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Are BDNF and glucocorticoid activities calibrated?

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Abstract

One hypothesis to account for the onset and severity of neurological disorders is the loss of trophic support. Indeed, changes in the levels and activities of brain-derived neurotrophic factor (BDNF) occur in numerous neurodegenerative and neuropsychiatric diseases. A deficit promotes vulnerability whereas a gain of function facilitates recovery by enhancing survival, synapse formation and synaptic plasticity. Implementation of 'BDNF therapies', however, faces numerous methodological and pharmacokinetic issues. Identifying BDNF mimetics that activate the BDNF receptor or downstream targets of BDNF signaling represent an alternative approach. One mechanism that shows great promise is to study the interplay of BDNF and glucocorticoid hormones, a major class of natural steroid secreted during stress reactions and in synchrony with circadian rhythms. While small amounts of glucocorticoids support normal brain function, excess stimulation by these steroid hormones precipitate stress-related affective disorders. To date, however, because of the paucity of knowledge of underlying cellular mechanisms, deleterious effects of glucocorticoids are not prevented following extreme stress. In the present review, we will discuss the complementary roles share by BDNF and glucocorticoids in synaptic plasticity, and delineate possible signaling mechanisms mediating these effects.

Keywords

Dendritic spine; plasticity; HPA axis; rhythms; glucocorticoid resistance; transcription; FKBP5; MKP-1

I. Introduction

The brain is capable of considerable structural and functional plasticity during development that persists in the adult (Grutzendler et al., 2002, Yang et al., 2009, Liston and Gan, 2011). As a functional interface between neurons, synapses are involved in computation of circuits and information processing. Emerging evidence indicates that once established, synapses and dendrites can be maintained for long periods of time. But they can also be eliminated or rewired to address environmental changes (Walsh and Lichtman, 2003). In effect, the dynamic brain architecture can be modified by new life experience and behavior (Xu et al., 2009, Yang et al., 2009). The study of hormone actions in the brain has contributed to our understanding of this important phenomenon (de Kloet et al., 2005). In particular, stress-related hormones such as glucocorticoids (cortisol in humans and corticosterone in rodents)

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cause reversible remodeling of neuronal connections in several brain regions that modulate the hypothalamic pituitary adrenal (HPA) neuro-endocrine circuit (McEwen, 1999). Glucocorticoids coordinate diverse physiological processes in response to environmental stressors to facilitate learning and memory, behavioral adaptation and reinstatement of homeostasis.

Stress activates the HPA axis, in which secretion of glucocorticoids is a consequence (Holsboer and Ising, 2010). Classically, termination of the stress response involves a negative feedback, mainly at the hypothalamus and pituitary (De Kloet et al., 1975, de Kloet et al., 2005). Impaired control of HPA activation or negative feedback may result in hypo- or hypercortisolism. Reduced synaptic connectivity and dendritic atrophy are hallmarks of several pathologies of the central nervous system in which the regulation of the HPA axis is impaired (Duman, 2009, Holsboer and Ising, 2010). An emerging theme is that the pathophysiological changes responsible for these diseases act by specifically targeting mechanisms of synapse and dendritic maintenance (Lin and Koleske, 2010).

Pathological hypercortisolism as observed in Cushing's disease, results in mood disorders and produces marked cortical and subcortical brain atrophy (Patil et al., 2007). Exposure to excess glucocorticoids decreases dendritic arborization and synapse density in the hippocampus as well as in the pre-frontal cortex (Wellman, 2001, Tata et al., 2006). Several studies provided a useful framework for a common pathway to cognitive impairment by neural re-organization of dendritic territories as a result of exposure to excess stress or glucocorticoids (McEwen, 1999, Wellman, 2001, Liston et al., 2006). In this review, we will discuss the effects of glucocorticoids on structural plasticity of synapses. There is a large body of evidence suggesting that glucocorticoid and neurotrophin activities are calibrated. How glucocorticoid and neurotrophin signaling intersect to regulate synaptic plasticity and behavior? And, what can be learned from the molecular mechanisms involved to restore synaptic plasticity and behavior in disorders featuring disrupted glucocorticoid rhythms?

II. Glucocorticoids are critical regulators of postsynaptic dendritic spine plasticity

2.1 Dendritic spines are highly motile structures

Dendritic spines are post-synaptic specialized neuronal compartments that physically connect individual neurons into a complex neural circuit organization. Changes in neuronal connectivity are believed to play a critical role in adaptation to environmental changes, learning and memory. Post-synaptic dendritic spines are highly motile structures that undergo continuous remodeling during development (Bhatt et al., 2009). Spinogenesis occurs during embryogenesis and also rapidly after birth. There is an overproduction of dendritic spines during the early stages of life that is corrected by activity-dependent pruning processes later during adolescence. Such selection of dendritic spines may serve to refine neural circuits that are functional at the time. About 40 to 50% of total spine number is lost during the adolescent pruning process (Rakic et al., 1986, Markus et al., 1987, Zuo et al., 2005). The spines that survive this developmental step are very stable during adulthood. From this perspective, it seems that we are born with a surplus of spines that are lost over time. However, the responses of spines are actually much more plastic. Because of new life experiences, learning enhances the formation of new dendritic spines. For instance, enrichment living increases the formation of new dendritic spines at least in the somatosensory cortex (Yang et al., 2009). Stimulation of whiskers also results in an increased formation of dendritic spines in the barrel cortex where primary somatosensory information is processed (Yang et al., 2009). Also, motor learning enhances dendritic spine formation in the corresponding motor cortex (Yang et al., 2009). These new sets of

experience-dependent dendritic spines are also subjected to activity-dependent pruning process in order to select the most relevant ones. In consequence, only a tiny fraction of dendritic spines survives life-long, suggesting that new life experiences help shape a synaptic code that is relevant for behavioral adaptation. This model provides an integrated and structural basis for life-long memory storage.

Live imaging of the brain has revealed that dendritic spines undergo continuous remodeling (Figure 1A). Some spines form quickly before they disappear; some are very stable over time while others are eliminated. Why are dendritic spines continuously remodeled if most of the newly formed spines are rapidly eliminated? Which spines are formed and which spines are eliminated is a highly debated question, particularly in the context of learning and memory. How do neurons constantly change morphology to integrate new information while retaining long-term memories? These are questions of considerable experimental interest.

Changes in dendritic spines occur in numerous genetic and psychiatric disorders where the density and also the morphology of spines are dramatically altered (Purpura, 1974, Fiala et al., 2002). In genetic and developmental disorders with highly penetrant mutations such as Down's syndrome, Rett syndrome and Fragile X syndrome, these defects can be reproduced in animal models, suggesting a causal and conserved relationship (Kaufmann and Moser, 2000, Kojima and Shirao, 2007, Rachidi and Lopes, 2008, Matijevic et al., 2009, Riise et al., 2011, Troca-Marin et al., 2012). However, many psychiatric disorders are caused by a complex interaction between susceptibility genes and the environment. Environmental factors modulate dendritic spine remodeling during critical periods and intrinsic factors that sense environmental changes can regulate dendritic spine remodeling.

2.2 Glucocorticoid enhance dendritic spine remodeling capacity

Glucocorticoids, the major class of stress hormones, affect the density and the morphology of dendritic spines (Conrad et al., 1999, Mitra et al., 2005, Bloss et al., 2011). Application of corticosterone to hippocampal organotypic slice cultures resulted in atrophic dendrites and reduced spine density (Alfarez et al., 2009). In contrast, other studies reported that corticosterone can increase dendritic spine density in hippocampal organotypic slice cultures in a NMDA receptor-dependent fashion via the MAPK, PKA and PI3K signaling pathways (Komatsuzaki et al., 2012). Rapid changes in dendritic spine morphology involve the reorganization of the actin cytoskeleton via the phosphorylation of actin-binding proteins (Lin and Koleske, 2010). Small GTPases, like Rho destabilize dendritic spines, whereas Rac facilitates spine growth. Rho and Rac activities converge to regulate actin-binding proteins, like cofilin, that participate in the stabilization of the actin filaments. Whereas phosphorylated cofilin enhances spine formation, it destabilizes dendritic spines when dephosphorylated due to depolymerization of actin filaments (Lin and Koleske, 2010). Using cofilin phosphorylation as a marker of actin remodeling, a recent study provided evidence that glucocorticoids enhance the stabilization and growth of actin filaments (Jafari et al., 2012). The molecular mechanisms that bridge glucocorticoid signaling to the reorganization of the actin cytoskeleton are unknown, but several studies reported that transcription of regulatory genes might be related (like LIMK1, the major kinase for cofilin (Morsink et al., 2006) and caldesmon, a calcium sensing actin binding protein (Mayanagi et al., 2008). Several studies also indicate that glucocorticoids can rapidly enhance the polymerization of actin filaments in non-neuronal cell types (Rubenstein et al., 2003, Clark et al., 2005, Mayanagi et al., 2008).

Using transcranial two-photon imaging of the living cortex, Liston and Gan (2011) described an unexpected finding. Administration of a single dose of glucocorticoids enhanced the formation as well as the elimination of dendritic spines within hours of treatment (Figure 1B). Corticosterone enhanced both the formation and elimination of spines

in a dose dependent fashion and occurred independently of changes in filipodia, which turnover rate was not affected. In adolescent mice (1 month old), when dendritic spine turnover approximates 9% over a 3-day period, glucocorticoids enhance the turnover rate to about 15%. In adult mice (5 month old), when dendritic spine turnover approximates 3% over a 3-day period, glucocorticoids enhance the turnover rate to about 7%. Although dendritic spine turnover rate diminishes during aging (Grutzendler et al., 2002, Zuo et al., 2005, Yang et al., 2009, Bloss et al., 2011), the adult brain retains the capacity for dendritic spine remodeling in response to corticosterone treatment (Liston and Gan, 2011). Glucocorticoids enhance dendritic spine formation and elimination in all cortical regions tested: the barrel cortex, the motor cortex and the frontal cortex. Remarkably, the extent of formation and elimination of dendritic spines is equilibrated to mitigate net changes in spine number.

Why glucocorticoids change spine remodeling in opposite directions is unknown. Which spines are maintained and which spines are eliminated remains an open question. Further studies are needed to address whether glucocorticoids open structural plasticity windows favorable for experience-dependent adaptation to different behavioral contexts.

2.3 Comparison with other steroid hormones

Although a majority of studies focused on the role of glucocorticoids upon morphological and functional plasticity of neural circuits involved in psychiatric disorders, changes in gonadal or other steroid hormones synthesized in the central nervous system like neurosteroids, dehydroepiandrosterone (DHEA), allopregnanolone may prove equally important. For instance, DHEA increased dendritic spine density in pyramidal CA1 neurons (Hajszan et al., 2004). DHEA is a precursor for the synthesis of testosterone and estradiol by specific enzymes expressed in the hippocampus (3 β -hydroxysteroid dehydrogenase, 17 β -hydroxysteroid dehydrogenase III and P450 aromatase). The question is whether DHEA is converted to androgens and estrogens to produce synaptogenic effects? And if so, are they similar in both sexes?

Blocking the P450 aromatase with the inhibitor Letrozole is sufficient to prevent the production of estrogen in the brain as well as the DHEA-mediated spinogenesis in ovariectomized females, but not in gonadectomized males (MacLusky et al., 2004). Changes in the number of dendritic spine, the size of the spine head and the length of the spine neck after treatment with estrogen are well characterized in ovariectomized female rats (Gould et al., 1990, Yankova et al., 2001). Activation of the androgen receptor with testosterone increased also the number of spines at apical dendrites of CA1 pyramidal neurons of both males and females (Leranth et al., 2004, MacLusky et al., 2006). Direct application of testosterone or estradiol to hippocampal slice preparations increased dendritic spine density *in vitro* to an extent similar to that observed *in vivo* (Mukai et al., 2011). So, the spinogenic effects of DHEA are probably mediated by androgens in both sexes and also by estrogens in females.

III. The neuro-endocrine circuit of stress is a major target of glucocorticoid spine plasticity

3.1 The limbic-hypothalamic-pituitary-adrenal (LHPA) axis

Mixed signals from the environment are integrated by way of interactions between the limbic brain circuitry and the neuro-endocrine axis. The neuro-endocrine hypothalamic-pituitary adrenal (HPA) axis consists of a linear chain of reactions initiated by the secretion of corticotrophin-releasing hormone (CRH), which controls the secretion of adrenocorticotropin (ACTH) from the anterior pituitary and glucocorticoids from the adrenal

glands as endpoint. Glucocorticoid hormones are secreted under stress and in synchrony with circadian rhythms. Once secreted, glucocorticoids are buffered by corticoid-binding globulin (CBG) and circulate in the blood to act on various target organs, including the brain to shape neuronal and behavioral adaptation to environmental changes (emotions, predation, arousal, reward, etc.) at least via alteration of gene transcription (de Kloet et al., 2005).

There are three cardinal systems that coordinate adrenal secretions during homeostatic and stress responses (Figure 2) (De Kloet et al., 1998, Herman et al., 2005). The first is a circadian rhythm of basal activity derived from the suprachiasmatic nucleus (SCN). The second is via polysynaptic limbic circuits that converge on the hypothalamic paraventricular nucleus (PVN) to activate CRH-producing neurons. These input circuits involve multiple brain regions including the hippocampus, prefrontal cortex, amygdala, bed nucleus of the stria terminalis (BNST), and locus ceruleus (LC). The intricacy of these circuits allow for a diversity of stressor specific responses like physical stress or emotionally arousing experiences. The third mechanism involves feedback inhibitory actions of adrenal steroids to prevent the escalation of glucocorticoids to toxic levels. Feedback control is characterized by the downregulation of CRH and ACTH exerted through corticosteroid receptors, which can act as nuclear transcription factors.

Two types of corticosteroid receptors have been identified and cloned (De Kloet and Reul, 1987): The mineralocorticoid receptor (MR) has approximately a ten-fold higher affinity than does the glucocorticoid receptor (GR). GR is mostly ubiquitous in the brain and abundant in hypothalamic CRH neurons and pituitary corticotrophs (De Kloet et al., 1998). MR is expressed in the hypothalamus, but highest expression is found in hippocampal neurons (Van Eekelen et al., 1988). This dual receptor system senses variations of corticosteroid concentrations that can increase by 10-100 times during circadian cycle and by 200 times during stress (Reul and de Kloet, 1985). Therefore, it has been postulated that MR mediates its effects when levels of circulating glucocorticoids are low (circadian troughs) whereas GR appears to produce effects at glucocorticoid peaks (circadian peaks and stress levels).

3.2 Genetic studies of the glucocorticoid receptor

Genetic ablation of the glucocorticoid receptor (GR) in specific brain regions has provided valuable information regarding the role of limbic circuits in the control of the HPA axis (Gass et al., 2001, Howell and Muglia, 2006, Kolber et al., 2008). Mice with complete knockout of the *Gr* gene die because of lung maturation defects (Tronche et al., 1999, Kellendonk et al., 2002a, Kellendonk et al., 2002b). In contrast, mice harboring the knockout of *Gr* in the entire CNS survive adulthood with a disinhibited HPA axis, symptoms of Cushing disease and decreased anxiety (Tronche et al., 1999). Deletion of the *Gr* gene in the forebrain only recapitulated the disinhibition of the HPA axis but increased anxiety, suggesting that the forebrain structures participate in the maintenance of HPA axis activity (Boyle et al., 2005, Boyle et al., 2006). Additional studies characterized the primary site of glucocorticoids on anxiety, the central nucleus of the amygdala, where the deletion of the *Gr* gene decreased learned but not innate anxiety without affecting HPA axis parameters (Kolber et al., 2008). Targeted deletion of the *Gr* gene in the PVN or the pituitary using Sim1-cre and POMC-cre mouse lines, respectively, produced similar disinhibition of the HPA axis with no effect on anxiety or cognition (Schmidt et al., 2009, Jeanneteau et al., 2012). Finally, deletion of GR in dopaminergic neurons, but not in dopamine-releasing neurons, decreased drug seeking behavior without affecting anxiety or HPA axis reactivity (Ambroggi et al., 2009). Altogether, these studies indicate that GR mediates pleiotropic glucocorticoid responses like stress-coping behavior, anxiety and cognition via distinct regions of the brain. These studies also indicate that glucocorticoid receptors modify a large

array of behavior through different neuronal populations that may not necessarily impinge on HPA axis reactivity.

