60 YEARS OF NEUROENDOCRINOLOGY

Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation

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Abstract

The discovery of steroid hormone receptors in brain regions that mediate every aspect of brain function has broadened the definition of 'neuroendocrinology' to include the reciprocal communication between the brain and the body via hormonal and neural pathways. The brain is the central organ of stress and adaptation to stress because it perceives and determines what is threatening, as well as the behavioral and physiological responses to the stressor. The adult and developing brain possess remarkable structural and functional plasticity in response to stress, including neuronal replacement, dendritic remodeling, and synapse turnover. Stress causes an imbalance of neural circuitry subserving cognition, decision-making, anxiety and mood that can alter expression of those behaviors and behavioral states. This imbalance, in turn, affects systemic physiology via neuroendocrine, autonomic, immune and metabolic mediators. In the short term, as for increased fearful vigilance and anxiety in a threatening environment, these changes may be adaptive. But, if the danger passes and the behavioral state persists along with the changes in neural circuitry, such maladaptation may need intervention with a combination of pharmacological and behavioral therapies, as is the case for chronic anxiety and depression. There are important sex differences in the brain responses to stressors that are in urgent need of further exploration. Moreover, adverse early-life experience, interacting with alleles of certain genes, produce lasting effects on brain and body over the life-course via epigenetic mechanisms. While prevention is most important, the plasticity of the brain gives hope for therapies that take into consideration brain–body interactions.

Introduction

The fundamental discovery of the communication between hypothalamus and pituitary, by Geoffrey Harris, established the basis for understanding brain–body communication via the neuroendocrine system (Harris 1970).

As originally conceived and confirmed by the releasing factors in the hypothalamus for pituitary hormones (Schally *et al*. 1973, Guillemin 1978, Vale *et al*. 1981), the field of neuroendocrinology has flourished. At the

same time, steroid hormones were shown to bind to intracellular receptors that regulate gene expression in tissues such as liver, or the prostate and uterus in the case of sex hormones (Jensen & Jacobson 1962). The focus of steroid hormone feedback to regulate neuroendocrine function was naturally upon the pituitary and the hypothalamus and this important work continues to uncover essential aspects of neuroendocrine regulation (Meites 1992).

The McEwen laboratory entered this field by serendipitously discovering adrenal steroid, and later estrogen receptors, in the hippocampal formation of the rat (McEwen *et al.* 1968, McEwen & Plapinger 1970, Gerlach & McEwen 1972, Loy *et al.* 1988, Milner *et al.* 2001) and we, and others, extended these findings to the infrahuman primate brain, as well as to other regions of the brain involved in cognitive and emotional regulation (Gerlach *et al.* 1976). This has catalyzed studies that look at actions of hormonal feedback on the brain not only to regulate hypothalamic functions but also to influence neurological, cognitive and emotional functions of the whole brain, with translation to the human brain in relation to aging, mood disorders and the impact of the social environment. This article describes research in our, and other laboratories, that redefined neuroendocrinology as a field that also studies two-way brain body communication via the neuroendocrine, autonomic, immune and metabolic systems. This research has uncovered the remodeling of brain architecture mediated by hormones working together with other cellular mediators. These actions occur via epigenetic mechanisms involving both genomic and non-genomic processes over the life course, and there is ongoing translation of the findings in animal models to the human condition, including the effects of adverse early-life experiences and the relationship of socioeconomic status and health through the development of the concept of allostatic load.

Receptors outside of the hypothalamus

By administering ^{3}H corticosterone into adrenalectomized rats, we discovered receptors for adrenal steroids in the hippocampal formation of the rat and, later, the rhesus monkey (McEwen *et al.* 1968, McEwen & Plapinger 1970, Gerlach & McEwen 1972, Gerlach *et al.* 1976; Fig. 1). Other work revealed such receptors in the hippocampal equivalent in other species, including birds (McEwen 1976, Dickens *et al.* 2009). In retrospect, these findings broadened the perspective that glucocorticoids provided negative feedback control of the HPA axis to include actions of adrenal steroids on other brain functions such as memory, learning, control of mood, and other aspects of behavior (McEwen 2010).

Work by Reul and de Kloet demonstrated that there are two types of adrenal steroid receptors, mineralocorticoid (type 1 or MR) and glucocorticoid (type 2 or GR), in hippocampus and other brain regions (Reul & DeKloet 1985). This was further elaborated by immunocytochemical mapping of the receptors (Ahima & Harlan 1990, Ahima *et al.* 1991). Studies in our laboratory, as well as by Diamond
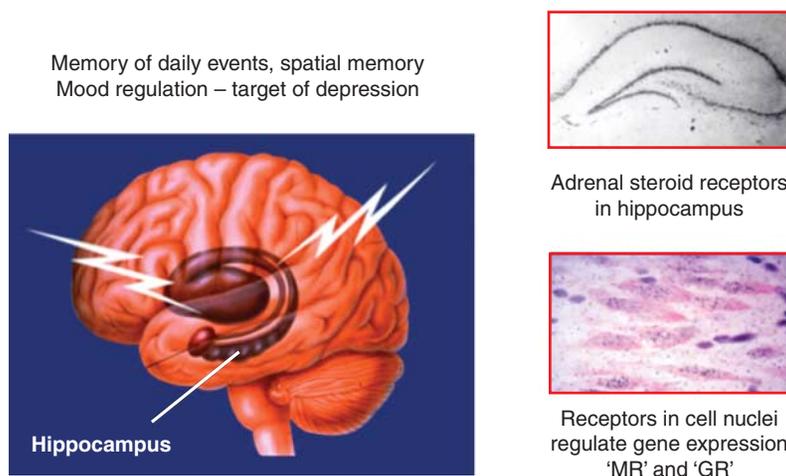

Memory of daily events, spatial memory
Mood regulation – target of depression

Hippocampus

Adrenal steroid receptors
in hippocampus

Receptors in cell nuclei
regulate gene expression
'MR' and 'GR'

Figure 1
The hippocampal formation is a target of adrenocortical steroids and is involved in spatial and episodic memory, as well as mood regulation. Both pyramidal neurons in Ammon's horn and neurons of the dentate express type I or mineralocorticoid (MR) and type 2 or glucocorticoid (GR) receptors.

and Joëls, have shown biphasic effects mediated by MR and GR (Diamond *et al.* 1992, Pavlides *et al.* 1995, Joels 2006). Ultradian fluctuations of glucocorticoids drive GR activation and reactivation, while MR occupancy for nuclear activation is more constant and promotes excitability (Stavreva *et al.* 2009). Moreover, membrane associated GR and MR are linked to the direct stimulation of excitatory amino acid release (Karst *et al.* 2005, Popoli *et al.* 2012).

Much of this information was obtained via studies on the hippocampus, which has become a gateway into the study of hormone effects on other brain regions involved in cognitive and emotional regulation and other behaviors. The hippocampus is important for episodic and spatial memory and is now also recognized for its role in mood regulation, as will be explained in the following section. For spatial memory (Fig. 2), the hippocampus becomes active in London cab drivers during functional MRI imaging when they remember a route from one place to another (Maguire *et al.* 1997) and the hippocampus is also important for food caching behavior in squirrels and birds (Biegler *et al.* 2001, Clayton 2001, Burger *et al.* 2013).

The hippocampus is also 'the canary in the coal mine' as far as conditions such as ischemia and seizures that cause brain damage as well as brain aging (Sapolsky 1990). And the hippocampus responds to sex hormones with effects on spatial memory and other functions (Sandstrom & Williams 2001), as discussed later in this review.

Output to multiple interacting mediators and the concept of allostatic load

As originally defined, neuroendocrinology refers to the hypothalamic and pituitary control of neuroendocrine function. The McEwen laboratory has focused upon the return loop of feedback of steroid hormones on the brain to affect molecular, cellular, physiological and behavioral processes throughout the entire brain. This feedback now includes action in the brain of metabolic hormones such as insulin, ghrelin, insulin-like growth factor 1 (IGF1) and leptin via specific uptake systems and acting upon receptors residing in hippocampus and other brain regions (McEwen 2007; Fig. 3). Moreover, given the influence of

Maguire *et al.* 2000

London Cab Drivers

Sex Hormones!

Sandstrom & Williams 2001

Biegler *et al.* 2001

Food cacheing birds

Hippocampus – the 'canary' of wear and tear on the brain with aging

Figure 2
The hippocampal formation is activated in spatial memory as in the London Cab Driver's study (Maguire *et al.* 1997), as well as in spatial location of food in food-caching birds and squirrels. The hippocampus is also a target of sex hormones that affect spatial memory (Sandstrom & Williams 2004).

The hippocampus is also sensitive to damage by seizures, ischemia and head trauma in which glucocorticoids synergize effects of excitatory amino acid overload (Sapolsky 1990).
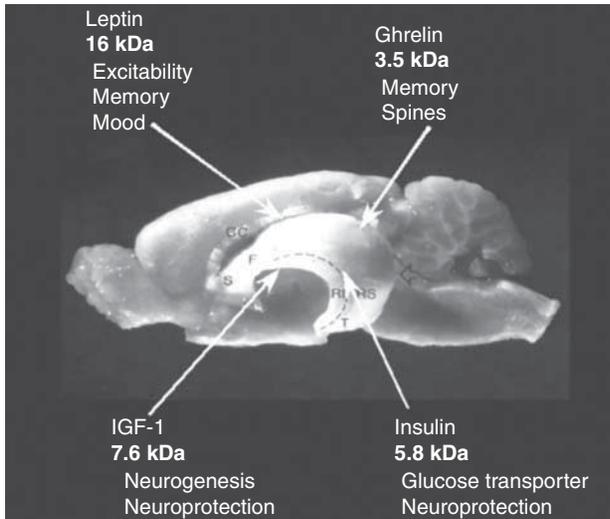
Figure 3
Four peptide/protein hormones, insulin-like growth factor 1 (IGF1), insulin, ghrelin, and leptin, are able to enter the brain and affect structural remodeling or other functions in the hippocampus. A transport process is involved, and specific receptors are expressed in hippocampus, as well as in other brain regions. Molecular sizes are indicated for each hormone in kDa: ghrelin, 3.5 kDa; leptin, 16 kDa; insulin, 5.8 kDa; IGF1, 7.6 kDa. Reproduced, with permission, from McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews* **87** 873–904. Copyright 2007 the American Physiological Society.

hormones and autonomic outflow from the brain upon activity of the immune system, the direct and indirect feedback actions of circulating cytokines on the brain must also be considered in a broader definition of neuroendocrinology (Maier & Watkins 1998). Furthermore, the autonomic nervous system itself, both parasympathetic and sympathetic arms, is a partner of neuroendocrine regulation as is here more broadly defined (Sloan *et al*. 1999, Tracey 2002).

Within this broader view of neuroendocrinology in relation to brain–body communication, we modified the concept of allostasis (Sterling & Eyer 1988) to refer to the active process of maintaining homeostasis via output of hormones and autonomic nervous system (ANS) activity, and we developed the concept of allostatic load and overload as a means of better understanding the cumulative and potentially damaging, as well as protective, effects of stressors on the brain and body (McEwen & Stellar 1993, McEwen 1998, McEwen & Wingfield 2003, McEwen & Gianaros 2011). Because the mediators of allostasis interact and affect each other's activity and because each mediator system has biphasic effects in dose and time, the 'network of allostasis' is nonlinear (McEwen 2006). When one mediator system changes, the others

adjust, and the resulting output can be distorted, as in chronic inflammation or a flat cortisol diurnal rhythm caused by sleep deprivation or depression.

