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The adaptive and maladaptive continuum of stress responses – a hippocampal perspective

Abstract: Exposure to stressors elicits a spectrum of responses that span from potentially adaptive to maladaptive consequences at the structural, cellular and physiological level. These responses are particularly pronounced in the hippocampus where they also appear to influence hippocampal-dependent cognitive function and emotionality. The factors that influence the nature of stress-evoked consequences include the chronicity, severity, predictability and controllability of the stressors. In addition to adult-onset stress, early life stress also elicits a wide range of structural and functional responses, which often exhibit life-long persistence. However, the outcome of early stress exposure is often contingent on the environment experienced in adulthood, and could either aid in stress coping or could serve to enhance susceptibility to the negative consequences of adult stress. This review comprehensively examines the consequences of adult and early life stressors on the hippocampus, with a focus on their effects on neurogenesis, neuronal survival, structural and synaptic plasticity and hippocampal-dependent behaviors. Further, we discuss potential factors that may tip stress-evoked consequences from being potentially adaptive to largely maladaptive.

Keywords: anxiety; cognition; dendritic atrophy; glucocorticoids; hippocampal neurogenesis; long-term potentiation.

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Introduction

Exposure to stressors evokes a variety of responses that primarily aim at buffering and restoring to normalcy the disruption of homeostasis induced following stress. However, under conditions where stress responses are driven repeatedly or fail to re-establish homeostasis, they can contribute to the generation of an alternative 'allostatic state', thus eventually resulting in 'allostatic load' (McEwen, 2003). Stress responses in an individual can span the range from potentially adaptive to predominantly maladaptive, with adaptive responses enhancing resilience and facilitating coping mechanisms against future stressors, and maladaptive responses leading to a disruption of stress coping and the establishment of vulnerability to stress-associated pathology. However, it is important to note that the entire ensemble of stress responses cannot be discretely parcellated into either an adaptive or maladaptive end state. Rather, stress responses are likely a continuum, with the conclusion of an adaptive or maladaptive consequence often determined in the context of future experience, and influenced strongly by the timing, intensity, duration, predictability and controllability of the stressor, as well as the genetic background and life history of the individual (Kavushansky et al., 2006; McEwen, 2007; Lupien et al., 2009).

Animals exposed to chronic or unpredictable stress often demonstrate adverse effects including a dysregulation of the stress-activated hypothalamo-pituitary-adrenocortical (HPA) axis (Mizoguchi et al., 2008; Christiansen et al., 2012), heightened anxiety and depressive behavior (Strekalova et al., 2004; Bessa et al., 2009; Koike et al., 2009) and impairments in cognitive function (Pawlak et al., 2005; Kallarackal et al., 2013). Concomitantly, marked molecular, structural and synaptic alterations are also noted in multiple regions of the brain involved in emotional and cognitive processing such as the hippocampus, amygdala and prefrontal cortex (Czeh et al., 2001; Vyas et al., 2002; Goldwater et al., 2009; reviewed in Leuner and Shors 2013). In stark contrast, exposure to mild, acute, controllable or predictable stressors has been linked to adaptive outcomes with decreases in anxiety, fear and depressive behavior (Baratta et al., 2007; Christianson et al., 2009; Parihar et al., 2011), improved hippocampal-dependent cognitive function (Lyons et al., 2010; Parihar et al., 2011), amygdalar spine loss (Marcuzzo et al., 2007), hippocampal dendritic spinogenesis and enhanced hippocampal neurogenesis (Lyons et al., 2010; Parihar et al., 2011). These studies suggest

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that the nature of the stressor is a key factor in determining the eventual consequences of stress, with the duration, intensity and the perception of control serving as critical decisive variables. However, it is important to factor in the individual variation in stress responses noted from both clinical and preclinical studies. Clinical studies highlight the fact that even severe stress exposure exacerbates/precipitates psychopathology in a relatively limited subset of individuals (Shalev et al., 1998). Preclinical studies in both rodent and non-human primate models recapitulate the individual variation in stress responses, with genetic background (Uher, 2009; Chaudhury et al., 2014; O'Leary et al., 2014) and life history, in particular early-life experience (Cirulli et al., 2009), serving as the backdrop that can strongly alter or modify the nature of outcomes evoked by stressors. Further, it is also necessary to draw attention to the fact that the same stressor can elicit opposing effects on structural versus synaptic changes, and different forms of anxiety and cognitive behaviors, thus indicative of differential vulnerability of these readouts to the same stressors. It is our goal in this review to delineate the maladaptive versus adaptive effects of adult- and early-onset stress in animal models, at the cellular, structural, network and behavioral level, with a special emphasis on the hippocampus, and hence gain a better mechanistic understanding of the continuum and diversity of responses that ensue from stressor experience.

Stress responsive neuroendocrine axis

Exposure to adverse experience activates a variety of neuroendocrine and neurotransmitter systems, key among them being the HPA axis (Smith and Vale, 2006) and adrenomedullary-sympathetic pathway (reviewed in Morilak et al., 2005). Physiological and psychological stressors activate the brain stem nuclei and the amygdala to induce the release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus (Smith et al., 1995; Pan et al., 1999; reviewed in Jankord and Herman, 2008). Hypothalamic CRH then enhances pituitary release of adrenocorticotrophic hormone (ACTH) that stimulates adrenocortical glucocorticoid (GC) secretion (reviewed in Herman and Cullinan, 1997). GCs are steroid hormones, predominant among which are corticosterone in rodents and cortisol in humans, which aid physiological stress coping by mobilizing energy stores to fuel fight and flight responses, and suppress non-vital body functions (reviewed in Sapolsky et al., 2000). In addition, GCs via their receptors present at the level of the hypothalamus, the pituitary (Bradbury et al., 1991), and other cortical and subcortical structures (reviewed in Jankord and Herman, 2008; Radley and Sawchenko, 2011) are also responsible for imposing feedback regulation on the HPA axis. The high-affinity mineralocorticoid receptor (MR) is predominantly expressed in limbic areas and is saturated under basal GC levels, whereas the more ubiquitously present low affinity glucocorticoid receptor (GR) (Reul and de Kloet, 1985; Arriza et al., 1988; Chao et al., 1989) is recruited by stress-elevated and peak circadian levels of GCs (Reul and de Kloet, 1985; Kitchener et al., 2004). GCs exert their action both via relatively slow-onset genomic effects and rapid-onset non-genomic action via a putative membrane-associated GC receptor (reviewed in Evanson et al., 2010).

Amongst cortical brain regions, the hippocampus has the highest expression of MRs and GRs (Reul and de Kloet, 1985; Chao et al., 1989), and is known to exert feedback inhibition on the HPA axis via multisynaptic inputs (reviewed in Jankord and Herman, 2008). The hippocampus is also particularly sensitive to the damaging effects of elevated GCs, which in conjunction with other stress-induced factors enhance neuronal damage and vulnerability to neuronal insults (Sunanda et al., 1997; Christian et al., 2011). Stress-evoked hippocampal damage in combination with the elevated GC-mediated downregulation of hippocampal GR expression (Herman and Spencer, 1998) could impair negative feedback of the HPA axis, resulting in sustained elevations of circulating GCs, thus compounding their damaging effects (reviewed in Stokes, 1995). This stress-evoked hippocampal dysfunction has also been suggested to contribute to the development of vulnerability for psychopathology (McEwen, 2004, reviewed in Stokes, 1995). Indeed, studies indicate that 50% patients with recurrent major depressive disorder (MDD) exhibit elevated basal salivary and plasma GC levels (Lopez-Duran et al., 2009), possibly mediated by impaired hippocampal feedback regulation of the HPA axis (Young et al., 1991).

In addition to the HPA axis, exposure to stress also activates the sympatho-adrenomedullary system resulting in enhanced norepinephrine (NE) levels in multiple brain regions, including the hippocampus (reviewed in Pacak et al., 1995; Morilak et al., 2005). Stress-evoked NE release, along with CRH, is known to influence central nervous system stress responses (reviewed in Morilak et al., 2005; Lloyd and Nemeroff, 2011). Together adrenergic neurotransmission, hypothalamic CRH and circulating GCs also act as the primary mediators of the peripheral

stress response and are responsible for mediating a major component of the physiological effects of stress.

