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Glucocorticoid mechanisms of functional connectivity changes in stress-related neuropsychiatric disorders

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ABSTRACT

Stress—especially chronic, uncontrollable stress—is an important risk factor for many neuropsychiatric disorders. The underlying mechanisms are complex and multifactorial, but they involve correlated changes in structural and functional measures of neuronal connectivity within cortical microcircuits and across neuroanatomically distributed brain networks. Here, we review evidence from animal models and human neuroimaging studies implicating stress-associated changes in functional connectivity in the pathogenesis of PTSD, depression, and other neuropsychiatric conditions. Changes in fMRI measures of corticocortical connectivity across distributed networks may be caused by specific structural alterations that have been observed in the prefrontal cortex, hippocampus, and other vulnerable brain regions. These effects are mediated in part by glucocorticoids, which are released from the adrenal gland in response to a stressor and also oscillate in synchrony with diurnal rhythms. Recent work indicates that circadian glucocorticoid oscillations act to balance synapse formation and pruning after learning and during development, and chronic stress disrupts this balance. We conclude by considering how disrupted glucocorticoid oscillations may contribute to the pathophysiology of depression and PTSD in vulnerable individuals, and how circadian rhythm disturbances may affect non-psychiatric populations, including frequent travelers, shift workers, and patients undergoing treatment for autoimmune disorders.

Stress is an important risk factor for many neuropsychiatric disorders. However, most individuals who are exposed to a stressor do not go on to develop a clinical disorder. Mechanisms of resilience and vulnerability to the harmful consequences of chronic stress have received increasing attention and are thought to involve a complex interaction between multiple genetic, environmental, and psychosocial factors (Feder et al., 2009; McEwen, 2012; Zhu et al., 2014). In vulnerable individuals, these factors converge to trigger pathophysiological processes that may lead to psychiatric symptoms. Increasingly, neuroimaging studies indicate that changes in functional connectivity across neuroanatomically distributed brain networks are an important element of that pathophysiology. Abnormal patterns of corticocortical connectivity are a common feature of depression, anxiety disorders, post-traumatic stress disorder, and other stress-related neuropsychiatric conditions (Anand et al., 2005; Etkin and Wager, 2007; Greicius et al., 2007; Milad et al., 2007; Zhao et al., 2007; Liberzon and Sripada, 2008; Monk et al., 2008; Broyd et al., 2009). Functional connectivity changes, in turn, have been linked to specific symptoms and to recovery during treatment (Etkin et al., 2009; Fox et al., 2012; Liston et al., 2014; Salomons et al., 2014)

How chronic stress leads to pathological patterns of functional connectivity in vulnerable individuals is not fully understood. The underlying mechanisms are complex and multifactorial, involving dynamic changes in glutamatergic signaling and synaptic strength; direct effects on neurotrophins and cell adhesion molecules; and interactions with noradrenergic, dopaminergic, and serotonergic neuromodulators (Sandi, 2004; Duman and Monteggia, 2006; Arnsten, 2009; Popoli et al., 2012). In clinical populations, in particular, it is likely that no single mechanism can account for stress-related changes in functional connectivity, which emerge from complex interactions with genetic and neurodevelopmental factors that influence risk and resilience (Duman et al., 1997; de Kloet et al., 2005a; Lupien et al., 2009).

Here, we review recent advances in our understanding of just one of these mechanisms: how glucocorticoid stress hormones

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affect dendritic remodeling and postsynaptic dendritic spine plasticity in susceptible brain regions, including the hippocampus, prefrontal cortex, and amygdala (Leuner and Shors, 2013). Glucocorticoids are released by the hypothalamic-pituitary-adrenal (HPA) axis in response to a stressor and serve to mobilize resources to maintain homeostasis (Woolley et al., 1990; Watanabe et al., 1992; Magariños and McEwen, 1995a, 1995b). Importantly, glucocorticoid activity also oscillates in synchrony with circadian and ultradian rhythms, independent of external stressors (de Kloet, 1991; Droste et al., 2008). Recent work indicates that chronic stress disrupts these glucocorticoid rhythms, which play critical roles in regulating synaptic remodeling after learning and during development (Liston et al., 2013). This review will focus on understanding how disrupted glucocorticoid oscillations and synergistic interactions with associated signaling pathways may contribute to the development of stress-related psychiatric disorders in vulnerable individuals.

1. Stress effects on structural and functional connectivity

Disruptions in connectivity across distributed neural networks are common features of stress-related neuropsychiatric conditions, and understanding how they arise may yield new insights into mechanisms of resilience and vulnerability. Stress has potent effects on apical dendrites and postsynaptic dendritic spines in multiple brain regions. In the hippocampus, which plays an important negative feedback role in HPA axis regulation, chronic stress causes atrophy of apical dendrites in CA1 and CA3 pyramidal cells and a decrease in the density of postsynaptic dendritic spines (Jacobson and Sapolsky, 1991; Magariños and McEwen, 1995a, 1995b; Magariños et al., 1996, 1997; Sousa et al., 2000; Vyas et al., 2002). Chronic stress also disrupts neurogenesis in the dentate gyrus (Gould et al., 1997; Shors, 2006). Other studies have identified associated behavioral deficits in spatial learning and memory tasks such as the radial arm and Y mazes (Luine et al., 1994; Conrad et al., 1996; Liston et al., 2006). In contrast, in the amygdala, which upregulates HPA axis activity, chronic stress causes hypertrophy of dendritic arbors, accompanied by a facilitation of aversive learning and heightened fear and anxiety (Vyas et al., 2002, 2003).