Another important feature of the allostatic load concept is the notion that the mediators that normally help the body and brain adapt to stressors can also become distorted and contribute to cumulative, pathophysiological change such as atherosclerosis or obesity and diabetes (McEwen 1998). Finally, and importantly, the allostatic load concept emphasizes the central role of the brain in response to adaptation to stressors because of its central role in regulating and responding to the broader-defined 'neuroendocrine' system (McEwen 1998; Fig. 4). Both the physical and social environment contribute to experiences that require adaptation of brain architecture and physiological processes (McEwen & Gianaros 2011), as is discussed later in this review. Quite recently, the epigenetic allostasis concept has introduced another feature of the allostatic load to emphasize the influence of early-life experiences on the development of mood disorders in susceptible individuals and this also points to the key role of MR receptors in the communication with the glutamate system (Nasca *et al*. 2014), as discussed in the next section.

Structural plasticity of brain regions mediating cognition and affect

A remarkable feature of the adult, as well as the developing brain, is its capacity for remodeling of dendrites, turnover of synapses and neurogenesis. We discovered that remodeling of dendrites in the hippocampus in response to chronic stress caused shrinking of dendrites in the CA3 subfield that was also mimicked by chronic glucocorticoid treatment, but also involved mediation by excitatory amino acids and other cellular mediators (McEwen 1999; Fig. 5). Similar shrinkage of dendrites was found in medial prefrontal cortex after chronic stress, whereas expansion of dendrites in basolateral amygdala was found under the same conditions (Vyas *et al*. 2002, Radley *et al*. 2004). In hippocampus of hibernating animals, rapid shrinkage of CA3 apical dendrites is seen with onset of hibernation while regrowth of those dendrites occurs within hours of termination of hibernation, suggesting that the cytoskeleton can rapidly depolymerize and repolymerize when needed via a mechanism in which tau phosphorylation is involved (Arendt *et al*. 2003, Magarinos *et al*. 2006).

The turnover of spine synapses also occurs in response to stressors and this was shown quite recently in the case of the HPA axis to be dependent on the ultradian pulses of glucocorticoids (Liston & Gan 2011, Liston *et al*. 2013).
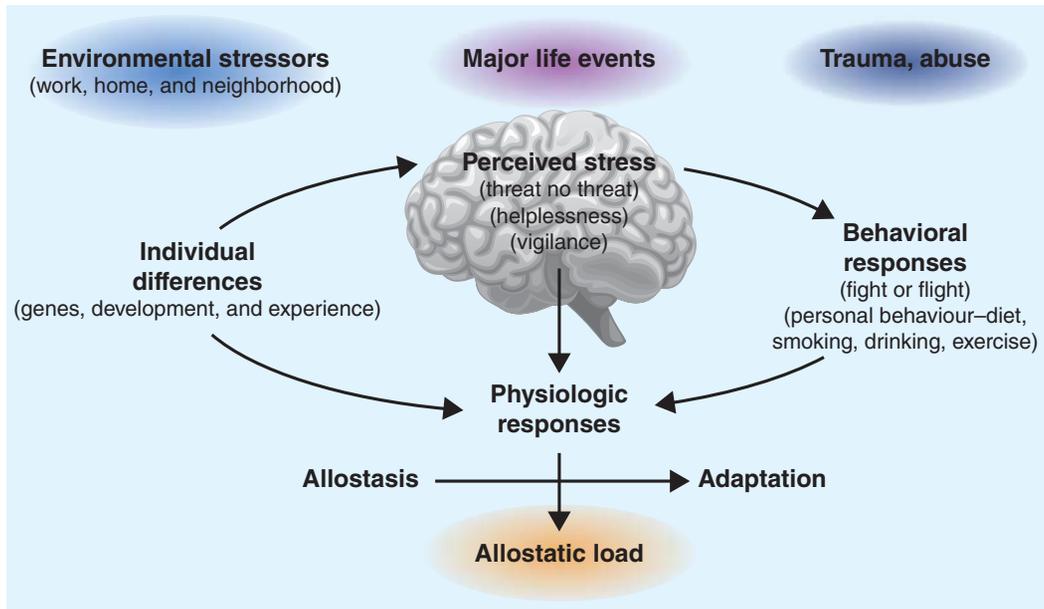
Figure 4

The stress response and development of allostatic load. The perception of stress is influenced by one's experiences, genetics, and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated, leading to allostasis and adaptation. Over time, allostatic load can accumulate, and the overexposure to mediators of neural, endocrine, and immune stress can have adverse effects on various organ systems, leading to disease. Reproduced, with permission, from McEwen BS (1998) Protective and damaging effects of stress mediators. *New England Journal of Medicine* **338** 171–179. Copyright 1998 Massachusetts Medical Society.

Chronic stress causes reduced spine density in hippocampus and medial prefrontal cortex, as well as medial amygdala, and increased spine density occurs in basolateral amydala (McEwen & Chattarji 2007). Sex hormones also regulate spine synapse turnover in hippocampus, hypothalamus, and prefrontal cortex of female rats and rhesus monkeys by a mechanism involving not only estradiol (E_2), but also excitatory amino acids and NMDA receptors (Frankfurt *et al.* 1990, McEwen *et al.* 1995, Woolley 1999, Dumitriu *et al.* 2010; Fig. 6).

Structural plasticity also occurs among interneurons involving spine turnover and dendritic remodeling, as well as neurogenesis (Cameron & Dayer 2008, Nacher *et al.* 2013). As first suggested by Altman (1962), there is turnover and neurogenesis of inhibitory interneurons in the adult cortex occurring at about the same rate as that of granule neurons in the dentate gyrus (Cameron & Dayer 2008). Spine synapse turnover and dendritic remodeling is evident in a class of interneurons that express polysialated neural cell adhesion molecule (PSA-NCAM) and which are widely distributed in the telencephalon of rodents and humans (Nacher *et al.* 2013). Dopamine acting via D2 receptors affects PSA-NCAM expression and some dopamine effects are blocked by the depletion of PSA (Nacher *et al.* 2013).

Neurogenesis in the dentate gyrus of the adult hippocampus was rediscovered by Elizabeth Gould and Heather Cameron based upon earlier work by Altman and Kaplan and findings in the songbird brain by Nottebohm and colleagues (Cameron & Gould 1994, Kaplan 2001, Alvarez-Buylla & Garcia-Verdugo 2002, Nottebohm 2002, Gould 2007). Glucocorticoids and excitatory amino acids are both involved in stress-induced suppression of neurogenesis, which was found not only in rodents, but also in tree shrews and rhesus monkeys (Cameron & Gould 1994, Gould *et al.* 1997, 1998). Yet, glucocorticoid levels do not predict the direction of neurogenesis, as shown by studies of male sexual behavior in which increased neurogenesis is found with high glucocorticoid levels; oxytocin appears to play an important role in glucocorticoid mediated neurogenesis (Leuner *et al.* 2010, 2012).

Repeated stress in rats has been shown to lead to reduced cell proliferation and neuron number in the dentate gyrus along with reduced dentate gyrus volume (Pham *et al.* 2003). Conversely, physical activity increases neurogenesis and dentate gyrus volume (van Praag *et al.* 1999), as also does living in an enriched environment (Kempermann *et al.* 1997). Hippocampal volume increases in elderly 'couch potatoes' who engage in regular, moderate exercise, such as walking (Erickson *et al.* 2011).
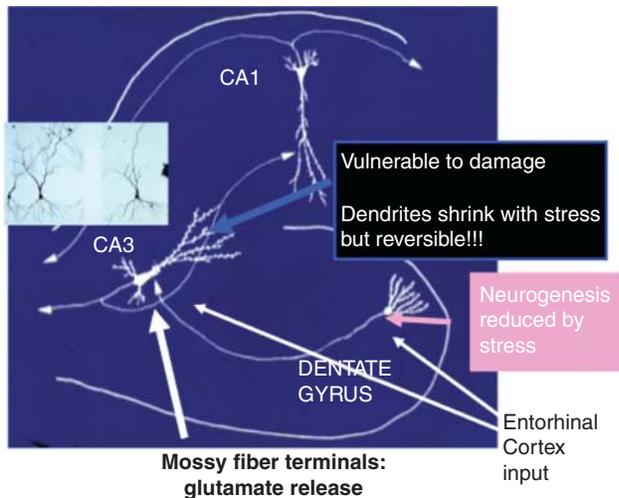
Figure 5
The trisynaptic organization of the hippocampus showing input from the entorhinal cortex to both CA3 and dentate gyrus (DG), with feed forward and feedback connections between these two regions that promote memory formation in space and time but, at the same time, makes the CA3 vulnerable to seizure-induced excitatory (McEwen 1999). Chronic stress causes apical dendrites of CA3 neurons to debranch and shorten in a reversible manner, and glutamate release by giant mossy fiber terminals is a driving force. Chronic stress also inhibits neurogenesis in DG and can eventually reduce DG neuron number and DG volume.

Mechanisms of action of glucocorticoids and estrogens

As is now recognized for all steroid hormones, glucocorticoids produce effects on their target cells via both direct and indirect genomic effects, as well as non-genomic actions (Fig. 7). Direct actions involve binding of the dimerized GR to the glucocorticoid response element, whereas indirect genomic actions involve tethering of the GR to other transcription factors such as AP1, NfkB or Stat5 (Yamamoto 1985, Ratman et al. 2013). There are also actions of GR on the mitochondrial genome (Du et al. 2009a). Non-genomic actions include the stimulation of endocannabinoid production and direct stimulation of glutamate release, as summarized next.

The role of glucocorticoids and estrogens in structural remodeling of the adult brain also involves multiple interacting mediators (McEwen 2010). In the case of stress and adrenal steroids, tissue plasminogen activator is involved as a mediator of stress induced changes in medial amygdala and CA1 hippocampal spine density, along with corticotrophin releasing hormone (CRH), which is able to stimulate its release (Pawlak et al. 2003, 2005, Chen et al. 2006a). Reduced BDNF expression in haploinsufficiency and in the val66met polymorphism is linked to reduced

dendritic growth in hippocampus and lack of response to chronic stress (Chen et al. 2006b, Magarinos et al. 2011), whereas BDNF over-expression is associated with longer dendrites in both hippocampus and amygdala and failure to respond to chronic stress with retraction in hippocampus and elongation in basolateral amygdala (Govindarajan et al. 2006). Lipocalin-2 is induced by acute stress and modulates actin dynamics and it down-regulates mushroom spines in hippocampus after 3d restraint stress, while deletion of Lipocalin-2 increases the proportion of mushroom spines along with increased neuronal excitability and anxiety (Mucha et al. 2011). In amygdala, 3d restraint stress up-regulates spine density and this effect is lost in lipocalin-2-ko mice (Skrzypiec et al. 2013).