3.3 Role of glucocorticoid receptors on spine plasticity

Antagonism of GR with mifepristone *in vivo* prevented spine formation whereas blockade of the MR with spironolactone prevented both the formation and elimination of spines afforded by endogenous glucocorticoids and also following acute corticosterone treatment (Liston and Gan, 2011). *In vitro*, activation of GR using the selective synthetic agonist, dexamethasone, rapidly increases the density of mushroom and thin spines without significantly affecting the density of filopodia and stubby spines (Komatsuzaki et al., 2005). Dexamethasone also enhances the size of the spine head diameter, indicating that GR activation may facilitate the maintenance or the maturation of spines (Komatsuzaki et al., 2005, Komatsuzaki et al., 2012).

To better understand how glucocorticoid receptors modulate dendritic spine structure, the time scale within which they operate may provide clues about the site of actions. But, the speed of glucocorticoid-mediated spine remodeling (from 30 minutes onwards) cannot discriminate between synaptic and somatic receptor signaling. Would glucocorticoid receptors need to be located within spines to affect their morphology and density? Synaptic GR was highlighted at basolateral amygdala neurons *in vivo* using immuno-electron microscopy and at CA1 stratum radiatum where it only partially co-localized with PSD95 *in vivo* using confocal deconvoluted microscopy (Johnson et al., 2005, Jafari et al., 2012, Komatsuzaki et al., 2012). Synaptic GR was also detected in a synaptosomal fraction purified from primary cultured cortical neurons (Komatsuzaki et al., 2005). The abundance of both GR messenger RNA and protein in dendritic spines was downregulated in Fragile X mental retardation protein (FMRP) knockout mice, suggesting that GR can be synthesized at synapses (Miyashiro et al., 2003, Jafari et al., 2012). However, additional studies will be required to address the roles of synaptic versus somatic GR and MR in regulating spine dimension and synaptic response.

The relation between structure and function of synapses in central spiny neurons asserts that larger spines produce larger synaptic currents, longer spines produce smaller postsynaptic currents, and the number of spines correlates with the frequency of postsynaptic currents (Yuste and Bonhoeffer, 2001, Segal, 2010). Corticosterone modulates the strength of synaptic transmission and plasticity at both excitatory and inhibitory synapses (Karst and Joels, 2005, Maggio and Segal, 2009). These effects are determined by the time, the context at exposure, the duration of the stimulation and dose of corticosteroid (Diamond et al., 1992). For instance, direct application of dexamethasone in the hypothalamic PVN nucleus rapidly suppresses glutamate excitatory postsynaptic currents in CRH producing neurons, an effect that even persisted in the presence of the GR antagonist mifepristone (Di et al., 2003, Tasker et al., 2005). Rapid effects are now believed to occur via membrane-tethered glucocorticoid receptors that differ from their intracellular counterpart with respect to their subcellular location, affinity and signaling responses coupled to small heterotrimeric G-proteins (Tasker et al., 2006, Groeneweg et al., 2011). Glucocorticoids (or stress) rapidly increase glutamate release from both neuronal and glial origins in the hippocampus, amygdala and prefrontal cortex in a GR and endocannabinoid dependent manner (Lowy et al., 1993, Bagley and Moghaddam, 1997, Venero and Borrell, 1999, Wang and Wang, 2009, Hascup et al., 2010, Hill et al., 2011). When activated, GR can facilitate the insertion of voltage-gated calcium channels and ionotropic glutamate receptors into synapses (Groc et al., 2008, Joels and Karst, 2012). So, glutamate signaling may also contribute to glucocorticoid-mediated spine plasticity (Karst et al., 2005, de Kloet et al., 2008). Activation of MR enhances excitability of hippocampal CA1 neurons whereas GR activation depresses their excitability (Joels and de Kloet, 1989, Joels and Vreugdenhil, 1998). Corticosterone,

when applied to the dorsal hippocampus, depresses NMDA receptor-mediated LTP in a dose-dependent and GR-dependent fashion. In contrast, corticosterone, when applied in the ventral hippocampus, enhances LTP via a MR-dependent mechanism (Krugers et al., 2005, Maggio and Segal, 2007). Not only glutamate but also serotonin and dopamine release is enhanced by glucocorticoids (Gartside et al., 2003, Butts et al., 2011). These effects may be especially important in the pathophysiology of depression, antidepressant response and in the pathophysiology of stimulant drug abuse (Schatzberg et al., 1985, Piazza and Le Moal, 1996, Wolkowitz et al., 1997, Chaouloff, 2000). By regulating monoaminergic neurotransmission, glucocorticoids may sensitize neurons to activity-dependent stimuli (Gartside et al., 2003). However, such plasticity critically depends on the duration, the amplitude and time at exposure to glucocorticoids.

IV. Disruption of glucocorticoid rhythms impairs dendritic spine plasticity and behavior

While small oscillating amounts of glucocorticoids support normal brain function, extreme excess or deficit of these hormones can precipitate cognitive and mood disorders (Table 1). Not only increased but also decreased glucocorticoid signaling can lead to pathological conditions (Kim and Diamond, 2002, Raison and Miller, 2003). Disruption of glucocorticoid rhythms occurs in Alzheimer's disease (AD) (Swanwick et al., 1998), resulting in sustained increased cortisol levels from early stages of the disease. Chronic glucocorticoid exposure worsens neuropathological features of AD and a polymorphism in glucocorticoid biosynthetic enzyme 11 β -hydroxysteroid dehydrogenase (11 β HSD1) is associated with a six-fold increased risk for sporadic AD (de Quervain et al., 2004, Green et al., 2006). Reduced synaptic connectivity and dendritic atrophy along the limbic-HPA neuro-endocrine axis are hallmarks of several pathologies of the nervous system (Duman, 2009).

A hypercortisol state as observed in Cushing's disease and major depression produces marked cortical and subcortical brain atrophy (Patil et al., 2007). Exposure to excess glucocorticoids decreases dendritic arborization and synapse density in the hippocampus as well as in the pre-frontal cortex (Watanabe et al., 1992, Wellman, 2001, Tata et al., 2006). In clear contrast, exposure to excess glucocorticoids increases dendritic arborization and synapse density in the amygdala (Vyas et al., 2002, Mitra et al., 2005). Reduction of hippocampal volume may impair cognition whereas enlargement of the amygdala volume correlates with anxiety and hyperactivation of the neural circuitry of fear. However, little is known about the molecular mechanisms involved in structural remodeling produced by chronic stress and glucocorticoids. Repeated administration of corticosterone over the course of 10 days to artificially maintain a hypercortisol state prevents dendritic spine formation and enhances dendritic spine elimination. Therefore, excess glucocorticoid shifts the balance of formation and elimination to widespread loss of spines (Figure 3). Excess glucocorticoids increases the elimination of spines formed after treatment as well as pre-existing spines that were formed before treatment. Such abnormal loss of stable spines established early in life following chronic glucocorticoid excess may underlie the severe behavioral and cognitive impairments observed in stress-related disorders. Biochemical analysis of synaptosomes composition confirmed that chronic glucocorticoids administration to naïve rats profoundly diminished the abundance of the post-synaptic markers PSD95, NR1 and synaptopodin at least in the hippocampus (Cohen et al., 2011). Moreover, glucocorticoids are the mainstay of treatment for numerous inflammatory and immunological disorders among which neurological and psychiatric side effects have been reported (Barnes and Adcock, 2009). In contrast, antagonism of the HPA axis alleviates some of the symptomatology of depression but also produces a wide range of side effects (Holsboer and Ising, 2008).

A hypocorticotid state is observed in several pathologies like Addison's disease, chronic fatigue, antisocial aggressiveness, atypical depression and post-traumatic stress disorder (Gold et al., 2002, Kim and Haller, 2007). What are the effects of hypocortisolism upon dendritic spine density and remodeling? Removal of the adrenal glands, termed adrenalectomy, depletes the majority of endogenous corticosterone from the entire organism. Total spine density measured in the hippocampal formation showed no difference between sham-operated and adrenalectomized animals (Komatsuzaki et al., 2012). Because the extent of formation and elimination of dendritic spines is similar, the lack of effects on spine number in fixed tissue preparations provides little information about the consequences of glucocorticoid depletion. The use of longitudinal imaging studies will provide a better understanding of the effects of glucocorticoid depletion upon dendritic spine dynamics. For instance, suppression of endogenous glucocorticoid secretion by chemical adrenalectomy (low dose dexamethasone to activate the negative feedback of the HPA axis) diminished spine remodeling capacity from 15% to 2%, indicating clearly the critical role of glucocorticoids on spine plasticity (Liston and Gan, 2011). Both the formation and elimination of dendritic spines are diminished to similar extent, suggesting that pre-existing neural circuits are maintained but incapable of structural plasticity as long as the hypocorticotid state lasts (Figure 3). This finding contrasts with the elimination of pre-existing spines that result from prolonged hypercorticotid state. As much as the dose and duration of exposure, the rhythmic secretion of glucocorticoids with peaks and troughs is critical in health and disease.

V. Glucocorticoid resistance in psychiatric disorders

Disruption of the HPA axis is a major risk factor of neuropsychiatric disorders (Pariante, 2009, Holsboer and Ising, 2010). Elevated plasma level of glucocorticoids (hypercorticotid state) is a major endocrine hallmark of psychiatric and neurodegenerative diseases (Nemeroff et al., 1984, Holsboer, 2000, Pariante et al., 2003). Approximately 40% of depressed patients are resistant to the cortisol-suppressing effect of dexamethasone, suggesting a dysfunctional negative feedback control of the HPA axis (Holsboer, 2000). Decreased responsiveness to glucocorticoids like dexamethasone, a phenomenon known as glucocorticoid resistance, has been proposed as an underlying mechanism to explain mood disorders and deterioration of cognitive functions (Pariante, 2006, Carvalho and Pariante, 2008, Anacker et al., 2011).

What is glucocorticoid resistance? Resistant target-tissues are characterized by their inability to respond to glucocorticoids and can be generalized or tissue-specific, transient or permanent, partial or complete (Chrousos et al., 1982, Chrousos et al., 1993). Glucocorticoid resistance was first described in inflammatory diseases (Barnes and Adcock, 2009). Approximately 25% of cases of severe asthma are unresponsive to the therapeutic use of steroids. Even more patients develop reduced sensitivity that requires an increased dosage in treatment modalities that can produce a wide range of side effects (Table 1) (Barnes and Adcock, 2009).

What are the clinical and genetic evidence that support a role of glucocorticoid resistance in depression (Table 2)? Experiencing chronic stress facilitates the development of glucocorticoid resistance that interferes with appropriate regulation of inflammation, and increases the sensitivity to develop a common cold (Cohen et al., 2012). Moreover, genomic profiling of RNA transcripts in peripheral red blood cells stimulated with dexamethasone *in vivo* led to the identification of 2670 dexamethasone-regulated genes in controls and only 1151 transcripts in depressed patient cases with a hypercorticotid diagnosis (Menke et al., 2012). The number of genes regulated by the dexamethasone was diminished despite similar glucocorticoid level in control and depressed patients at the time of blood collection (Menke

et al., 2012). This study emphasized that several genes including *fkbp51* and *mkp-1*, previously associated with the pathophysiology of depression, are reliable markers of GR activation (Binder, 2009, Duric et al., 2010, Menke et al., 2012). By inhibiting GR nuclear transport and genomic responses, FKBP51 contributes to glucocorticoid resistance (Wohnik et al., 2005, Zhang et al., 2008b). Indeed, there is positive correlation between glucocorticoid resistance and *fkbp51* expression in multiple models (Denny et al., 2000, Binder, 2009, Attwood et al., 2011, Touma et al., 2011, Hartmann et al., 2012). Other GR-regulated genes like *bdnf*, *hdac2* and *p11* may also contribute of glucocorticoid sensitivity and responsiveness (Ito et al., 2005, Zhang et al., 2008a, Barnes, 2009, Chen et al., 2010, Autry and Monteggia, 2012). In particular, the central role of BDNF upon glucocorticoid activities will be discussed in the next sections.

Familial and sporadic cases of glucocorticoid resistance have been reported (Charmandari et al., 2004). Mutations in the human *Gr* gene impair glucocorticoid transcriptional capabilities altering tissue sensitivity to these hormones (van Rossum and Lamberts, 2004). However, these mutations are rare and cannot account for the glucocorticoid resistance observed in psychiatric and mood disorders. Reduced GR expression was reported in postmortem brain biopsies collected from depressed patients (Webster et al., 2002). A similar downregulation of GR protein was detected in the rat brain following chronic stress (Kitraki et al., 1999). Downregulation of GR may represent a protective mechanism to limit the toxic effects of prolonged high glucocorticoid exposure on cell survival, synaptic connectivity, synaptic strength and neurogenesis (McEwen and Seeman, 1999, Sapolsky, 2000b, a, Liston et al., 2006, Mirescu and Gould, 2006, Joels et al., 2007). Alternatively, several studies firmly support a strong genetic association between polymorphisms in the human *fkbp51* gene and stress-related mood disorders like depression, suicide and bipolar depression (Schmidt et al., 2012). These *fkbp51* risk alleles are linked to stronger expression following stress/ glucocorticoid exposure that may contribute to glucocorticoid resistance (Lavebratt et al., 2010).

Antidepressants increase GR mRNA and protein expression in the brain (Carvalho and Pariante, 2008, Anacker et al., 2011). Antidepressants also increase dexamethasone-induced gene transcription *in vitro* (Pepin et al., 1992a, b, Pariante et al., 2001, Pariante et al., 2003). Depressive patients treated with antidepressants that do not normalize their plasma glucocorticoid levels have increase risk of relapse (Holsboer and Ising, 2010). Changes in the expression of the MDR1A p-glycoprotein, which transports glucocorticoids across blood brain barrier affect glucocorticoid availability in the central nervous system. However, genetic ablation of MDR1A does not affect cortisol transport in response to antidepressant treatments (Holsboer and Ising, 2010, Mason et al., 2011). How a single, conserved hormone can elicit complex, distinct, specific and developmentally regulated actions on synaptic plasticity is a major area for future work.

Hans Selye, the famous endocrinologist who introduced the concept of stress in biology proposed the idea that pleiotropic hormonal actions may rely upon conditioning factors (Selye, 1956, 1971). He wrote already in the 1950s: "Under the influence of such conditioning factors, a normally well-tolerated degree of stress can even become pathogenic". His concept may explain why some individuals are more vulnerable than others to mood disorders despite similar stressful experiences. He further explained that such conditioning factors might be endogenous (genetic predisposition, age or sex) or exogenous (treatment with certain hormones, drugs, or dietary factors). Are glucocorticoid actions regulated by such conditioning factors?

VI. How conditioning factors modulate glucocorticoid receptor signaling?

Glucocorticoids do not display significant effects under baseline conditions upon resting membrane potential and membrane resistance of hippocampal neurons. It is only when neurons are stimulated (e.g. by neurotransmitters) that these effects become apparent (De Kloet et al., 1998). Actions of glucocorticoids are influenced by the co-incidence of different signaling systems. For instance, the enhancement of emotionally arousing memories by glucocorticoids requires co-incident norepinephrine signaling in the basolateral amygdala (Rubenstein et al., 2003). Norepinephrine is capable of potentiating ligand-induced GR transcriptional capabilities and DNA binding in a PI3K-dependent manner (Schmidt et al., 2001). Also, adrenergic receptor agonists, generally used in the treatment of asthma, synergistically enhance GR-dependent transcription in a cAMP/PKA-dependent manner (Kaur et al., 2008). Maximal GR transcriptional capabilities are achieved approximately at ten-fold lower glucocorticoid concentrations in the presence of cAMP-elevating drugs (Kaur et al., 2008). Another set of factors that may also play a role in altered GR function in major depression is proinflammatory cytokines, such as interleukin IL1, IL-2, IL-6, TNF- α , and interferon (IFN)- α , and their signaling pathways, may influence neuroendocrine function through the impairment of GR function (Miller et al., 1999, Pearce et al., 2001, Raison et al., 2006). Co-incident growth factor signaling may also intersect with GR actions. For instance, bFGF and IGF1 can enhance ligand-induced GR transcriptional capabilities in a PI3K-dependent manner (Schmidt et al., 2001).