Maladaptive effects of adult chronic stress exposure on the hippocampus

Chronic stress and hippocampal neuron dendritic architecture

The hippocampus is particularly vulnerable to the damaging effects of stress on structural plasticity, possibly a consequence of high GC receptor expression in this brain region. Exposure to diverse stressors including chronic restraint stress (2–6 h, 10–21 days), chronic unpredictable stress (CUS) and psychosocial stress (1 h/day, 28 days of subordinate stress) in animal models results in apical dendritic atrophy and reduced dendritic arborization of hippocampal CA3 pyramidal neurons (Watanabe et al., 1992; Magariños et al., 1996; Vyas et al., 2002; Wang et al., 2011a) (Figure 1B). The dendritic atrophy observed in CA3 neurons is accompanied by alteration in dentate gyrus (DG) mossy fiber terminals that synapse onto these cells (Magariños et al., 1997). These terminals exhibit a reorganization of presynaptic vesicles accompanied by enhancement in mitochondrial density in the vicinity of active zones (Magariños et al., 1997), indicating enhanced glutamatergic input from the DG to the CA3. Indeed, both acute and chronic stressors (1 h acute immobilization and 40 days of CUS) have been reported to enhance glutamate levels (Lowy et al., 1993; de Vasconcellos-Bittencourt et al., 2011) in the hippocampus, possibly resulting in excitotoxic damage and contributing to the stress-mediated dendritic atrophy (Magariños et al., 1996; Sunanda et al. 1997; Christian et al., 2011). Though stress-induced dendritic

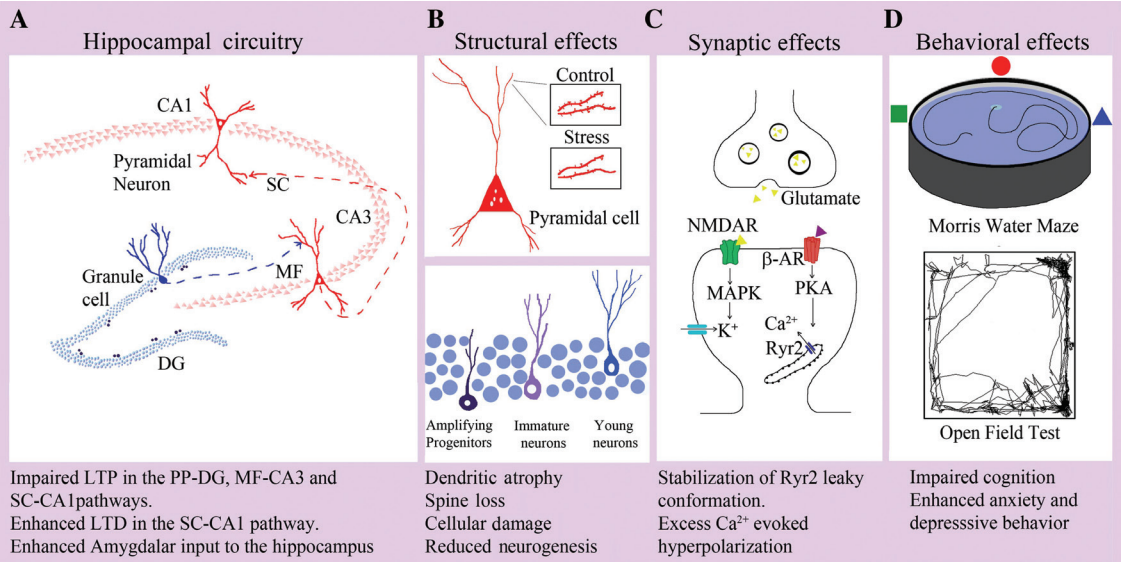

Figure 1: Maladaptive consequences of chronic adult stressors on hippocampal structural plasticity, physiological responses and hippocampus-dependent behaviors. Chronic, unpredictable or uncontrollable stressors elicit a number of maladaptive consequences that manifest themselves as changes in hippocampal structural and synaptic plasticity and hippocampal-dependent behaviors. (A) A representation of the different hippocampal subfields and the pathways that constitute the hippocampal circuitry. Exposure to chronic stressors differentially influences plasticity in different hippocampal cellular subfields and synaptic pathways. (B) Exposure to multiple chronic or severe stressors mediates hippocampal CA3 apical dendritic atrophy and reduces spine density in the CA1 and dentate gyrus (DG) neurons. Severe stressor exposure also induces CA3 cell loss, cellular damage and nuclear fragmentation. Chronic stressors reduce hippocampal progenitor proliferation, survival and differentiation. (C) Exposure to stress impairs long-term potentiation (LTP) in the CA3-CA1 Schaffer collateral (SC) pathway, the mossy fiber (MF)-CA3 synapses and the medial perforant pathway to the DG. This impairment in LTP is possibly a consequence of enhanced intracellular calcium (Ca^{2+}) levels resulting from enhanced NMDA receptor (NMDAR) activation and the beta-adrenergic receptor (b-AR)/protein kinase A (PKA)-mediated stabilization of the ryanodine receptor 2 (Ryr2) leaky conformation. (D) In addition to maladaptive consequences on hippocampal structural and physiological responses, chronic stress also evokes alterations in hippocampal-dependent cognitive, anxiety and depressive and behaviors. Animals subjected to chronic or severe stressors exhibit impairments in acquisition, consolidation and retrieval of hippocampal-dependent tasks of learning and memory. Further exposure to chronic stressors evokes anxiogenic behavior, anhedonia and learned helplessness. MAPK, mitogen-activated protein kinase; K^+, potassium ions.

remodeling has been relatively less well examined for the other hippocampal subfields, a few studies have observed dendritic retraction and decreases in spine density in CA1 and DG neurons following chronic stress (restraint stress 6 h daily, 21 days or 1 month of CUS) (Sousa et al., 2000; Pawlak et al., 2005; Christian et al., 2011) (Figure 1B).

These stress-induced structural changes are thought to involve multiple mediators including elevated GC levels (Magariños and McEwen, 1995; Alfarez et al., 2008), CRH (Chen et al., 2010b) and reduced trophic support (reviewed in Schmidt and Duman, 2007). Pharmacological blockade of steroid synthesis (Magariños and McEwen, 1995) prior to stress exposure or the absence of the forebrain CRH1 receptor (CRHR1) (Wang et al., 2011a) renders animals resistant to chronic stress-mediated CA3 neuron dendritic atrophy. CRH has been demonstrated to act via Rho GTPases to block the activity-mediated actin polymerization and induce a loss of thin dendritic spines (Chen et al., 2013). Other molecular mediators that are implicated in the chronic stress-evoked hippocampal dendritic atrophy include neuronal cell adhesion molecules such as polysialylated neural cell adhesion molecule (PSA-NCAM) (McCall et al., 2013), neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Magariños et al., 2011), the filopodia-associated transmembrane glycoprotein M6a (Alfonso et al., 2005) and the extracellular proteases tissue plasminogen activator and plasminogen (Pawlak et al., 2005). Studies have also indicated altered monoaminergic and GABAergic responses in mediating stress-induced adverse effects on dendritic atrophy (Magariños et al., 1999; McKittrick et al., 2000).

While the functional consequences of such structural changes are unclear, it has been hypothesized that stress-mediated dendritic remodeling may potentially contribute to hippocampal-dependent cognitive dysfunction and an enhanced vulnerability to psychopathology. However, viewed from another perspective hippocampal dendritic remodeling may be a compensatory response evoked to limit stress-induced excitotoxic damage. Indeed, studies have demonstrated that the stress-mediated molecular changes such as the enhancement in lipocalin2 (Mucha et al., 2011) and decline in PSA-NCAM (McCall et al., 2013), which contribute to hippocampal dendritic spine retraction and dendritic atrophy, exert a protective role against the damaging effects of stressors. A reversal of the above molecular effects is reported to heighten anxiety (Mucha et al., 2011) and increase damage by excitotoxic agents (McCall et al., 2013). These studies highlight the interesting possibility that many of the perceived maladaptive effects of stress may actually be offshoots of an attempt to achieve homeostasis and restrict stress-induced damage.

Chronic stress and hippocampal neuronal damage

Non-human primates exposed to severe social or physical stressors exhibit accelerated damage and finally a loss of hippocampal CA3 pyramidal neurons (Uno et al., 1989; Mizoguchi et al., 1992). A sustained increase in GCs also results in CA2/3 pyramidal neuron dendritic atrophy, cell layer irregularity, soma shrinkage and condensation, and nuclear pyknosis, suggesting GCs to be the primary mediators of stress-induced cell damage and loss (Sapolsky et al., 1990) (Figure 1B). However, studies in rodents (CUS and chronic restraint stress) (Sousa et al., 1998; Heine et al., 2004) and tree shrews (28 days of subordinate stress) (Vollmann-Honsdorf et al., 1997; Lucassen et al., 2001) have been unable to recapitulate the severe stress-evoked cellular damage observed in primates. Further, while reduced hippocampal volume has been observed in children suffering from childhood maltreatment (Teicher et al., 2012) and patients suffering from psychiatric conditions such as MDD (Sheline et al., 1996; Cole et al., 2011) and post-traumatic stress disorder (PTSD) (Bonne et al., 2008), these volumetric alterations have been largely thought to be a consequence of hippocampal cell soma shrinkage and neuropil reductions (Rosoklija et al., 2000; Stockmeier et al., 2004; but also see Boldrini et al., 2013). These contrasting findings about the effects of stress on adult neuronal loss and damage point towards possible species-specific differences in the hippocampal vulnerability to stressors. While hippocampal cell loss has largely been thought of as an adverse consequence of stress, we cannot preclude the possibility that by eliminating cells that have accumulated stress-evoked damage these changes help restore the normal function and excitability of hippocampal circuitry.

In addition to cellular damage, prolonged stress (40 days of CUS, 21 days of restraint stress – 6 h daily or 7 days of CUS) or GC exposure enhances hippocampal neuronal susceptibility to insults such as hypoxia (Koide et al., 1986; de Vasconcellos-Bittencourt et al., 2011), epileptogenic agents (Stein-Behrens et al., 1994), metabolic insults (Sapolsky, 1985; de Vasconcellos-Bittencourt et al., 2011) and excitotoxic and oxidative damage (Roy and Sapolsky, 2003; Atif et al., 2008). Mechanistic insight into this neuronal vulnerability is provided by studies that indicate that stress-induced elevations in GCs may impede normal neuronal metabolism (reviewed in Reagan and McEwen, 1997). While stress exposure (CUS) results in dissipation of mitochondrial membrane potential and damages mitochondrial ultrastructure in the hippocampus (Gong et al., 2011), high levels of GCs have been

demonstrated to interfere with neuronal glucose uptake (Piroli et al., 2007).