Endocannabinoids generated postsynaptically via acute glucocorticoid stimulation inhibit either glutamate or GABA release presynaptically (Hill & McEwen 2010) and this affects not only prefrontal and amygdala control of HPA activity, but also effects of stress on medial prefrontal cortex (mPFC) and basolateral amygdala dendritic branching. Deletion of CB1 receptors exacerbates stress-induced retraction of mPFC dendrites (Hill et al. 2011a), whereas deletion of a degradative enzyme, fatty acid amide hydrolase, prevents stress induced dendrite expansion in basolateral amygala neurons (Hill et al. 2013). Endocannabinoids also play a role in shut-off of HPA function, as well as basal CORT (cortisol, human; corticosterone, rodent) levels after chronic stress and habituation of the CORT response to chronic stress and they appear to do so via the prefrontal cortex and amygdala (Hill et al. 2011b).

With regard to estrogen actions, there are multiple targets of genomic and non-genomic actions of E_2. E_2 stimulates both acetylcholine (Towart et al. 2003) and neuropeptide Y release (Ledoux et al. 2009) via presynaptic estrogen receptors and it induces actin polymerization and filopodial formation and translation of PSD95 mRNA via PI3kinase (Fig. 8; Dumitriu et al. 2010). E_2 stimulated acetylcholine release that inhibit inhibitory interneurons is believed to be responsible for up-regulation of NMDA receptors that are required for estrogen-induced synapse formation (Weiland 1992, Daniel & Dohanich 2001, Rudick et al. 2003).

For both E_2 and glucocorticoids, mitochondria are targets that affect Ca^{++} sequestration and regulate free radical formation (Brinton 2008, Du et al. 2009b). Both ERβ and glucocorticoid receptors translocate to mitochondria where they affect metabolic activity that, at physiological levels, promotes Ca^{++} sequestration and regulates free radical formation (Moutsatsou et al. 2001, Rettberg et al. 2014). At high levels of glucocorticoids, the
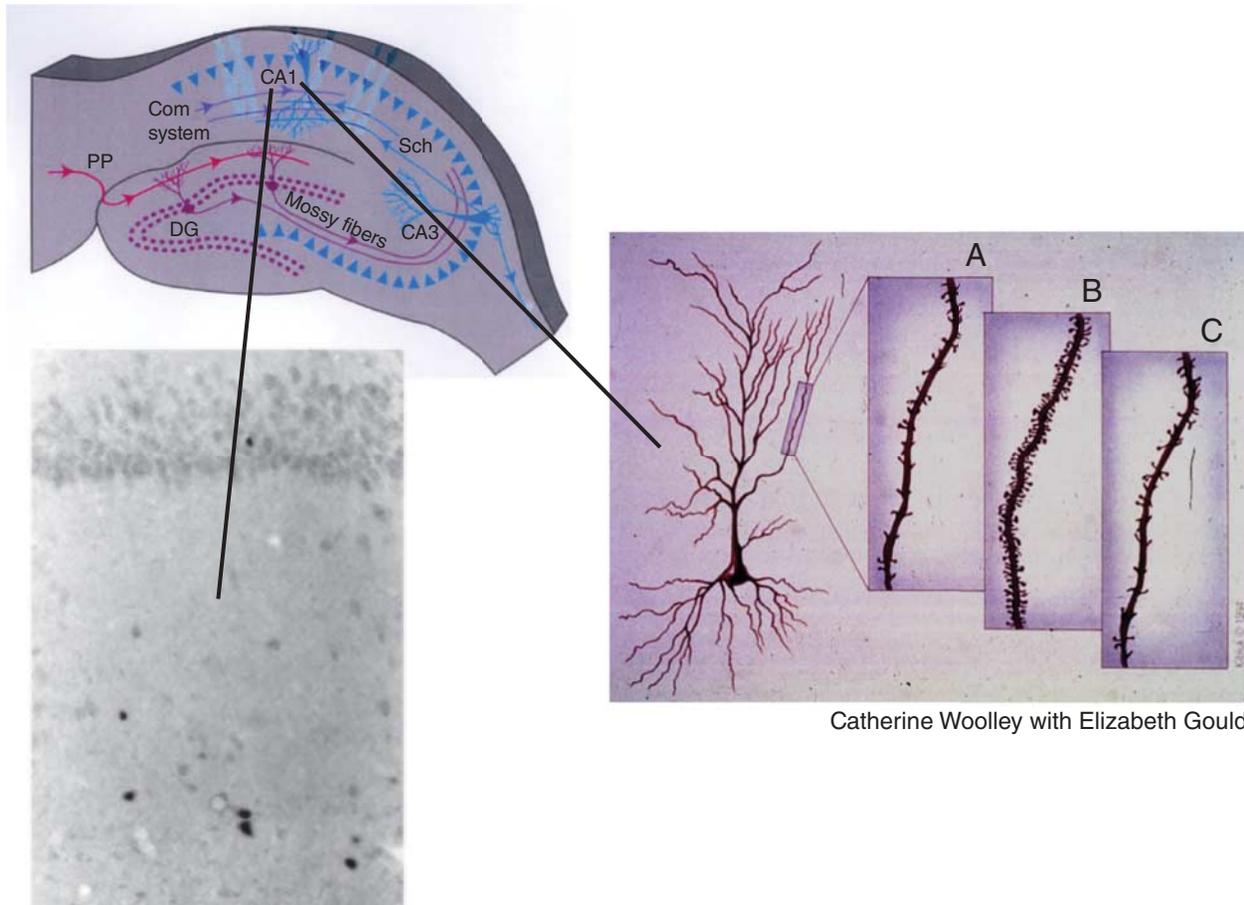
Catherine Woolley with Elizabeth Gould

Figure 6

Cyclic ovarian function regulates spine synapse turnover in the CA1 regions of the rat hippocampus and it does so via a combination of nuclear and non-nuclear estrogen receptors. The cell nuclear estrogen receptors are found in a subset of inhibitory interneurons whereas the non-nuclear receptors are expressed in presynaptic cholinergic and NPY terminals, in dendrites and mitochondria (McEwen & Milner 2007, Nilsen et al. 2007, Ledoux et al. 2009).

sequestration mechanism fail and free radicals and oxidative damage takes place (Du et al. 2009a).

Sex differences

There are important sex differences in the effects of stress and sex hormones on the hippocampus and prefrontal cortex, extending the seminal work of Harris & Levine (1965). Chronic stressors in females do not cause dendrites to shrink in CA3 neurons or in medial prefrontal cortex neurons (Galea et al. 1997). In medial prefrontal cortex, neurons that project cortically shrink with chronic stress in males but not in females, whereas neurons that project to the amygdala extend dendrites in females, but not in males, with chronic stress (Shansky et al. 2009, 2010). For the females to respond in this way, there must be circulating estrogens (Shansky et al. 2009).

That such sex differences exist in a brain region like prefrontal cortex not previously thought to be responsive to sex hormones means that there may be sex difference throughout the brain. Indeed, membrane associated estrogen receptors have been found widely throughout the brain (McEwen & Milner 2007). Studies in men and women of the functional imaging responses of human brain to tests of emotional recognition in which men and women score the same, nevertheless, reveal different patterns of activation across brain regions between the sexes (Derntl et al. 2010).

Reversal of sex differences by manipulations during the critical period for sexual differentiation have shown that males treated with an aromatase inhibitor at birth are able to respond to estrogens to induce synapses in the hippocampus, whereas normally males do not respond to E_2, but do respond to testosterone and dihydrotestosterone
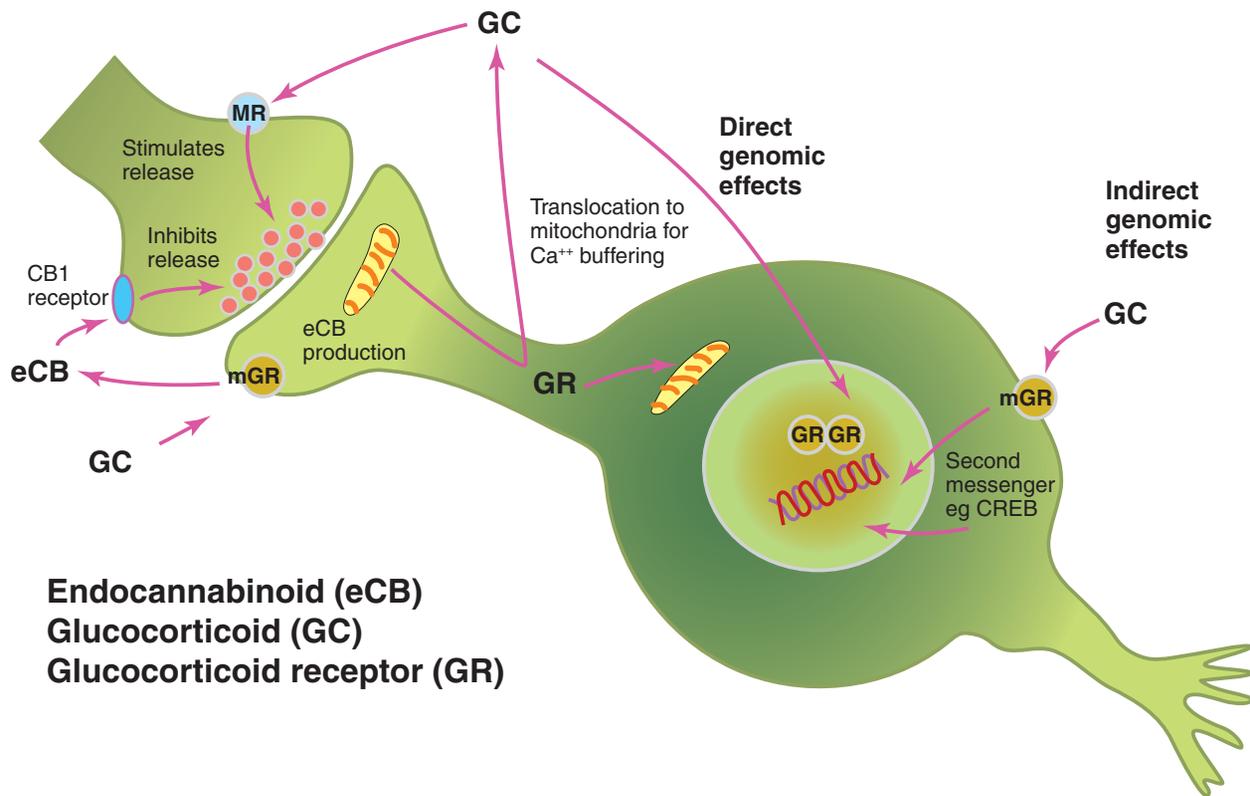
Figure 7

Glucocorticoids produce both direct and indirect genomic effects, and actions via translocation into mitochondria, as well as direct stimulation of presynaptic glutamate release and other non-genomic actions via signaling pathways that activate endocannabinoid synthesis.

for spine synapse induction (Lewis *et al*. 1995, Leranth *et al*. 2003). This is the converse of testosterone treatment of newborn females which defeminizes the ability of ovulation and respond with lordosis (Goy & McEwen 1980). It is important to note that aromatization of testosterone plays a key role in the defeminizing aspects of sexual differentiation postnatally, whereas conversion of testosterone to dihydrotestosterone is involved in masculinizing aspects of brain sexual differentiation that generally occur before birth in the rodent (Naftolin *et al*. 1971, McEwen *et al*. 1977, Naftolin 1994).

