyas et al., 2002). Accompanying these structural changes, there is increased anxiety-like behavior (Vyas et al., 2003). Even the single traumatic stress of putting a rat into a plastic immobilization cone, such as is used to draw blood from the tail, causes increased

anxiety with a 10d delay and an increase in spine density on neurons in basolateral amygdala (BlA) but no increase in dendritic length (Mitra et al., 2005). The increase in dendritic length with chronic stress can be mimicked by a single large dose of glucocorticoids (Mitra and Sapolsky, 2008), although the ability of a single traumatic stressor to cause increased spine density 10d later may involve a different mechanism (Rao et al., 2012). Indeed, a timed mild stressor or elevated glucocorticoids in the drinking water prevent the delayed effects of an acute traumatic stressor to induce anxiety and new spines in BlA neurons 10d later (Rao et al., 2012). These findings are consistent with studies on human post-traumatic stress disorder (PTSD) showing that elevated glucocorticoids during or immediately after a traumatic event blocks PTSD symptoms (Yehuda et al., 1998; Schelling et al., 2004; Zohar et al., 2011).

Although the mechanisms for these changes are not clearly elucidated, BDNF is also involved, and BDNF over expression leads to hypertrophy of dendrites in basolateral amygdala and failure to increase further after chronic stress (Govindarajan et al., 2006). Together with the finding that BDNF under expression impairs the ability of chronic stress to cause dendrites of CA3 hippocampal neurons to shrink after chronic stress, it would appear that BDNF may have a facilitative role in stress-induced remodeling with a floor and a ceiling effect (Magarinos et al., 2011).

At the same time as those changes in basolateral amygdala, tissue plasminogen activator (tPA), which is released from excitatory nerve terminals, also plays a role in the increased anxiety induced by an acute restraint stress (Pawlak et al., 2003) and does so by a mechanism initiated by corticotrophin-releasing hormone receptor stimulation (Matys et al., 2004). These alterations that are dependent on tPA occur in the medial amygdala, which also is involved in the stress-induced anxiety and shows chronic stress-induced reduction in dendritic spines, opposite to those changes in basolateral amygdala (Bennur et al., 2007).

Consistent with the studies on animal models, the human amygdala is hyperactive in chronic anxiety disorders and major depression (Drevets, 2000). Structural imaging has demonstrated increased volume in acute major depression (Frodl et al., 2002), but decreased volume in long-term chronic depression (Sheline et al., 1998). In anxiety disorders, successful cognitive behavior therapy has been associated with a decrease in amygdala volume, implying an increase related to the prior anxiety (Holzel et al., 2009). Clearly, these findings should encourage further work on the plasticity of the human amygdala and on the top-down efficacy of behavioral therapies for anxiety disorders.

Stress and the Prefrontal Cortex

Although the prefrontal cortex never stood out as a target of adrenal steroids, glucocorticoid receptors and some mineralocorticoid receptors are expressed

there (Ahima and Harlan, 1990; Ahima et al., 1991). Moreover, the prefrontal cortex (PFC) is implicated in feedback control of hypothalamic-pituitary-adrenal (HPA) activity (Diorio et al., 1993), as well as in downstream control of autonomic nervous system function (Buchanan et al., 2010). The PFC is a very sensitive target of stress in animal models and in humans, as well as being a brain structure that shows sex differences in stress responsiveness and response to estrogens (i.e., a nexus of many aspects discussed in this review concerning sex and stress effects above the hypothalamus). We shall discuss the stress effects first and then devote a separate section to discussing sex differences.