What molecular mechanisms of co-incidence detection could modulate glucocorticoid actions (Table 2)? Phosphorylation of GR by PKA and MAPK regulates transcription capabilities (Haske et al., 1994, Ismaili and Garabedian, 2004). De-acetylation of GR and histones by HDAC2 regulate glucocorticoid transcriptional capabilities (Govindan, 2010). Ectopic expression of hippocampal *hdac2* was reported in Alzheimer's disease brains and pharmacological blockade of HDAC2 activity suppressed cognitive deficits produced by prolonged GR activation (Graff et al., 2012). Glucocorticoid-induced toxic effects upon cognitive and neurochemical features of Alzheimer's disease, such as amyloid plaque formation, may depend on elevated expression of HDAC2 (Swanwick et al., 1998, de Quervain et al., 2004, Green et al., 2006). In contrast, the expression of HDAC2 is downregulated in glucocorticoid-resistant cases of severe asthma and pharmacological activation of HDAC2 with theophylline and antioxidants present therapeutic value (Ito et al., 2005, Barnes, 2009). Too much or too little HDAC2 expression may similarly impinge on glucocorticoid actions. Expression of glucocorticoid-sensitive genes like *mkip-1* (MAP kinase phosphatase-1) and *crh* (Corticotrophin releasing hormone) depends on co-incidence detection mechanisms that involve cAMP and growth factor signaling. The CREB co-activator CRTC2 is a co-incidence detector in hypothalamic neurons, where CRTC2 phosphorylation and nuclear translocation determines the ability of neurotrophins and glucocorticoids to activate or suppress CRH expression, respectively (Altarejos and Montminy, 2011, Jeanneteau et al., 2012).

To produce synaptic plasticity, glucocorticoids use both genomic and non-genomic mechanisms together with ongoing neural activity mediated by excitatory neurotransmitters like glutamate and norepinephrine, neuropeptides like CRH and growth factors like neurotrophins (Lynch, 2004, McGaugh, 2004, Roozendaal et al., 2006). We will further discuss whether Brain-Derived Neurotrophic Factor (BDNF), a prominent neurotrophin in the brain, is a conditioning factor of glucocorticoid actions.

VII. Does the neurotrophin BDNF condition glucocorticoid activities?

Decreased spine density induced by chronic stress seems to be mediated by a stress/glucocorticoid-induced downregulation of BDNF expression (Duman et al., 1997). BDNF has well-established synaptogenic properties and loss of neurotrophic support impinges on the formation and maintenance of neural circuits (Jeanneteau and Chao, 2012). According to the neurotrophic hypothesis of depression (Duman et al., 1997, Duman and Monteggia, 2006), downregulation of BDNF mediates the toxic effects of prolonged GR activation on neuronal survival, synaptic plasticity and behavior. However, several lines of evidence challenge the dogmatic view that BDNF and glucocorticoids have antagonistic actions in the sense that too little BDNF is not just a reflection of loss of trophic support for brain cells but also serves a molecular switch that controls glucocorticoid actions.

We propose that BDNF and glucocorticoid activities are calibrated (Figure 4). On the one hand, *bdnf* is a stress sensitive gene. More BDNF is synthesized in response to acute glucocorticoid treatment (or stress) when spinogenesis is maximal, whereas less BDNF is produced following chronic stress/glucocorticoid exposure when spine elimination prevails (Tapia-Arancibia et al., 2004, Liston and Gan, 2011). On the other hand, BDNF like the other growth factors bFGF and IGF1, can enhance GR-mediated transcription (Our unpublished microarray and RNA sequencing data). Therefore, scaling both BDNF and glucocorticoid activities may determine a wide range of effects upon synaptic structure, strength and function. Our model predicts that transient increase in glucocorticoid levels enhances not only BDNF levels but also dendritic spine remodeling that both correlate with cognitive improvements. In contrast, chronic increase in glucocorticoid levels decreases BDNF levels, dendritic spine remodeling capacity that correlate with cognitive impairments. If these changes can be precipitated by chronic stress, they are reversible. Antidepressant therapies can normalize BDNF and glucocorticoid levels, and restore the complexity of dendritic territories with amelioration of depression-like behavioral symptoms. How BDNF and glucocorticoids signals are integrated in order to sculpt neural circuits and dendritic territories will be discussed in the following sections.

VII.1 Neurogenesis fennels BDNF and antidepressant effects upon endocrine and behavioral reactivity to stress

Glucocorticoids (or stress) strongly inhibit adult neurogenesis in the hippocampus (Mirescu and Gould, 2006). Adult-born hippocampal granule neurons regulate adaptation to stress both at the level of endocrine and behavioral responses (Surget et al., 2011). Indeed, excessive stress-induced glucocorticoid peaks and depressive-like phenotypes develop when adult neurogenesis is impaired using either genetic tools or X-irradiation (Snyder et al., 2011). Blocking hippocampal neurogenesis also diminishes the behavioral effects of antidepressants (Santarelli et al., 2003, Warner-Schmidt and Duman, 2006, Wang et al., 2008, David et al., 2009). Several studies have also described the importance of the BDNF-TrkB pathway in the regulation of adult neurogenesis and the effect of antidepressants. Infusion of BDNF in the hippocampus increased neurogenesis and elicited antidepressant responses (Shirayama et al., 2002, Scharfman et al., 2005). Adult hippocampal neurogenesis is compromised in BDNF heterozygous mice (Rossi et al., 2006). Moreover, antidepressants failed to induce hippocampal neurogenesis in TrkB heterozygous mice (Sairanen et al., 2005, Li et al., 2008). Reduced BDNF signaling in BDNF heterozygous mice or via over-expression of the dominant negative TrkB.T1 isoform prevented antidepressant effects in the forced swim test (Saarelainen et al., 2003). Conditional knockout of BDNF in adult mice also diminished the effects of antidepressants in the forced swim test (Monteggia et al., 2004, Monteggia et al., 2007). Further experiments demonstrated that manipulation of the BDNF-TrkB signaling during adulthood does not affect proliferation of hippocampal progenitor cells *in vivo* but rather determined their differentiation, migration and growth

(Bergami et al., 2008, Taliaz et al., 2010). Similar effects are expected to occur in the hypothalamus where adult neurogenesis is stimulated by intraventricular administration of BDNF (Pencea et al., 2001, Kokoeva et al., 2005, Lee et al., 2012).

When sustained, a hypercorticotid state reduces the clinical efficacy of antidepressants, diminishes BDNF hippocampal expression (see section VII.4), attenuates adult neurogenesis and its inhibitory tone on the HPA axis (Gartside et al., 2003). This suggests a vicious circle through which stress, by inhibiting BDNF and neurogenesis, elevates stress-evoked glucocorticoid levels that persist in absence of stress and is resistant to antidepressant treatments.

VII.2 Neurotrophins and the integration of neural circuits

Neurotrophins can affect a variety of higher-order brain functions that modulate different behaviors, such as feeding, learning and memory and anxiety (Snider, 1994, Lu et al., 2008, Minichiello, 2009). In particular, BDNF has emerged as a key regulator of synaptic plasticity in the adult nervous system. For example, BDNF can modulate behavioral responses by regulating the activity of a number of neurotransmitter systems, including dopaminergic (Guillin et al., 2001, Gallo and Letourneau, 2004, Graham et al., 2009), glutamatergic (Rattiner et al., 2004, Raison et al., 2006) and serotonergic (Lyons et al., 1999) pathways. Experimental manipulations of neurotrophin signaling alter both neurotransmission and neural circuit architecture with a rapid and slow time scale, respectively (Poo, 2001). A single nucleotide polymorphism in the BDNF gene (val66met) observed with a 4-20% prevalence (depending on ethnicity) in general human population is associated with impaired cognitive function with structural and functional dendritic defects of hippocampal neurons (Egan et al., 2003, Chen et al., 2006, Ninan et al., 2010). Neurotrophin signaling may participate in the molecular mechanisms that translate structural synaptic changes into function. Several examples illustrate the role of neurotrophins as central molecular actors of the transition between structure to function and vice versa. First, neurotrophins have been implicated in synaptic scaling of both excitatory and inhibitory neurons in several preparations (Gottmann et al., 2009). Second, pharmacological and genetic manipulations indicate neurotrophin signaling is involved in several steps of synaptic long-term potentiation, including the induction, maintenance and consolidation phases (Poo, 2001). For instance, BDNF can convert weak synaptic activity into robust potentiation by post-synaptic mechanisms (Figurov et al., 1996, Kovalchuk et al., 2002, Wierenga et al., 2005).

According to Hebb's theory, adjacent synapses that repeatedly take part in the firing of post-synaptic cells will be strengthened (Hebb, 1949). Inactive or silent synapses undergo elimination. One way to restrict neurotrophin responsiveness to active synapses is to pair neurotrophin signaling to neuronal activity (Boulanger and Poo, 1999). Neuronal activity originating from both pre- and postsynaptic sides can stimulate the secretion of BDNF, which may result in strengthening and maintenance of active synapses. In contrast, synapses with unsynchronized activity between the pre- and post-synaptic terminals do not receive neurotrophin support and are weakened (Snider and Lichtman, 1996, Poo, 2001).

Neuronal network activity contributes to the expression of neurotrophin genes. Most notably, BDNF expression is sensitive to sensory information within the attributed neural circuits in several circumstances such as physical activity, experimental seizure, fear conditioning, food restriction and visual cues (Lu, 2003). For instance, stimulation of a single whisker results in an increase in *Bdnf* gene expression in the cortical barrel corresponding to that whisker (Genoud et al., 2004). It was proposed that BDNF expression reflects the level of activation of a specific neuronal network.

Scaling the activity of individual synapses to the overall neural network activity is an important mechanism that impacts indirectly upon the number of synapses and vice versa (Turrigiano, 2007, Ibata et al., 2008). The strength of neuronal networks is controlled by homeostatic regulatory mechanisms that can adjust the level of activity (Turrigiano, 2007). Chronic activity blockade scales up the amplitude of post-synaptic responses, whereas raising firing rates with bicuculine, an inhibitor of GABA receptors, scale down the amplitude of post-synaptic currents (Turrigiano et al., 1998). Meta-plasticity is a term originally coined to refer to the changes in synaptic plasticity based upon recent events of neuronal activity (Abraham and Bear, 1996). BDNF prevents increased scaling of post-synaptic responses upon blockade of neuronal activity (Rutherford et al., 1998). BDNF can also counteract compensatory meta-plasticity changes occurring within the visual cortex after sensory deprivation (Mandolesi et al., 2005). Therefore, BDNF produces meta-plasticity changes to adjust the activity of neuronal networks within homeostatic range.

VII.3 BDNF and glucocorticoids sculpt dendritic arborization

BDNF and glucocorticoids modulate the formation and the refinement of dendritic territories and connectivity in the central nervous system (See earlier sections II.2, III.3 and IV). Sholl analyzes of excitatory neurons in hippocampus, cortex and amygdala *in vivo* demonstrated convincingly that BDNF and glucocorticoids alter dendritic arborization. On one hand, mice lacking one copy of the *bdnf* gene display 50% less BDNF in the brain, smaller hippocampal volume and excitatory granular neurons of the dentate with atrophic dendrites (Chen et al., 2006). On the other hand, chronic immobilization stress (via glucocorticoids) causes the growth of dendrites in the amygdala but dendritic atrophy in the hippocampus and prefrontal cortex (Liston et al., 2006, McEwen, 2007). Activation of GR can decrease the complexity of apical dendrites while preserving the integrity of basal dendrites in pyramidal neurons of hippocampal CA3 formation and layer II/III of the prefrontal cortex (Liston et al., 2006, Alfarez et al., 2009, Magarinos et al., 2011). Similarly, only apical dendrites of CA3 pyramidal neurons are atrophied in haplo-insufficient BDNF mice (Magarinos et al., 2011). These findings indicate that stress, glucocorticoids and BDNF regulate unique but common neural circuits. BDNF contributes to the rewiring and maintenance of established circuits, and glucocorticoids help restore homeostasis when challenged by new experiences (de Kloet et al., 2005, Cohen-Cory et al., 2010, Jeanneteau and Chao, 2012). So, remodeling of dendritic territories may help maintain circuit's excitability within physiological range without damaging neurons. For instance, spines protect neurons from uncontrolled rises of intracellular calcium into mitochondria-containing dendrites, which may otherwise activate apoptotic processes leading to cell death (Segal, 2010). So, debranching hippocampal neurons from hyperactive inputs as observed in response to stress may represent a protective mechanism. Short-term plasticity may rely on morphological changes that depend on gene expression (Kandel, 2001, Greer and Greenberg, 2008).

VII.4 Glucocorticoids regulate the expression of BDNF

Among the many genes regulated by glucocorticoids and chronic stress, repression of the *bdnf* gene captured attention since BDNF levels reinforce the maintenance of synapses, dendritic fields and ameliorate behavior in animal models of stress-related disorders (Horch and Katz, 2002, Schmidt and Duman, 2007, Datson et al., 2008). Indeed, BDNF haplo-deficient mice show decreased dendritic tree and spine density in several brain regions involved in the control of the HPA axis (Magarinos et al., 2011). Consequently, BDNF haplo-insufficient mice or conditional BDNF forebrain knockout mice decrease HPA axis circadian and stressed activities (Autry et al., 2009, Jeanneteau et al., 2012). The expression of BDNF is tissue-specific, sensitive to various environmental factors and dependent on neuronal activity.

The genomic organization of the *bdnf* gene is complex with multiple promoters, each of which can be tissue-specific, activity-dependent and sensitive to distinct environmental factors (Timmusk et al., 1994, Aid et al., 2007, Pruunsild et al., 2007, Cunha et al., 2010). There are 8 alternative exons (namely I to VIII) upstream of the last exon IX shared to all transcripts. Some *bdnf* transcripts are actively transported to particular subcellular compartments and the length of the 3'-UTR sequence determines the stability of each isoform (An et al., 2008, Lau et al., 2010). Consequently, net changes in BDNF protein levels reflect the sum of all promoter-specific *bdnf* transcripts since they all share the last protein-encoding exon. Chronic stress and glucocorticoids downregulate BDNF protein levels and exon IV *bdnf* transcript in the hippocampus contrary to exon II and III specific transcripts that remained unaffected (Smith et al., 1995b, a, de Quervain et al., 1998, Hansson et al., 2006, Nicholas et al., 2006, Prickaerts et al., 2006). In contrast, adrenalectomy up-regulates exon IV *bdnf* transcript and protein level in the hippocampus (Funakoshi et al., 1993, Duman and Monteggia, 2006, Tahera et al., 2007).

Genetic manipulation of GR expression in mice produces profound effects on the mRNA and protein levels of BDNF. Hypomorphic mice with 50% reduction of GR downregulate BDNF protein level in the hippocampus without changing NGF levels (Ridder et al., 2005). In contrast, transgenic mice overexpressing GR two-fold increase BDNF protein level in the hippocampus without changing NGF levels (Ridder et al., 2005). Because brain expression of BDNF is sensitive to circadian rhythms (Schaaf et al., 2000, Tapia-Arancibia et al., 2004, Allen and Earnest, 2005), further investigations revealed that hypomorphic GR mice resulted in downregulation of BDNF protein in the hippocampus during inactive periods (daytime). Increases in BDNF protein in the hypothalamus occur during the active period (nighttime) (Schulte-Herbruggen et al., 2007). The parietal cortex displayed higher BDNF protein levels in GR +/- mice both in daytime and nighttime periods, whereas other brain regions (frontal cortex, the amygdala and striatum) were not sensitive to both GR expression and the circadian cycle (Schulte-Herbruggen et al., 2007). Similarly, BDNF protein levels were upregulated in the hypothalamic PVN of conditional GR knockout targeted to the hypothalamic PVN, suggesting a possible cell autonomous regulation of BDNF expression by GR (Jeanneteau et al., 2012). To date, GR DNA-binding responsive elements have not been identified in the many promoters of the *bdnf* gene (Dwivedi et al., 2006, Hansson et al., 2006). How do glucocorticoids regulate BDNF expression? What is the effect of acute stress compared to chronic stress?