Chronic stress and hippocampal neurogenesis

Though the DG granule cell neurons appear to be predominantly resistant to stress-evoked dendritic atrophy and hippocampal cellular damage, an alternate form of cellular plasticity that is compromised in this hippocampal subfield is neurogenesis (reviewed in Schoenfeld and Gould, 2012). The hippocampal DG is amongst the major neurogenic regions in the adult mammalian brain. The DG subgranular zone (SGZ) harbors quiescent neural stem cells that proliferate and eventually mature into granule cells, and integrate into DG neurocircuitry (reviewed in Ming and Song, 2005). Chronic exposure to diverse stressors (CUS, chronic restraint stress, social defeat, chronic foot shock) reduces the proliferation (Dagyte et al., 2009; Lagace et al., 2010; Hillerer et al., 2013), survival (Lee et al., 2006; Veena et al., 2009; Hillerer et al., 2013) and differentiation (Veena et al., 2009; Hillerer et al., 2013) of new neurons in the adult hippocampal DG (Figure 1B). Giving credence to the idea that GCs may be the primary mediators of the neurogenic effects of stress, exposure to high levels of GCs also impairs hippocampal progenitor proliferation (Brummelte and Galea, 2010; Anacker et al., 2013a) and reduces the immature neuron number (Brummelte and Galea, 2010; Diniz et al., 2013). Further, adrenalectomy (Tanapat et al., 2001) or GR antagonist pretreatment (Oomen et al., 2007) reverses the stress-induced decline in hippocampal progenitor proliferation. GCs may regulate hippocampal neurogenesis either through GC receptors present in hippocampal progenitors (Anacker et al., 2013b), or alternatively via perturbing glutamatergic signaling which is known to regulate neurogenesis (Gould et al., 1997; Cameron et al., 1998). Studies have also implicated the reduction of trophic factors such as vascular endothelial growth factor (vEGF) (Heine et al., 2005), increased signaling by inflammatory cytokine pathway molecules like interleukin-1β and nuclear factor-κB (Koo and Duman, 2008; Koo et al., 2010) and a decline in telomerase activity (Zhou et al., 2011), in the chronic stress-mediated reduction of hippocampal neurogenesis.

Newborn neurons are thought to contribute to hippocampal feedback regulation of the HPA axis, with animals lacking hippocampal neurogenesis exhibiting impaired normalization of stress-evoked corticosterone secretion (Schloesser et al., 2009; Snyder et al., 2011). In this regard, it is tempting to speculate that a decline in hippocampal neurogenesis may contribute to the dysregulated HPA axis feedback regulation observed in animals exposed to chronic or severe stressors (Mizoguchi et al., 2008; Christiansen et al., 2012).

Stress and adverse effects on hippocampal long-term potentiation

Stress can exert contrasting effects on cellular excitability and forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) (Figure 1A), depending on the severity and timing of the stressor. While LTP is defined as a sustained increase in synaptic transmission following a brief tetanic stimulation of afferent pathways, LTD is characterized by a decrease in synaptic efficiency following the low-frequency stimulation of afferent fibers. Together, LTP and LTD are forms of synaptic plasticity widely considered as potential mechanisms contributing to learning and memory (reviewed in Howland and Wang, 2008). Exposure to chronic or acute uncontrollable or intense stressors (chronic social defeat, inescapable shock, CUS or exposure to mixed restraint and swim stress) impairs induction of LTP in the Schaffer collateral-CA1 pathway (Kim et al., 1996; Ryan et al., 2010; Liu et al., 2012), commissural/associational input to the CA3 (Pavlides et al., 2002; Chen et al., 2010b), mossy fiber-CA3 synapses (Takeda et al., 2009; Chen et al., 2010a) and the medial perforant pathway to the DG (Pavlides et al., 2002). The stress-evoked impairment in LTP is noted to be more pronounced in the dorsal hippocampus, which plays a pivotal role in learning and memory, rather than the ventral hippocampus which is implicated in emotional processing (Maggio and Segal, 2009). These stress-evoked LTP deficits are fairly long-lasting and are noted up to 4 weeks following cessation of stressor experience (Ryan et al., 2010). However, whether chronic/severe stressors impair the early, late or both phases of LTP is currently unclear. Concomitant with impairments in LTP, multiple stressors potentiate hippocampal LTD at the Schaffer collateral-CA1 pathway (Xu et al., 1997; Holderbach et al., 2007). Furthermore, exposure to chronic stress also reduces α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated currents in the temporoammonic-CA1 synapses (Kallarackal et al., 2013). Behavioral studies are consistent with these synaptic plasticity deficits, demonstrating impairments on hippocampal-dependent cognitive tasks under conditions of stress (Kallarackal et al., 2013; Wagner et al., 2013).

Chronic stress-induced impairments in memory and synaptic plasticity are in part thought to result from

elevations in levels of GCs that act via the GRs to suppress LTP (Pavlides et al., 1996; Pavlides and McEwen, 1999) and impair hippocampal-dependent memory (Roozendaal et al., 2003). The attenuation of LTP by GRs is thought to involve extracellular signal-regulated kinase 1/2 (Erk1/2) activation (Yang et al., 2004) and N-methyl-D-aspartate (NMDA) receptor-mediated enhancement in intracellular calcium levels (Takahashi et al., 2002). Enhanced intracellular calcium via calcium-sensitive potassium channels has been suggested to suppress hippocampal excitatory activity (Joels and de Kloet, 1989; reviewed in Joels, 2001) (Figure 1C). Chronic stress-mediated stabilization of the leaky conformation of the ryanodine receptor also contributes to the disrupted calcium homeostasis and has been implicated in deficits in hippocampal LTP and cognitive dysfunction (Liu et al., 2012) (Figure 1C). A role for GRs in chronic stress-evoked impairment in hippocampal LTP is further strengthened by findings that demonstrate the reversal of these synaptic changes in the presence of a GR antagonist (Cazakoff and Howland, 2010) or post-adrenalectomy (Chen et al., 2010a). Other factors that possibly contribute to the stress-evoked impairment in LTP include enhanced CRH signaling via CRHR1 (Chen et al., 2010b; Wang et al., 2011a) and reduced trophic signaling (BDNF-TrkB) (Radecki et al., 2005; Aleisa et al., 2006) in the hippocampus.

In addition to changes that occur at the level of the hippocampus, modulatory inputs from multiple limbic circuits also influence hippocampal LTP in response to negative emotional experience. Enhanced and prolonged amygdalar input to the hippocampus, as under situations of stress, impair LTP in the DG and the CA1 subfield (Kim et al., 2005; Li and Richter-Levin, 2012), and such an impairment has been suggested to be dependent on both GCs and NE (Akirav and Richter-Levin, 2002).

Behavioral effects of chronic stress

Chronic stress and hippocampal-dependent cognitive function

Exposure to stress exerts a gamut of effects on various aspects of hippocampal-dependent cognitive behavior, influencing the acquisition, consolidation and retrieval of memory. These effects are dependent not only on the nature of the stress but also on the specific learning task employed, and the timing of the stressor with respect to the phase of learning (reviewed in Sandi and Pinelo-Nava, 2007). While stressors that are intrinsic to the learning task predominantly potentiate learning and memory (Sandi et al., 1997; Salehi et al., 2010), the effects of exogenous acute or chronic stressors are contingent on the nature of learning task. Severe acute or chronic stressors impair acquisition (Luine et al., 1994; Pawlak et al., 2005), consolidation (Park et al., 2008; Kallarackal et al., 2013) and retrieval (Wong et al., 2007; Park et al., 2008) of hippocampal-dependent spatial and non-spatial memory as tested on the Morris water maze (MWM) task, radial arm maze and novel object recognition task (Figure 1D). In contrast, both acute and chronic stressors evoke a potentiation of Pavlovian conditioned learning (Conrad et al., 1999; Shors, 2001; Cordero et al., 2003). The selective impairment of emotionally neutral memories, and potentiation of stressful memories, by temporally coincident severe adverse experience, possibly allows the consolidation of emotionally salient information at the expense of non-relevant information (Diamond et al., 2005).