Chronic stress of the same type that causes the changes in the hippocampus and amygdale, discussed earlier, leads to remodeling of neurons in the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). In mPFC (cingulate, prelimbic, and infralimbic regions), layer II/III neurons undergo apical dendritic retraction and reduction of spine density after 21 days of chronic restraint stress (CRS) (Cook and Wellman, 2004; Radley et al., 2004), whereas CRS causes increased dendritic length and complexity in neurons of the OFC (Liston et al., 2006). The behavioral effects of CRS on an attention set shifting task of cognitive flexibility are of similar magnitude to the effects of lesions of the mPFC (Birrell and Brown, 2000). Other measures of cognitive flexibility and decision making also show impairment from chronic stress (Dias-Ferreira et al., 2009). However, the morphological changes caused by CRS are reversible within two to three weeks of stress cessation, at least in young adult rats (Radley et al., 2005; Bloss et al., 2010). In middle-aged and aged (20-month) rats, the dendritic retraction caused by CRS in mPFC neurons is similar in magnitude to that in young adult rats, but it is only partially reversible in middle-aged rats and not at all reversible in old rats within the three-week recovery time frame (Bloss et al., 2010). We are hoping to see if this age-related loss of resilience can be prevented by pharmacological, dietary, and behavior means.

There are several other fascinating features of the stress-induced changes in mPFC neurons. First, they are accompanied by a reduction in spine synapse density, as well as the shape of remaining spines, suggesting that younger spines may be selectively eliminated (Radley et al., 2008). Second, in young rats, the CRS-induced dendritic changes are accompanied by a reduction of D1 dopamine receptors and loss of D1 enhancement of long-term potentiation (LTP) (Goldwater et al., 2009), both of which reappear during the recovery phase; however, the recovery of dendritic length is more proximal to the cell body than the stress-induced loss of distal dendritic material, suggesting that these neurons are somehow "different" from those before chronic stress (Goldwater et al., 2009). Third, in young male rats, the mPFC neurons that lose dendritic material do not project to amygdala, based on retrograde tracing studies, but are most likely projecting to cortical targets (Shansky et al., 2009). Fourth, circadian disruption

is also able to cause dendritic shrinkage in the prefrontal cortex along with increasing cognitive rigidity (Karatsoreos et al., 2011).

The human PFC also shows adaptive plasticity that is consistent with the story described here. Medical students, including some studying for the medical board exam and exhibiting different degrees of perceived stress, showed deficits on an attention set shifting task related to their perceived stress score; moreover, a functional connectivity circuit involving the PFC that was defined by activation in the attention set shifting task, showed slower functional connectivity in those students with high levels of perceived stress (Liston et al., 2009). These effects on behavior and functional connectivity disappeared after the students had a vacation! The human PFC is also benefited by physical exercise and cognitive behavioral therapy. Daily moderate aerobic exercise in sedentary adults over a six-month to one-year period increased blood flow measured by fMRI in mPFC and the parietal cortex associated with attention and also improved performance on tasks of executive function (Kramer et al., 1999; Colcombe et al., 2004). Brain volume increases also have been reported from regular physical activity (Colcombe et al., 2006), including increased hippocampal volume, as noted earlier (Erickson et al., 2009; Erickson et al., 2011). Increases in PFC volume have also been reported in a longitudinal study as a result of beneficial cognitive behavioral therapy for chronic fatigue syndrome (de Lange et al., 2008).

Sex Differences and What This Means for the Rest of the Brain

All of the animal model studies of stress effects summarized here were carried out on male rodents. From the first section of this review, we know that sex hormones have their own powerful effects on neuronal structure and function. Thus, it is perhaps not surprising that female rodents do not show the same pattern of neural remodeling after chronic stress as do males. The first realization of this was for the hippocampus, in which the remodeling of CA3 dendrites did not occur in females after CRS, even though all the measures of stress hormones and other factors indicated that the females were experiencing the stress as much as males (Galea et al., 1997). Females and males also differ in the cognitive consequences of repeated stress, with males showing impairment of hippocampal-dependent memory, with females not showing the same impairment (Luine et al., 1994; Bowman et al., 2001; Luine et al., 2007).

In contrast, acute tail shock stress during classical eyeblink conditioning improves performance in males but suppresses it in females (Wood and Shors, 1998) by mechanisms influenced by gonadal hormones in development and in adult life (Wood et al., 2001; Shors and Miesegaes, 2002). However, giving male and female rats control over the shock abolishes the stress effects and the sex differences (Leuner et al., 2004). These findings

suggest that sex differences involve brain systems that mediate how males and females interpret stressful stimuli, and that a sense of control is paramount to coping with those stimuli.