Spine synapse induction, that is produced by E_2 in adult female hippocampus and by dihydrotestosterone in male hippocampus, involves somewhat different mechanisms. In the female, as previously described, there are multiple mechanisms involving both genomic and non-genomic actions of E_2 and both cholinergic and GABAergic, as well as NMDA receptor mediated activity and E_2 stimulated signaling via PI3kinase (McEwen *et al*. 2001). In the male, where there are genomic androgen receptors in the CA1 region, as well as non-genomic receptors, the cholinergic system does not appear to be involved while androgens

upregulate NMDA receptors; this is a topic that needs more in-depth investigation (Romeo *et al*. 2005).

Gene expression in an ever-changing brain

We have found that the expression of genes in the brain is changing continuously with experiences and that novel stressors have different effects upon gene expression in a naïve brain, a chronically stressed brain and a brain recovered from chronic stress. High throughput gene expression profiling of the hippocampal response to an acute forced swim stress revealed a distinct pattern of gene regulation between stress-naïve mice and mice subjected to a forced swim after exposure to 3 weeks of chronic restraint stress (Gray *et al*. 2014). Further, mice allowed 3 weeks of recovery from chronic stress, which exhibited a normalization of anxiety-like behaviors, still revealed a gene expression profile that was different from the stress naïve state and produced a still different gene expression profile in response to a novel stress. An acute CORT challenge given to either stress naïve or chronically stressed rats also revealed highly different gene expression profiles,
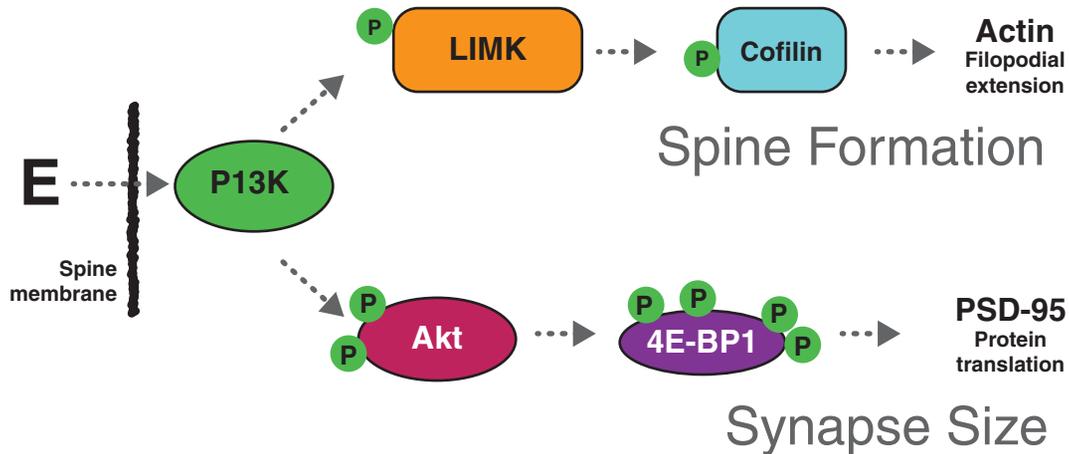
Figure 8

Non-genomic effects of estrogen. Estrogen initiates a complex set of signal transduction pathways in the hippocampal neuron via several membrane-bound receptors. Above are two examples of estrogen-initiated signal transduction leading to spinogenesis and changes in synapse size. Rapid activation of Akt (protein kinase B) via PI3K is thought to be mediated by ERα. Subsequently, activated Akt initiates translation of PSD-95 by removing the repression of the initiation factor 4E-binding protein1 (4E-BP1). Estradiol-mediated phosphorylation of cofilin has been shown to occur via activation of LIMK. Cofilin is an actin depolymerization factor and it is inactivated by phosphorylation. Therefore, in the presence of estrogen, cofilin repression of actin polymerization is removed, resulting in an increase in filopodial density. The signal transduction pathways illustrated here are an oversimplification of a large body of work done in an *in vitro* cell line. Reproduced, with permission, from Dumitriu D, Rapp PR, McEwen BS & Morrison JH (2010) Estrogen and the aging brain: an elixir for the weary cortical network. *Annals of the New York Academy of Sciences* **1204** 104–112. Copyright 2010 New York Academy of Sciences.

depending on the stress history of the animal; while ∼200 of the genes altered by CORT were the same irrespective of stress history, over 500 were different after a chronic stress exposure (Datson *et al.* 2013; Fig. 9). Together, these studies suggest that while the brain can recover, there remains considerable imprint of past stress experiences which alters future reactivity at the molecular level.

Yet a CORT challenge is not equivalent to replicating the complex network of pathways activated during an *in vivo* stress exposure. Expression profiles resulting from a bolus of corticosterone were found to be highly distinct from that of an acute stressor that elevates CORT (Gray *et al.* 2014; Fig. 9). While many of the well-established genes, such as c-Fos and Arc responded the same, there remains a widely unexplored set of new gene targets that have been identified, which are activated by stress, but function outside of traditional CORT or inflammatory signaling pathways.

Epigenetic regulation: search for rapidly acting treatments

Although the action of steroid hormones on cellular processes involves both genomic and non-genomic mechanisms of action, the cumulative actions of the interacting mediators result in changes in gene expression via epigenetic mechanisms involving histone modifications, methylation of cytosine bases on DNA, and the regulatory actions of non-coding RNA's (Mehler 2008). Regarding histone modifications that either repress gene expression and DNA activity or enhance such activity, Reul and colleagues have shown that the forced swimming-induced behavioral immobility response requires histone H3 phospho-acetylation and c-Fos induction in distinct dentate granule neurons through recruitment of the NMDA/ERK/MSK 1/2 pathway (Chandramohan *et al.* 2008).

Another histone mark change in hippocampus, and most prominently in the dentate gyrus, is the dramatic induction by an acute restraint stress of trimethylation of lysine 9 on histone H3, which is associated with repression of a number of retrotransposon elements and reduction of the coding and non-coding RNA normally produced by the repressed DNA (Hunter *et al.* 2009). This repression is lost with repeated stress, suggesting the possibility that those retrotransposon elements may impair genomic stability under conditions of chronic stress (Hunter *et al.* 2014).

A current practical application of this is the investigation of rapidly acting antidepressants, because classical antidepressants work slowly and are not effective on every depressed individual. In the course of these studies, we are learning more about epigenetic mechanisms that connect excitatory amino acid function with neural remodeling and stress-related behaviors. One novel agent
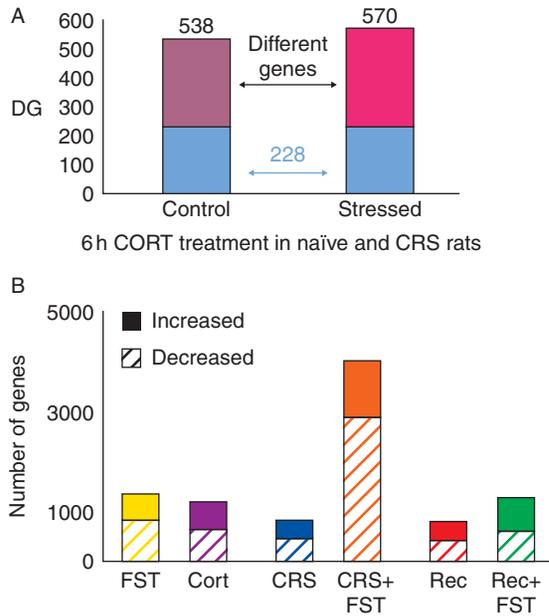
Figure 9

Effects of stress and acute glucocorticoid treatment on gene expression in hippocampus. (A) Naïve and 21d chronically restraint stressed (CRS) rats respond differently to a 6 h bolus of corticosterone in which more than half of the genes turned on or turned off are different (Datson *et al.* 2013). (B) Naïve mice given acute forced swim stress (FST) show a largely different pattern of gene expression (up and down) from naïve mice given an acute corticosterone bolus. Moreover, mice that are either naïve, or 21d CRS or 21d CRS plus 21d recovery respond, in large, differently to acute FST with respect to gene expression levels. There is a core of genes that always respond to the acute FST. Reproduced, with permission, from Gray JD, Rubin TG, Hunter RG & McEwen BS 2014 Hippocampal gene expression changes underlying stress sensitization and recovery. *Molecular Psychiatry* **19** 1171–1178. Copyright 2014, Rights Managed by Nature Publishing Group.

is acetyl-L-carnitine (LAC) that decreases depressive-like behavior within 3 days of treatment in a stress-induced and a genetic model of depression-like behavior while SSRI's and tricyclic drugs have no effect in that time frame (Nasca *et al.* 2013). Antidepressant effects of LAC have been shown in other animal models that mimic features of the spectrum of depressive disorders in humans (Cuccurazzu *et al.* 2013) and need to be expanded to human treatment resistant depression (Flight 2013, Russo & Charney 2013). The rapid antidepressant action of LAC is mediated by acetylation of the histone H3K27 bound to the promoter gene of the metabotropic glutamate receptor, mGlu2, which inhibits glutamate release to the synapse (Fig. 10A). Furthermore, a single injection of the HDAC inhibitor, MS-275, mimicked the action of LAC in enhancing mGlu2 receptor expression in Flinders Sensitive Line (FSL) rats. Among other mechanisms, LAC also promotes acetylation of the p65, the major component of the NFkB transcription factor, to exert fast antidepressant responses (Cuccurazzu *et al.* 2013).

In the course of this work, we become aware that lower mGlu2 expression in hippocampus increases the vulnerability to stress (Nasca *et al.* 2014).

Translation to the human brain

The revelations about how acute and chronic stress affect the brain in animal models has been used by researchers and clinicians to show changes in function within the human brain that result from stress and trauma, and correspond to effects seen in the research on animal models (McEwen 2007, McEwen & Gianaros 2011, McEwen & Morrison 2013). These include changes in brain structure and functional activity in depression, post traumatic stress disorder (PTSD), Cushing's disease and type 2 diabetes, as well as effects of jet lag and shift work, chronic life stress, perceived stress and the beneficial effects of physical activity (Sheline 2003, McEwen & Gianaros 2011). For perceived stress, medical students who had high scores on the ten item perceived stress scale showed impaired functional connectivity by fMRI in a brain circuit involving the prefrontal cortex, as well as impaired performance on a test of mental flexibility (Liston *et al.* 2009); these effects were reversed by a month vacation and we know from animal studies that prefrontal cortical and hippocampal dendrite shrinkage is reversible in young adult animals (Conrad *et al.* 1999, Radley *et al.* 2005). Regarding physical activity, previously sedentary older adults who walk an hour a day for 6 months to a year show enlargement of the hippocampal formation (Erickson *et al.* 2011) and this is likely due, at least in part, to the increased dentate gyrus neurogenesis that is stimulated by exercise and by an enriched environment (Kempermann *et al.* 1997, van Praag *et al.* 1999). It is also noteworthy that hippocampal volume increases with intense learning (Draganski *et al.* 2006), but is also decreased in Cushing's disease (Starkman *et al.* 1992).

However, there is age-related loss of resilience of the dendrite shrinkage in prefrontal cortex (Bloss *et al.* 2010), as well as age-related memory impairment, which, however, can be reduced by pharmacological intervention (Bloss *et al.* 2008, Pereira *et al.* 2014). These treatments may find their way into treating human mild cognitive impairment and perhaps also dementia.

Another translational application of structural plasticity and the actions of stress mediators is the somewhat surprising role of glucocorticoid elevation at the time of trauma in reducing the risk for PTSD (Schelling *et al.* 2004, Zohar *et al.* 2011, Rao *et al.* 2012). One possibility is that glucocorticoid stimulation of endocannabinoid production may be involved in this protection (Hill & McEwen 2010).