The neural basis of this seemingly-contrasting effect of stress on different forms of learning and memory is currently unknown but can possibly be a consequence of the different brain regions recruited (Akirav et al., 2001; van Stegeren et al., 2010), and the modulatory neurotransmitters as well as levels of stress hormones released on exposure to the different learning tasks (van Stegeren et al., 2007). The memory impairing effects of stress have been attributed to elevated GC levels. Indeed, conditions in humans that result in hypercortisolism including aging (Shors, 2006) and depression (Marazziti et al., 2010) are associated with hippocampal-dependent cognitive dysfunction. Amongst the GC receptors, MRs are implicated in the reactivity to environmental stimuli and selection of behavioral strategies (Oitzl and de Kloet, 1992; Oitzl et al., 1994), whereas the GR function is thought to be required for consolidation of memories (Oitzl and de Kloet, 1992). A balance of GCs involving saturation of MRs and mild stimulation of GRs, as observed under conditions of mild stress, is thought to facilitate synaptic plasticity (Diamond et al., 1992; Rey et al., 1994). In contrast, predominant recruitment of the GRs as observed in severe stress strongly impairs hippocampal-dependent learning and memory (Segev et al., 2012). In addition to GCs, the chronic stress-mediated decline in levels of BDNF (Song et al., 2006) and growth hormone (Vander Weele et al., 2013), and the structural, cellular and network plasticity impairments noted in response to adverse experience (reviewed in Maras and Baram, 2012, Maras et al., 2014), also contribute to the stress-evoked spatial memory deficits. These findings are supported by similar temporal trajectories of recovery of hippocampal CA3 dendritic architecture and cognitive performance on hippocampus-dependent tasks following cessation of chronic stress (Luine et al., 1994; Sousa et al., 2000).

Chronic stress-mediated impairments in memory are mediated by various limbic regions in addition to the hippocampus, including the medial prefrontal cortex (mPFC) (reviewed in Holmes and Wellman, 2009) and the amygdala (reviewed in Roozendaal et al., 2009). In particular, the cross-talk between the amygdala and the hippocampus is thought to play an important role in stress-mediated impairment in memory retrieval (reviewed in Richter-Levin, 2004). Recent studies have demonstrated that chronic stress enhances functional connectivity between the amygdala and the hippocampus concomitantly reducing intra-hippocampal connectivity, thus possibly contributing to dysregulated emotionality and cognitive impairments (Ghosh et al., 2013).

Chronic stress and anxiety, depressive and social behavior

Repeated exposure to severe stressors is thought to precipitate psychopathological states in vulnerable individuals, including depressive and anxiety disorders. Indeed, many of the structural and molecular changes, including a decline in dendritic complexity and spine number (Soetanto et al., 2010), hippocampal atrophy (Sheline et al., 1996), reduced BDNF expression (Shimizu et al., 2003) and dysregulated HPA activity (Young et al., 1991), observed in rodent models of chronic stress exposure are mimicked in patients suffering from major depressive disorders (reviewed in Duman and Monteggia, 2006). These changes in dendritic architecture and spine morphology possibly affect synaptic and local circuit organization, and thus comprise a cellular substrate for altered emotional responses. Indeed, a strong negative correlation has been reported in rodents for anxiety responses to acute stress exposure (predator stress) and dorsal hippocampal DG neuron spine density (Adamec et al., 2012). Multiple animal models of chronic stress, including social defeat (Rygula et al., 2005), restraint stress (Strekalova et al., 2004; Wood et al., 2008) and CUS (Kompagne et al., 2008; Bessa et al., 2009), exhibit behavioral endophenotypes of major depression including behavioral despair, anhedonia and social avoidance (Figure 1D). Further, animals subjected to social isolation or CUS also exhibit enhanced anxiety (Koike et al., 2009; Ma et al., 2011) (Figure 1D), and potentiated fear and startle behavior (McGuire et al., 2010). While exposure to a variety of chronic or acute severe stressors evokes depressive and anxiogenic behavioral phenotypes, it is important to note that the nature and intensity of behavioral effects are dependent on both the specific stressor paradigm (Table 1), and the genetic background and epigenetic landscape of the animal (Chaudhury et al., 2014; O'Leary et al., 2014).

The stress-responsive hormonal mediators, namely GCs (Calvo et al., 1998; Jakovcevski et al., 2011), CRH (Smith et al., 1998; Kozlovsky et al., 2012) and acetylcholine (Mark et al., 1996; Mineur et al., 2013), are thought to contribute to enhanced emotionality observed following chronic stressors. Hippocampal infusion of antisense oligonucleotides for CRHR1 (Kozlovsky et al., 2012) post-stressor experience or loss of forebrain CRHR1 (Smith et al., 1998; Timpl et al., 1998) prevents stress-evoked anxiety behavior. Stress-mediated enhancement in emotionality is also mitigated by pharmacological blockade of adrenal steroid synthesis (Calvo et al., 1998) and hippocampal GR activity (Jakovcevski et al., 2011), prior to stressor experience. Multiple trophic factors and activity-associated genes whose hippocampal expression is repressed by stress (CUS, chronic restraint stress) such as the immediate early gene neuritin (Son et al., 2012), BDNF (Schmidt and Duman, 2010) and neuropeptide Y (NPY) (Thorsell et al., 2000; Cohen et al., 2012) also likely influence alterations in emotionality.

Thus far we have discussed the maladaptive effects that arise as a consequence of chronic or severe stress exposure. The various structural, cellular and physiological changes evoked by commonly used preclinical models of chronic stress are summarized in Table 1. While the field has largely focused on the adverse effects of stress, only recently has there been a growing understanding of the potentially positive consequences that arise in response to adult-onset stress exposure. The next section of this review examines the putative adaptive effects of stress at the molecular, structural and cellular level and explores the neuroendocrine, neurotransmitter and molecular factors that evoke such consequences.

Adaptive effects of adult mild stress exposure on the hippocampus

Acute mild stress, dendritic architecture and neuronal damage

Relatively few studies have examined if short-duration, mild or predictable stressors influence hippocampal neuronal structural remodeling. Acute restraint or tail shock stress enhances hippocampal CA1 neuron spinogenesis in males (Shors et al., 2001) (Figure 2B). While it is unclear if acute stress-mediated spinogenesis exerts an adaptive

Table 1: Maladaptive structural, synaptic and behavioral effects of adult stressors.

Stressor	Structural and cellular consequences	Synaptic plasticity and circuit changes	Behavioral consequences	References
Chronic restraint stress (6 h, 21 days, 2 h 10–12 days, 6 h, 1 day)	Reorganization of presynaptic vesicles and enhanced mitochondrial density in the vicinity of active zones in Mossy fibers, CA3 apical dendrite atrophy and decreased dendritic complexity, CA1 spine loss. Enhanced vulnerability to hypoxic, neurotoxic and metabolic insult. Reduced cell proliferation, survival, differentiation	Impaired LTP at the SC-CA1 pathway, the PP input to the DG, commissural/ associational input to the CA3	Impaired acquisition and retrieval in the MWM, and 8 arm radial arm maze test. Enhanced anxiety behavior, enhanced depressive behavior, anhedonia, novelty-induced hyperlocomotion	Watanabe et al., 1992; Luine et al., 1994; Magarinos et al., 1997; Pavlides et al., 2002; Strekalova et al., 2004; Pawlak et al., 2005; Atif et al., 2008; Wood et al., 2008; Veena et al., 2009; Christian et al., 2011; Liu et al., 2012; Hillerer et al., 2013
CUS (5 h single day, 1 month, 3–5 weeks)	CA3 neuron apical spine loss, CA1 neuron dendritic atrophy. Decreased DG granule cell dendritic length, MF synapse degeneration, MF synapse number and area. Enhanced vulnerability to hypoxic, metabolic insult. Reduced hippocampal neurogenesis	Impaired LTP in commissural-CA3 pathway. Enhanced CA1 LTD.	Impaired memory in the NOR. Impaired acquisition on the MWM. Anhedonia, social avoidance, learned helpless behavior on the FST. No change in anxiety behavior	Stein-Behrens et al., 1994; Sousa et al., 2000; Lee et al., 2006; Holderbach et al., 2007; Kompagne et al., 2008; Bessa et al., 2009; de Vasconcellos-Bittencourt et al., 2011; Gong et al., 2011; Ma et al., 2011
Social stressors (social defeat, severe fatal social stressor)	Decreased dendritic complexity, decreased CA3 neuron dendritic length. Depleted area of MF terminals, dendritic atrophy, nuclear pyknosis in the CA3, soma shrinkage and cell loss in the CA1, CA3 subfields. Reduced hippocampal proliferation and survival	Enhanced LTP threshold and potentiated LTD in the CA1	Impaired memory in the NOR task and the Y maze test	Uno et al., 1989; Magarinos et al., 1996; McKittrick et al., 2000; Czeh et al., 2001; Rygula et al., 2005; Lagace et al., 2010; Wang et al., 2011a; Wagner et al., 2013
Uncontrollable stress (inescapable shock)	Reduced hippocampal proliferation	Impaired LTP, enhanced LTD in the CA1	Impaired object recognition memory in long acquisition to retrieval delay test	Shors et al., 1989; de Quervain et al., 1998; Dagyte et al., 2009
Mixed stress	Cell loss in the CA1, CA3 subfields	Impaired SC/ commissural-CA1 LTP	–	Mizoguchi et al., 1992; Kim et al., 1996

Listed are the potential maladaptive structural, cellular, physiological and behavioral consequences evoked by various animal models of adult chronic or severe stressors, including chronic restraint stress, chronic unpredictable stress, social defeat, uncontrollable stressors and mixed/combination stressors. DG, dentate gyrus; FST, forced swim test; LTD, long-term depression; LTP, long-term potentiation; MF, mossy fiber; PP, perforant pathway; MWM, Morris water maze; NOR, novel object recognition; SC, Schaffer collateral.

or adverse influence on neuronal function, it is nevertheless interesting to note its striking dissimilarity to the hippocampal spine retraction observed following chronic stress (Pawlak et al., 2005). This effect of acute stress on spinogenesis is potentially mediated by GCs, which via GR-mediated activation of Erk1/2 signaling influence actin dynamics and enhance dendritic spine density (Jafari et al., 2012). Studies have also suggested a role for multiple kinases including mitogen-activated protein kinase, phosphophatidylinositiol-3 kinase, protein kinase A and protein kinase C (PKC) in the GC-mediated enhanced spinogenesis (Komatsuzaki et al., 2012). It is important to note here that while the hippocampus shows an increase in spine density in response to acute stressors, the very same stressor precipitates spine retraction in the amygdala (Marcuzzo et al., 2007), suggesting that the adaptive outcomes of stress are a consequence of its synergistic effects on multiple stress and fear processing circuits.