More recently, in collaboration with John Morrison, Becca Shansky showed that female rats fail to show the mPFC dendritic remodeling seen in males after CRS in those neurons that do not project to amygdala, but they do show, after CRS, an *expansion* of the dendritic tree in the subset of neurons that project to the basolateral amygala (Shansky et al., 2010). Moreover, ovariectomy prevented these CRS effects on dendritic length and branching. Furthermore, estradiol treatment of ovariectomized (OVX) females increased spine density in mPFC neurons, irrespective of where they were projecting (Shansky et al., 2010).

Taken together with the fact that estrogen, as well as androgen effects are widespread in the central nervous system, these findings indicate that there are likely to be many more examples of sex × stress interactions related to many brain regions and multiple functions, as well as developmentally programmed sex differences that affect how the brain responds to stress, such as in the locus ceruleus (Bangasser et al., 2010; Bangasser et al., 2011). Clearly, the impact of sex and sex differences has undergone a revolution and much more is to come (Meites, 1992; McEwen and Lasley, 2005; Cahill, 2006; Laje et al., 2007; McEwen, 2009), including insights into X and Y chromosome contributions to brain sex differences (Carruth et al., 2002).

Early Life Stress and Brain Development and Function

Brain development has always fascinated me, but my lab did not work very much on that topic, with the important exception of early gonadal hormone actions and brain sexual differentiation (McEwen 1983; Pfaff and McEwen, 1983). However, Akaysha Tang initiated a collaboration, and Lisa Eiland joined my lab, and these colleagues set us off on some fascinating studies of early life experiences and brain development, in which we are now collaborating with the Huda Akil–Stan Watson laboratory in Ann Arbor.

Akaysha Tang, a faculty member in psychology at the University of New Mexico, spent several short periods in our lab and initiated a long-distance collaboration that also involves Russ Romeo, a former postdoc in my lab and now a faculty member in psychology at Columbia/Barnard. With our input, Akaysha and her lab colleagues have developed the "maternal modulation hypothesis" that emphasizes the role of the mother in providing consistency of maternal care, not just quantity but also the importance for infant cognitive and social, as well as physical, development of exposure to novelty while under consistent maternal care (Akers et al., 2008; Tang et al., 2011; Tang et al., 2012).

Lisa Eiland, an MD neonatalogist at Weill/Medical College of Cornell University and now at Roosevelt Hospital, introduced the maternal separation (MS)

model in rats (three hours per day separation from mother rat on postnatal days 2–12) as a model of some of the things that happen to premature neonates in the neonatal intensive care unit (NICU). Her work showed that development of the hippocampus was impaired by MS as was spatial memory in young adults and that chronic stress led to more anxiety in the MS rats (Eiland and McEwen, 2012). These findings have led to collaboration with the Akil-Watson laboratory to compare MS versus non-MS rats with rats from high and low responding (HR and LR) strains developed in Ann Arbor. With the treatment of neonates of all four groups with FGF2 on postnatal day one (based upon the finding that this treatment makes LR rats less anxious and more exploratory than HR rats), we expect that FGF2 will reverse the MS effect (Turner et al., 2011).

Stress and Brain–Body Interactions and Social Neuroscience

So far, I have summarized how useful steroid hormones have been in elucidating mechanisms of adaptive plasticity of the adult and developing brain. Let us now look at a bigger picture, related to how the brain is the master organ of adaptation to a changing external and internal environment and an active and malleable participant in those adaptive changes. Because we are the "Laboratory of Neuroendocrinology," we deal with the interactions between brain and body, a subject that has matured considerably with progress in endocrinology and neuroscience and with advances in many aspects of physiology and medicine, particularly at the molecular level. As a parallel to laboratory research, I have become involved in applying some of this knowledge to understanding mechanisms of how the social, as well as physical, environment affects human health.