Importantly, analogous effects have been observed in parallel rodent and human neuroimaging studies of the prefrontal cortex (Fig. 1). Many of these studies have focused on the dorsolateral prefrontal cortex in humans, and the medial prefrontal cortex in rodents, as these regions share important functional and neuroanatomical similarities (Ongur and Price, 2000; Dalley et al., 2004), although it should be noted that rodents do have a dorsal prefrontal cortex, which may contribute to associated cognitive functions (Lai et al., 2012). In rats, pyramidal cells in layer II/III of the medial PFC show a pattern of structural changes similar to what has been observed in the hippocampus: retraction of apical dendritic branches and reduced spine density after repeated stress exposure (Cook and Wellman, 2004; Radley et al., 2004, 2006, 2013; Izquierdo et al., 2006; Shansky et al., 2009). These changes were associated with specific deficits in an extradimensional attentional set shifting task that correlated with individual differences in the degree of dendritic atrophy (Liston et al., 2006). In another study, chronic stress caused deficits in spatial working memory that correlated with spine loss on the apical dendrites of prelimbic pyramidal cells (Hains et al., 2009).

The apical dendrites of layer II/III pyramidal cells are important recipients of long-range corticocortical projections, so apical dendritic atrophy would be expected to impair functional connectivity across neuroanatomically distributed brain networks (Dehaene et al., 1998). This is exactly what was observed in a related functional neuroimaging study (Liston et al., 2009). Here, chronically stressed but otherwise healthy human subjects were tested on an

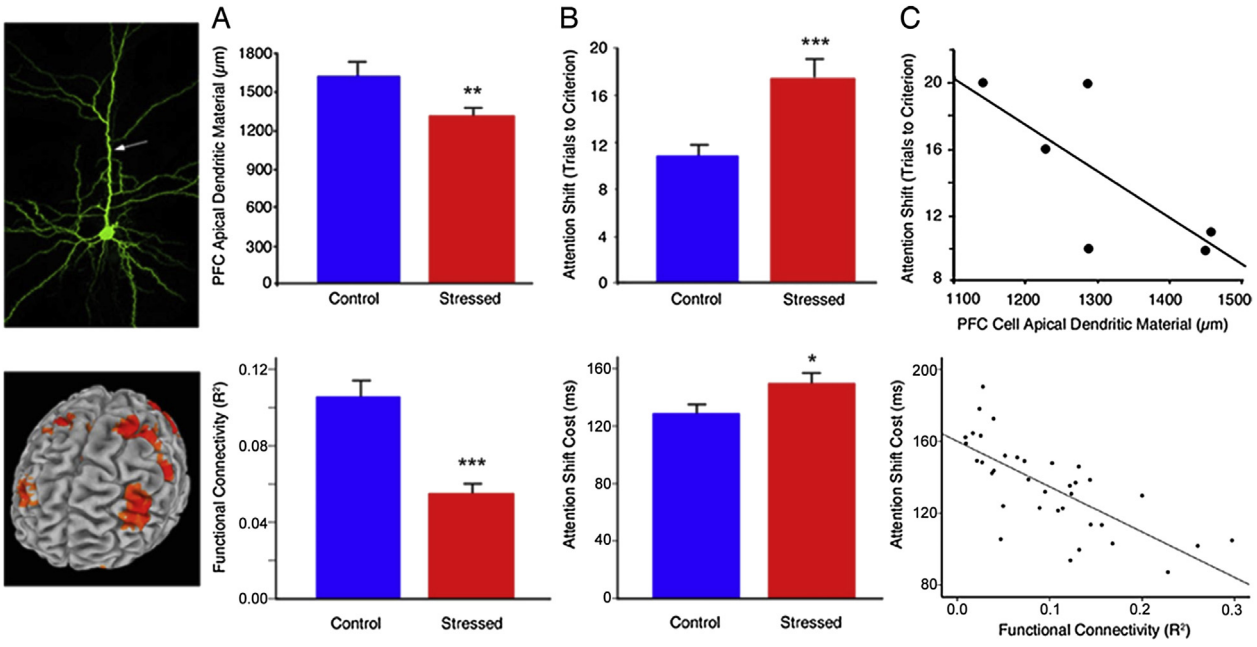

Fig. 1. Analogous effects of chronic stress in parallel rodent and human neuroimaging studies. In both rats (upper panels) and healthy human subjects (lower panels), chronic stress (A) disrupted measures of prefrontal cortical connectivity, and (B) interfered with attention shifting performance. (C) In both studies, individual differences in attention shifting performance were correlated with stress-related connectivity deficits. In the upper panels, rats were exposed to 21 days of repeated restraint stress, and then tested on an extradimensional attentional set-shifting task. Apical dendritic arborization was quantified in layer II/III pyramidal cells of the medial prefrontal cortex after iontophoretic injections of a fluorescent dye (Lucifer Yellow). In the lower panels, healthy human subjects were tested on an analogous attention shifting task after ~1 month of chronic stress caused by preparing for a major exam. Stress was quantified using the Cohen Perceived Stress Scale and a salivary cortisol assay. Functional connectivity between dorsolateral prefrontal cortex and a frontoparietal attention network was quantified using fMRI measures of correlated activity between network nodes. Figure reproduced from (Liston et al., 2009); permission pending.

attention shifting task during fMRI scanning. They exhibited deficits in fMRI measures of functional connectivity between dorsolateral prefrontal cortex and a frontoparietal attention network that were correlated with stress levels and attention shifting impairments. Similar effects were also observed in the medial prefrontal cortex in another human neuroimaging study, in which stressful life events were associated with decreased gray matter volume in the medial prefrontal, anterior cingulate, and subgenual cingulate cortex (Ansell et al., 2012). Thus, chronic stress has been linked to deficits in structural and functional connectivity measures and associated attentional impairments in both rodent models and human neuroimaging studies.