Like glucocorticoids, stress has profound effect on *bdnf* gene expression, which depend upon of dose and duration (Tapia-Arancibia et al., 2004). Single immobilization stress for 2 to 8 hours session each can downregulate *bdnf* mRNA in the hippocampus (Smith et al., 1995a, Ueyama et al., 1997). In contrast, shorter stress sessions (15 min and 1 hour) increase *bdnf* transcripts exon I, II, III throughout the hippocampus though transiently only (Marmigere et al., 2003). Similar data were reported in the hypothalamus where short exposition to inescapable stress increases BDNF transcripts and protein whereas longer exposure to the stressor diminished BDNF expression (Marmigere et al., 2001, Rage et al., 2002). How sustainable are these changes? Plasma corticosterone levels remained dramatically elevated 3 weeks after the cessation of restrain stress if chronic (for 10 consecutive days) but not when acute (Lakshminarasimhan and Chattarji, 2012). In these mice, BDNF levels are downregulated in the hippocampus but upregulated in the amygdala regardless of the duration of the stress. But increased amygdalar BDNF persisted even 3 weeks after cessation of stress whereas downregulated hippocampal BDNF returned to baseline rather quickly (Lakshminarasimhan and Chattarji, 2012). Consequently, persistent ectopic BDNF and glucocorticoid co-activities in the amygdala, which contrast with ectopic glucocorticoid and co-incident BDNF deficit in the hippocampus may explain distinct morphological, physiological and behavioral effects of stress. Are distinct repertoires of

genes regulated in such a context? As much as glucocorticoids are involved in behavioral and cellular adaptation to stress and restoration of homeostasis (de Kloet et al., 2005, Karatsoreos and McEwen, 2011), *bdnf* is a stress sensitive gene involved in similar behavioral and cellular adaptation to environmental changes. For instance, BDNF protein is upregulated in the hypothalamic PVN shortly after stress to restore CRH protein stocks that are depleted upon activation of the HPA axis (Givalois et al., 2004, Naert et al., 2006, Jeanneteau et al., 2012).

VII.5 Does BDNF mediate or occlude the effects of glucocorticoids on synaptic plasticity and behavior?

BDNF has well characterized synaptogenic effects and loss of BDNF expression due to prolonged glucocorticoid exposure decreases synaptic density that correlates with cognitive deficits and mood disorders (Duman et al., 1997, Nestler et al., 2002, Duman and Monteggia, 2006, McEwen, 2007, Krishnan and Nestler, 2008, McEwen, 2008). Do BDNF deficits increase susceptibility to the toxic effects of glucocorticoids? Deficits of BDNF in hypomorphic mice or in the forebrain do not give rise to depressive-like symptoms, suggesting that BDNF alone is not a mediator of depression (Martinowich et al., 2007). Female mice harboring conditional knockout of BDNF in the forebrain developed depressive-like symptoms indicating a strong interaction with sex hormones (Monteggia et al., 2007). Reactivity of the HPA axis following chronic stress was increased only in female mice carrying a conditional deletion of BDNF in the forebrain (Autry et al., 2009, Autry and Monteggia, 2012).

Can BDNF deficits be such a conditioning factor under which a normally well-tolerated degree of stress can even become pathogenic? Several studies suggest that BDNF deficits may lower the threshold to develop anxiogenic and anhedonic behaviors in specific hormonal or environmental context. Indeed, mice with reduced BDNF function display depressive behavior only when exposed to mild stress that has no effect on wildtypes (Duman et al., 2007). Four weeks after priming a stressful event, plasma glucocorticoid levels return to control baseline in all rats among which 40% (the susceptible) decreased hippocampal BDNF levels, diminished dendritic arborization and developed depressive-like symptoms after exposition to inescapable chronic stress. In contrast, the other 60% resilient maintained normal hippocampal BDNF levels, dendritic arborization and behavior (Blugeot et al., 2011).

A genetic variation G196A (Val66Met polymorphism) in the human population also impairs reactivity of the HPA axis with depressive and cognitive defects. Human carriers of the BDNF Met66 polymorphism, which are predisposed to reduced levels of activity-dependent BDNF, display a reduction in hippocampal volume and cognitive disabilities (Egan et al., 2003, Yeo et al., 2004). The BDNF Met66 allele also impairs HPA axis reactivity by an inability to cope with stress (Egan et al., 2003, Chen et al., 2006). Similar to humans, a knock-in animal model of the Val66met polymorphism results in reduced BDNF levels and an increase in HPA axis reactivity to stress (Yu et al., 2012). In contrast, elevating BDNF levels in the forebrain of an animal model by genetic methods protected against stress-induced morphological and behavioral defects (Govindarajan et al., 2006). Therefore, BDNF levels may establish vulnerability and recovery in stress-related disorders (Duman et al., 1997, Greenberg et al., 2009). BDNF deficits may underlie or occlude the toxic effects of glucocorticoids, since mice with reduced BDNF function (BDNF hypomorphs) display fewer spines and dendrites in hippocampal formation CA3 with no further atrophy by excess stress (Magarinos et al., 2011).

VII.6 Glucocorticoids can activate the BDNF receptor, TrkB in absence of neurotrophins

A single acute administration of a synthetic glucocorticoid, dexamethasone, did not significantly alter the abundance or secretion of the neurotrophins NGF, BDNF and NT3 proteins at least in cortical and hippocampal tissue as well as primary neurons (Jeanneteau et al., 2008). Nevertheless, a single acute administration of dexamethasone can enhance TrkB phosphorylation in the brain and some peripheral tissues of young developing rats (Figure 5), suggesting that glucocorticoids can elicit Trk activation in absence of neurotrophins. Unlike corticosterone, dexamethasone does not cross the blood brain barrier at low doses because of active transport out of the brain by the MDR1A p-glycoprotein (De Kloet, 1997, Meijer et al., 1998). But at high doses, dexamethasone penetrates the brain where it enhances the phosphorylation of TrkB and GR, a surrogate marker of its activity (Wang et al., 2002, Wang et al., 2007). Phosphorylation of the NGF receptor, TrkA was enhanced in the septum of rats shortly after administration of a single high dose of dexamethasone (Saporito et al., 1994, Shi et al., 1998). Dexamethasone and other synthetic or natural glucocorticoids consistently elicited TrkA, TrkB and TrkC phosphorylation in reconstituted culture systems (Jeanneteau et al., 2008). Phosphorylation of TrkA, TrkB and TrkC in response to GR activation is weak and delayed when compared to stimulation with their cognate neurotrophin ligands. Phosphorylation of Trk by glucocorticoids required GR binding to DNA as well as GR transcriptional capabilities (Jeanneteau et al., 2008). Phosphorylation of TrkB receptors can be also elicited by imipramine or fluoxetine in BDNF conditional knockout mice. These observations suggest that *bdnf* is not necessarily required for TrkB activation (Rantamaki et al., 2011). Indeed, several mechanisms of TrkB activation in absence of neurotrophins have now been characterized (Lee et al., 2002a, Chao, 2003). Imipramine, fluoxetine, zinc, adenosine, dopamine, the neuropeptide PACAP can also trigger Trk activation via neurotrophin-independent mechanisms (Lee and Chao, 2001, Lee et al., 2002b, Jeanneteau and Chao, 2006, Huang et al., 2008, Iwakura et al., 2008, Rantamaki et al., 2011). The ability of glucocorticoids to use TrkB as signaling platform is another example of the convergence of neurotrophin and glucocorticoid actions.

VII.7 *Mkp-1*, a glucocorticoid- and BDNF-sensitive gene

Among the many genes regulated by glucocorticoids, *mkp-1* presents the peculiarity of being co-responsive to BDNF and dexamethasone, which induces MKP-1 expression beyond additive effects of a single treatment (Figure 6A). MKP-1 is a phosphatase involved in feedback control of MAPK signal duration. MAPKs are central in the control of cytoskeleton dynamics because they phosphorylate a large array of microtubule- and actin-associated proteins. Sustained gain-of-function of MKP-1 destabilizes microtubules filaments because of persistent deactivation of the JNK kinase (Duric et al., 2010, Jeanneteau et al., 2010, Jeanneteau and Deinhardt, 2011). In contrast, loss of MKP-1 resulted in an inability of BDNF and neuronal activity to produce new axon branches (Jeanneteau et al., 2010). Hence, regulation of MKP-1 levels by BDNF and glucocorticoids can result in discrete changes in axon arborization. With low basal expression, high inducibility, rapid turnover and the opportunity for stabilization, MKP-1 displays the necessary attributes to control MAPK signaling and cytoskeletal remodeling at defined cellular locations in a temporal fashion. As the strength of MAPK signaling determines the duration of biological responses and many physiological outcomes, spatio-temporal titration of MKP-1 plays a pivotal regulatory role. It is tempting to speculate that stabilization of MKP-1 protein levels by BDNF signaling may instruct and determine precise axonal branching and connectivity. To date, the role of MKP-1 on dendritic tree and spine remodeling remains unknown.

If titration of MKP-1 levels is important for neuronal signal transduction, what may result from the deregulation of its expression during higher order behaviors? Enhanced expression

of MKP-1 has recently been reported in postmortem hippocampal tissues from individuals with major depression (Duric et al., 2010). Induction of *mkp-1* in the hippocampus also occurs in animal models following chronic severe stress or seizures (Qian et al., 1994, Duric et al., 2010). Whether upregulation of MKP-1 is a cause or consequence of these conditions is presently unknown. However, viral overexpression of MKP-1 levels in the hippocampus produced depressive-like effects in mice in absence of stress (Duric et al., 2010). At the cellular level, neither overexpression nor genetic ablation of *mkp-1* affected neuronal survival, but impaired cell differentiation (Figure 6). If the chronic misexpression of MKP-1 contributes to the gradual development of depression, then restoring baseline MKP-1 levels may prove beneficial. Two lines of evidence support this idea. First, the persistent overexpression of MKP-1 induced by chronic stress is reversed by antidepressant treatment (Duric et al., 2010). Second, *mkp-1* knock out mice are resilient to severe stressful experiences compared to wildtype littermates. Therefore, if the molecular mechanisms that disrupt the expression of *mkp-1* are causal to mood disorders, transient antagonism of MKP-1 phosphatase activity may represent therapeutic value.

VIII. Summary and future directions

Prolonged glucocorticoid exposure over weeks has been linked to dendritic atrophy and spine loss in fixed tissue preparations. But the short-term effects of glucocorticoids are more difficult to assess in fixed tissue preparations and several studies have provided mixed results (Conrad et al., 1999, Mitra et al., 2005, Bloss et al., 2011). To determine the extent to which glucocorticoids regulate dendritic spine plasticity, two-photon imaging of the living brain to track remodeling of spines *in vivo* after treatment with glucocorticoids provided unexpected results. Glucocorticoids enhanced dendritic spine remodeling capacity. Disruption of glucocorticoid rhythms, a major endocrine hallmark of numerous psychiatric and neurodegenerative disorders, has profound deleterious effects on dendritic spine morphological plasticity and behavior (Duman et al., 1997, De Kloet et al., 1998, McEwen, 1998, Berton et al., 2006). Behavioral experience may be encoded by patterns of dendritic spines that result from the processes of formation and elimination. More dendritic spines are pruned than formed in response to chronic stress, which may set the stage for cognitive impairments, neuropsychiatric illnesses and normal aging.

Normalization of glucocorticoid rhythms is possible with antidepressant therapies (Holsboer and Ising, 2010). However, patients that fail to normalize glucocorticoids rhythms despite antidepressant treatments have increased risk of relapse, suggesting the important role of glucocorticoids in mood disorders (Holsboer and Ising, 2010). Because BDNF mediates the effects of antidepressant therapies (Saarelainen et al., 2003, Castren and Rantamaki, 2010, Autry et al., 2011), imbalance of the glucocorticoid and neurotrophic systems may impair neural connectivity and precipitate the development of psychiatric disorders as previously proposed (Duman et al., 1997, Krishnan and Nestler, 2008). Numerous studies have reported reduced sensitivity to glucocorticoids, also termed glucocorticoid resistance, which may present the underlying foundations of psychiatric disorders featuring disrupted glucocorticoid rhythms. Within normal range, glucocorticoids support normal brain function but too much or too little glucocorticoids produce numerous detrimental effects in the central nervous system but also in peripheral organs.

How can glucocorticoid actions be changed from protective to harmful outcomes? To produce synaptic plasticity, glucocorticoids use both genomic and non-genomic mechanisms together with ongoing neural activity mediated by neurotransmitters, neuropeptides and neurotrophins. BDNF is the most abundant neurotrophin in the brain, but how BDNF and glucocorticoids signals are integrated to shape specific changes in morphology and plasticity is not fully understood. Of many studies of glucocorticoids actions upon BDNF activities,

very few investigated the role of BDNF on glucocorticoid function. Does BDNF regulate glucocorticoid actions? What is the role of glucocorticoid and BDNF regulated genes on the consolidation, maturation and elimination of dendritic spines in the brain structures that control the maintenance of the HPA axis? Are BDNF and glucocorticoid activities calibrated remains an open question. Since morphological and quantitative alterations of dendritic spines by chronic stress/glucocorticoids are reversible, future studies will address these questions and raise new opportunities for therapeutic interventions. For instance, would restoring dendritic spine number in the hippocampus and prefrontal cortex be a potential therapeutic avenue for chronic stress? So far, experimental strategies have been limited to the prevention of dendritic atrophy by overexpressing BDNF in target tissues like the hippocampus (Govindarajan et al., 2006, Taliaz et al., 2011). If manipulating the glucocorticoid system can restore BDNF expression, would dendritic spine loss recover? Anti-glucocorticoid therapies (chemical adrenalectomy with low dose dexamethasone, inhibition of glucocorticoid synthesis with metyrapone or GR antagonism with mifepristone) may represent effective adjuncts, accelerating the onset of antidepressant action (Arana et al., 1995, Jahn et al., 2004, DeBattista et al., 2006, McIsaac and Young, 2009). Presently, it is unknown whether anti-glucocorticoid strategies would affect BDNF expression and dendritic spine dynamics. Elucidating the molecular mechanisms by which glucocorticoid and BDNF signaling intersect may provide targets to counteract the toxic effects of glucocorticoids and prime the resilience and recovery from severe stressful experiences.