Chronic stress, in addition to evoking hippocampal structural reorganization, also enhances adult neuron vulnerability to neurotoxic insults. However, whether exposure to mild, predictable, controllable or acute stressors can serve to enhance cellular resilience or provide possible immunizing effects against future stressor experiences is currently unknown. A single prior study has demonstrated that diverse mild stressors (acute immobilization, cold stress or handling) enhance hippocampal glucose utilization in an NMDA receptor-dependent fashion (Schasfoort et al., 1988). This suggests the possibility that acute stressors can impinge on signaling pathways to influence cellular metabolism. In this regard, parallels can be drawn with studies where prior exposure to a mild stressor (mild hypoxia, mild oxidative stress, mild heat shock) primes cellular stress pathways and thus buffers cells from the damaging effects of strong stressors (Fonager et al., 2002; Kitagawa, 2012; Yoshiike et al., 2012). It is interesting to speculate that similar protective mechanisms may also be evoked by preconditioning with mild environmental stressors that then enable hippocampal neurons to cope with a future severe stressor. This tantalizing and hitherto unexplored area of investigation could unveil whether prior history of mild stressors allows for improved buffering for vulnerable hippocampal neurons from the damaging effects of severe stressors.

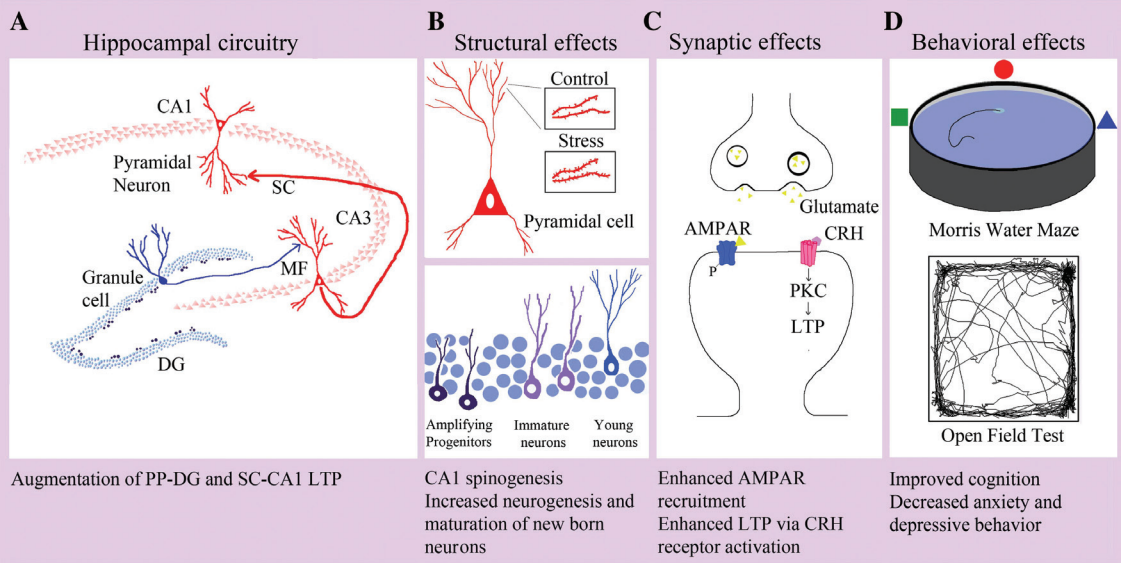

Figure 2: Adaptive consequences of acute, mild or predictable adult stressors on hippocampal structural plasticity, physiological responses and hippocampus-dependent behaviors. Exposure to acute, mild or predictable stressors elicits several potentially adaptive responses at the level of hippocampal structural and synaptic plasticity and hippocampal-dependent behaviors. (A) A graphical representation of the hippocampal circuitry. Acute stressors mediate an augmentation of perforant pathway – dentate gyrus (DG) and Schaffer collateral (SC)-CA1 long-term potentiation (LTP). (B) Exposure to acute stressors enhances spinogenesis in the hippocampal CA1 in males. In addition, enhanced hippocampal progenitor proliferation, morphological maturation of new born neurons and their recruitment by learning paradigms are also elicited by acute and predictable stressors. (C) The acute stress-evoked augmentation of LTP is thought to result from norepinephrine (NE)-mediated enhancement in GluR1 containing AMPA receptor (AMPAR) phosphorylation and its recruitment to synaptic sites, and corticotrophin releasing hormone (CRH)-mediated activation of protein kinase C (PKC). (D) Exposure to acute or predictable stressors evokes behavioral alteration including an improvement in the acquisition and retrieval in trace conditioning, contextual fear conditioning and spatial memory tasks. Further, animals exposed to predictable or controllable stressors exhibit anxiolytic and antidepressant behavior and resilience to the anxiogenic effects of future stressors. MF, mossy fiber.

Acute mild stress and hippocampal neurogenesis

Multiple recent studies have shown facilitatory effects of mild stressors on hippocampal neurogenesis. Exposure to chronic mild or predictable stressors, such as 5 min of daily restraint stress for 28 days in rodent models, or repeated disruption of social pairings in primate models, enhances hippocampal progenitor proliferation (Parihar et al., 2011) and neurogenesis (Lyons et al., 2010) (Figure 2B). Further, exposure to acute stressors (3 h immobilization) also enhances hippocampal progenitor proliferation (Kirby et al., 2013). Interestingly, these results are at variance with previous reports that demonstrated either no change (Thomas et al., 2007; Dagyte et al., 2009) or a decline (Gould et al., 1997) in hippocampal progenitor proliferation following acute stress exposure. A possible determinant of these contrasting findings is the handling of animals prior to the stress exposure and the nature of stress paradigm. It can be envisioned that prior handling of animals mitigates the novelty-associated stress of the paradigm, thus allowing for the adaptive aspects of the acute stressors to emerge. In addition to enhancing progenitor proliferation and hippocampal neurogenesis, exposure to acute or predictable stressors also accelerates the morphological maturation of newborn neurons (Parihar et al., 2011) and enhances their functional recruitment by learning paradigms (Kirby et al., 2013).

Recent evidence has shed some light on the possible molecular mediators of the neurogenic effects of acute/mild stress. Hippocampal expression of trophic factors such as fibroblast growth factor-2 (FGF-2) (Kirby et al., 2013), BDNF and insulin-like growth factor 1 (Lyons et al., 2010) is elevated following acute/mild stress experience. Given the robust proneurogenic effects of these trophic factors (reviewed in Lee and Son, 2009) an enhancement in their levels may contribute to the acute stress-evoked increased neurogenesis. Enhanced hippocampal neurogenesis and trophic signaling is a common feature of multiple forms of environmental stressors and cues that evoke adaptive neurological and behavioral consequences. Indeed behavioral models of learned safety that evoke antidepressant-like behavior also enhance hippocampal neurogenesis and BDNF expression (Pollak et al., 2008). A moderate rise in GCs and CRH in response to mild stressors may also act to increase hippocampal neurogenesis. GCs mediate a dose-dependent effect on hippocampal progenitor turnover, with low doses exerting potential proneurogenic effects in contrast to the high dose GC-evoked decline in progenitor turnover (Anacker et al., 2013a). *In vitro* studies demonstrate that GCs by activation of the MRs and notch signaling pathway (Anacker et al., 2013a) and via the astrocytic release of FGF-2 (Kirby et al., 2013) in the hippocampus increase the proliferation of adult hippocampal progenitors. CRH potentiates hippocampal neurogenesis *in vitro*, and *in vivo* can exert a protective effect against an elevated GC-induced decline in hippocampal progenitor proliferation (Koutmani et al., 2013). Given the correlation between hippocampal neurogenesis and hippocampal-dependent behaviors, enhanced neurogenesis coupled with accelerated maturation of new neurons may contribute to putative adaptive behavioral effects observed following mild stress.