These studies also indicate that connectivity in cortical networks is highly plastic and is often capable of recovering after a change in stress exposure. In rats, four weeks after cessation of the stressor, spine densities fully recovered to unstressed levels (Radley et al., 2005). Similarly, when the same human subjects were re-scanned after a month of rest and reduced stress, both functional connectivity deficits and attention shifting impairments normalized and were no different from unstressed control subjects (Liston et al., 2009). The reversibility of these stress effects underscores the striking capacity for resilience that is evident in the healthy brain.

While the healthy human brain demonstrates a remarkable capacity for adaptation and recovery from stressors in daily life, patients with neuropsychiatric disorders often do not. In a recent clinical neuroimaging study, we found that patients with depression exhibited a similar pattern of functional connectivity deficits between dorsolateral prefrontal cortex and a frontoparietal control network that may contribute to rumination, executive control deficits, and other cognitive symptoms (Liston et al., 2014). However, in contrast to the study of chronically stressed but otherwise healthy subjects, when depressed patients were re-scanned after five weeks of antidepressant treatment, frontoparietal connectivity deficits persisted (Liston et al., 2014). In conjunction with findings in animal models, these results are consistent with the hypothesis that stress-associated changes in connectivity in large-scale brain networks are an important feature of depression and other stress-related neuropsychiatric disorders, and that resilience and vulnerability may be determined in part by individual differences in the capacity for plasticity within these circuits.

2. Neuroendocrine mechanisms: glucocorticoid oscillations regulate synaptic remodeling in cortical circuits

Understanding the mechanisms by which stress alters connectivity in vulnerable circuits may reveal new avenues for treatment. Undoubtedly, many factors are involved, and some of them have been reviewed elsewhere (de Kloet et al., 1998a; McEwen, 2000; de Kloet et al., 2005b; Arnsten, 2009; Joëls and Baram, 2009; Chen et al., 2010). Here we focus on a factor that has received relatively little attention, namely, endogenous glucocorticoid oscillations and their role in regulating synaptic plasticity. Glucocorticoids are hormones that are released from the adrenal gland in response to signals originating in the pituitary and hypothalamus, which receives projections from distinct circuits for detecting physiological and psychosocial stressors (Herman and Cullinan, 1997; Ulrich-Lai and Herman, 2009) (Fig. 2**a**). In the short term, glucocorticoids serve to mobilize energy resources and facilitate sympathetic nervous system responses to maintain homeostasis and adapt to stress. In the long term, however, prolonged exposure to glucocorticoids in chronic stress states can have maladaptive effects, mediated in part by disruptions in negative feedback mechanisms (McEwen, 1998, 2003).

Glucocorticoid activity also oscillates with diurnal activity rhythms, independent of external stressors (Fig. 2b): glucocorticoid secretion tends to peak in the early morning in diurnal animals (early evening in nocturnal animals), remains relatively elevated for most of the active period of the animal's day, and becomes relatively suppressed for most of the night. In addition, recent reports (Stavreva et al., 2009; Lightman and Conway-Campbell, 2010) have shown that an ultradian oscillation with a period of 1–2 h is superimposed on this circadian rhythm and has equally important consequences for glucocorticoid signaling (reviewed below). In previous fixed tissue studies, stress and glucocorticoid effects on dendritic arborization and spine density took weeks to develop (Magariños et al., 1996; Wellman, 2001; Vyas et al., 2002; Radley et al., 2004, 2006), which would imply that glucocorticoid oscillations occurring on a timescale of minutes to hours were unlikely to play a direct role in these changes.

However, recent studies indicate that glucocorticoids and related signaling molecules can have much more rapid effects on dendritic spines than were previously suspected. For example, in hippocampal organotypic cultures, corticotropin-releasing hormone (CRH)—a peptide hormone neurotransmitter and upstream regulator of glucocorticoid synthesis—rapidly increased the retraction and elimination of apical dendritic spines after just 30 min of exposure (Chen et al., 2008), providing one potential mechanism for stress-induced deficits in memory recall (Chen et al., 2010). Similarly, using transcranial two-photon microscopy to image the dynamic remodeling of postsynaptic dendritic spines in the living, developing cortex (Liston and Gan, 2011), we found that glucocorticoids have rapid effects on both spine formation and elimination within hours of exposure. Surprisingly, low-dose dexamethasone (0.1 mg/kg), a synthetic glucocorticoid that inhibits endogenous corticosteroid synthesis without penetrating the blood/brain barrier (Karssen et al., 2005), effectively prevented developmental spine formation and pruning. It is important to note that studies in neuronal cultures and in the developing cortex are investigating spine remodeling under conditions of heightened plasticity, so additional work will be needed to understand how the results apply to the adult brain. However, these experiments indicate that glucocorticoids play an unexpected, necessary role in facilitating physiological spine maturation in the developing adolescent brain, acting on timescale of minutes to hours to facilitate spine remodeling. These unexpectedly rapid effects also suggest that circadian glucocorticoid oscillations may contribute to synaptic plasticity during learning and development.