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References

- Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* 1996; 19:126–130. [PubMed: 8658594]
- Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. *Journal of neuroscience research.* 2007; 85:525–535. [PubMed: 17149751]
- Alfarez DN, De Simoni A, Velzing EH, Bracey E, Joels M, Edwards FA, Krugers HJ. Corticosterone reduces dendritic complexity in developing hippocampal CA1 neurons. *Hippocampus.* 2009; 19:828–836. [PubMed: 19235231]
- Allen GC, Earnest DJ. Overlap in the distribution of TrkB immunoreactivity and retinohypothalamic tract innervation of the rat suprachiasmatic nucleus. *Neuroscience letters.* 2005; 376:200–204. [PubMed: 15721221]
- Altarejos JY, Montminy M. CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. *Nat Rev Mol Cell Biol.* 2011; 12:141–151. [PubMed: 21346730]
- Ambroggi F, Turiault M, Milet A, Deroche-Gamonet V, Parnaudeau S, Balado E, Barik J, van der Veen R, Maroteaux G, Lemberger T, Schutz G, Lazar M, Marinelli M, Piazza PV, Tronche F. Stress and addiction: glucocorticoid receptor in dopaminergic neurons facilitates cocaine seeking. *Nature neuroscience.* 2009; 12:247–249.
- An JJ, Gharami K, Liao GY, Woo NH, Lau AG, Vanevski F, Torre ER, Jones KR, Feng Y, Lu B, Xu B. Distinct role of long 3' UTR BDNF mRNA in spine morphology and synaptic plasticity in hippocampal neurons. *Cell.* 2008; 134:175–187. [PubMed: 18614020]
- Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology.* 2011; 36:415–425. [PubMed: 20399565]
- Arana GW, Santos AB, Laraia MT, McLeod-Bryant S, Beale MD, Rames LJ, Roberts JM, Dias JK, Molloy M. Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. *The American journal of psychiatry.* 1995; 152:265–267. [PubMed: 7840362]

- Attwood BK, Bourgognon JM, Patel S, Mucha M, Schiavon E, Skrzypiec AE, Young KW, Shiosaka S, Korostynski M, Piechota M, Przewlocki R, Pawlak R. Neuropsin cleaves EphB2 in the amygdala to control anxiety. *Nature*. 2011; 473:372–375. [PubMed: 21508957]
- Autry AE, Adachi M, Cheng P, Monteggia LM. Gender-specific impact of brain-derived neurotrophic factor signaling on stress-induced depression-like behavior. *Biological psychiatry*. 2009; 66:84–90. [PubMed: 19358977]
- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; 475:91–95. [PubMed: 21677641]
- Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacological reviews*. 2012; 64:238–258. [PubMed: 22407616]
- Bagley J, Moghaddam B. Temporal dynamics of glutamate efflux in the prefrontal cortex and in the hippocampus following repeated stress: effects of pretreatment with saline or diazepam. *Neuroscience*. 1997; 77:65–73. [PubMed: 9044375]
- Bao AM, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: focus on the human hypothalamus. *Brain Res Rev*. 2008; 57:531–553. [PubMed: 17524488]
- Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. *Annu Rev Physiol*. 2009; 71:451–464. [PubMed: 18817512]
- Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. *Lancet*. 2009; 373:1905–1917. [PubMed: 19482216]
- Bergami M, Rimondini R, Santi S, Blum R, Gotz M, Canossa M. Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105:15570–15575. [PubMed: 18832146]
- Berton O, McClung CA, Dileone RJ, Krishnan V, Renthall W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science*. 2006; 311:864–868. [PubMed: 16469931]
- Bhatt DH, Zhang S, Gan WB. Dendritic spine dynamics. *Annu Rev Physiol*. 2009; 71:261–282. [PubMed: 19575680]
- Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*. 2009; 34(Suppl 1):S186–195. [PubMed: 19560279]
- Bloss EB, Janssen WG, Ohm DT, Yuk FJ, Wadsworth S, Saardi KM, McEwen BS, Morrison JH. Evidence for reduced experience-dependent dendritic spine plasticity in the aging prefrontal cortex. *J Neurosci*. 2011; 31:7831–7839. [PubMed: 21613496]
- Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel JJ, Becker C. Vulnerability to depression: from brain neuroplasticity to identification of biomarkers. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2011; 31:12889–12899. [PubMed: 21900567]
- Boulanger L, Poo MM. Gating of BDNF-induced synaptic potentiation by cAMP. *Science*. 1999; 284:1982–1984. [PubMed: 10373115]
- Boyle MP, Brewer JA, Funatsu M, Wozniak DF, Tsien JZ, Izumi Y, Muglia LJ. Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. *Proc Natl Acad Sci U S A*. 2005; 102:473–478. [PubMed: 15623560]
- Boyle MP, Kolber BJ, Vogt SK, Wozniak DF, Muglia LJ. Forebrain glucocorticoid receptors modulate anxiety-associated locomotor activation and adrenal responsiveness. *J Neurosci*. 2006; 26:1971–1978. [PubMed: 16481429]
- Butts KA, Weinberg J, Young AH, Phillips AG. Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. *Proceedings of the National Academy of Sciences of the United States of America*. 2011; 108:18459–18464. [PubMed: 22032926]
- Carvalho LA, Pariante CM. In vitro modulation of the glucocorticoid receptor by antidepressants. *Stress*. 2008; 11:411–424. [PubMed: 19065455]

- Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol.* 2010; 70:289–297. [PubMed: 20186711]
- Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci.* 2003; 4:299–309. [PubMed: 12671646]
- Chaouloff F. Serotonin, stress and corticoids. *J Psychopharmacol.* 2000; 14:139–151. [PubMed: 10890308]
- Charmandari E, Kino T, Chrousos GP. Familial/sporadic glucocorticoid resistance: clinical phenotype and molecular mechanisms. *Annals of the New York Academy of Sciences.* 2004; 1024:168–181. [PubMed: 15265781]
- Chen G, Henter ID, Manji HK. Translational research in bipolar disorder: emerging insights from genetically based models. *Molecular psychiatry.* 2010; 15:883–895. [PubMed: 20142820]
- Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL, Lee FS. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science.* 2006; 314:140–143. [PubMed: 17023662]
- Chrousos GP, Detera-Wadleigh SD, Karl M. Syndromes of glucocorticoid resistance. *Ann Intern Med.* 1993; 119:1113–1124. [PubMed: 8239231]
- Chrousos GP, Vingerhoeds A, Brandon D, Eil C, Pugeat M, DeVroede M, Loriaux DL, Lipsett MB. Primary cortisol resistance in man. A glucocorticoid receptor-mediated disease. *The Journal of clinical investigation.* 1982; 69:1261–1269. [PubMed: 6282933]
- Clark AF, Brotchie D, Read AT, Hellberg P, English-Wright S, Pang IH, Ethier CR, Grierson I. Dexamethasone alters F-actin architecture and promotes cross-linked actin network formation in human trabecular meshwork tissue. *Cell Motil Cytoskeleton.* 2005; 60:83–95. [PubMed: 15593281]
- Cohen JW, Louneva N, Han LY, Hodes GE, Wilson RS, Bennett DA, Lucki I, Arnold SE. Chronic corticosterone exposure alters postsynaptic protein levels of PSD-95, NR1, and synaptopodin in the mouse brain. *Synapse.* 2011; 65:763–770. [PubMed: 21190219]
- Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America.* 2012; 109:5995–5999. [PubMed: 22474371]
- Cohen-Cory S, Kidane AH, Shirkey NJ, Marshak S. Brain-derived neurotrophic factor and the development of structural neuronal connectivity. *Dev Neurobiol.* 2010; 70:271–288. [PubMed: 20186709]
- Conrad CD, LeDoux JE, Magarinos AM, McEwen BS. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behav Neurosci.* 1999; 113:902–913. [PubMed: 10571474]
- Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? *Front Mol Neurosci.* 2010; 3:1. [PubMed: 20162032]
- Datson NA, Morsink MC, Meijer OC, de Kloet ER. Central corticosteroid actions: Search for gene targets. *Eur J Pharmacol.* 2008; 583:272–289. [PubMed: 18295201]
- David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I, Drew M, Craig DA, Guiard BP, Guilloux JP, Artymyshyn RP, Gardier AM, Gerald C, Antonijevic IA, Leonardo ED, Hen R. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron.* 2009; 62:479–493. [PubMed: 19477151]
- De Kloet ER. Why Dexamethasone Poorly Penetrates in Brain. *Stress.* 1997; 2:13–20. [PubMed: 9787252]
- de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci.* 2005; 6:463–475. [PubMed: 15891777]
- de Kloet ER, Karst H, Joels M. Corticosteroid hormones in the central stress response: quick-and-slow. *Frontiers in neuroendocrinology.* 2008; 29:268–272. [PubMed: 18067954]
- De Kloet ER, Reul JM. Feedback action and tonic influence of corticosteroids on brain function: a concept arising from the heterogeneity of brain receptor systems. *Psychoneuroendocrinology.* 1987; 12:83–105. [PubMed: 3037584]

- De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr Rev.* 1998; 19:269–301. [PubMed: 9626555]
- De Kloet R, Wallach G, McEwen BS. Differences in corticosterone and dexamethasone binding to rat brain and pituitary. *Endocrinology.* 1975; 96:598–609. [PubMed: 163728]
- de Quervain DJ, Poirier R, Wollmer MA, Grimaldi LM, Tsolaki M, Streffer JR, Hock C, Nitsch RM, Mohajeri MH, Papassotiropoulos A. Glucocorticoid-related genetic susceptibility for Alzheimer's disease. *Hum Mol Genet.* 2004; 13:47–52. [PubMed: 14583441]
- de Quervain DJ, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature.* 1998; 394:787–790. [PubMed: 9723618]
- DeBattista C, Belanoff J, Glass S, Khan A, Horne RL, Blasey C, Carpenter LL, Alva G. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biological psychiatry.* 2006; 60:1343–1349. [PubMed: 16889757]
- Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG. Squirrel monkey immunophilin FKBP51 is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology.* 2000; 141:4107–4113. [PubMed: 11089542]
- Di S, Malcher-Lopes R, Halmos KC, Tasker JG. Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J Neurosci.* 2003; 23:4850–4857. [PubMed: 12832507]
- Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus.* 1992; 2:421–430. [PubMed: 1308198]
- Duman CH, Schlesinger L, Kodama M, Russell DS, Duman RS. A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. *Biological psychiatry.* 2007; 61:661–670. [PubMed: 16945347]
- Duman RS. Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression. *Dialogues Clin Neurosci.* 2009; 11:239–255. [PubMed: 19877493]
- Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry.* 1997; 54:597–606. [PubMed: 9236543]
- Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biological psychiatry.* 2006; 59:1116–1127. [PubMed: 16631126]
- Duric V, Banasr M, Licznarski P, Schmidt HD, Stockmeier CA, Simen AA, Newton SS, Duman RS. A negative regulator of MAP kinase causes depressive behavior. *Nat Med.* 2010; 16:1328–1332. [PubMed: 20953200]
- Dwivedi Y, Rizavi HS, Pandey GN. Antidepressants reverse corticosterone-mediated decrease in brain-derived neurotrophic factor expression: differential regulation of specific exons by antidepressants and corticosterone. *Neuroscience.* 2006; 139:1017–1029. [PubMed: 16500030]
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell.* 2003; 112:257–269. [PubMed: 12553913]
- Fiala JC, Spacek J, Harris KM. Dendritic spine pathology: cause or consequence of neurological disorders? *Brain Res Brain Res Rev.* 2002; 39:29–54. [PubMed: 12086707]
- Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature.* 1996; 381:706–709. [PubMed: 8649517]
- Funakoshi H, Frisen J, Barbany G, Timmusk T, Zachrisson O, Verge VM, Persson H. Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. *The Journal of cell biology.* 1993; 123:455–465. [PubMed: 8408225]
- Gallo G, Letourneau PC. Regulation of growth cone actin filaments by guidance cues. *J Neurobiol.* 2004; 58:92–102. [PubMed: 14598373]
- Gartside SE, Leitch MM, Young AH. Altered glucocorticoid rhythm attenuates the ability of a chronic SSRI to elevate forebrain 5-HT: implications for the treatment of depression. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology.* 2003; 28:1572–1578. [PubMed: 12784107]

- Gass P, Reichardt HM, Strekalova T, Henn F, Tronche F. Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: models for depression and anxiety? *Physiol Behav.* 2001; 73:811–825. [PubMed: 11566214]
- Genoud C, Knott GW, Sakata K, Lu B, Welker E. Altered synapse formation in the adult somatosensory cortex of brain-derived neurotrophic factor heterozygote mice. *J Neurosci.* 2004; 24:2394–2400. [PubMed: 15014114]
- Givalois L, Naert G, Rage F, Ixart G, Arancibia S, Tapia-Arancibia L. A single brain-derived neurotrophic factor injection modifies hypothalamo-pituitary-adrenocortical axis activity in adult male rats. *Mol Cell Neurosci.* 2004; 27:280–295. [PubMed: 15519243]
- Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. *Endocrinol Metab Clin North Am.* 2002; 31:37–62. vi. [PubMed: 12055990]
- Gottmann K, Mittmann T, Lessmann V. BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. *Exp Brain Res.* 2009; 199:203–234. [PubMed: 19777221]
- Gould E, Woolley CS, Frankfurt M, McEwen BS. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *The Journal of neuroscience: the official journal of the Society for Neuroscience.* 1990; 10:1286–1291. [PubMed: 2329377]
- Govindan MV. Recruitment of cAMP-response element-binding protein and histone deacetylase has opposite effects on glucocorticoid receptor gene transcription. *The Journal of biological chemistry.* 2010; 285:4489–4510. [PubMed: 20018896]
- Govindarajan A, Rao BS, Nair D, Trinh M, Mawjee N, Tonegawa S, Chattarji S. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. *Proc Natl Acad Sci U S A.* 2006; 103:13208–13213. [PubMed: 16924103]
- Graff J, Rei D, Guan JS, Wang WY, Seo J, Hennig KM, Nieland TJ, Fass DM, Kao PF, Kahn M, Su SC, Samiei A, Joseph N, Haggarty SJ, Delalle I, Tsai LH. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature.* 2012; 483:222–226. [PubMed: 22388814]
- Graham DL, Krishnan V, Larson EB, Graham A, Edwards S, Bachtell RK, Simmons D, Gent LM, Berton O, Bolanos CA, DiLeone RJ, Parada LF, Nestler EJ, Self DW. Tropomyosin-related kinase B in the mesolimbic dopamine system: region-specific effects on cocaine reward. *Biol Psychiatry.* 2009; 65:696–701. [PubMed: 18990365]
- Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci.* 2006; 26:9047–9056. [PubMed: 16943563]
- Greenberg ME, Xu B, Lu B, Hempstead BL. New insights in the biology of BDNF synthesis and release: implications in CNS function. *J Neurosci.* 2009; 29:12764–12767. [PubMed: 19828787]
- Greer PL, Greenberg ME. From synapse to nucleus: calcium-dependent gene transcription in the control of synapse development and function. *Neuron.* 2008; 59:846–860. [PubMed: 18817726]
- Groc L, Choquet D, Chaouloff F. The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. *Nature neuroscience.* 2008; 11:868–870.
- Groeneweg FL, Karst H, de Kloet ER, Joels M. Rapid non-genomic effects of corticosteroids and their role in the central stress response. *J Endocrinol.* 2011; 209:153–167. [PubMed: 21357682]
- Grutzendler J, Kasthuri N, Gan WB. Long-term dendritic spine stability in the adult cortex. *Nature.* 2002; 420:812–816. [PubMed: 12490949]
- Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature.* 2001; 411:86–89. [PubMed: 11333982]
- Hajszan T, MacLusky NJ, Leranth C. Dehydroepiandrosterone increases hippocampal spine synapse density in ovariectomized female rats. *Endocrinology.* 2004; 145:1042–1045. [PubMed: 14645116]
- Hansson AC, Sommer WH, Metsis M, Stromberg I, Agnati LF, Fuxe K. Corticosterone actions on the hippocampal brain-derived neurotrophic factor expression are mediated by exon IV promoter. *Journal of neuroendocrinology.* 2006; 18:104–114. [PubMed: 16420279]

- Hartmann J, Wagner KV, Liebl C, Scharf SH, Wang XD, Wolf M, Hausch F, Rein T, Schmidt U, Touma C, Cheung-Flynn J, Cox MB, Smith DF, Holsboer F, Muller MB, Schmidt MV. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. *Neuropharmacology*. 2012; 62:332–339. [PubMed: 21839098]
- Hascup ER, Hascup KN, Stephens M, Pomerleau F, Huettl P, Gratton A, Gerhardt GA. Rapid microelectrode measurements and the origin and regulation of extracellular glutamate in rat prefrontal cortex. *Journal of neurochemistry*. 2010; 115:1608–1620. [PubMed: 20969570]
- Haske T, Nakao M, Moudgil VK. Phosphorylation of immunopurified rat liver glucocorticoid receptor by the catalytic subunit of cAMP-dependent protein kinase. *Molecular and cellular biochemistry*. 1994; 132:163–171. [PubMed: 7969099]
- Hebb, D. The organization of behavior. Wiley; 1949.
- Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005; 29:1201–1213. [PubMed: 16271821]
- Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TT, Karatsoreos IN, Mackie K, Viau V, Pickel VM, McEwen BS, Liu QS, Gorzalka BB, Hillard CJ. Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2011; 31:10506–10515. [PubMed: 21775596]
- Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2000; 23:477–501. [PubMed: 11027914]
- Holsboer F, Ising M. Central CRH system in depression and anxiety--evidence from clinical studies with CRH1 receptor antagonists. *Eur J Pharmacol*. 2008; 583:350–357. [PubMed: 18272149]
- Holsboer F, Ising M. Stress hormone regulation: biological role and translation into therapy. *Annu Rev Psychol*. 2010; 61:81–109. C101–111. [PubMed: 19575614]
- Horch HW, Katz LC. BDNF release from single cells elicits local dendritic growth in nearby neurons. *Nat Neurosci*. 2002; 5:1177–1184. [PubMed: 12368805]
- Howell MP, Muglia LJ. Effects of genetically altered brain glucocorticoid receptor action on behavior and adrenal axis regulation in mice. *Frontiers in neuroendocrinology*. 2006; 27:275–284. [PubMed: 16814372]
- Huang YZ, Pan E, Xiong ZQ, McNamara JO. Zinc-mediated transactivation of TrkB potentiates the hippocampal mossy fiber-CA3 pyramid synapse. *Neuron*. 2008; 57:546–558. [PubMed: 18304484]
- Ibata K, Sun Q, Turrigiano GG. Rapid synaptic scaling induced by changes in postsynaptic firing. *Neuron*. 2008; 57:819–826. [PubMed: 18367083]
- Ismaili N, Garabedian MJ. Modulation of glucocorticoid receptor function via phosphorylation. *Ann N Y Acad Sci*. 2004; 1024:86–101. [PubMed: 15265775]
- Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, Barczyk A, Hayashi S, Adcock IM, Hogg JC, Barnes PJ. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *The New England journal of medicine*. 2005; 352:1967–1976. [PubMed: 15888697]
- Iwakura Y, Nawa H, Sora I, Chao MV. Dopamine D1 receptor-induced signaling through TrkB receptors in striatal neurons. *The Journal of biological chemistry*. 2008; 283:15799–15806. [PubMed: 18381284]
- Jafari M, Seese RR, Babayan AH, Gall CM, Lauterborn JC. Glucocorticoid Receptors are Localized to Dendritic Spines and Influence Local Actin Signaling. *Molecular neurobiology*. 2012
- Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Archives of general psychiatry*. 2004; 61:1235–1244. [PubMed: 15583115]
- Jeanneteau F, Chao MV. Promoting neurotrophic effects by GPCR ligands. *Novartis Found Symp*. 2006; 276:181–189. discussion 189–192, 233–187, 275–181. [PubMed: 16805430]
- Jeanneteau F, Chao MV. Chapter 107: Neurotrophins and synaptogenesis. *Comprehensive Developmental Neuroscience*. 2012; 2