Individual differences, stressful early life events and the life course perspective

What happens early in life determines the trajectory of development for the rest of the individual's life and biomedical science and medical practice are beginning to recognize this (Halfon *et al.* 2014). The original definition of epigenetics that referred to the emergence of characteristics of an organism with development (Waddington 1942) implied that there was no turning back, but that each stage of development offers possibilities to change the trajectory of brain and body function.

Adverse childhood experiences produce a lifelong vulnerability to mental and physical health disorders and prevention is paramount (Felitti *et al.* 1998, Shonkoff *et al.* 2009, Anda *et al.* 2010). Where adverse events have happened, it is important to find ways of compensatory remediation. This is an enormous challenge and the newer use of the term 'epigenetics', meaning 'above the genome' and referring to the ability to change expression of genetic traits via physical, behavioral and pharmacological intervention as previously described, offers some hope that the brain and body remain dynamic over the lifespan (Bavelier *et al.* 2010, McEwen 2012).

Even without adversity in childhood, individuals with the same genes turn out differently and this is reflected in divergent epigenetic profiles of CpG methylation patters of chromosomes of identical twins as they age (Fraga *et al.* 2005). Cloned mice raised in an enriched environment develop differences in locomotor activity correlated with levels of dentate gyrus neurogenesis (Freund *et al.* 2013). And genetically similar rats screened for anxiety-like behavior early in life show consistent individual anxiety profiles over their life course, and the more anxious rats die 200 days sooner than the less anxious ones (Cavigelli & McClintock 2003, Cavigelli *et al.* 2006). Reduced prefrontal cortical dendrite length and branching is a neuroanatomical feature of elevated anxiety-like behavior in rats (Miller *et al.* 2012).

Arising out of the studies of the antidepressant-like actions of LAC is new insight into at least one possible mechanism involving mineralocorticoid receptors (MR) in hippocampus by which individual differences arise in susceptibility to stressors for developing anxiety- and depressive-like behaviors. Mice with a mGlu2 knock-out subjected to chronic unpredictable stressors show more signs of coat deterioration, reduced body weight and increased immobility at the forced swim test compared to WT animals subjected to the same regimen of stress (Nasca *et al.* 2014). In WT mice, a simple light–dark test revealed a subset with higher anxiety that have elevated hippocampal MR. Those mice with higher MR showed a greater stress-induced reduction in mGlu2 accompanied by more anxiety and depressive-like behaviors; this effect is mediated by a
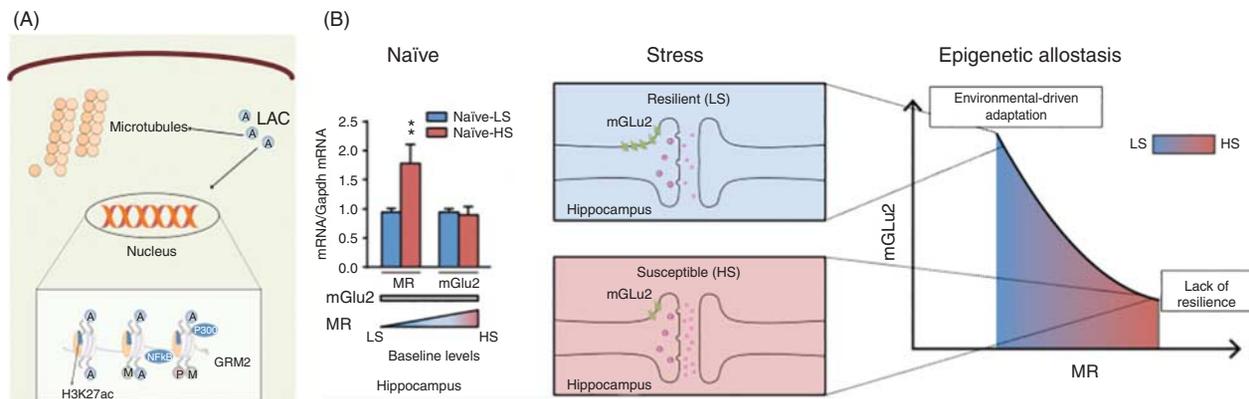

Figure 10
Novel mechanisms for rapidly acting medications to treat stress-related disorders. (A) The novel antidepressant candidate acetyl-L-carnitine (LAC) may act inside and outside the nucleus to exert fast antidepressant responses: it has been shown that LAC corrects mGlu2 deficits in vulnerable animal models by increasing acetylation of either the histone H3K27 bound to Grm2 promoter gene or the NFkB-p65 member (Nasca *et al.* 2013). (B) The use of the light–dark test as a screening method allows identification of clusters of animals with a different baseline susceptibility along with differences in mineralocorticoid receptor (MR) levels in hippocampus. The susceptible mice (HS, high susceptible) that are characterized by higher baseline MR levels show reduced hippocampal mGlu2 expression associated with exacerbation of anxious and of depressive-like behaviors after acute and chronic stress respectively. Conversely, individuals (LS, low susceptible) with lower baseline MR levels cope better with stress and show adaptation in mGlu2 receptor expression in hippocampus. The epigenetic allostasis model points to the developmental origins of these individual differences, suggesting that unknown epigenetic influences early in life may lead to alterations in MR hippocampal levels. Reproduced, with permission, from Nasca C, Bigio B, Zelli D, Nicoletti F & McEwen BS (2014) Mind the gap: glucocorticoids modulate hippocampal glutamate tone underlying individual differences in stress susceptibility. *Molecular Psychiatry* 20 755–763. Copyright 2014, Rights Managed by Nature Publishing Group.

stress-induced reduction of the epigenetic enzyme P300, which regulates acetylation of the histone H3K27 that promotes mGlu2 expression (Nasca *et al.* 2014).

The ability of MR activation to mediate enhanced anxiety and depression-like behavior after acute and chronic stress by down-regulating mGlu2 is consistent with evidence showing a role of MR in anxiety-like behavior (Korte *et al.* 1995) in hippocampus (Smythe *et al.* 1997, Bitran *et al.* 1998) and particularly the ventral hippocampus (McEown & Treit 2011). Despite high baseline cortisol levels, patients with major depression show high functional activity of the MR system along with decreased sensitivity to GR agonists, suggesting an imbalance in the MR/GR ratio (Young *et al.* 2003). Indeed, the MR/GR balance is important not only for emotional regulation but also for cognitive function and HPA regulation (de Kloet 2014).

The epigenetic allostasis model in Fig. 10 proposes that early-life epigenetic influences, program each individual to different trajectories of behavioral and physiological responses to later stressful life events, and it remains to be determined whether the higher MR-levels reflect epigenetic influences of maternal care or other experiences early in life. Indeed, the role of consistent and disrupted maternal care, as well as prenatal stress, have been investigated in animal models and should be considered (Francis *et al.* 1999, Weinstock 2005, Moriceau & Sullivan 2006, Maccari & Morley-Fletcher 2007, Akers *et al.* 2008, Molet *et al.* 2014).

Impact of the social environment

The emerging field of epigenetics, along with the reversible remodeling of brain architecture, has provided a new way of conceptualizing the influence of the social and physical environment on the brain and body. As shown in Fig. 4, the brain is the central organ of stress and adaptation because it determines what is threatening and, therefore, stressful. And the brain controls autonomic and neuroendocrine signals that affect the rest of the body to promote adaptation ('allostasis') and also allostatic load and overload (McEwen & Stellar 1993, McEwen 1998, McEwen & Wingfield 2003). Health behaviors ('lifestyle'), including choice and amount of food intake, smoking, alcohol intake, physical activity, or lack thereof, and social interactions also feed into and contribute to allostasis and allostatic load/overload (McEwen 2006). Finally, the genetic endowment and experiential factors throughout the life course, but especially early in life, influence the trajectory of brain and body function (Danese & McEwen 2012, Halfon *et al.* 2014).

Low socioeconomic status is associated with increased risk for the common diseases of modern life and is associated with increased inflammatory tone and altered white matter structure (Seeman *et al.* 2010, Gianaros *et al.* 2013). Likewise, type 2 diabetes, which is more common at lower levels of socioeconomic status (SES), is also associated with altered myelin and impaired cognitive function (Yau *et al.* 2012). On the positive side, meaning and purpose in life appear to have a considerable ability to promote health and ward off cognitive decline, including dementia (Carlson *et al.* 2009, Boyle *et al.* 2010). Likewise, regular physical activity has many benefits for brain and body health (Colcombe *et al.* 2004).

Conclusions

With the discovery of circulating hormone actions throughout the brain on virtually every aspect of brain function, the original definition of 'neuroendocrinology' based upon the work of Geoffrey Harris has expanded to encompass many aspects of reciprocal brain–body communication. With the new appreciation of the life-course perspective for human health and disease, along with the emerging field of gene x environment interactions now called 'epigenetics' (Halfon *et al.* 2014), the reciprocal communication between the brain and body via hormonal and neural mediators takes a central role in facilitating progress in understanding how the social and physical environment 'gets under the skin' to alter trajectories of health and disease. Given the central role of the brain, there is now impetus for interventions that involve policies of government and the private sector, as well as psychosocial interventions at the individual level that produce a 'top–down' improvement in the physiological processes that are dysregulated by stress and adversity (Acheson 1998). The emerging recognition of the ability of the brain to change its architecture and function via these top–down interventions involving brain–body communication, where pharmaceutical agents or behavioral interventions that open up 'windows of plasticity,' gives hope for redirecting individual trajectories towards better physical and mental health.

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References

Acheson SD 1998 *Independent Inquiry into Inequalities in Health Report*. London, UK: The Stationary Office.

Ahima RS & Harlan RE 1990 Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. *Neuroscience* **39** 579–604. (doi:10.1016/0306-4522(90)90244-X)

Ahima R, Krozowski Z & Harlan R 1991 Type I corticosteroid receptor-like immunoreactivity in the rat CNS: distribution and regulation by corticosteroids. *Journal of Comparative Neurology* **313** 522–538. (doi:10.1002/cne.903130312)

Akers KG, Yang Z, DelVecchio DP, Reeb BC, Romeo RD, McEwen BS & Tang AC 2008 Social competitiveness and plasticity of neuroendocrine function in old age: influence of neonatal novelty exposure and maternal care reliability. *PLoS ONE* **3**(7) e2840. (doi:10.1371/journal.pone.0002840)

Altman J 1962 Are new neurons formed in the brains of adult mammals? *Science* **135** 1127–1128. (doi:10.1126/science.135.3509.1127)

Alvarez-Buylla A & Garcia-Verdugo JM 2002 Neurogenesis in adult subventricular zone. *Journal of Neuroscience* **22** 629–634.

Anda RF, Butchart A, Felitti VJ & Brown DW 2010 Building a framework for global surveillance of the public health implications of adverse childhood experiences. *American Journal of Preventive Medicine* **39** 93–98. (doi:10.1016/j.amepre.2010.03.015)

Arendt T, Stieler J, Strijkstra AM, Hut RA, Rudiger J, Van der Zee EA, Harkany T, Holzer M & Härtig W 2003 Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals. *Journal of Neuroscience* **23** 6972–6981.