Acute mild stress and hippocampal LTP

Stress exerts a bimodal effect on synaptic plasticity, with exposure to mild stressors (acute immobilization, handling and brief restraint stress) potentiating LTP both in the Schaffer collateral-CA1 and perforant pathway-DG synapses (Blank et al., 2002; Korz and Frey, 2003; Spyrka et al., 2011) (Figure 2A) and severe stress impairing hippocampal LTP in the very same circuits (Kim et al., 1996; Takeda et al., 2009). In particular, mild stressors (acute swim stress) prolong the perforant pathway-DG LTP by converting the early protein synthesis-independent phase of LTP to the stable protein synthesis-dependent late LTP (Korz and Frey, 2003). The contrasting effects of mild and severe stress on LTP possibly result from differences in the duration and frequency of elevated GC exposure, and stoichiometry of GRs and MRs recruited. The acute activation of both MRs and GRs by short-duration mild stressors likely plays a role in the induction of LTP, as this form of stress-evoked synaptic plasticity is lost in animals administered either GR or MR antagonists prior to the stressors (Spyrka et al., 2011). Other stress-evoked factors such as CRH and NE also contribute to enhanced hippocampal LTP. The acute stress (1 h immobilization stress) mediated induction of LTP in the Schaffer collateral-CA1 pathway (Blank et al., 2002) is blocked by a CRH receptor antagonist (Blank et al., 2002) (Figure 2C). Further, acute stress (predator odor) evoked NE release enhances phosphorylation of GluR1-containing AMPA receptors and their recruitment to synaptic sites, thus lowering the threshold for both DG LTP and contextual learning (Hu et al., 2007) (Figure 2C). An additional cellular mechanism that may add to the induction of LTP is the upregulation of the neuronal readthrough splice variant of acetylcholine esterase (AChE) in response to stress exposure. This particular AChE splice variant interacts with and activates PKCbetaII and promotes hippocampal LTP and contextual fear conditioning

(Nijholt et al., 2004). Taken together, these studies suggest that there is a narrow window of stressor intensity in which adverse experience may prime hippocampal synaptic plasticity and promote cognitive functioning. Such an idea naturally raises questions about what defines the range in which stress experience can be potentially beneficial. Also, given the individual variation that exists in stress responses, it would be interesting to explore the critical mechanisms that define the tipping point when stress experience shifts from beneficial to maladaptive.

Behavioral effects of acute mild stress

Acute mild stress and hippocampal-dependent cognitive function

It is generally accepted that individuals exhibit facilitated recall for events that are emotionally salient (Olff et al., 2005), which may also underlie the development of psychopathological conditions such as PTSD. While exposure to severe chronic or even acute severe stressors reliably impairs learning and memory, studies in animal models have shown that mild stress facilitates learning and memory (Sandi et al., 1997) (Figure 2D). To reconcile these contrasting effects of stress on memory, Joels et al. have proposed a theory that suggests that stress intrinsically linked to or temporally coincident with a learning task facilitates cognitive function (reviewed in Joels et al., 2006). Studies have shown that mild stress that forms an intrinsic aspect of the cognitive task facilitates learning (Sandi et al., 1997; Cordero et al., 1998; Salehi et al., 2010). However, the impact of stress on learning demonstrates a U-shaped dose dependence curve with very low or high stress-associated tasks eliciting lower performance (Sandi et al., 1997; Salehi et al., 2010). In addition to cognitive task-associated stressors, uncorrelated mild stress that temporally overlaps closely with learning paradigms also enhances hippocampal learning (Shors et al., 1992; Cordero et al., 2003; Ježek et al., 2010). Exposure to a single acute stressor (low intensity tail shock or 2 h restraint stress) prior to testing facilitates hippocampal associative learning as assessed by trace fear conditioning (Shors et al., 1992; Beylin and Shors, 2003) and contextual fear conditioning (Cordero et al., 2003; Rodríguez Manzanares et al., 2005). Further, exposure to mild stressors (immobilization for 15 min or 1 h but not 3 h, single forced swim stress, repeated 5 min restraint stress) also enhances consolidation and persistence of memory (Ježek et al., 2010; Parihar et al., 2011; Parfitt et al., 2012; Giachero et al., 2013). Stress-induced NE levels (Hu et al., 2007) and CRH (Blank et al., 2002) play an important role in mediating the beneficial effects of stress on cognitive function. NE in addition to enhancing arousal and attention to external cues potentiates hippocampal synaptic plasticity (Akirav and Richter-Levin, 2002) and learning (Quirarte et al., 1997), especially when released in a temporally overlapping fashion with corticosterone. Although stress hormones generally act in a facilitatory fashion when they are present around the time of learning, they have opposite effects on learning and recall of memory when present in high amounts either before or a considerable time after a learning task (de Quervain et al., 1998, 2000).

Acute mild stress and anxiety, depressive and social behavior

Though the positive effects of mild or acute stressors on learning and memory have been the focus of attention, the putative beneficial effects of such stressors on anxiety, mood and social behavior are relatively less well documented. A recent study has demonstrated that chronic exposure to a predictable mild stressor, comprising 5 min of daily restraint stress for 28 days, decreased anxiety and depressive behavior soon after the cessation of the stress paradigm (Parihar et al., 2011). Strikingly, these adaptive effects of predictable mild stress on emotionality are also observed long after stress exposure indicating the lasting nature of these consequences (Parihar et al., 2011). Behavioral paradigms that allow the animal to predict periods of safety from the stressors also result in the emergence of adaptive behavioral consequences. Exposure to learned safety, where the presence of a cue or a context predicts safety from a stressor, results in antidepressant and anxiolytic behavior in the presence of the safety signal (Pollak et al., 2008). These adaptive behavioral effects emerge even in the complete absence of the primary stressor, indicating generalization of the safety signal (Pollak et al., 2008).

In addition to predictability, controllability of the stressor also strongly influences stress responses. Studies in which two animals are yoked such that one animal of the pair controls the tail shocks administered to both, have demonstrated striking effects of behavioral controllability in mitigating the adverse effects of stress (Amat et al., 2005, 2006). While animals exposed to uncontrollable tailshocks exhibit a significant impairment in hippocampal LTP and demonstrate behavioral learned helplessness, exposure to the same duration and intensity of controllable tailshocks prevents the emergence of these adverse synaptic and behavioral

consequences (Shors et al., 1989; Amat et al., 2006). Further, prior exposure to controllable stressors results in an accelerated extinction of fear memories (Baratta et al., 2007), and prevents swim stress-induced enhancement in anxiety behavior (Christianson et al., 2009). While the role of the hippocampus in mediating the protective effects of controllable stressors on emotional behavior is unknown, the mPFC-raphe circuit has been particularly well studied in this regard (Amat et al., 2005; Christianson et al., 2009).

It is important to note here that both adaptive and maladaptive structural, cellular, physiological and behavioral changes mediated by adult stressors involve a role for the same set of neuroendocrine and neurotransmitter mediators, namely, GCs, CRH and NE. This suggests that the downstream signaling and receptor recruitment evoked by these factors within the hippocampus may vary quite significantly based on the levels of these neuroendocrine hormones and neurotransmitters, and their combinatorial states, both of which are determined by the nature of the stressor.

Thus far this review has focused on the bimodal effects of adult-onset stressors on hippocampal-dependent behaviors and hippocampal structural, cellular and synaptic plasticity (Tables 1 and 2). Furthermore, we have also discussed how the chronicity, severity, predictability and controllability of stressors may alter the nature of changes from being potentially adaptive to predominantly maladaptive. While the nature of adult stressors can dictate the short-term consequences of stress exposure (Heine et al., 2004; Lin et al., 2008), a key determinant of the persistence of these responses is often the timing of exposure to the stressor. Adult stress-evoked effects are relatively short lived, reverting to baseline soon after the cessation of the stressor; in contrast, adverse early life experiences mediate neuroendocrine and behavioral consequences that often exhibit life-long persistence (Champagne et al., 2008). The following segment of this review delves into the consequences of stressor exposure in early postnatal life and the manner in which the trajectory of its consequences is shaped both by the stressor paradigm and by the future environmental context.

Effects of early life stress exposure on the hippocampus

The effects of exposure to severe stress during early postnatal life have been examined using various rodent models including natural variations in quality of maternal care, maternal stress due to limited nesting material and prolonged durations of maternal separation (MS) (24 h single separation, or chronic 3–6 h separation during the first 1–3 weeks of postnatal life) (Tables 3 and 4). In addition, the effects of juvenile stress on hippocampal structural and functional plasticity have also been the focus of recent interest. Animals subject to such early life stressors exhibit certain common behavioral phenotypes including heightened anxiety, enhanced fearfulness and altered cognitive behavior that are observed long after the cessation of the stress. The relatively persistent nature of changes induced by early postnatal and adolescent adverse experiences has been linked to their temporal overlap with critical periods of limbic neurocircuit development (Sapolsky and Meaney, 1986; Schmidt et al., 2003). Although the HPA axis is hyporesponsive to environmental stressors in early postnatal life (Sapolsky and Meaney, 1986; van Oers et al., 1998), it is likely that exposure to early life adversity triggers additional responses which adversely influence limbic neurocircuit development (Korosi et al., 2010), thus programming life-long perturbations in emotional behavior. In this context, studies have implicated altered serotonergic neurotransmission including 5-HT_{1A} (Goodfellow et al., 2009) and 5-HT_{2A} receptor signaling (Benekareddy et al., 2010), and enhanced hippocampal CRH (Ivy et al., 2010; Wang et al., 2011b) as possible candidates that influence the development of emotionality and underlie the effects of early adverse experience.