- Jeanneteau F, Deinhardt K. Fine-tuning MAPK signaling in the brain: The role of MKP-1. *Communicative and Integrative Biology*. 2011; 4:1–3. [PubMed: 21509167]
- Jeanneteau F, Deinhardt K, Miyoshi G, Bennett AM, Chao MV. The MAP kinase phosphatase MKP-1 regulates BDNF-induced axon branching. *Nat Neurosci*. 2010; 13:1373–1379. [PubMed: 20935641]
- Jeanneteau F, Garabedian MJ, Chao MV. Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. *Proc Natl Acad Sci U S A*. 2008; 105:4862–4867. [PubMed: 18347336]
- Jeanneteau F, Lambert WM, Ismaili N, Bath KG, Lee FS, Garabedian MJ, Chao MV. BDNF and glucocorticoids control corticotrophin-releasing hormone (CRH) homeostasis in the hypothalamus. *PNAS* In review. 2012
- Joels M, de Kloet ER. Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. *Science*. 1989; 245:1502–1505. [PubMed: 2781292]
- Joels M, Karst H. Corticosteroid effects on calcium signaling in limbic neurons. *Cell Calcium*. 2012; 51:277–283. [PubMed: 22153720]
- Joels M, Karst H, Krugers HJ, Lucassen PJ. Chronic stress: implications for neuronal morphology, function and neurogenesis. *Frontiers in neuroendocrinology*. 2007; 28:72–96. [PubMed: 17544065]
- Joels M, Vreugdenhil E. Corticosteroids in the brain. Cellular and molecular actions. *Molecular neurobiology*. 1998; 17:87–108. [PubMed: 9887448]
- Johnson LR, Farb C, Morrison JH, McEwen BS, LeDoux JE. Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience*. 2005; 136:289–299. [PubMed: 16181741]
- Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. *Science*. 2001; 294:1030–1038. [PubMed: 11691980]
- Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. *Trends Cogn Sci*. 2011; 15:576–584. [PubMed: 22078931]
- Karst H, Berger S, Turiault M, Tronche F, Schutz G, Joels M. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:19204–19207. [PubMed: 16361444]
- Karst H, Joels M. Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. *J Neurophysiol*. 2005; 94:3479–3486. [PubMed: 16033944]
- Kaufmann WE, Moser HW. Dendritic anomalies in disorders associated with mental retardation. *Cerebral cortex*. 2000; 10:981–991. [PubMed: 11007549]
- Kaur M, Chivers JE, Gienbycz MA, Newton R. Long-acting beta2-adrenoceptor agonists synergistically enhance glucocorticoid-dependent transcription in human airway epithelial and smooth muscle cells. *Mol Pharmacol*. 2008; 73:203–214. [PubMed: 17901197]
- Kellendonk C, Eiden S, Kretz O, Schutz G, Schmidt I, Tronche F, Simon E. Inactivation of the GR in the nervous system affects energy accumulation. *Endocrinology*. 2002a; 143:2333–2340. [PubMed: 12021198]
- Kellendonk C, Gass P, Kretz O, Schutz G, Tronche F. Corticosteroid receptors in the brain: gene targeting studies. *Brain Res Bull*. 2002b; 57:73–83. [PubMed: 11827739]
- Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. *Nature reviews Neuroscience*. 2002; 3:453–462.
- Kim JJ, Haller J. Glucocorticoid hyper- and hypofunction: stress effects on cognition and aggression. *Annals of the New York Academy of Sciences*. 2007; 1113:291–303. [PubMed: 17513462]
- Kitraki E, Karandrea D, Kittas C. Long-lasting effects of stress on glucocorticoid receptor gene expression in the rat brain. *Neuroendocrinology*. 1999; 69:331–338. [PubMed: 10343174]
- Koenig JI, Kirkpatrick B, Lee P. Glucocorticoid hormones and early brain development in schizophrenia. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2002; 27:309–318. [PubMed: 12093605]

- Kojima N, Shirao T. Synaptic dysfunction and disruption of postsynaptic drebrin-actin complex: a study of neurological disorders accompanied by cognitive deficits. *Neuroscience research*. 2007; 58:1–5. [PubMed: 17379343]
- Kokoeva MV, Yin H, Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science*. 2005; 310:679–683. [PubMed: 16254185]
- Kolber BJ, Roberts MS, Howell MP, Wozniak DF, Sands MS, Muglia LJ. Central amygdala glucocorticoid receptor action promotes fear-associated CRH activation and conditioning. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105:12004–12009. [PubMed: 18695245]
- Komatsuzaki Y, Hatanaka Y, Murakami G, Mukai H, Hojo Y, Saito M, Kimoto T, Kawato S. Corticosterone induces rapid spinogenesis via synaptic glucocorticoid receptors and kinase networks in hippocampus. *PloS one*. 2012; 7:e34124. [PubMed: 22509272]
- Komatsuzaki Y, Murakami G, Tsurugizawa T, Mukai H, Tanabe N, Mitsuhashi K, Kawata M, Kimoto T, Ooishi Y, Kawato S. Rapid spinogenesis of pyramidal neurons induced by activation of glucocorticoid receptors in adult male rat hippocampus. *Biochemical and biophysical research communications*. 2005; 335:1002–1007. [PubMed: 16111661]
- Kovalchuk Y, Hanse E, Kafitz KW, Konnerth A. Postsynaptic Induction of BDNF-Mediated Long-Term Potentiation. *Science*. 2002; 295:1729–1734. [PubMed: 11872844]
- Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008; 455:894–902. [PubMed: 18923511]
- Krusters HJ, Alfarez DN, Karst H, Parashkouhi K, van Gemert N, Joels M. Corticosterone shifts different forms of synaptic potentiation in opposite directions. *Hippocampus*. 2005; 15:697–703. [PubMed: 15959917]
- Lakshminarasimhan H, Chattarji S. Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. *PloS one*. 2012; 7:e30481. [PubMed: 22272355]
- Lau AG, Irier HA, Gu J, Tian D, Ku L, Liu G, Xia M, Fritsch B, Zheng JQ, Dingledine R, Xu B, Lu B, Feng Y. Distinct 3'UTRs differentially regulate activity-dependent translation of brain-derived neurotrophic factor (BDNF). *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:15945–15950. [PubMed: 20733072]
- Lavebratt C, Aberg E, Sjöholm LK, Forsell Y. Variations in FKBP5 and BDNF genes are suggestively associated with depression in a Swedish population-based cohort. *J Affect Disord*. 2010; 125:249–255. [PubMed: 20226536]
- Lee DA, Bedont JL, Pak T, Wang H, Song J, Miranda-Angulo A, Takiar V, Charubhumi V, Balordi F, Takebayashi H, Aja S, Ford E, Fishell G, Blackshaw S. Tanycytes of the hypothalamic median eminence form a diet-responsive neurogenic niche. *Nature neuroscience*. 2012; 15:700–702.
- Lee FS, Chao MV. Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc Natl Acad Sci U S A*. 2001; 98:3555–3560. [PubMed: 11248116]
- Lee FS, Rajagopal R, Chao MV. Distinctive features of Trk neurotrophin receptor transactivation by G protein-coupled receptors. *Cytokine Growth Factor Rev*. 2002a; 13:11–17. [PubMed: 11750876]
- Lee FS, Rajagopal R, Kim AH, Chang PC, Chao MV. Activation of Trk neurotrophin receptor signaling by pituitary adenylate cyclase-activating polypeptides. *J Biol Chem*. 2002b; 277:9096–9102. [PubMed: 11784714]
- Leranth C, Prange-Kiel J, Frick KM, Horvath TL. Low CA1 spine synapse density is further reduced by castration in male non-human primates. *Cerebral cortex*. 2004; 14:503–510. [PubMed: 15054066]
- Lewis LD, Cochrane GM. Psychosis in a child inhaling budesonide. *Lancet*. 1983; 2:634. [PubMed: 6136789]
- Li Y, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron*. 2008; 59:399–412. [PubMed: 18701066]
- Lin YC, Koleske AJ. Mechanisms of synapse and dendrite maintenance and their disruption in psychiatric and neurodegenerative disorders. *Annu Rev Neurosci*. 2010; 33:349–378. [PubMed: 20367247]

- Liston C, Gan WB. Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. *Proc Natl Acad Sci U S A*. 2011; 108:16074–16079. [PubMed: 21911374]
- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci*. 2006; 26:7870–7874. [PubMed: 16870732]
- Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. *Int J Psychophysiol*. 2006; 59:195–202. [PubMed: 16434116]
- Lowy MT, Gault L, Yamamoto BK. Adrenalectomy attenuates stress-induced elevations in extracellular glutamate concentrations in the hippocampus. *Journal of neurochemistry*. 1993; 61:1957–1960. [PubMed: 7901339]
- Lu B. BDNF and activity-dependent synaptic modulation. *Learn Mem*. 2003; 10:86–98. [PubMed: 12663747]
- Lu Y, Christian K. BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiol Learn Mem*. 2008; 89:312–323. [PubMed: 17942328]
- Lynch MA. Long-term potentiation and memory. *Physiol Rev*. 2004; 84:87–136. [PubMed: 14715912]
- Lyons WE, Mamounas LA, Ricaurte GA, Coppola V, Reid SW, Bora SH, Wihler C, Koliatsos VE, Tessarollo L. Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc Natl Acad Sci U S A*. 1999; 96:15239–15244. [PubMed: 10611369]
- MacLusky NJ, Hajszan T, Leranth C. Effects of dehydroepiandrosterone and flutamide on hippocampal CA1 spine synapse density in male and female rats: implications for the role of androgens in maintenance of hippocampal structure. *Endocrinology*. 2004; 145:4154–4161. [PubMed: 15178643]
- MacLusky NJ, Hajszan T, Prange-Kiel J, Leranth C. Androgen modulation of hippocampal synaptic plasticity. *Neuroscience*. 2006; 138:957–965. [PubMed: 16488544]
- Magarinos AM, Li CJ, Gal Toth J, Bath KG, Jing D, Lee FS, McEwen BS. Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. *Hippocampus*. 2011; 21:253–264. [PubMed: 20095008]
- Maggio N, Segal M. Unique regulation of long term potentiation in the rat ventral hippocampus. *Hippocampus*. 2007; 17:10–25. [PubMed: 17094146]
- Maggio N, Segal M. Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2009; 29:2857–2866. [PubMed: 19261881]
- Mandolesi G, Menna E, Harauzov A, von Bartheld CS, Caleo M, Maffei L. A role for retinal brain-derived neurotrophic factor in ocular dominance plasticity. *Curr Biol*. 2005; 15:2119–2124. [PubMed: 16332537]
- Markus EJ, Petit TL, LeBoutillier JC. Synaptic structural changes during development and aging. *Brain research*. 1987; 432:239–248. [PubMed: 3676839]
- Marmigere F, Givalois L, Rage F, Arancibia S, Tapia-Arancibia L. Rapid induction of BDNF expression in the hippocampus during immobilization stress challenge in adult rats. *Hippocampus*. 2003; 13:646–655. [PubMed: 12921353]
- Marmigere F, Rage F, Tapia-Arancibia L. Regulation of brain-derived neurotrophic factor transcripts by neuronal activation in rat hypothalamic neurons. *Journal of neuroscience research*. 2001; 66:377–389. [PubMed: 11746355]
- Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nature neuroscience*. 2007; 10:1089–1093.
- Mason BL, Thomas SA, Lightman SL, Pariente CM. Desipramine treatment has minimal effects on the brain accumulation of glucocorticoids in P-gp-deficient and wild-type mice. *Psychoneuroendocrinology*. 2011; 36:1351–1360. [PubMed: 21481537]
- Matijevic T, Knezevic J, Slavica M, Pavelic J. Rett syndrome: from the gene to the disease. *Eur Neurol*. 2009; 61:3–10. [PubMed: 18948693]

- Mayanagi T, Morita T, Hayashi K, Fukumoto K, Sobue K. Glucocorticoid receptor-mediated expression of caldesmon regulates cell migration via the reorganization of the actin cytoskeleton. *The Journal of biological chemistry*. 2008; 283:31183–31196. [PubMed: 18772142]
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998; 338:171–179. [PubMed: 9428819]
- McEwen BS. Stress and hippocampal plasticity. *Annu Rev Neurosci*. 1999; 22:105–122. [PubMed: 10202533]
- McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007; 87:873–904. [PubMed: 17615391]
- McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European journal of pharmacology*. 2008; 583:174–185. [PubMed: 18282566]
- McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences*. 1999; 896:30–47. [PubMed: 10681886]
- McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual review of neuroscience*. 2004; 27:1–28.
- McIsaac SA, Young AH. The role of hypothalamic pituitary-adrenal axis dysfunction in the etiology of depressive disorders. *Drugs Today (Barc)*. 2009; 45:127–133. [PubMed: 19343232]
- Meijer OC, de Lange EC, Breimer DD, de Boer AG, Workel JO, de Kloet ER. Penetration of dexamethasone into brain glucocorticoid targets is enhanced in *mdr1A* P-glycoprotein knockout mice. *Endocrinology*. 1998; 139:1789–1793. [PubMed: 9528963]
- Menke A, Arloth J, Putz B, Weber P, Klengel T, Mehta D, Gonik M, Rex-Haffner M, Rubel J, Uhr M, Lucae S, Deussing JM, Muller-Myhsok B, Holsboer F, Binder EB. Dexamethasone stimulated gene expression in peripheral blood is a sensitive marker for glucocorticoid receptor resistance in depressed patients. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2012; 37:1455–1464. [PubMed: 22237309]
- Meyboom RH, de Graaf-Breederveld N. Budesonide and psychic side effects. *Ann Intern Med*. 1988; 109:683. [PubMed: 3421583]
- Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. Glucocorticoid resistance and relevance to depression. *Advances in experimental medicine and biology*. 1999; 461:107–116. [PubMed: 10442170]
- Minichiello L. TrkB signalling pathways in LTP and learning. *Nat Rev Neurosci*. 2009; 10:850–860. [PubMed: 19927149]
- Mirescu C, Gould E. Stress and adult neurogenesis. *Hippocampus*. 2006; 16:233–238. [PubMed: 16411244]
- Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proc Natl Acad Sci U S A*. 2005; 102:9371–9376. [PubMed: 15967994]
- Miyashiro KY, Beckel-Mitchener A, Purk TP, Becker KG, Barret T, Liu L, Carbonetto S, Weiler IJ, Greenough WT, Eberwine J. RNA cargoes associating with FMRP reveal deficits in cellular functioning in *Fmr1* null mice. *Neuron*. 2003; 37:417–431. [PubMed: 12575950]
- Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101:10827–10832. [PubMed: 15249684]
- Monteggia LM, Luikart B, Barrot M, Theobald D, Malkovska I, Nef S, Parada LF, Nestler EJ. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol Psychiatry*. 2007; 61:187–197. [PubMed: 16697351]
- Morsink MC, Steenbergen PJ, Vos JB, Karst H, Joels M, De Kloet ER, Datson NA. Acute activation of hippocampal glucocorticoid receptors results in different waves of gene expression throughout time. *J Neuroendocrinol*. 2006; 18:239–252. [PubMed: 16503919]
- Mukai H, Hatanaka Y, Mitsuhashi K, Hojo Y, Komatsuzaki Y, Sato R, Murakami G, Kimoto T, Kawato S. Automated analysis of spines from confocal laser microscopy images: application to

the discrimination of androgen and estrogen effects on spinogenesis. *Cerebral cortex*. 2011; 21:2704–2711. [PubMed: 21527787]