Bavelier D, Levi DM, Li RW, Dan Y & Hensch TK 2010 Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *Journal of Neuroscience* **30** 14964–14971. (doi:10.1523/JNEUROSCI.4812-10.2010)

Biegler R, McGregor A, Krebs JR & Healy SD 2001 A larger hippocampus is associated with longer-lasting spatial memory. *PNAS* **98** 6941–6944. (doi:10.1073/pnas.121034798)

Bitran D, Shiekh M, Dowd JA, Dugan MM & Renda P 1998 Corticosterone is permissive to the anxiolytic effect that results from the blockade of hippocampal mineralocorticoid receptors. *Pharmacology, Biochemistry, and Behavior* **60** 879–887. (doi:10.1016/S0091-3057(98)00071-9)

Bloss EB, Hunter RG, Waters EM, Munoz C, Bernard K & McEwen BS 2008 Behavioral and biological effects of chronic S18986, a positive AMPA receptor modulator, during aging. *Experimental Neurology* **210** 109–117. (doi:10.1016/j.expneurol.2007.10.007)

Bloss EB, Janssen WG, McEwen BS & Morrison JH 2010 Interactive effects of stress and aging on structural plasticity in the prefrontal cortex. *Journal of Neuroscience* **30** 6726–6731. (doi:10.1523/JNEUROSCI.0759-10.2010)

Boyle PA, Buchman AS, Barnes LL & Bennett DA 2010 Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. *Archives of General Psychiatry* **67** 304–310. (doi:10.1001/archgenpsychiatry.2009.208)

Brinton RD 2008 The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. *Trends in Neurosciences* **31** 529–537. (doi:10.1016/j.tins.2008.07.003)

Burger DK, Saucier JM, Iwaniuk AN & Saucier DM 2013 Seasonal and sex differences in the hippocampus of a wild rodent. *Behavioural Brain Research* **236** 131–138. (doi:10.1016/j.bbr.2012.08.044)

Cameron HA & Gould E 1994 Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* **61** 203–209. (doi:10.1016/0306-4522(94)90224-0)

Cameron HA & Dayer AG 2008 New interneurons in the adult neocortex: small, sparse, but significant? *Biological Psychiatry* **63** 650–655. (doi:10.1016/j.biopsych.2007.09.023)

Carlson MC, Erickson KI, Kramer AF, Voss MW, Bolea N, Mielke M, McGill S, Rebok GW, Seeman T & Fried LP 2009 Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* **64** 1275–1282. (doi:10.1093/gerona/glp117)

Cavigelli SA & McClintock MK 2003 Fear of novelty in infant rats predicts adult corticosterone dynamics and an early death. *PNAS* **100** 16131–16136. (doi:10.1073/pnas.2535721100)

Cavigelli SA, Yee JR & McClintock MK 2006 Infant temperament predicts life span in female rats that develop spontaneous tumors. *Hormones and Behavior* **50** 454–462. (doi:10.1016/j.yhbeh.2006.06.001)

Chandramohan Y, Droste SK, Arthur JS & Reul JM 2008 The forced swimming-induced behavioural immobility response involves histone H3 phospho-acetylation and c-Fos induction in dentate gyrus granule neurons via activation of the *N*-methyl-D-aspartate/extracellular signal-regulated kinase/mitogen- and stress-activated kinase signalling pathway. *European Journal of Neuroscience* **27** 2701–2713. (doi:10.1111/j.1460-9568.2008.06230.x)

Chen Y, Fenoglio KA, Dube CM, Grigoriadis DE & Baram TZ 2006*a* Cellular and molecular mechanisms of hippocampal activation by acute stress are age-dependent. *Molecular Psychiatry* **11** 992–1002.

Chen Z-Y, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C & McEwen BS 2006*b* Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* **314** 140–143. (doi:10.1126/science.1129663)

Clayton NS 2001 Hippocampal growth and maintenance depend on food-caching experience in juvenile mountain chickadees (Poecile gambeli). *Behavioral Neuroscience* **115** 614–625. (doi:10.1037/0735-7044.115.3.614)

Colcombe SJ, Kramer AF, McAuley E, Erickson KI & Scalf P 2004 Neurocognitive aging and cardiovascular fitness. *Journal of Molecular Neuroscience* **24** 9–14. (doi:10.1385/JMN:24:1:009)

Conrad CD, Magarinos AM, LeDoux JE & McEwen BS 1999 Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behavioral Neuroscience* **113** 902–913. (doi:10.1037/0735-7044.113.5.902)

Cuccurazzu B, Bortolotto V, Valente MM, Ubezio F, Koverech A, Canonico PL & Grilli M 2013 Upregulation of mGlu2 receptors via NF-κB p65 acetylation is involved in the proneurogenic and antidepressant effects of acetyl-L-carnitine. *Neuropsychopharmacology* **38** 2220–2230. (doi:10.1038/npp.2013.121)

Danese A & McEwen BS 2012 Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior* **106** 29–39. (doi:10.1016/j.physbeh.2011.08.019)

Daniel JM & Dohanich GP 2001 Acetylcholine mediates the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and the associated improvement in working memory. *Journal of Neuroscience* **21** 6949–6956.

Datson NA, van den Oever JM, Korobko OB, Magarinos AM, de Kloet ER & McEwen BS 2013 Previous history of chronic stress changes the transcriptional response to glucocorticoid challenge in the dentate gyrus region of the male rat hippocampus. *Endocrinology* **154** 3261–3272. (doi:10.1210/en.2012-2233)

Derntl B, Finkelmeyer A, Eickhoff S, Kellermann T, Falkenberg DI, Schneider F & Habel U 2010 Multidimensional assessment of empathic abilities: neural correlates and gender differences. *Psychoneuroendocrinology* **35** 67–82. (doi:10.1016/j.psyneuen.2009.10.006)

Diamond DM, Bennett MC, Fleshner M & Rose GM 1992 Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* **2** 421–430. (doi:10.1002/hipo.450020409)

Dickens M, Romero LM, Cyr NE, Dunn IC & Meddle SL 2009 Chronic stress alters glucocorticoid receptor and mineralocorticoid receptor mRNA expression in the European starling (*Sturnus vulgaris*) brain. *Journal of Neuroendocrinology* **21** 832–840. (doi:10.1111/j.1365-2826.2009.01908.x)

Draganski B, Gaser C, Kempermann G, Kuhn HG, Winkler J, Büchel C & May A 2006 Temporal and spatial dynamics of brain structure changes during extensive learning. *Journal of Neuroscience* **26** 6314–6317. (doi:10.1523/JNEUROSCI.4628-05.2006)

Du J, McEwen BS & Manji HK 2009*a* Glucocorticoid receptors modulate mitochondrial function. *Communicative & Integrative Biology* **2** 1–3. (doi:10.4161/cib.2.4.8554)

Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C, Khairova R, Zhou R, Yuan P & Machado-Vieira R 2009*b* Dynamic regulation of mitochondrial function by glucocorticoids. *PNAS* **106** 3543–3548. (doi:10.1073/pnas.0812671106)

Dumitriu D, Rapp PR, McEwen BS & Morrison JH 2010 Estrogen and the aging brain: an elixir for the weary cortical network. *Annals of the New York Academy of Sciences* **1204** 104–112. (doi:10.1111/j.1749-6632.2010.05529.x)

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H & White SM 2011 Exercise training increases size of hippocampus and improves memory. *PNAS* **108** 3017–3022. (doi:10.1073/pnas.1015950108)

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP & Marks JS 1998 Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *American Journal of Preventive Medicine* **14** 245–258. (doi:10.1016/S0749-3797(98)00017-8)

Flight MH 2013 Antidepressant epigenetic action. *Nature Reviews. Neuroscience* **14** 226. (doi:10.1038/nrn3466)

Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suñer D, Cigudosa JC, Urioste M & Benitez J 2005 Epigenetic differences arise during the lifetime of monozygotic twins. *PNAS* **102** 10604–10609. (doi:10.1073/pnas.0500398102)

Francis D, Diorio J, Liu D & Meaney MJ 1999 Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **286** 1155–1158. (doi:10.1126/science.286.5442.1155)

Frankfurt M, Gould E, Wolley C & McEwen BS 1990 Gonadal steroids modify dendritic spine density in ventromedial hypothalamic neurons: a golgi study in the adult rat. *Neuroendocrinology* **51** 530–535. (doi:10.1159/000125387)

Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, Krüger A, Sachser N, Lindenberger U & Kempermann G 2013 Emergence of individuality in genetically identical mice. *Science* **340** 756–759. (doi:10.1126/science.1235294)

Galea LAM, McEwen BS, Tanapat P, Deak T, Spencer RL & Dhabhar FS 1997 Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* **81** 689–697. (doi:10.1016/S0306-4522(97)00233-9)

Gerlach J & McEwen BS 1972 Rat brain binds adrenal steroid hormone: radioautography of hippocampus with corticosterone. *Science* **175** 1133–1136. (doi:10.1126/science.175.4026.1133)

Gerlach J, McEwen BS, Pfaff DW, Moskovitz S, Ferin M & Waters EM 1976 Cells in regions of rhesus monkey brain and pituitary retain radioactive estradiol, corticosterone and cortisol differently. *Brain Research* **103** 603–612. (doi:10.1016/0006-8993(76)90463-7)

Gianaros PJ, Marsland AL, Sheu LK, Erickson KI & Verstynen TD 2013 Inflammatory pathways link socioeconomic inequalities to white matter architecture. *Cerebral Cortex* **23** 2058–2071. (doi:10.1093/cercor/bhs191)

Gould E 2007 How widespread is adult neurogenesis in mammals? *Nature Reviews. Neuroscience* **8** 481–488. (doi:10.1038/nrn2147)

Gould E, McEwen BS, Tanapat P, Galea LAM & Fuchs E 1997 Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *Journal of Neuroscience* **17** 2492–2498.

Gould E, Tanapat P, McEwen BS, Flugge G & Fuchs E 1998 Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *PNAS* **95** 3168–3171. (doi:10.1073/pnas.95.6.3168)

Govindarajan A, Rao BSS, Nair D, Trinh M, Mawjee N, Tonegawa S & Chattarji S 2006 Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. *PNAS* **103** 13208–13213. (doi:10.1073/pnas.0605180103)

Goy R & McEwen BS, Eds 1980 *Sexual Differentiation of the Brain*. Cambridge, MA, USA: MIT Press.

Gray JD, Rubin TG, Hunter RG & McEwen BS 2014 Hippocampal gene expression changes underlying stress sensitization and recovery. *Molecular Psychiatry* **19** 1171–1178. (doi:10.1038/mp.2013.175)

Guillemin R 1978 Peptides in the brain: the new endocrinology of the neuron. *Science* **202** 390–402. (doi:10.1126/science.212832)

Halfon N, Larson K, Lu M, Tullis E & Russ S 2014 Lifecourse health development: past, present and future. *Maternal and Child Health Journal* **18** 344–365. (doi:10.1007/s10995-013-1346-2)

Harris GW 1970 Effects of the nervous system on the pituitary-adrenal activity. *Progress in Brain Research* **32** 86–88.