Early life stressors such as maternal separation and low maternal care program life-long dysregulation in the basal and stress-evoked HPA axis responses. Animals that experience maternal separation, inadequate maternal care during postnatal life or acute stress during adolescence exhibit potentiated HPA axis activity on adult stress exposure, and an inability to normalize these responses following stressor termination (Liu et al., 1997; Kalinichev et al., 2002; Isgor et al., 2004). These perturbations are a consequence of enhanced PVN CRH expression (Ladd et al., 2005) and long-term transcriptional repression of hippocampal GR expression (Meaney et al., 1996; Weaver et al., 2004) that together impair feedback regulation of the HPA axis (Meaney et al., 1996; Ladd et al., 2004). In contrast, pups that received augmented maternal care during early postnatal life exhibit reduced excitatory input to the PVH (Korosi et al., 2010) and transcriptional repression of CRH during early life (Liu et al., 1997; Korosi et al., 2010). It has been suggested that the dysregulated HPA axis responses observed in animals with an early stress history adversely impact GC-sensitive limbic neurocircuits, such as the hippocampus, to mediate changes at the structural, cellular and synaptic level. These early

Table 2: Adaptive structural, synaptic and behavioral effects of adult stressors.

Stressor	Structural and cellular consequences	Synaptic plasticity and circuit changes	Behavioral consequences	References
Acute stress (restraint, tailshock)	Enhanced progenitor proliferation and enhanced recruitment of new born neurons in learning tasks. Enhanced CA1 neuron spinogenesis	Enhanced hippocampus SC-CA1 LTP. Decreased LTD in the DG	Enhanced contextual fear conditioning. Enhanced associative learning in trace fear conditioning. Enhanced memory recall	Shors et al., 2001; Blank et al., 2002; Nijholt et al., 2004; Ježek et al., 2010; Spyrka et al., 2011; Kirby et al., 2013
Predictable stress (5 min restraint daily for 28 days, repeated social instability)	Enhanced progenitor proliferation, enhanced neurogenesis and accelerated maturation of new born neurons	–	Improved learning and retention on the spatial memory tasks. Decreased anxiety and depressive behavior	Lyons et al., 2010; Parihar et al., 2011
Controllable stress	–	Prevents stress-induced impairment in hippocampal LTP	Enhanced fear extinction, decreased stress, evoked learned helplessness and anxiety behavior	Shors et al., 1989; Amat et al., 2006; Baratta et al., 2007; Christianson et al., 2009
Learned safety	Enhanced survival of new born neurons	–	Anxiolytic and antidepressant behavior in the presence of safety cue	Pollak et al., 2008
Mild stress	–	Enhanced PP-DG LTP, enhanced synaptic AMPAR recruitment, reduced SC-CA1 LTP threshold	Improved spatial learning, enhanced trace conditioning, enhanced contextual learning	Shors et al., 1992; Sandi et al., 1997; Korz and Frey, 2003; Hu et al., 2007

Listed are the potential adaptive structural, cellular, physiological and behavioral consequences evoked by various models of stressors, including acute stressors (tailshock, restraint, swim stress), predictable stressors, controllable stressors and mild stressors (predator odor, platform stress, mild tailshock). AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; DG, dentate gyrus; LTD, long-term depression; LTP, long-term potentiation; SC, Schaffer collateral.

stress-evoked changes could then mechanistically contribute to the life-long perturbations in anxiety, depressive and cognitive behavior observed in these animals.

Early life stress and hippocampal neuron dendritic architecture

Mimicking the hippocampal dendritic atrophy evoked by chronic adult stressors, exposure to adverse early life experiences such as unpredictable or prolonged maternal separation, inadequate maternal care and juvenile chronic restraint stress result in decreased hippocampal neuron dendrite arborization and spine density in the DG, CA3 and CA1 subfields in adulthood (Champagne et al., 2008; Bagot et al., 2009; Monroy et al., 2010; Oomen et al., 2010; Wang et al., 2011a, Eiland et al., 2012). Further, animals exposed to maternal separation in the first two weeks of postnatal life (3 h daily) also exhibit reduced adult mossy fiber density (Huot et al., 2002). Many of these structural changes evoked by adverse early environment are evident as late as in middle-aged life (Brunson et al., 2005) highlighting the persistent nature of the effects. Since all of the above postnatal stress models involve a disruption of mother-pup interactions, these findings also highlight the importance of maternal care in normal limbic neurocircuit development. Indeed, CA1 apical branch length, dendritic complexity and hippocampal GR expression in male rats are noted to be positively correlated with the quality of maternal care received (van Hasselt et al., 2012).

Early life stress and hippocampal neuronal damage

In addition to alterations in dendritic architecture, animals exposed to early life and juvenile adverse experience (prolonged maternal separation and 4 weeks of CUS, respectively) exhibit alterations at the cellular level, including a decline in hippocampal DG granule cell number (Fabricius et al., 2008; Oomen et al., 2011; Wang and Gondré-Lewis, 2013) and reduced hippocampal volume (Isgor et al., 2004). The reduction in hippocampal volume observed in response to adolescent stressors is a cumulative consequence of decreased developmental growth of the hippocampal CA1, CA3 and DG cell layers (Isgor et al., 2004).

Table 3: Maldaptive structural, synaptic and behavioral effects of early life stressors.

Stressor	Structural and cellular consequences	Synaptic plasticity and circuit changes	Behavioral consequences	References
Maternal separation (24 h single day, 3–6 h/days, P2-14 or P2-21)	Reduced CA1 dendritic arborization, reduced MF density. Reduced DG cell number. Enhanced postnatal neurogenesis, reduced or unaltered neurogenesis in young adulthood and reduced neurogenesis in middle-aged life. Decreased dendritic spine number in new born neurons	Impaired LTP at the SC-CA1 synapses. Reduced expression of multiple glutamatergic receptors	Age- and paradigm-dependent effects on hippocampal memory. Potentiated stress-evoked exacerbations in anxiety memory. Enhanced anxiety and fear	Lehmann et al., 1999; Huot et al., 2002; Roceri et al., 2002; Pickering et al., 2006; Aisa et al., 2008, 2009; Monroy et al., 2010; Oomen et al., 2010, 2011; Leslie et al., 2011; Herpfer et al., 2012; Suri et al., 2013, 2014
Low maternal care	Decreased CA1 dendritic length and spine number. Increased CA1 and DG apoptosis. Reduced hippocampal new born neuron survival and differentiation	Impaired SC-CA1 and DG synaptic LTP. Reduced excitatory synapses on the CA1 and CA3 neurons, decreased inhibitory synapses on the CA3 neurons	Impaired hippocampal-dependent spatial learning. Enhanced fear and anxiety behavior	Caldji et al., 1998; Weaver et al., 2002; Bredy et al., 2003; Menard et al., 2004; Champagne et al., 2008; Bagot et al., 2009
Low nesting material	Decreased dendritic spines in CA1 neurons, CA1 neuronal dendritic atrophy	Impaired CA3-commissural/associational LTP. Impaired SC-CA1 LTP in middle-aged life	Impaired hippocampal-dependent spatial memory in young adulthood and middle-aged life. High anxiety behavior	Brunson et al., 2005; Rice et al., 2008; Ivy et al., 2010; Wang et al., 2011b; Dalle Molle et al., 2012
Juvenile stress	Decreased CA3 dendritic complexity, decreased hippocampal volume. Decreased progenitor survival in adolescence and adulthood	Impaired dorsal hippocampal CA1 LTP. Augmented ventral hippocampal CA1 LTP. Impaired CA1 LTP in middle-aged life	Impaired hippocampal-dependent spatial memory. Anhedonia. Increased locomotion in response to novelty. Enhanced anxiety behavior	Isgor et al., 2004; Vidal et al., 2007; McCormick et al., 2010; Sterlemann et al., 2010; Barha et al., 2011; Maggio and Segal, 2011; Eiland et al., 2012

Listed are the potential maladaptive structural, cellular, physiological and behavioral consequences evoked by various models early life stress. The early life stressors discussed include maternal separation, low maternal care, limited nesting material model of maternal neglect and juvenile/adolescent stressors. DG, dentate gyrus; LTP, long-term potentiation; SC, Schaffer collateral.

Maternal neglect during early life also enhances apoptosis in both the DG and CA1 subfields of the hippocampus in adulthood (Weaver et al., 2002). Although the molecular underpinnings of these structural and cellular changes are not completely understood, factors similar to those implicated in the effects of adult stress such as elevated circulating levels of GCs (Lajud et al., 2012), increased hippocampal CRH signaling (Ivy et al., 2010; O'Malley et al., 2011; Wang et al., 2011b) and reduced trophic support (Lippmann et al., 2007; Aisa et al., 2009) in adulthood have been implicated.

Early life stress and hippocampal neurogenesis

The effects of early stress on hippocampal neurogenesis seem to vary depending on both the age of observation and the stressor paradigm employed. While maternal separation evokes enhanced hippocampal progenitor proliferation in postnatal life, at P15 (Nair et al., 2007) and P21 (Nair et al., 2007; Oomen et al., 2009; Suri et al., 2013; Loi et al., 2014), its influence on adult hippocampal neurogenesis is less clear. Studies have reported both a decline (Aisa et al., 2009; Hulshof et al., 2011) and no change (Oomen et al., 2011; Suri et al., 2013) in hippocampal progenitor proliferation in adult animals with a history of maternal separation. This discrepancy between studies could be a consequence of differences in strains and species of animals, the separation paradigms or the experimental controls used. The disparity in the effects of maternal separation also hints towards possible differences in vulnerability of different animal species and strains to early adverse experiences. Studies that have examined the influence of other models of early life stress (inadequate maternal care) on

Table 4: Adaptive structural, synaptic and behavioral effects of early life stressors.