To test this hypothesis, we conducted a series of two-photon imaging studies in mice before and after training on a RotaRod motor skill-learning paradigm, and found that circadian glucocorticoid peaks and troughs play critical, complementary roles in facilitating experience-dependent spine remodeling (Fig. 2c–g) (Liston et al., 2013). Specifically, circadian glucocorticoid peaks enhanced spine formation rapidly in the hours after learning, acting through a glucocorticoid receptor-dependent, non-transcriptional mechanism. In accord with prior reports (Yang et al., 2009), training increased formation rates but only if it occurred during the circadian peak. In mice that were trained during the circadian trough, spine formation rates were equivalent to those of untrained mice, and memory retention was reduced one week later. Furthermore, circadian troughs were necessary for stabilizing a subset of learning-related spines and pruning a corresponding set of pre-existing synapses. Memory retention and the long-term survival of learning-related spines required intact circadian troughs in the days after learning, which enhanced learning-related spine pruning through a distinct, mineralocorticoid receptor-dependent, transcriptional mechanism. In this way, circadian glucocorticoid oscillations were critical for maintaining homeostasis in synaptic density, by balancing formation and pruning after learning to

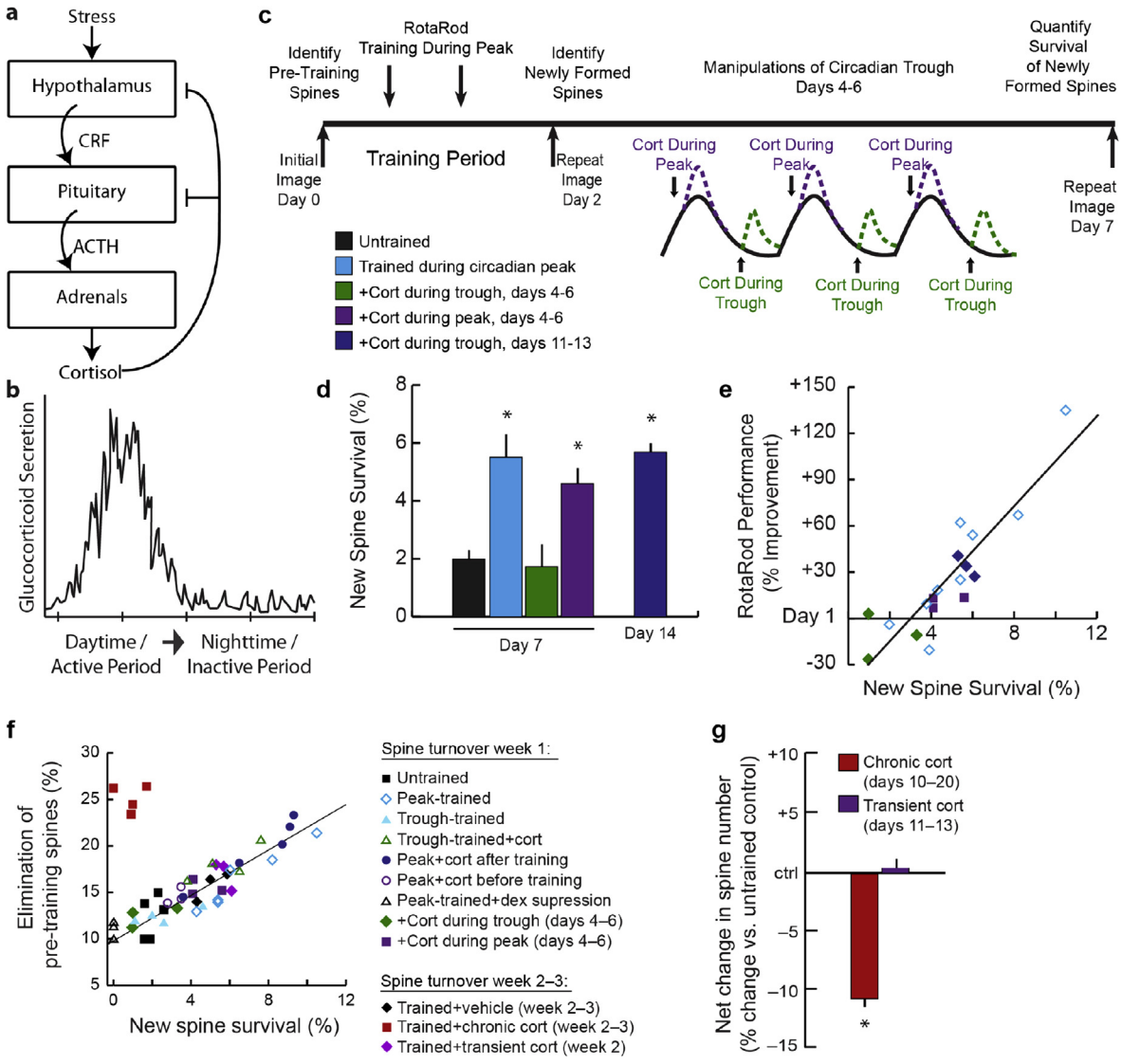

Fig. 2. Glucocorticoid oscillations and stress-induced glucocorticoid secretion are regulated by the HPA Axis. (a) Physiological and psychosocial stressors are detected by circuits that project to the hypothalamus, stimulating corticotropin releasing factor (CRF) secretion, which causes the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn is transported by the circulation to the adrenal glands, stimulating the synthesis and release of cortisol, the principal glucocorticoid in humans. Negative feedback mechanisms prevent excessive glucocorticoid activity and may contribute to oscillations in hormonal activity. (b) Schematic. In physiological circumstances, glucocorticoid secretion also oscillates in synchrony with the 24-h rhythm of day and night, independent of external stressors. In diurnal animals, glucocorticoid secretion is elevated during the daytime (active period) and suppressed at night (inactive period). The opposite is generally true in nocturnal animals. Superimposed on this 24-h circadian cycle are rapid ultradian oscillations with a period of 1–2 h. Ultradian oscillations generate circumscribed pulses in gene expression that are tightly coupled to natural fluctuations in glucocorticoid secretion. (c) Schematic of experiments for investigating how circadian glucocorticoid troughs affect the survival of newly formed spines. Two-photon imaging was performed before and after two days of