As I said earlier, around 1990 I was recruited into the MacArthur Foundation Health and Behavior Network, an interdisciplinary group of researchers that introduced me to larger questions of how brain, behavior, and physiology interact with each other and with the social environment. After several years, this network was gradually transformed into the MacArthur Foundation Research Network on Socioeconomic Status (SES) and Health (www.macses.ucsf.edu), to address the important and challenging question of how income and education "get under the skin" to produce the linear gradients of health and mortality seen in Western societies, with the higher SES population doing better on the average than the lowest SES, and with the middle SES levels being truly in the middle on an almost linear relationship with high and low SES. This line of research has been summarized nicely in an edited volume (Adler et al. 1999) and PDFs that are available online ("Reaching for a Healthier Life" and "The Biology of Disadvantage" from another edited volume: www.macses.ucsf.edu).

The types of stress and impacts of stressful experiences, as well as choice of lifestyle, are influenced by education, social environment, and access to

resources. Based on the idea that the brain is the central organ of stress and adaptation because it perceives what is stressful and controls physiological and behavioral responses that then also influence the brain in ways described earlier, with input from my friend and mentor, Eliot Stellar, and Teresa Seeman of UCLA, we formulated a concept referred to as "allostatic load" that has helped to bridge the gap between biology and biomedicine, health psychology and behavior, and sociology and economics.

Indeed a field of "social neuroscience" (http://s4sn.org/drupal) is beginning to take shape because it recognizes how important the social, as well as physical, environment are in shaping brain function, behavior, and in influencing systemic physiology. A prominent example is the recent publication in the *Proceedings of the National Academy of Sciences* of the Sackler Colloquium on the "Biological Embedding of Early Social Adversity: From Fruit Flies to Kindergartners," which was held in the National Academy's facility on the campus of the University of California, Irvine, in December 2011.

Following is a brief synopsis of the concepts of allostasis and allostatic load (McEwen and Gianaros, 2010; McEwen and Gianaros, 2011). Whereas many physiological parameters, such as blood oxygen and pH, are maintained in a narrow range (homeostasis–essential for life), many other parameters vary in their functionality with time of day and in response to external and internal demands, including those mediators that help the organism adapt. Allostasis, originally created as a concept by Sterling and Eyer (Sterling and Eyer, 1988) and modfied by McEwen and Stellar (McEwen and Stellar, 1993), is the active process of responding to a challenge to the body by triggering chemical mediators of adaptation (HPA, autonomic, metabolic, immune) that operate in a nonlinear network (McEwen, 2006). Allostasis is essential for maintaining homeostasis in the face of challenges or demands imposed by changes in (a) the environment and (b) an individual's behavioral state that is registered by the brain. Thus, the dynamic mediators of allostasis expressing marked variability facilitate adaptation, whereas the parameters associated with homeostasis do not express comparable variability as a means of promoting adaptation. Allostasis is essential for maintaining homeostasis in the face of external and internal demands that are registered by the brain. Critically, however, this dynamic adaptation has a price, and the cost of this adaptation is called allostatic load—the wear and tear on the body and brain that results from chronic dysregulation (overactivity or inactivity) of mediators of allostasis (McEwen and Stellar, 1993; McEwen, 1998).

The MacArthur experience and the concepts of allostasis and allostatic load set us in an unexpected direction, namely, how the brain and immune system communicate. Arising out of the Health and Behavior Network, the MacArthur Foundation provided grant support for several years to a brain behavior and immunity group that explored topics related to how the stress

hormone axis interacts with the immune system (McEwen et al., 1997). This had at least two major consequences. First, Firdaus Dhabhar, a graduate student and now faculty member at Stanford, used this as a catalyst for his PhD thesis work showing, for the first time, that acute stressors enhance acquired immunity, its formation and expression, and do so via the ability of cortisol and adrenalin to promote "trafficking" of immune cells from the blood and from storage organs like the spleen into sites in the body where they are needed to defend against a pathogen or to repair a wound; at the same time, chronic stress has the opposite effect, namely, to suppress immune function (Dhabhar et al., 2012). The latter concept is well known while the enhancement of immune function is surprisingly counter-intuitive and is still working its way into biomedical thinking, in large part due to the continuing elegant work of Firdaus Dhabhar, who has shown its applicability in recovery from knee surgery (Rosenberger et al., 2009) and in defending against certain types of immune-sensitive cancers (Dhabhar et al., 2010).