- Naert G, Ixart G, Tapia-Arancibia L, Givalois L. Continuous i.c.v. infusion of brain-derived neurotrophic factor modifies hypothalamic-pituitary-adrenal axis activity, locomotor activity and body temperature rhythms in adult male rats. *Neuroscience*. 2006; 139:779–789. [PubMed: 16457953]
- Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*. 1984; 226:1342–1344. [PubMed: 6334362]
- Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron*. 2002; 34:13–25. [PubMed: 11931738]
- Nicholas A, Munhoz CD, Ferguson D, Campbell L, Sapolsky R. Enhancing cognition after stress with gene therapy. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2006; 26:11637–11643. [PubMed: 17093085]
- Ninan I, Bath KG, Dagar K, Perez-Castro R, Plummer MR, Lee FS, Chao MV. The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus. *J Neurosci*. 2010; 30:8866–8870. [PubMed: 20592208]
- Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? *J Psychopharmacol*. 2006; 20:79–84. [PubMed: 16785275]
- Pariante CM. Risk factors for development of depression and psychosis. Glucocorticoid receptors and pituitary implications for treatment with antidepressant and glucocorticoids. *Ann N Y Acad Sci*. 2009; 1179:144–152. [PubMed: 19906237]
- Pariante CM, Kim RB, Makoff A, Kerwin RW. Antidepressant fluoxetine enhances glucocorticoid receptor function in vitro by modulating membrane steroid transporters. *Br J Pharmacol*. 2003; 139:1111–1118. [PubMed: 12871829]
- Pariante CM, Makoff A, Lovestone S, Feroli S, Heyden A, Miller AH, Kerwin RW. Antidepressants enhance glucocorticoid receptor function in vitro by modulating the membrane steroid transporters. *Br J Pharmacol*. 2001; 134:1335–1343. [PubMed: 11704655]
- Patil CG, Lad SP, Katznelson L, Laws ER Jr. Brain atrophy and cognitive deficits in Cushing's disease. *Neurosurg Focus*. 2007; 23:E11. [PubMed: 17961025]
- Pavlaki, A.; Magiakou, MA.; Chrousos, GP. Chapter 14 - Glucocorticoid Therapy and Adrenal Suppression. 2011. www.endotext.org
- Pearce BD, Biron CA, Miller AH. Neuroendocrine-immune interactions during viral infections. *Adv Virus Res*. 2001; 56:469–513. [PubMed: 11450310]
- Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2001; 21:6706–6717. [PubMed: 11517260]
- Pepin MC, Pothier F, Barden N. Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression. *Mol Pharmacol*. 1992a; 42:991–995. [PubMed: 1480137]
- Pepin MC, Pothier F, Barden N. Impaired type II glucocorticoid-receptor function in mice bearing antisense RNA transgene. *Nature*. 1992b; 355:725–728. [PubMed: 1741058]
- Phelan MC. Beclomethasone mania. *Br J Psychiatry*. 1989; 155:871–872. [PubMed: 2620226]
- Piazza PV, Le Moal. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol*. 1996; 36:359–378. [PubMed: 8725394]
- Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2001; 2:24–32. [PubMed: 11253356]
- Prickaerts J, van den Hove DL, Fierens FL, Kia HK, Lenaerts I, Steckler T. Chronic corticosterone manipulations in mice affect brain cell proliferation rates, but only partly affect BDNF protein levels. *Neuroscience letters*. 2006; 396:12–16. [PubMed: 16326007]
- Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics*. 2007; 90:397–406. [PubMed: 17629449]

- Purpura DP. Dendritic spine “dysgenesis” and mental retardation. *Science*. 1974; 186:1126–1128. [PubMed: 4469701]
- Qian Z, Gilbert M, Kandel ER. Temporal and spatial regulation of the expression of BAD2, a MAP kinase phosphatase, during seizure, kindling, and long-term potentiation. *Learning & memory*. 1994; 1:180–188. [PubMed: 10467595]
- Rachidi M, Lopes C. Mental retardation and associated neurological dysfunctions in Down syndrome: a consequence of dysregulation in critical chromosome 21 genes and associated molecular pathways. *Eur J Paediatr Neurol*. 2008; 12:168–182. [PubMed: 17933568]
- Rage F, Givalois L, Marmigere F, Tapia-Arancibia L, Arancibia S. Immobilization stress rapidly modulates BDNF mRNA expression in the hypothalamus of adult male rats. *Neuroscience*. 2002; 112:309–318. [PubMed: 12044449]
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006; 27:24–31. [PubMed: 16316783]
- Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *The American journal of psychiatry*. 2003; 160:1554–1565. [PubMed: 12944327]
- Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science*. 1986; 232:232–235. [PubMed: 3952506]
- Rantamaki T, Vesa L, Antila H, Di Lieto A, Tammela P, Schmitt A, Lesch KP, Rios M, Castren E. Antidepressant drugs transactivate TrkB neurotrophin receptors in the adult rodent brain independently of BDNF and monoamine transporter blockade. *PloS one*. 2011; 6:e20567. [PubMed: 21666748]
- Rattiner LM, Davis M, Ressler KJ. Differential regulation of brain-derived neurotrophic factor transcripts during the consolidation of fear learning. *Learn Mem*. 2004; 11:727–731. [PubMed: 15537738]
- Reul JM, de Kloet ER. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology*. 1985; 117:2505–2511. [PubMed: 2998738]
- Ridder S, Chourbaji S, Hellweg R, Urani A, Zacher C, Schmid W, Zink M, Hortnagl H, Flor H, Henn FA, Schutz G, Gass P. Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2005; 25:6243–6250. [PubMed: 15987954]
- Riise R, Brox JI, Sorensen R, Skjeldal OH. Spinal deformity and disability in patients with Rett syndrome. *Dev Med Child Neurol*. 2011; 53:653–657. [PubMed: 21501153]
- Roozendaal B, Okuda S, Van der Zee EA, McGaugh JL. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103:6741–6746. [PubMed: 16611726]
- Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, Fabbri ME, Tessarollo L, Maffei L, Berardi N, Caleo M. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *The European journal of neuroscience*. 2006; 24:1850–1856. [PubMed: 17040481]
- Rubenstein NM, Guan Y, Woo PL, Firestone GL. Glucocorticoid down-regulation of RhoA is required for the steroid-induced organization of the junctional complex and tight junction formation in rat mammary epithelial tumor cells. *The Journal of biological chemistry*. 2003; 278:10353–10360. [PubMed: 12525486]
- Rutherford LC, Nelson SB, Turrigiano GG. BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. *Neuron*. 1998; 21:521–530. [PubMed: 9768839]
- Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castren E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J Neurosci*. 2003; 23:349–357. [PubMed: 12514234]

- Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2005; 25:1089–1094. [PubMed: 15689544]
- Saleh N, Moutereau S, Durr A, Krystkowiak P, Azulay JP, Tranchant C, Broussolle E, Morin F, Bachoud-Levi AC, Maison P. Neuroendocrine disturbances in Huntington's disease. *PloS one*. 2009; 4:e4962. [PubMed: 19319184]
- Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003; 301:805–809. [PubMed: 12907793]
- Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of general psychiatry*. 2000a; 57:925–935. [PubMed: 11015810]
- Sapolsky RM. Stress hormones: good and bad. *Neurobiol Dis*. 2000b; 7:540–542. [PubMed: 11042072]
- Saporito MS, Brown ER, Hartpence KC, Wilcox HM, Robbins E, Vaught JL, Carswell S. Systemic dexamethasone administration increases septal Trk autophosphorylation in adult rats via an induction of nerve growth factor. *Mol Pharmacol*. 1994; 45:395–401. [PubMed: 8145726]
- Schaaf MJ, De Kloet ER, Vreugdenhil E. Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation. *Stress*. 2000; 3:201–208. [PubMed: 10938581]
- Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Exp Neurol*. 2005; 192:348–356. [PubMed: 15755552]
- Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO. A corticosteroid/dopamine hypothesis for psychotic depression and related states. *J Psychiatr Res*. 1985; 19:57–64. [PubMed: 2859366]
- Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav Pharmacol*. 2007; 18:391–418. [PubMed: 17762509]
- Schmidt MV, Paez-Pereda M, Holsboer F, Hausch F. The Prospect of FKBP51 as a Drug Target. *ChemMedChem*. 2012; 7:1351–1359. [PubMed: 22581765]
- Schmidt MV, Sterlemann V, Wagner K, Niederleitner B, Ganea K, Liebl C, Deussing JM, Berger S, Schutz G, Holsboer F, Muller MB. Postnatal glucocorticoid excess due to pituitary glucocorticoid receptor deficiency: differential short- and long-term consequences. *Endocrinology*. 2009; 150:2709–2716. [PubMed: 19213843]
- Schmidt P, Holsboer F, Spengler D. Beta(2)-adrenergic receptors potentiate glucocorticoid receptor transactivation via G protein beta gamma-subunits and the phosphoinositide 3-kinase pathway. *Molecular endocrinology*. 2001; 15:553–564. [PubMed: 11266507]
- Schulte-Herbruggen O, Hellweg R, Chourbaji S, Ridder S, Brandwein C, Gass P, Hortnagl H. Differential regulation of neurotrophins and serotonergic function in mice with genetically reduced glucocorticoid receptor expression. *Exp Neurol*. 2007; 204:307–316. [PubMed: 17208231]
- Segal M. Dendritic spines, synaptic plasticity and neuronal survival: activity shapes dendritic spines to enhance neuronal viability. *The European journal of neuroscience*. 2010; 31:2178–2184. [PubMed: 20550565]
- Selye, H. *The stress of life*. McGrawHill; New York: 1956.
- Selye, H. *Hormones and Resistance*. Springer-Verlag; BerlinHeidelberg-New York: 1971.
- Shi B, Rabin SJ, Brandoli C, Mocchetti I. Dexamethasone induces hypertrophy of developing medial septum cholinergic neurons: potential role of nerve growth factor. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 1998; 18:9326–9334. [PubMed: 9801371]
- Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J Neurosci*. 2002; 22:3251–3261. [PubMed: 11943826]

- Smith MA, Makino S, Kvetnansky R, Post RM. Effects of stress on neurotrophic factor expression in the rat brain. *Annals of the New York Academy of Sciences*. 1995a; 771:234–239. [PubMed: 8597402]
- Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 1995b; 15:1768–1777. [PubMed: 7891134]
- Snider WD. Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. *Cell*. 1994; 77:627–638. [PubMed: 8205613]
- Snider WD, Lichtman JW. Are neurotrophins synaptotrophins? *Mol Cell Neurosci*. 1996; 7:433–442. [PubMed: 8875427]
- Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*. 2011; 476:458–461. [PubMed: 21814201]
- Surget A, Tanti A, Leonardo ED, Laugeray A, Rainer Q, Touma C, Palme R, Griebel G, Ibarguen-Vargas Y, Hen R, Belzung C. Antidepressants recruit new neurons to improve stress response regulation. *Molecular psychiatry*. 2011; 16:1177–1188. [PubMed: 21537331]
- Swanwick GR, Kirby M, Bruce I, Buggy F, Coen RF, Coakley D, Lawlor BA. Hypothalamic-pituitary-adrenal axis dysfunction in Alzheimer's disease: lack of association between longitudinal and cross-sectional findings. *Am J Psychiatry*. 1998; 155:286–289. [PubMed: 9464214]
- Tahera Y, Meltser I, Johansson P, Salman H, Canlon B. Sound conditioning protects hearing by activating the hypothalamic-pituitary-adrenal axis. *Neurobiol Dis*. 2007; 25:189–197. [PubMed: 17056263]
- Taliaz D, Loya A, Gersner R, Haramati S, Chen A, Zangen A. Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2011; 31:4475–4483. [PubMed: 21430148]
- Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Molecular psychiatry*. 2010; 15:80–92. [PubMed: 19621014]
- Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Physiology of BDNF: focus on hypothalamic function. *Front Neuroendocrinol*. 2004; 25:77–107. [PubMed: 15571756]
- Tasker JG, Di S, Malcher-Lopes R. Rapid central corticosteroid effects: evidence for membrane glucocorticoid receptors in the brain. *Integr Comp Biol*. 2005; 45:665–671. [PubMed: 21676815]
- Tasker JG, Di S, Malcher-Lopes R. Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology*. 2006; 147:5549–5556. [PubMed: 16946006]
- Tata DA, Marciano VA, Anderson BJ. Synapse loss from chronically elevated glucocorticoids: relationship to neuropil volume and cell number in hippocampal area CA3. *J Comp Neurol*. 2006; 498:363–374. [PubMed: 16871536]
- Timmusk T, Belluardo N, Persson H, Metsis M. Developmental regulation of brain-derived neurotrophic factor messenger RNAs transcribed from different promoters in the rat brain. *Neuroscience*. 1994; 60:287–291. [PubMed: 8072683]
- Touma C, Gassen NC, Herrmann L, Cheung-Flynn J, Bull DR, Ionescu IA, Heinzmann JM, Knapman A, Siebertz A, Depping AM, Hartmann J, Hausch F, Schmidt MV, Holsboer F, Ising M, Cox MB, Schmidt U, Rein T. FK506 binding protein 5 shapes stress responsiveness: modulation of neuroendocrine reactivity and coping behavior. *Biological psychiatry*. 2011; 70:928–936. [PubMed: 21907973]
- Troca-Marin JA, Alves-Sampaio A, Montesinos ML. Deregulated mTOR-mediated translation in intellectual disability. *Progress in neurobiology*. 2012; 96:268–282. [PubMed: 22285767]
- Tronche F, Kellendonk C, Kretz O, Gass P, Anlag K, Orban PC, Bock R, Klein R, Schutz G. Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety. *Nature genetics*. 1999; 23:99–103. [PubMed: 10471508]
- Tsigos C, Chrousos GP. Differential diagnosis and management of Cushing's syndrome. *Annu Rev Med*. 1996; 47:443–461. [PubMed: 8712794]