Harris GW & Levine S 1965 Sexual differentiation of the brain and its experimental control. *Journal of Physiology* **181** 379–400. (doi:10.1113/jphysiol.1965.sp007768)

Hill MN & McEwen BS 2010 Involvement of the endocannabinoid system in the neurobehavioural effects of stress and glucocorticoids. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **34** 791–797. (doi:10.1016/j.pnpbp.2009.11.001)

Hill MN, Hillard CJ & McEwen BS 2011*a* Alterations in corticolimbic dendritic morphology and emotional behavior in cannabinoid CB1 receptor-deficient mice parallel the effects of chronic stress. *Cerebral Cortex* **21** 2056–2064. (doi:10.1093/cercor/bhq280)

Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TT, Karatsoreos IN, Mackie K, Viau V & Pickel VM 2011*b* Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *Journal of Neuroscience* **31** 10506–10515. (doi:10.1523/JNEUROSCI.0496-11.2011)

Hill MN, Kumar SA, Filipski SB, Iverson M, Stuhr KL, Keith JM, Cravatt BF, Hillard CJ, Chattarji S & McEwen BS 2013 Disruption of fatty acid amide hydrolase activity prevents the effects of chronic stress on anxiety and amygdalar microstructure. *Molecular Psychiatry* **18** 1125–1135. (doi:10.1038/mp.2012.90)

Hunter RG, McCarthy KJ, Milne TA, Pfaff DW & McEwen BS 2009 Regulation of hippocampal H3 histone methylation by acute and chronic stress. *PNAS* **106** 20912–20917. (doi:10.1073/pnas.0911143106)

Hunter RG, Gagnidze K, McEwen BS & Pfaff DW 2015 Stress and the dynamic genome: steroids, epigenetics, and the transposome. *PNAS* **112** 6828–6833. (doi:10.1073/pnas.1411260111)

Jensen E & Jacobson H 1962 Basic guides to the mechanism of estrogen action. *Recent Progress in Hormone Research* **18** 387–408.

Joels M 2006 Corticosteroid effects in the brain: U-shape it. *Trends in Pharmacological Sciences* **27** 244–250. (doi:10.1016/j.tips.2006.03.007)

Kaplan MS 2001 Environment complexity stimulates visual cortex neurogenesis: death of a dogma and a research career. *Trends in Neurosciences* **24** 617–620. (doi:10.1016/S0166-2236(00)01967-6)

Karst H, Berger S, Turiault M, Tronche F, Schutz G & Joels M 2005 Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *PNAS* **102** 19204–19207. (doi:10.1073/pnas.0507572102)

Kempermann G, Kuhn HG & Gage FH 1997 More hippocampal neurons in adult mice living in an enriched environment. *Nature* **586** 493–495. (doi:10.1038/386493a0)

de Kloet ER 2014 From receptor balance to rational glucocorticoid therapy. *Endocrinology* **155** 2754–2769. (doi:10.1210/en.2014-1048)

Korte SM, de Boer SF, de Kloet ER & Bohus B 1995 Anxiolytic-like effects of selective mineralocorticoid and glucocorticoid antagonists on fear-enhanced behavior in the elevated plus-maze. *Psychoneuroendocrinology* **20** 385–394. (doi:10.1016/0306-4530(94)00069-7)

Ledoux VA, Smejkalova T, May RM, Cooke BM & Woolley CS 2009 Estradiol facilitates the release of neuropeptide Y to suppress

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hippocampus-dependent seizures. *Journal of Neuroscience* **29** 1457–1468. (doi:10.1523/JNEUROSCI.4688-08.2009)

Leranth C, Petnehazy O & MacLusky NJ 2003 Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. *Journal of Neuroscience* **23** 1588–1592.

Leuner B, Glasper ER & Gould E 2010 Sexual experience promotes adult neurogenesis in the hippocampus despite an initial elevation in stress hormones. *PLoS ONE* **5** e11597. (doi:10.1371/journal.pone.0011597)

Leuner B, Caponiti JM & Gould E 2012 Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. *Hippocampus* **22** 861–868. (doi:10.1002/hipo.20947)

Lewis C, McEwen BS & Frankfurt M 1995 Estrogen-induction of dendritic spines in ventromedial hypothalamus and hippocampus: effects of neonatal aromatase blockade and adult castration. *Developmental Brain Research* **87** 91–95. (doi:10.1016/0165-3806(95)00052-F)

Liston C & Gan WB 2011 Glucocorticoids are critical regulators of dendritic spine development and plasticity *in vivo*. *PNAS* **108** 16074–16079. (doi:10.1073/pnas.1110444108)

Liston C, McEwen BS & Casey BJ 2009 Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *PNAS* **106** 912–917. (doi:10.1073/pnas.0807041106)

Liston C, Cichon JM, Jeanneteau F, Jia Z, Chao MV & Gan WB 2013 Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. *Nature Neuroscience* **16** 698–705. (doi:10.1038/nn.3387)

Loy R, Gerlach J & McEwen BS 1988 Autoradiographic localization of estradiol-binding neurons in rat hippocampal formation and entorhinal cortex. *Developmental Brain Research* **39** 245–251. (doi:10.1016/0165-3806(88)90028-4)

Maccari S & Morley-Fletcher S 2007 Effects of prenatal restraint stress on the hypothalamus–pituitary–adrenal axis and related behavioural and neurobiological alterations. *Psychoneuroendocrinology* **32** S10–S15. (doi:10.1016/j.psyneuen.2007.06.005)

Magarinos AM, McEwen BS, Saboureau M & Pevet P 2006 Rapid and reversible changes in intrahippocampal connectivity during the course of hibernation in European hamsters. *PNAS* **103** 18775–18780. (doi:10.1073/pnas.0608785103)

Magarinos AM, Li CJ, GalToth J, Bath KG, Jing D, Lee FS & McEwen BS 2011 Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. *Hippocampus* **21** 253–264. (doi:10.1002/hipo.20744)

Maguire EA, Frackowiak RSJ & Frith CD 1997 Recalling routes around London: activation of the right hippocampus in taxi drivers. *Journal of Neuroscience* **17** 7103–7110.

Maier SF & Watkins LR 1998 Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review* **105** 83–107. (doi:10.1037/0033-295X.105.1.83)

McEown K & Treit D 2011 Mineralocorticoid receptors in the medial prefrontal cortex and hippocampus mediate rats' unconditioned fear behaviour. *Hormones and Behavior* **60** 581–588. (doi:10.1016/j.yhbeh.2011.08.007)

McEwen BS 1976 Steroid hormone receptors in developing and mature brain tissue. In *Neurotransmitters, Hormones and Receptors: Novel Approaches*, pp. 50–66. Eds S Snyder & BS McEwen. Bethesda, MA, USA: Society of Neuroscience.

McEwen BS 1998 Protective and damaging effects of stress mediators. *New England Journal of Medicine* **338** 171–179. (doi:10.1056/NEJM199801153380307)

McEwen BS 1999 Stress and hippocampal plasticity. *Annual Review of Neuroscience* **22** 105–122. (doi:10.1146/annurev.neuro.22.1.105)

McEwen BS 2006 Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in Clinical Neuroscience* **8** 367–381.

McEwen BS 2007 Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews* **87** 873–904. (doi:10.1152/physrev.00041.2006)

McEwen BS 2010 Stress, sex, and neural adaptation to a changing environment: mechanisms of neuronal remodeling. *Annals of the New York Academy of Sciences* **1204** (Suppl) E38–E59. (doi:10.1111/j.1749-6632.2010.05568.x)

McEwen BS 2012 Brain on stress: how the social environment gets under the skin. *PNAS* **109** (Suppl 2) 17180–17185. (doi:10.1073/pnas.1121254109)

McEwen BS & Plapinger L 1970 Association of corticosterone-1,2 3H with macromolecules extracted from brain cell nuclei. *Nature* **226** 263–264. (doi:10.1038/226263a0)

McEwen BS & Stellar E 1993 Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine* **153** 2093–2101. (doi:10.1001/archinte.1993.00410180039004)

McEwen BS & Wingfield JC 2003 The concept of allostasis in biology and biomedicine. *Hormones and Behavior* **43** 2–15. (doi:10.1016/S0018-506X(02)00024-7)

McEwen BS & Chattarji S 2007 Neuroendocrinology of stress. In *Handbook of Neurochemistry and Molecular Neurobiology*, pp. 572–593. New York, NY, USA: Springer–Verlag.

McEwen BS & Milner TA 2007 Hippocampal formation: shedding light on the influence of sex and stress on the brain. *Brain Research Reviews* **55** 343–355. (doi:10.1016/j.brainresrev.2007.02.006)

McEwen BS & Gianaros PJ 2011 Stress- and allostasis-induced brain plasticity. *Annual Review of Medicine* **62** 431–445. (doi:10.1146/annurev-med-052209-100430)

McEwen BS & Morrison JH 2013 The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron* **79** 16–29. (doi:10.1016/j.neuron.2013.06.028)

McEwen BS, Weiss J & Schwartz L 1968 Selective retention of corticosterone by limbic structures in rat brain. *Nature* **220** 911–912. (doi:10.1038/220911a0)

McEwen BS, Lieberburg I, Chaptal C & Krey L 1977 Aromatization: important for sexual differentiation of the neonatal rat brain. *Hormones and Behavior* **9** 249–263. (doi:10.1016/0018-506X(77)90060-5)

McEwen BS, Gould E, Orchinik M, Weiland NG & Woolley CS 1995 Oestrogens and the structural and functional plasticity of neurons: implications for memory, ageing and neurodegenerative processes. In *Ciba Foundation Symposium #191 The Non-reproductive Actions of Sex Steroids*, pp 52–73. Ed. J Goode. London: CIBA Foundation.

McEwen B, Akama K, Alves S, Brake WG, Bulloch K, Lee S, Li C, Yuen G & Milner TA 2001 Tracking the estrogen receptor in neurons: implications for estrogen-induced synapse formation. *PNAS* **98** 7093–7100. (doi:10.1073/pnas.121146898)

Mehler MF 2008 Epigenetic principles and mechanisms underlying nervous system functions in health and disease. *Progress in Neurobiology* **86** 305–341. (doi:10.1016/j.pneurobio.2008.10.001)

Meites J 1992 Short history of neuroendocrinology and the International Society of Neuroendocrinology. *Neuroendocrinology* **56** 1–10. (doi:10.1159/000126201)

Miller MM, Morrison JH & McEwen BS 2012 Basal anxiety-like behavior predicts differences in dendritic morphology in the medial prefrontal cortex in two strains of rats. *Behavioural Brain Research* **229** 280–288. (doi:10.1016/j.bbr.2012.01.029)

Milner TA, McEwen BS, Hayashi S, Li CJ, Reagen L & Alves SE 2001 Ultrastructural evidence that hippocampal α estrogen receptors are located at extranuclear sites. *Journal of Comparative Neurology* **429** 355–371. (doi:10.1002/1096-9861(20010115)429:3<355::AID-CNE1>3.0.CO;2-)

Molet J, Maras PM, Avishai-Eliner S & Baram TZ 2014 Naturalistic rodent models of chronic early-life stress. *Developmental Psychobiology* **56** 1675–1688. (doi:10.1002/dev.21230)

Moriceau S & Sullivan R 2006 Maternal presence serves as a switch between learning fear and attraction in infancy. *Nature Neuroscience* **8** 1004–1006. (doi:10.1038/nn1733)

Moutsatsou P, Psarra A-MG, Tsiapara A, Paraskevakou H, Davaris P & Sekeris CE 2001 Localization of the glucocorticoid receptor in rat brain

mitochondria. *Archives of Biochemistry and Biophysics* **386** 69–78. (doi:10.1006/abbi.2000.2162)

Mucha M, Skrzypiec AE, Schiavon E, Attwood BK, Kucerova E & Pawlak R 2011 Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation. *PNAS* **108** 18436–18441. (doi:10.1073/pnas.1107936108)

Nacher J, Guirado R & Castillo-Gomez E 2013 Structural plasticity of interneurons in the adult brain: role of PSA-NCAM and implications for psychiatric disorders. *Neurochemical Research* **38** 1122–1133. (doi:10.1007/s11064-013-0977-4)

Naftolin F 1994 Brain aromatization of androgens. *Journal of Reproductive Medicine* **39** 257–261.