A second major consequence of our foray into the immune system is the study of the immune system of the brain, namely, microglial and brain dendritic cells via the elegant work of Karen Bulloch and her neuroimmune physiology and inflammation program at Rockefeller. Dr. Bulloch, an expert in the thymus and its innervation (Bulloch, 1985) and function of modulators such as calcitonin gene related peptide (CGRP) (Bulloch et al., 1991; Bulloch et al., 1998), was a member of the brain behavior immunity group and transferred her research program to Rockefeller where she shifted her interests, first to study CGRP in relation to brain damage (Bulloch et al., 1997) and then to study microglial cells in the context of aging and inflammation (Sierra et al., 2007) and presently to discover that within the population of "microglia" in the brain is a heterogeneous class of "brain dendritic cells" (Bulloch et al., 2008) that are activated in aging (Kaunzner et al., 2012), after stroke (Felger et al., 2010), and during intranasal viral infections (D'Agostino et al., 2012). It appears that some come in from outside but others are resident in the brain and become activated after insult or with aging, but whether they protect or cause problems remains unclear.

Thus the basic concept of allostasis and allostatic load, whether pertaining to the immune system, the brain, or to other systems of the body, is that the same systems that help the body and brain adapt can also contribute to pathophysiology when overused and out of synchrony with each other (McEwen, 1998). This is so because each regulatory mediator (HPA, autonomic, metabolic, immune) system influences the other mediator systems, directly or indirectly; moreover, each mediator system can have positive and also negative effects (i.e., a U-shaped dose response) depending on level and timing of their activity (McEwen, 2006). There are many implications, but two of them are worth noting here.

First, pharmaceutical agents that enhance or inhibit one mediator system will influence the activity of other mediators, as well as run the risk of tipping the balance on the U-shaped dose curve from good to bad effects (Calabrese, 2008). This is the challenge of drug development for many disorders of modern life, from hypertension to arthritis to metabolic syndrome to depression—to interfere with a process that is either inadequate or overactive but not to the point of either shutting it off completely or of overstimulating it.

This leads to the second point. I have referred to examples of the abilty of physical activity and successful cognitive behavior therapy to change brain structure and function. Indeed, "top-down" interventions such as physical activity, adequate sleep, and postive social interactions, including cognitive therapies, are in some cases a better way to intervene and to help the system of allostasis correct itself and to re-achieve a balance that favors adaptation over pathophysiology (McEwen and Gianaros, 2010, McEwen and Gianaros, 2011). A further example is found in the Experience Corps, in Baltimore, Md., in which elderly volunteers, serving as elementary school teachers' aides, show benefits to their prefrontal cortical function as well as improved mood and physical health, as a result of participating in this program, which provides positive social interactions, physical activity, and a meaning and purpose in life, as well as benefiting the education of children (Fried et al., 2004; Carlson et al., 2009).

A major contributor to allostatic load and poor mental and physical health over the lifespan is adverse experiences early in life (Anda et al., 2010) that affect brain development and, thereby, alter brain and body health through neuroendocrine, neural and immune mechanisms (Shonkoff et al., 2009). Interventions that improve parent-child interactions at the family level, such as the Nurse-Family Partnership, can have an enormous benefit and have a significant return on investment (Eckenrode et al., 2010) (http://developingchild.harvard.edu/initiatives/council; see also www.dana.org/news/reportonprogress/detail.aspx?id=31362).

Looking Back and Looking Forward

Because I chose to work on hormones, I have been acutely aware over the years of the tendency of neuroscientists to be brain-centric and to largely ignore the influences of the rest of the body via hormones and immune system chemicals, while those interested in endocrinology and internal medicine tend to ignore the brain and its pervasive influence on systemic health. Fortunately, this is changing, and I believe that our work has helped to make this change. For example, it is hard to ignore the fact that the entire brain is a target for sex hormones via genomic and non-genomic mechanisms that affect reacting times, pain sensitivity, mood, and higher cognitive functions, or that the hippocampus is a target not only of stress and sex hormones but also of metabolic hormones such as leptin, insulin,

ghrelin, and IGF-1 (McEwen, 2007). Yet, there is still a reluctance to think of a systemic disorder as also a brain disorder. A case in point is Type 2 diabetes that we now know damages the brain, particularly the hippocampus, starting early in life (Yau et al., 2010; Yau et al., 2012) and in adult life and aging (Convit et al, 2003; Gold et al., 2007) with increased risk for dementia later in life (Arvanitakis et al., 2004; Rasgon and Jarvik, 2004).