- Turrigiano G. Homeostatic signaling: the positive side of negative feedback. *Curr Opin Neurobiol.* 2007; 17:318–324. [PubMed: 17451937]
- Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature.* 1998; 391:892–896. [PubMed: 9495341]
- Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. *Neuroscience research.* 1997; 28:103–110. [PubMed: 9220467]
- Van Eekelen JA, Jiang W, De Kloet ER, Bohn MC. Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the rat hippocampus. *Journal of neuroscience research.* 1988; 21:88–94. [PubMed: 2851057]
- van Rossum EF, Lamberts SW. Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Prog Horm Res.* 2004; 59:333–357. [PubMed: 14749509]
- Venero C, Borrell J. Rapid glucocorticoid effects on excitatory amino acid levels in the hippocampus: a microdialysis study in freely moving rats. *The European journal of neuroscience.* 1999; 11:2465–2473. [PubMed: 10383636]
- Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *The Journal of neuroscience: the official journal of the Society for Neuroscience.* 2002; 22:6810–6818. [PubMed: 12151561]
- Walsh MK, Lichtman JW. In vivo time-lapse imaging of synaptic takeover associated with naturally occurring synapse elimination. *Neuron.* 2003; 37:67–73. [PubMed: 12526773]
- Wang CC, Wang SJ. Modulation of presynaptic glucocorticoid receptors on glutamate release from rat hippocampal nerve terminals. *Synapse.* 2009; 63:745–751. [PubMed: 19484722]
- Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. *The Journal of neuroscience: the official journal of the Society for Neuroscience.* 2008; 28:1374–1384. [PubMed: 18256257]
- Wang Z, Chen W, Kono E, Dang T, Garabedian MJ. Modulation of glucocorticoid receptor phosphorylation and transcriptional activity by a C-terminal-associated protein phosphatase. *Mol Endocrinol.* 2007; 21:625–634. [PubMed: 17185395]
- Wang Z, Frederick J, Garabedian MJ. Deciphering the phosphorylation “code” of the glucocorticoid receptor in vivo. *J Biol Chem.* 2002; 277:26573–26580. [PubMed: 12000743]
- Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus.* 2006; 16:239–249. [PubMed: 16425236]
- Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain research.* 1992; 588:341–345. [PubMed: 1393587]
- Webster MJ, Knable MB, O’Grady J, Orthmann J, Weickert CS. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol Psychiatry.* 2002; 7:985–994. 924. [PubMed: 12399952]
- Wellman CL. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol.* 2001; 49:245–253. [PubMed: 11745662]
- Wierenga CJ, Ibata K, Turrigiano GG. Postsynaptic expression of homeostatic plasticity at neocortical synapses. *J Neurosci.* 2005; 25:2895–2905. [PubMed: 15772349]
- Wochnik GM, Ruegg J, Abel GA, Schmidt U, Holsboer F, Rein T. FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *The Journal of biological chemistry.* 2005; 280:4609–4616. [PubMed: 15591061]
- Wolkowitz OM, Reus VI, Canick J, Levin B, Lupien S. Glucocorticoid medication, memory and steroid psychosis in medical illness. *Annals of the New York Academy of Sciences.* 1997; 823:81–96. [PubMed: 9292035]
- Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, Tennant K, Jones T, Zuo Y. Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature.* 2009; 462:915–919. [PubMed: 19946267]
- Yang G, Pan F, Gan WB. Stably maintained dendritic spines are associated with lifelong memories. *Nature.* 2009; 462:920–924. [PubMed: 19946265]

- Yankova M, Hart SA, Woolley CS. Estrogen increases synaptic connectivity between single presynaptic inputs and multiple postsynaptic CA1 pyramidal cells: a serial electron-microscopic study. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:3525–3530. [PubMed: 11248111]
- Yehuda R. Post-traumatic stress disorder. *The New England journal of medicine*. 2002; 346:108–114. [PubMed: 11784878]
- Yehuda R, Seckl J. Minireview: Stress-related psychiatric disorders with low cortisol levels: a metabolic hypothesis. *Endocrinology*. 2011; 152:4496–4503. [PubMed: 21971152]
- Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O’Rahilly S, Farooqi IS. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci*. 2004; 7:1187–1189. [PubMed: 15494731]
- Yu H, Wang DD, Wang Y, Liu T, Lee FS, Chen ZY. Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2012; 32:4092–4101. [PubMed: 22442074]
- Yuste R, Bonhoeffer T. Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annual review of neuroscience*. 2001; 24:1071–1089.
- Zeiger MA, Nieman LK, Cutler GB, Chrousos GP, Doppman JL, Travis WD, Norton JA. Primary bilateral adrenocortical causes of Cushing’s syndrome. *Surgery*. 1991; 110:1106–1115. [PubMed: 1745978]
- Zhang L, Li H, Su TP, Barker JL, Maric D, Fullerton CS, Webster MJ, Hough CJ, Li XX, Ursano R. p11 is up-regulated in the forebrain of stressed rats by glucocorticoid acting via two specific glucocorticoid response elements in the p11 promoter. *Neuroscience*. 2008a; 153:1126–1134. [PubMed: 18440154]
- Zhang X, Clark AF, Yorio T. FK506-binding protein 51 regulates nuclear transport of the glucocorticoid receptor beta and glucocorticoid responsiveness. *Invest Ophthalmol Vis Sci*. 2008b; 49:1037–1047. [PubMed: 18326728]
- Zuo Y, Lin A, Chang P, Gan WB. Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron*. 2005; 46:181–189. [PubMed: 15848798]

Synopsis

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- VIII.** Summary and future directions

- Glucocorticoid oscillations enhance dendritic spine plasticity.
- Disruption of glucocorticoid rhythms precipitates neurological disorders.
- Normalization of glucocorticoid rhythms is possible with antidepressants.
- BDNF mediates the effects of antidepressants.
- Are BDNF and glucocorticoid activities calibrated?

Figure 1. Glucocorticoids enhance dendritic spine remodeling

(A) Dendritic spines are continuously remodeling over time. The formation and elimination of dendritic spines are sensitive to new behavioral experience and environmental change. This may help create a synaptic code relevant for behavioral adaptation to the environment. (B) Glucocorticoids are secreted under stress and in synchrony with circadian rhythms. A single application of glucocorticoids enhances dendritic spine formation and elimination within hours and in a dose-dependent fashion. The extent of formation and elimination is balanced to mitigate net changes in spine number. Administration of low dose dexamethasone diminishes the capacity to remodel dendritic spine without altering spine density. Prolonged administration of glucocorticoids diminishes the formation but enhances the elimination of dendritic spines resulting in widespread loss of dendritic spines.

Figure 2. The limbic-hypothalamic-pituitary-adrenal (LHPA) axis

Maintenance of the HPA axis rhythmic activity involves homeostatic equilibrium between the activation (Plain arrows) and inhibitory feedback (Dashed lines). The paraventricular nucleus of the hypothalamus (PVN) integrates input information conveyed by limbic brain structures. The main driving force of the HPA axis is corticotrophin-releasing hormone (CRH) acting in synergy with arginine-vasopressin peptide (AVP), to stimulate the release in the blood of pituitary pro-opiomelanocortin-derived peptides (ACTH). Subsequently, ACTH stimulates the secretion of adrenal corticosteroids in the circulatory system. The pituitary and PVN contain the primary inhibitory feedback sites that involve the glucocorticoid receptor (GR). Secondary GR sites can be recruited depending on the nature of the stressor and the afferent structure involved; the hippocampus (Hippo) if cognitive, the amygdala (Amyg) if affective, the suprachiasmatic nucleus (SCN) if rated by circadian rhythms or brain stem if arousing. Under systemic stress (blood loss, pain, hypoglycemia), brainstem catecholaminergic afferents from the nucleus of the solitary tract (NTS) and adrenergic afferences from the ventral medulla activate PVN neurons and glucocorticoid secretion. Serotonergic fibers from the dorsal raphe nucleus (DR) project to several limbic structures like the prefrontal cortex (PFC), Hippocampus and bed nucleus of the stria terminalis (BNST) to regulate PVN activity and glucocorticoid secretion. SCN pacemaker neurons project to the PVN to convey directly circadian excitatory and inhibitory activities. GABAergic neurons in the hypothalamus (peri-PVN) and the BNST govern inhibitory control of the PVN. Excitatory inputs from the hippocampus (subiculum) and PFC stimulate GABA inhibitory tone via the BNST or peri-PVN to suppress PVN activity. Signals from psychogenic stressors utilize multisynaptic pathways from sensory organs, the locus coeruleus (LC) and brainstem nuclei through limbic structures, including the PFC, BNST, and amygdala.

Figure 3. Glucocorticoids are critical regulators of dendritic spine remodeling

Glucocorticoids enhance the formation and elimination of dendritic spines in the living cortex. Hypercortisolism featured in Cushing's disease, major depression and bipolar disorder, diminishes dendritic spine formation but increases spine elimination. Consequently, chronic exposure to high glucocorticoid levels shifts the balance of formation and elimination of spines to widespread loss. Hypercortisolism is often associated with reduced glucocorticoid signaling or GR expression, which is also referred to as glucocorticoid resistance or insensitivity. In contrast, hypocortisolism, as observed in atypical depression and post-traumatic stress disorders (PTSD), dramatically diminishes dendritic spine formation and elimination. Deficits in circulating glucocorticoids diminish GR signaling and spine remodeling capacity to minimal level without impairing spine density.

Figure 4. Model describing how BDNF and glucocorticoid activities are calibrated

Scaling BDNF levels to glucocorticoid activities may determine a wide range of effects upon synaptic structure, strength and function. Our model represents a simplistic attempt to define how BDNF and glucocorticoid activities integrate at least in the cortex. On the one hand, more BDNF is synthesized at glucocorticoid circadian peaks than troughs when dendritic spine remodeling is maximal and BDNF signaling optimal for their maturation and maintenance. Spine size, shape and number are determined by input activity, BDNF and glucocorticoids, and correlate with behavioral performance. On the other hand, less BDNF is produced when glucocorticoid peaks are sustained like upon chronic stress, impinging upon the maintenance of dendritic spines and cognitive performances. Spine plasticity depends on the repertoire of glucocorticoid-sensitive genes, which are also regulated by BDNF (our unpublished microarray and RNA sequencing data). Long-term antidepressant treatments elevate BDNF levels and normalize glucocorticoid levels to baseline, which are necessary to restore dendritic spine remodeling capacity and behavioral performance.

Figure 5. Glucocorticoids can use the BDNF receptor, TrkB as a signaling platform

Acute treatment with high dose exogenous glucocorticoids can activate the Trk neurotrophin receptor family of proteins in a variety of experimental systems like PC12 cells, primary neurons, cortical and hippocampal slice explants and after *in vivo* administration. For instance, phosphorylation of TrkB, a surrogate activation mark (Y816-P) can be detected in a large panel of tissues biopsied from postnatal day 18 rats administered with intraperitoneal dexamethasone (10 mg/kg) for 6 hours compared to saline treated controls. This effect was observed in both males and females and correlated with increases phosphorylation of the glucocorticoid receptor, a surrogate activation mark (S211-P). Downregulation of GR protein level is typically observed upon stimulation with cognate ligands like dexamethasone. Phosphorylation of Trk receptors upon glucocorticoid treatment activates prototypical neurotrophic signaling cascades (MAPK, PI3K/Akt, PLCgamma) and promotes trophic effects *in vitro* in absence of neurotrophins. Indeed, a single acute administration of dexamethasone did not alter the expression or secretion of the neurotrophins NGF, BDNF and NT3 at least in cortical and hippocampal tissue as well as primary neurons, suggesting that glucocorticoids can elicit Trk activation in absence of neurotrophins. Compared to the robust and rapid signaling effects of BDNF, the effects of glucocorticoids upon Trk receptor activity are delayed, weaker, but last for several hours. Glucocorticoids activate TrkB, perhaps, to facilitate cellular adaptation to high dose glucocorticoids.

Figure 6. BDNF and glucocorticoid activities calibrate *mkp-1* expression and structural plasticity

(A) Expression of MKP-1 is low, but is highly inducible by glucocorticoids and BDNF. Expression of MKP-1 is robustly amplified upon BDNF (50 ng/ml) and glucocorticoid (1 μ M) co-stimulation for the indicated time whereas GILZ, a prototypical glucocorticoid-sensitive gene is not. Activity-dependent induction of *mkp-1* was observed in a variety of experimental systems like PC12 cells, primary neurons and *in vivo* following sensory stimuli. (B) MKP-1 levels impact morphological plasticity. Loss of *mkp-1* (KO) prevented activity-dependent branching of axons compared to wildtype (WT) neurons. Transient induction of MKP-1 using a promoter-inducible system mirrored the effects of neuronal activity upon axon branching, whereas prolonged expression prevented axon growth. Because too much or too little MKP-1 has deleterious effects on morphological plasticity, titration of MKP-1 levels with neuronal activity is critical. (C) Once expressed, MKP-1 protein is unstable due to rapid turnover. Degradation of MKP-1 protein is sensitive to the balance of phosphorylation and ubiquitination events. Abnormal expression of MKP-1 is a hallmark of several disorders, such as stress-related disorders and major depression.

Table 1
Disruption of glucocorticoid rhythms in health and diseases

Alterations of glucocorticoid secretion are frequently observed in human disorders (Koenig et al., 2002, Yehuda, 2002, Lovallo, 2006, Bao et al., 2008, Barnes and Adcock, 2009, Saleh et al., 2009, Holsboer and Ising, 2010, Pavlaki et al., 2011, Yehuda and Seckl, 2011). Cushing disease provides a good example of causal relationship (Zeiger et al., 1991, Tsigos and Chrousos, 1996). Glucocorticoid therapies also cause a wide range of side effects that are reminiscent of the disorders featuring disrupted glucocorticoid secretion (Lewis and Cochrane, 1983, Meyboom and de Graaf-Breederveld, 1988, Phelan, 1989). Therefore, the rhythmic secretion of glucocorticoids with peaks and troughs is critical both in pathogenesis as well as in treatment modalities.

Diseases featuring disrupted glucocorticoid rhythms	Side effects of glucocorticoid therapy	Medication interfering with glucocorticoid rhythms
<p>Heightened hypercorticotid oscillations:</p> <ul style="list-style-type: none"> • Major depression • Suicide • Cushing disease • Alzheimer disease • Huntington disease • Cognitive decline • Alcoholism • Schizophrenia 	<p>Rapid onset:</p> <ul style="list-style-type: none"> • Emotional lability • Increased appetite, weight gain, • Insomnia 	<p>Increasing glucocorticoid blood levels:</p> <ul style="list-style-type: none"> • Oral contraceptives • Cyclosporine • Anesthetics • Erythromycin • Cyclophosphamide
<p>Flattened hypocorticotid oscillations:</p> <ul style="list-style-type: none"> • Post-traumatic stress disorder • Melancholic depression • Bipolar depression • Chronic fatigue • Addison's disease • Antisocial aggressiveness • Addiction 	<p>Delayed due to cumulative dosage:</p> <ul style="list-style-type: none"> • Glucocorticoid resistance • Psychosis • Cushing syndrome • Growth retardation • Atherosclerosis • Osteoporosis, osteonecrosis • Cataract, glaucoma • Fatty liver, metabolic syndrome • Insulin resistance • Pancreatitis • Skin atrophy • Myopathy • Increased susceptibility to infections • Impaired wound healing 	<p>Decreasing glucocorticoid blood levels:</p> <ul style="list-style-type: none"> • Antidepressants • Insulin • Aspirin • Hypoglycemic agents • Antacids • Ephedrine • Phenytoin

Table 2
Glucocorticoid resistance and underlying mechanisms

Glucocorticoid resistance is characterized by reduced tissue sensitivity of the glucocorticoid receptor. Glucocorticoids are the mainstay of treatment for numerous inflammatory and immune diseases, and glucocorticoid insensitivity whether innate or acquired complicates clinical applications and management. Hyperactivation of the HPA axis compensates for the reduced sensitivity of peripheral tissues to glucocorticoids at the expense of the central nervous system. Hypercortisolism and hypersecretion of CRH and ACTH can precipitate cognitive impairments, mood disorders and psychiatric symptoms like psychosis. Several genes involved in glucocorticoid signaling and pleiotropic responses are listed.

Clinical evidences	Proposed mechanisms	Genes involved
Reduced sensitivity to glucocorticoid therapies Increased serum levels of glucocorticoids Side effects of hypercortisolism: <ul style="list-style-type: none"> Cognitive impairment Sleep disturbance Eating behavior Psychosis Anxiety Depression Cushingoid symptoms 	Familial glucocorticoid resistance: <ul style="list-style-type: none"> Polymorphisms 	Glucocorticoid availability: <ul style="list-style-type: none"> P-glycoprotein 11βHSD1
Decreased glucocorticoid receptor signaling: <ul style="list-style-type: none"> Genomic Epigenetic 	Glucocorticoid availability: <ul style="list-style-type: none"> Blood brain barrier Glucocorticoid receptor expression: <ul style="list-style-type: none"> Decreased GR in HPA structures Increased GRβ isoform Glucocorticoid receptor modifications: <ul style="list-style-type: none"> Phosphorylation Nitrosylation Ubiquitination Conditioning factors: <ul style="list-style-type: none"> Cytokines, growth factors Defective histone acetylation 	Glucocorticoid-mediated transcription: <ul style="list-style-type: none"> Hdac-2 Bag-1 Glucocorticoid signaling <ul style="list-style-type: none"> Fkbp-51 Mkp-1 Limk-1 Synaptic transmission and plasticity: <ul style="list-style-type: none"> Crh 5HT2a p11 Bdnf