training on a RotaRod motor skill-learning paradigm to identify newly formed, training-related spines, and subjects were imaged again on Day 7 to quantify spine survival rates. On Days 4, 5, and 6, intraperitoneal injections of corticosterone or vehicle were administered during the circadian peak or trough. (d) Circadian glucocorticoid troughs were critical for preserving newly formed spines. Disrupting the trough, but not the peak, reduced spine survival rates ($F(4,18) = 5.02$, $p = 0.007$), but only during the first week after training. Disrupting the trough on Days 11–13 had no effect on spine survival. (e) Across subjects, the survival of newly formed spines correlated with long-term retention of the motor skill ($r = 0.89$, $p = 0.001$). (f) Across subjects in many different experimental conditions, the survival of newly formed spines during training was strongly correlated with the elimination of pre-existing spines ($r = 0.91$, $p < 0.001$), but this balance was disrupted after chronic corticosterone exposure (red). (g) Chronic but not transient corticosterone exposure caused significant spine loss ($F(1,5) = 125.9$, $p < 0.001$). Panels (c–g) adapted from (Liston et al., 2013); permission pending. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

maintain relatively stable synaptic densities despite repeated bouts of learning-related remodeling.

Chronic stress states disrupt this balance. In the same RotaRod motor skill-learning study (Liston et al., 2013), prolonged glucocorticoid exposure—an important feature of chronic stress states—disrupted circadian troughs, reducing the survival of newly formed spines while simultaneously increasing the elimination of pre-existing synapses. Together, these two effects led to widespread spine loss and reduced spine densities, in striking contrast to the tight coupling between formation and pruning rates that was observed across all other experimental conditions in the study. Related effects were observed on spine maturation across adolescence (Liston and Gan, 2011), and in a mouse model of chronic circadian rhythm disruption (Karatsoreos et al., 2011), discussed in more detail below.

Notably, disrupted oscillations in chronic stress states have complex effects on synaptic remodeling that are modulated by the developmental trajectories of synapse formation (Fig. 3). Whereas

transient glucocorticoid activity increases the pruning mostly of young, recently formed spines, prolonged glucocorticoid exposure disrupts circadian troughs, eliminating synapses that formed progressively earlier in development (Liston and Gan, 2011; Liston et al., 2013). This finding may inform efforts to understand how stress effects interact with synaptic development across the lifespan of an organism. Stress has varying effects on brain function, behavior, and psychiatric risk that depend on when during