What our work and that of others on hormone actions has helped to uncover is that the adult brain is much more resilient and adaptable than previously believed, and neural architecture is modifiable. Indeed, adaptive, structural plasticity involves growth and shrinkage of dendritic trees of neurons, turnover of synapses and limited amounts of neurogenesis in the forebrain, especially the dentate gyrus of the hippocampal formation. Stress and sex hormones participate in adaptive structural plasticity in the hippocampus, prefrontal cortex, and amygdala—brain regions involved in memory, decision making, and self-regulatory behaviors such as emotional regulation and impulse control. These hormones exert their effects on brain structural remodeling through classical direct, as well as indirect, genomic mechanisms and also via non-genomic molecular mechanisms; they do so in collaboration with neurotransmitters and other intra- and extracellular mediators. Early life experiences and brain sexual differentiation determine the nature and degree of this plasticity.

Here is what I think is the most important lesson for neuroscience and medicine as we enter the era of "social neuroscience." Because hormones influence so many aspects of brain structure and function and because hormone secretion is governed by the cognitive and emotional brain acting through the hypothalamus, the role of brain plasticity must be considered in understanding how the social and physical environment "gets under the skin" to affect brain and body resilience and positive aspects of health, on the one hand, and vulnerability to disease, on the other.

Thus some of the lessons, looking forward, can be summarized as follows:

- First, the adult brain shows region-specific adaptive plasticity in response to stressful experiences, mediated in part by stress hormones, and this plasticity is also affected by sex hormones, which have their own effects on neuronal structure and function throughout the brain.
- Second, steroid hormones act classically via receptors that bind to response elements and act in the cell nucleus, but they also act in other parts of the cell independently of genomic actions or indirectly upon the genome via other signaling processes. In many cases, these non-genomic or indirect genomic actions involve the classical steroid receptor expressed in extra-nuclear sites. In other cases, there are other steroid-responsive receptors (e.g., those which are coupled to G proteins).

- Third, steroid hormone actions on structural and functional plasticity of the mature brain involve a convergence of multiple mediators, including neurotransmitters, neurotrophic factors, and signaling molecules, such as tissue plasminogen activator and endocannabinoids.
- Fourth, steroid hormone actions on structural and functional plasticity of the mature brain involve collaborations among multiple cell types (e.g., inhibitory interneurons, glial cells, principal neurons) and actions of hormones in multiple cellular compartments (e.g., presynaptic terminals, post-synaptic spines, mitochondria, endoplasmic reticulum, and cell nuclei).
- Sex hormones affect the whole nervous system and not just those brain regions involved in reproduction, and they affect multiple neural processes from cognitive function to emotional regulation to motor and sensory processing, as well as vulnerability to damage.
- There are developmentally programmed sex differences that affect many of the aforementioned processes.
- The brain and body are interconnected and affect each other in multiple ways so that brain and body health and wellness are intertwined, as codified in the allostatic load concept. Ignoring the brain while focusing on body systems invites problems, just as ignoring the body while focusing on the brain creates other problems.
- There is resilience in the aftermath of stress, and a healthy brain and body responds to stressors either by actively resisting their actions or by changing and then recovering when the stressor is over. A maladapted brain and body may not spontaneously recover from the stressor or may be adversely and even permanently damaged; early life adversity is a major cause of lifelong physical and mental health disorders.
- Finally, the plasticity of the adult, as well as the developing, brain offers opportunities for interventions that are "top down," that is, involving the activation of brain and body systems by behavioral and cognitive means. These can often be enhanced by pharmaceutical agents; however, these are not a substitute for the top-down intervention.

Acknowledgments

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