Naftolin F, Ryan KJ & Petro Z 1971 Aromatization of androstenedione by limbic system tissue from human foetuses. *Journal of Endocrinology* **51** 795–796. (doi:10.1677/joe.0.0510795)

Nasca C, Xenos D, Barone Y, Caruso A, Scaccianoce S, Matrisciano F, Battaglia G, Mathé AA, Pittaluga A & Lionetto L 2013 L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. *PNAS* **110** 4804–4809. (doi:10.1073/pnas.1216100110)

Nasca C, Bigio B, Zelli D, Nicoletti F & McEwen BS 2015 Mind the gap: glucocorticoids modulate hippocampal glutamate tone underlying individual differences in stress susceptibility. *Molecular Psychiatry* **20** 755–763.

Nilsen J, Irwin RW, Gallaher TK & Diaz Brinton R 2007 Estradiol *in vivo* regulation of brain mitochondrial proteome. *Journal of Neuroscience* **27** 14069–14077. (doi:10.1523/JNEUROSCI.4391-07.2007)

Nottebohm F 2002 Neuronal replacement in adult brain. *Brain research Bulletin* **57** 737–749. (doi:10.1016/S0361-9230(02)00750-5)

Pavlides C, Watanabe Y, Magarinos AM & McEwen BS 1995 Opposing role of adrenal steroid type I and type II receptors in hippocampal long-term potentiation. *Neuroscience* **68** 387–394. (doi:10.1016/0306-4522(95)00151-8)

Pawlak R, Magarinos AM, Melchor J, McEwen B & Strickland S 2003 Tissue plasminogen activator in the amygdala is critical for stress-induced anxiety-like behavior. *Nature Neuroscience* **6** 168–174. (doi:10.1038/nn998)

Pawlak R, Rao BSS, Melchor JP, Chattarji S, McEwen B & Strickland S 2005 Tissue plasminogen activator and plasminogen mediate stress-induced decline of neuronal and cognitive functions in the mouse hippocampus. *PNAS* **102** 18201–18206. (doi:10.1073/pnas.0509232102)

Pereira AC, Lambert HK, Grossman YS, Dumitriu D, Waldman R, Jannetty SK, Calakos K, Janssen WG, McEwen BS & Morrison JH 2014 Glutamatergic regulation prevents hippocampal-dependent age-related cognitive decline through dendritic spine clustering. *PNAS* **111** 18733–18738. (doi:10.1073/pnas.1421285111)

Pham K, Nacher J, Hof PR & McEwen BS 2003 Repeated, but not acute, restraint stress suppresses proliferation of neural precursor cells and increases PSA-NCAM expression in the adult rat dentate gyrus. *Journal of Neuroscience* **17** 879–886.

Popoli M, Yan Z, McEwen BS & Sanacora G 2012 The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews. Neuroscience* **13** 22–37.

van Praag H, Kempermann G & Gage FH 1999 Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience* **2** 266–270. (doi:10.1038/6368)

Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, McEwen BS & Morrison JH 2004 Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience* **125** 1–6. (doi:10.1016/j.neuroscience.2004.01.006)

Radley JJ, Rocher AB, Janssen WGM, Hof PR, McEwen BS & Morrison JH 2005 Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Experimental Neurology* **196** 199–203. (doi:10.1016/j.expneurol.2005.07.008)

Rao RP, Anilkumar S, McEwen BS & Chattarji S 2012 Glucocorticoids protect against the delayed behavioral and cellular effects of acute stress on the amygdala. *Biological Psychiatry* **72** 466–475. (doi:10.1016/j.biopsych.2012.04.008)

Ratman D, Vanden Berghe W, Dejager L, Libert C, Tavernier J, Beck IM & De Bosscher K 2013 How glucocorticoid receptors modulate the activity of other transcription factors: a scope beyond tethering. *Molecular and Cellular Endocrinology* **380** 41–54. (doi:10.1016/j.mce.2012.12.014)

Rettberg JR, Yao J & Brinton RD 2014 Estrogen: a master regulator of bioenergetic systems in the brain and body. *Frontiers in Neuroendocrinology* **35** 8–30. (doi:10.1016/j.yfrne.2013.08.001)

Reul JM & DeKloet ER 1985 Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* **117** 2505–2511. (doi:10.1210/endo-117-6-2505)

Romeo RD, Staub D, Jasnow AM, Karatsoreos IN, Thornton JE & McEwen BS 2005 Dihydrotestosterone increases hippocampal N-methyl-D-aspartate binding but does not affect choline acetyltransferase cell number in the forebrain or choline transporter levels in the CA1 region of adult male rats. *Endocrinology* **146** 2091–2097. (doi:10.1210/en.2004-0886)

Rudick CN, Gibbs RB & Woolley CS 2003 A role for the basal forebrain cholinergic system in estrogen-induced disinhibition of hippocampal pyramidal cells. *Journal of Neuroscience* **23** 4479–4490.

Russo SJ & Charney DS 2013 Next generation antidepressants. *PNAS* **110** 4441–4442. (doi:10.1073/pnas.1301593110)

Sandstrom NJ & Williams CL 2001 Memory retention is modulated by acute estradiol and progesterone replacement. *Behavioral Neuroscience* **115** 384–393. (doi:10.1037/0735-7044.115.2.384)

Sandstrom NJ & Williams CL 2004 Spatial memory retention is enhanced by acute and continuous estradiol replacement. *Hormones and Behavior* **45** 128–135. (doi:10.1016/j.yhbeh.2003.09.010)

Sapolsky R 1990 Glucocorticoids, hippocampal damage and the glutamatergic synapse. *Progress in Brain Research* **86** 13–23.

Schally AV, Arimura A & Kastin AJ 1973 Hypothalamic regulatory hormones. *Science* **179** 341–350. (doi:10.1126/science.179.4071.341)

Schelling G, Roozendaal B & De Quervain DJ-F 2004 Can posttraumatic stress disorder be prevented with glucocorticoids? *Annals of the New York Academy of Sciences* **1032** 158–166. (doi:10.1196/annals.1314.013)

Seeman T, Epel E, Gruenewald T, Karlamangla A & McEwen BS 2010 Socio-economic differentials in peripheral biology: cumulative allostatic load. *Annals of the New York Academy of Sciences* **1186** 223–239. (doi:10.1111/j.1749-6632.2009.05341.x)

Shansky RM, Hamo C, Hof PR, McEwen BS & Morrison JH 2009 Stress-induced dendritic remodeling in the prefrontal cortex is circuit specific. *Cerebral Cortex* **19** 2479–2484. (doi:10.1093/cercor/bhp003)

Shansky RM, Hamo C, Hof PR, Lou W, McEwen BS & Morrison JH 2010 Estrogen promotes stress sensitivity in a prefrontal cortex-amygdala pathway. *Cerebral Cortex* **20** 2560–2567. (doi:10.1093/cercor/bhq003)

Sheline YI 2003 Neuroimaging studies of mood disorder effects on the brain. *Biological Psychiatry* **54** 338–352. (doi:10.1016/S0006-3223(03)00347-0)

Shonkoff JP, Boyce WT & McEwen BS 2009 Neuroscience, molecular biology, and the childhood roots of health disparities. *Journal of the American Medical Association* **301** 2252–2259. (doi:10.1001/jama.2009.754)

Skrzypiec AE, Shah RS, Schiavon E, Baker E, Skene N, Pawlak R & Mucha M 2013 Stress-induced lipocalin-2 controls dendritic spine formation and neuronal activity in the amygdala. *PLoS ONE* **8** e61046. (doi:10.1371/journal.pone.0061046)

Sloan RP, Shapiro PA, Bagiella E, Myers MM & Gorman JM 1999 Cardiac autonomic control buffers blood pressure variability responses to challenge: a psychophysiologic model of coronary artery disease. *Psychosomatic Medicine* **61** 58–68. (doi:10.1097/00006842-199901000-00010)

Smythe JW, Murphy D, Timothy C & Costall B 1997 Hippocampal mineralocorticoid, but not glucocorticoid, receptors modulate anxiety-like behavior in rats. *Pharmacology, Biochemistry, and Behavior* **56** 507–513. (doi:10.1016/S0091-3057(96)00244-4)

Starkman MN, Gebarski SS, Berent S & Schteingart DE 1992 Hippocampal formation volume, memory dysfunction, and cortisol levels in partiens

with Cushing's syndrome. *Biological Psychiatry* **32** 756–765. (doi:10.1016/0006-3223(92)90079-F)

Stavreva DA, Wiench M, John S, Conway-Campbell BL, McKenna MA, Pooley JR, Johnson TA, Voss TC, Lightman SL & Hager GL 2009 Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. *Nature Cell Biology* **11** 1093–1102. (doi:10.1038/ncb1922)

Sterling P & Eyer J 1988 Allostasis: a new paradigm to explain arousal pathology. In *Handbook of Life Stress, Cognition and Health*, pp. 629—649. Eds S Fisher & J Reason. New York, NY: John Wiley & Sons.

Towart LA, Alves SE, Znamensky V, Hayashi S, McEwen BS & Milner TA 2003 Subcellular relationships between cholinergic terminals and estrogen receptor-α in the dorsal hippocampus. *Journal of Comparative Neurology* **463** 390–401. (doi:10.1002/cne.10753)

Tracey KJ 2002 The inflammatory reflex. *Nature* **420** 853–859. (doi:10.1038/nature01321)

Vale W, Spiess J, Rivier C & Rivier J 1981 Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. *Science* **213** 1394–1397. (doi:10.1126/science.6267699)

Vyas A, Mitra R, Rao BSS & Chattarji S 2002 Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience* **22** 6810–6818.

Waddington CH 1942 The epigenotype. *Endeavour* **1** 18–20.

Weiland NG 1992 Estradiol selectively regulates agonist binding sites on the *N*-methyl-D-aspartate receptor complex in the CA1 region of the hippocampus. *Endocrinology* **131** 662–668.

Weinstock M 2005 The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain, Behavior, and Immunity* **19** 296–308. (doi:10.1016/j.bbi.2004.09.006)

Woolley CS 1999 Effects of estrogen in the CNS. *Current Opinion in Neurobiology* **9** 349–354. (doi:10.1016/S0959-4388(99)80051-8)

Yamamoto K 1985 Steroid receptor regulated transcription of specific genes and gene networks. *Annual Review of Genetics* **19** 209–252. (doi:10.1146/annurev.ge.19.120185.001233)

Yau PL, Castro MG, Tagani A, Tsui WH & Convit A 2012 Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics* **130** e856–e864. (doi:10.1542/peds.2012-0324)

Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ & Akil H 2003 Mineralocorticoid receptor function in major depression. *Archives of General Psychiatry* **60** 24–28. (doi:10.1001/archpsyc.60.1.24)

Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, Yehuda R & Cohen H 2011 High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. *European Journal of Oral Sciences* **21** 796–809.