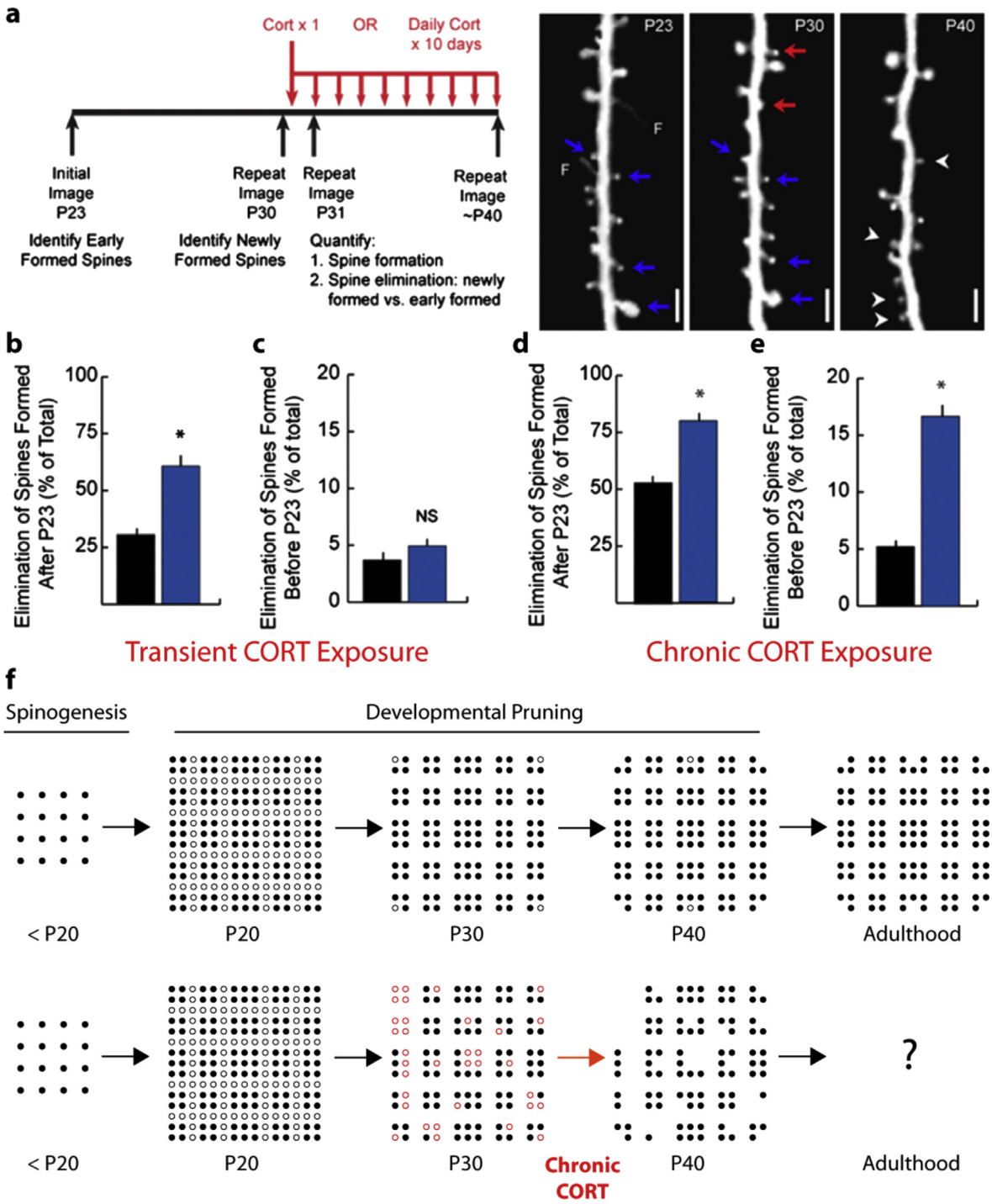

Fig. 3. Prolonged glucocorticoid exposure disrupts spine development. (a) We used transcranial two photon laser scanning microscopy to acquire images of the apical dendrites of cortical pyramidal cells at postnatal day 23 (P23) and again at P30, enabling us to identify spines formed early in life that were stably integrated into cortical circuits for at least one week. Subjects then received either a single injection of corticosterone (CORT) or repeated daily injections for ten days, followed by a third imaging session at P40. Spine formation (arrowheads) and elimination (arrows) were quantified before and after each CORT treatment. Scale bars = 2 micrometers. (b–c) Transient CORT exposure increased the elimination of recently formed spines (red arrows in panel a), but had no effect on spines formed prior to P23 (blue arrows). (d–e) In contrast, chronic corticosterone exposure eliminated >15% of spines formed early in life, as well as >75% of recently formed spines. (f) Schematic. Prolonged glucocorticoid exposure—a model of chronic stress—interferes with synaptic development. Normally (upper panels), rapid spinogenesis (solid circles) prior to P20 is followed by a period of accelerated spine pruning (hollow circles) during adolescence, but the vast majority of spines that formed early in life and survive this pruning process will persist into adulthood. Chronic CORT exposure (lower panels) disrupts this process, eliminating a significant proportion of spines formed early in development (hollow red circles). The long-term consequences of this synaptic reconfiguration in adulthood are unknown. Figure reproduced from (Liston and Gan, 2011); permission pending. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

development the stressor occurs (Lupien et al., 2009). This dependence may relate to the varying trajectories of synaptic development across different brain regions (Lupien et al., 2009). For example, during infancy and early childhood, the hippocampus is developing rapidly and may be particularly vulnerable to early-life stress, whereas protracted development in the prefrontal cortex during the transition from adolescence to early adulthood may increase its vulnerability during this period (Lupien et al., 2009). In accord with this hypothesis, a variety of early-life stressors can induce long-lasting changes in hippocampal corticosteroid receptor expression and HPA reactivity, heightened anxiety, and hippocampus-dependent memory deficits that persist into adulthood (Barbazanges et al., 1996; Vallée et al., 1999; Lemaire et al., 2000; Tsoory et al., 2007; Eiland and Romeo, 2012; Lui et al., 2012; Pattwell et al., 2012; Batalha et al., 2013).

Importantly, glucocorticoid activity oscillates not only with the circadian cycle of day and night, but also on a much faster time scale with a period of 1–2 h (Stavreva et al., 2009; Lightman and Conway-Campbell, 2010). These ultradian oscillations, which are superimposed on the slower circadian cycle (Fig. 2b), also have important effects. Recent studies have shown that ultradian glucocorticoid rhythms generate cycles of GR-mediated "gene pulsing," which regulate gene expression on faster timescales than was previously suspected (Stavreva et al., 2009). Facilitated by the rapid, chaperone-mediated recycling of nuclear GRs, ultradian gene pulses trigger changes in GR-regulated promoter activity that are tightly coupled to physiological oscillations (Stavreva et al., 2009). Ultradian glucocorticoid oscillations penetrate the blood/brain barrier and are preserved within stress-sensitive brain areas (Droste et al., 2008), where they probably play an important role in responding to stressors and other environmental stimuli in physiological circumstances. Conversely, in chronic stress models, disruptions of the ultradian oscillation alter gene expression responses in these regions and cause correlated changes in locomotor activity and risk assessment behaviors (Sarabdjitsingh et al., 2010a,b).

Whether and how these ultradian oscillations affect synaptic remodeling remains unclear, but they are likely to have important effects, acting potentially through both transcriptional and non-transcriptional mechanisms (McEwen, 1991; Makara and Haller, 2001; Lösel and Wehling, 2003; Groeneweg et al., 2011). As mentioned above, glucocorticoids can increase spine formation in cortical pyramidal cells by ten-fold in just 20 min, acting through non-genomic signaling pathways (Liston et al., 2013). Similarly, glucocorticoids can rapidly enhance the frequency of miniature excitatory postsynaptic potentials, increasing glutamate release probability by activating a non-genomic, MR-dependent signaling pathway (Karst et al., 2005). Similarly rapid effects have been observed in other studies in the prefrontal cortex, hippocampus, amygdala, and hypothalamus (Di et al., 2003; Groeneweg et al., 2011; Popoli et al., 2011; Tasker and Herman, 2011).

3. Molecular mechanisms of synaptic remodeling by glucocorticoids

The studies reviewed above indicate that stress and glucocorticoids have potent but complex effects on synaptic remodeling, and understanding the underlying molecular mechanisms is a rapidly emerging area of active investigation. These studies are challenging due in part to the fact that stress effects on dendritic remodeling, synaptic plasticity, and associated molecular signaling mechanisms vary with the region and developmental age under investigation (Lupien et al., 2009). However, one theme to emerge from this work is that glucocorticoids may engage distinct intracellular signaling mechanisms, depending on the timing of a stressor and the kinetics of the glucocorticoid response. For example, in response to an acute stressor, glucocorticoids promote memory consolidation and impair working memory (McGaugh and Roozendaal, 2002; Barsegyan et al., 2010) through a mechanism involving beta adrenergic- and cAMP-dependent activation of protein kinase A in the amygdala and prefrontal cortex (Roozendaal et al., 2002; Barsegyan et al., 2010). Acutely, glucocorticoids also promote long-term memory retention by enhancing learning-dependent spine formation, acting through a glucocorticoid receptor-dependent non-genomic signaling mechanism that increases LIM kinase and cofilin phosphorylation (Liston et al., 2013), which stabilizes actin polymers and promotes spine growth (Gu et al., 2010). Recent reviews underscore the point that acute glucocorticoid exposure modulates multiple additional molecular processes that are relevant in this context: acutely, glucocorticoids potentiate glutamate transmission by increasing presynaptic glutamate release and enhancing AMPA and NMDA receptor trafficking to postsynaptic membranes; they activate MAPK and CaMKII signaling pathways that have been linked to transcription-dependent mechanisms for memory consolidation; and they enhance endocannabinoid signaling, which in turns modulates the release of glutamate and other neurotransmitters (Arnsten, 2009; Campolongo et al., 2009; Hill et al., 2011; Sandi, 2011; Popoli et al., 2012).

In contrast, chronic glucocorticoid exposure engages a variety of molecular signaling mechanisms that are distinct from those engaged by an acute stressor. For example, chronic glucocorticoid exposure has effects on glutamate receptor expression that oppose those induced by an acute stressor, reducing the expression of the NMDA receptor subunit NR2B and the AMPA receptor subunits GluR2/3 in the prefrontal cortex (Gourley et al., 2009). Chronic stress effects on dendritic atrophy in the hippocampus and prefrontal cortex have also been linked to excessive protein kinase C signaling (Hains et al., 2009) and reduced expression of neural cell adhesion molecules (NCAM-140) (Sandi, 2004). And chronic glucocorticoid exposure suppresses BDNF transcription in the orbitofrontal cortex (Gourley et al., 2009) and reduces TrkB and ERK1/2 signaling in the hippocampus (Gourley et al., 2008). Although studies indicate that reduced activity-dependent BDNF secretion probably does not by itself cause spine loss or dendritic atrophy (Hill et al., 2005; Magarinos et al., 2011), it is likely that altered BDNF signaling plays a role through interactions with other factors.

4. Translational implications: circadian glucocorticoid oscillations and the pathogenesis of stress-related neuropsychiatric disorders

Stress—especially chronic, uncontrollable stress—is an important risk factor for depression, PTSD, and other anxiety disorders, and stress effects on glucocorticoid oscillations may contribute to this effect. Stress has varying effects on HPA axis activity and glucocorticoid secretion that depend on the timing and nature of the stressor; on the individual's subjective perception of the situation; and likely also on his genetic predisposition to developing stress-related psychiatric conditions (Miller et al., 2007). In a recent meta-analysis of 8521 subjects across 107 independent studies, the most consistent findings were that chronic stress increases the total daily output of cortisol (the principal glucocorticoid in humans), flattens the diurnal rhythm, and reduces the amplitude of the circadian peak (Miller et al., 2007). Together, these effects significantly alter both circadian and ultradian oscillations. The disruption may be particularly significant during the circadian trough, as unopposed MR activity typically occurs only during the trough when glucocorticoid secretion is low (Reul and de Kloet, 1985; de Kloet

et al., 1998b), and a relatively small increase in trough levels could have pronounced effects on glucocorticoid signaling. In conjunction with the studies cited above, these results suggest that chronic stress may predispose vulnerable individuals to a variety of neuropsychiatric disorders by disrupting the circadian oscillation and especially the circadian trough, reducing the survival of newly formed synapses, and destabilizing synapses formed early in development.

Converging evidence from both clinical studies and animal models lend support to this hypothesis. Disrupted circadian glucocorticoid cycling is a relatively consistent feature in clinical studies of patients with depression or PTSD (Heim et al., 2000; Holsboer, 2000; Yehuda, 2002; Miller et al., 2007). Blunted circadian cortisol oscillations are a feature common to both PTSD and depression (Yehuda et al., 1996). However, these two disorders appear to involve opposing changes in total cortisol secretion (decreased in PTSD, variably increased in depression): in PTSD, blunted oscillations are driven primarily by reduced circadian peaks (Yehuda et al., 1996), while in depression, they are driven primarily by elevated cortisol secretion during the circadian trough (Yehuda et al., 1996), especially in psychotic depression (Sachar et al., 1973; Keller et al., 2006). In both disorders, blunted corticol cycling is associated with hippocampal volume loss (Bremner et al., 1995, 2000; Sheline et al., 1996) and partially overlapping alterations in functional connectivity (Davidson et al., 2002; Lanius et al., 2004; Greicius et al., 2007; Sheline et al., 2010; Yin et al., 2011; Qin et al., 2012; Liston et al., 2014), which is consistent with results in animal models indicating that both peaks and troughs are necessary for balancing synaptic formation and pruning.

Similarly, animal models of mood disorders provide additional support for this hypothesis. Multiple animal models of depression—including chronic unpredictable stress, chronic social defeat stress, and early life stress—recapitulate neuroendocrine abnormalities found in patients, including blunted glucocorticoid oscillations, elevated glucocorticoid activity, and disrupted circadian troughs (Willner, 1997; Meaney, 2001; Krishnan et al., 2007; Nestler and Hyman, 2010). In at least one study, blunted circadian cycling was linked specifically to stress susceptibility: circadian rhythm amplitudes were blunted only in mice that exhibited a vulnerable behavioral phenotype in response to chronic social defeat stress, relative to resilient mice that did not develop depression-like symptoms (Krishnan et al., 2007).

In other studies, circadian rhythm disturbances have been causally related to mood symptoms. In a genetic model, mice carrying a mutation in the *Clock* gene showed a loss of circadian rhythms in locomotor activity and a host of mania-like behavioral symptoms (Roybal et al., 2007). And in an environmentally induced model of circadian rhythm disruption, mice that were housed on a shortened 20-h light–dark cycle exhibited learning and structural connectivity deficits comparable to those seen in chronic stress states, including apical dendritic atrophy in mPFC pyramidal cells and PFC-dependent cognitive deficits (Karatsoreos et al., 2011).

Studies like this also highlight implications for patients outside the psychiatric realm. For example, mice that were housed on a shortened 20-h light–dark cycle also developed metabolic problems, including obesity, increased leptin levels, and signs of insulin resistance. Shift workers and frequent travelers who suffer from chronic jet lag may experience analogous cognitive and metabolic changes (Sack et al., 2007; Lupien et al., 2009; McEwen, 2012), and in susceptible individuals, travel across time zones may even trigger severe mood episodes requiring psychiatric hospitalization (Jauhar and Weller, 1982). An increasing awareness of the importance of circadian and ultradian glucocorticoid oscillations in learning-related synaptic remodeling may also have implications for efforts to optimize training regimens for promoting motor skill learning, which is known to vary with the time of day in both adolescents and adults (Atkinson and Reilly, 1996; Miller et al., 2012). Similarly, disruptions in circadian glucocorticoid oscillations may be an important factor to consider in patients undergoing treatment with corticosteroids, which are frequently used in the management of a variety of common autoimmune disorders. Cognitive complaints and mood symptoms are extremely common but poorly understood side effects of treatment (Brown and Suppes, 1998; Otte et al., 2007; Cornelisse et al., 2011), which could potentially be mitigated by designing treatment regimens to preserve naturally occurring oscillations whenever possible.

5. Conclusions and future directions

Converging evidence from animal models and human neuroimaging studies indicates that stress-associated functional connectivity changes are a common feature of depression, PTSD, and other neuropsychiatric conditions and are associated with correlated structural changes in the prefrontal cortex, hippocampus, and other vulnerable brain regions. These, in turn, may be caused in part by circadian disturbances in glucocorticoid activity. Circadian glucocorticoid peaks and troughs are critical for generating and stabilizing new synapses after learning and pruning a corresponding subset of pre-existing synapses. Chronic stress disrupts this balance, interfering with glucocorticoid signaling during the circadian trough and leading to widespread synapse loss, dendritic remodeling, and behavioral consequences. These effects interact with synaptic development trajectories that vary across brain regions and may be particularly pronounced during the transition from adolescence to young adulthood, when major neuropsychiatric conditions most commonly emerge. Together these findings provide a model for understanding how stress effects on circadian glucocorticoid oscillations may contribute to connectivity changes and ultimately to the pathophysiology of depression, PTSD, and other disorders. Still, many questions remain, and we conclude by considering a few of them.

Perhaps most importantly, many of these links remain purely correlative, and it will be critical to test whether and how changes in synaptic remodeling directly affect the function of cortical microcircuits, the integration of information across neuroanatomically distributed networks, and the emergence of behavioral effects and psychiatric symptoms. To this end, the recent development of optogenetic tools for manipulating activity in specific neural circuits will be critical for establishing causal mechanisms (Yizhar et al., 2011; Tye and Deisseroth, 2012; Berndt et al., 2014). Likewise, recently developed imaging modalities provide a means for testing how structural changes within a given microcircuit affect functional circuit dynamics—another critical, unanswered question. These methods use genetically encoded calcium indicators (Tian et al., 2009) to quantify neuronal activity with single-cell precision in the living organism. In combination with implantable optical devices (Flusberg et al., 2008; Barretto et al., 2009; Chia and Levene, 2009; Andermann et al., 2013), these tools will extend the reach of conventional two-photon microscopy to enable *in vivo* imaging in the hippocampus, amygdala, medial prefrontal cortex, and other stress-sensitive limbic circuits, which tend to lie deep below the cortical surface. Finally, *in vivo* imaging tools may also prove useful for investigating the role of ultradian oscillations, which are superimposed on the circadian glucocorticoid rhythm. Whether and how these rapid oscillations affect synaptic remodeling is unknown. What is clear is that these oscillations trigger pulses of gene expression every 1–2 h (Stavreva et al., 2009), and that glucocorticoids are capable of regulating synapse function and facilitating synapse formation on a comparably rapid timescale

(Popoli et al., 2011; Liston et al., 2013). Together, these emerging technologies will enable investigators to ask fundamentally new questions about the links between circadian rhythm disruptions, structural measures of synaptic remodeling, and their functional consequences.

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