Stressor	Structural and cellular consequences	Synaptic plasticity and circuit changes	Behavioral consequences	References
Maternal separation (24 h single day, 3 h/day, P2-14)	Increased hippocampal BDNF expression in young adulthood and postnatal life. Enhanced postnatal hippocampal neurogenesis	Augmented DG LTP in the presence of high corticosterone	Improved acquisition on hippocampal-dependent stressful spatial learning tasks, but not on emotionally neutral learning tasks	Oomen et al., 2010; Suri et al., 2013
Low maternal care	–	Augmented SC-CA1 LTP in the presence of high corticosterone	Enhanced learning on contextual fear conditioning	Champagne et al., 2008
Novelty stress	–	–	Improved spatial working memory, improved HPA axis response to adult mild stressor exposure. Improved social coping and social recognition	Tang et al., 2003, 2006
Juvenile stress (predator odor, novelty exposure, social defeat, acute restraint acute footshock, social isolation)	Increased hippocampal BDNF and VEGF expression, increased supra-pyramidal MF volume, increased hippocampal CA1 and DG neuronal density	–	Improved hippocampal-dependent spatial memory. Enhanced fear memory. Decreased anxiety and depressive behavior. Improved behavioral and physiological coping in response to adult stress exposure	Frisone et al., 2002; Avital and Richter Levin, 2005; Miura et al., 2011; Oztan et al., 2011; Uysal et al., 2012; Buwalda et al., 2013; Reich et al., 2013

Listed are the potential adaptive structural, cellular, physiological and behavioral consequences evoked by various models early life stress. Early life stressors discussed include maternal separation, low maternal care, limited nesting material model of maternal neglect and juvenile/adolescent stressors. BDNF, brain-derived neurotrophic factor; DG, dentate gyrus; HPA, hypothalamo-pituitary-adrenal; LTP, long-term potentiation; PP, perforant pathway; SC, Schaffer collateral; VEGF, vascular endothelial growth factor.

hippocampal neurogenesis have noted a decline in hippocampal progenitor proliferation in young adulthood, concomitant with impaired progenitor survival and neuronal differentiation (Bredy et al., 2003; Koehl et al., 2012), reduced complexity of dendritic arborization and fewer dendritic spines (Leslie et al., 2011) in newborn neurons. Chronic restraint stress during adolescence (P30-52) also reduces hippocampal progenitor survival in female rats when assessed in adolescence (McCormick et al., 2010) and adulthood (Barha et al., 2011). The consequences of postnatal maternal separation on neurogenesis are also observed in aged life. As maternally separated animals age, they begin to demonstrate an accelerated age-dependent decline in hippocampal neurogenesis, including both a reduction in progenitor proliferation and a steep decline in immature neuron numbers (Suri et al., 2013). It is tempting to speculate that the postnatal induction in hippocampal progenitor proliferation noted in early stress animals may count out the limited number of cell divisions of quiescent stem cells (Kippin et al., 2005) and exhaust stem cell numbers, thus contributing to the eventual neurogenic decline noted in middle-aged life.

Early life stress and hippocampal LTP

Exposure to maternal separation (Herpfer et al., 2012), inadequate maternal care (Champagne et al., 2008; Bagot et al., 2009) and juvenile stress (Maggio and Segal, 2011) impairs hippocampal Schaffer collateral-CA1 and DG LTP. These adverse effects of early life and adolescent stressors on Schaffer collateral-CA1 synaptic plasticity are evident as late as in middle-aged life, concomitant with deficits in spatial learning (Ivy et al., 2010; Sterlemann et al., 2010, Sousa et al., 2014). Mimicking the adult stress-evoked effects, juvenile stress also evokes differential effects on dorsal and ventral hippocampal LTP. Juvenile stress impairs CA1 LTP in the cognitive function-associated dorsal hippocampus, while facilitating LTP in the emotional behavior-linked ventral hippocampus (Maggio and Segal, 2011). Additionally, in animals with a history

of juvenile adverse experience, the adult stress-mediated dissociation of the dorsal versus ventral hippocampal synaptic plasticity is enhanced and prolonged, hinting at an interaction of early life history and adult experience (Maggio and Segal, 2011).

Though the mechanistic underpinnings of the early stress-mediated impairments in synaptic plasticity are not well understood, alterations in excitatory and inhibitory inputs could potentially contribute to these changes. Indeed different models of early life stress exhibit differences in glutamate and GABA receptor expression and activity. Animals that receive low maternal care in postnatal life exhibit fewer excitatory synapses in the CA1 and CA3 subfields of the hippocampus with a concomitant reduction in the number of inhibitory synapses in the CA3 subfield (Wang et al., 2011b). In maternally separated animals, the hippocampal expression of multiple NMDA receptor subunits (NR2A, NR2B), AMPA receptors subunits (GluR1, GluR2) and metabotropic glutamate receptor mGluR4 is reduced, thus possibly influencing stoichiometry of glutamatergic receptors and glutamatergic receptor-driven electrophysiological responses and signaling (Roceri et al., 2002; Pickering et al., 2006; Martisova et al., 2012; O'Connor et al., 2013; Suri et al., 2014).

Behavioral effects of early life stress exposure

Early life stress and hippocampal-dependent cognitive function

In addition to the long-lasting alterations at the structural, cellular and circuit levels in the hippocampus, exposure to early stress also programs persistent changes in hippocampal-dependent cognitive behavior. However, the nature of these changes is largely dependent on the early stress paradigm in question. Exposure to the limited nesting material model of maternal neglect (Rice et al., 2008; Wang et al., 2011b) or severe adolescence stressors (social instability stress or CUS) (Isgor et al., 2004; McCormick et al., 2012) impairs hippocampal-dependent memory when tested using both spatial and non-spatial tasks. However, the effects of maternal separation on learning and memory have been less consistent, with multiple studies demonstrating either an impairment (Aisa et al., 2008; Oomen et al., 2010), no effect (Grace et al., 2009) or even an improvement (Makena et al., 2012; Suri et al., 2013) in cognitive function depending on the nature of separation paradigm, strain of the animal, emotional context of the learning task used and the age of testing. However, a consistent observation across diverse models of early stress is the hastening of age-associated impairments in performance on hippocampus-dependent spatial learning tasks (Ivy et al., 2010; Sterlemann et al., 2010; Suri et al., 2013). This suggests that a history of early stress may interact with the aging process, to hasten and accelerate age-induced neuronal damage and cognitive decline. While thus far studies have not directly assessed the effects of early stress on aging, clinical studies indicate shorter telomere lengths in individuals with a history of early life trauma (Tyrka et al., 2010).

Early life stress and anxiety, depressive and social behavior

The most robust and persistent effects of early adverse experience are noted on emotionality and stress coping. Inadequate maternal care or postnatal stressors (maternal separation, social intruder stress), in the first two weeks of postnatal life, result in enhanced anxiety responses (Lehmann et al., 1999; Kalinichev et al., 2002; Caldji et al., 2004; Dalle Molle et al., 2012) and potentiated fearfulness (Caldji et al., 1998; Kalinichev et al., 2002; Menard et al., 2004) in adulthood. Further, a history of maternal separation exacerbates the effects of adult chronic stressors on anxiety and depressive behavior (Aisa et al., 2008). Exposure to juvenile or adolescent stressors (resident intruder stress, or chronic restraint) also induces social avoidance (Vidal et al., 2007), anhedonia and increased novelty-induced locomotion (Eiland et al., 2012). However, similar to adult stressors, controllability over stress in adolescence prevents the emergence of maladaptive effects on anxiety behavior in adulthood (Kubala et al., 2012).

Accompanying the enhanced anxiety and depressive behavior are neurotransmitter and neuroendocrine changes that play a role in these behavioral consequences. Rats exposed to maternal separation exhibit enhanced 5-HT turnover (Daniels et al., 2004) and postnatal blockade of $5HT_{2A/2C}$ receptor signaling blocks the emergence of maternal separation-associated anxiety behavior (Benekareddy et al., 2011). In addition, the epigenetic repression of GR in the hippocampus and the resulting dysregulation of the hippocampal feedback control of the HPA axis have also been implicated in mediating enhanced emotionality in low maternal care animals (Weaver et al., 2006). The above causality is strengthened by the finding that blocking the epigenetic repression of GR expression reverses the anxiety behavior observed in these animals (Weaver et al., 2006). Adult blockade of GR and treatment with the beta-adrenoceptor antagonist propranolol (Aisa et al.,

2007) also completely reverse the depressive behavior and memory deficits observed in maternally separated animals.

Adaptive effects of early life stress exposure on the hippocampus

While early stress-evoked consequences have been predominantly classified as maladaptive, recent studies have explored the possibility that exposure to these stressors during early life may also induce potentially adaptive changes depending on the nature of the adult environmental context (Avital and Richter-Levin, 2005; Tang et al., 2006; Champagne et al., 2008; Suri et al., 2013) (Table 4). The 'tuning hypothesis' suggests that exposure to stress during early life can act as a predictor of future adversity and can fine tune neurocircuitry to enable future stress coping (Beery and Francis, 2011). A key determinant for the emergence of these adaptive effects, however, is the adult environmental context (Champagne et al., 2008; Suri et al., 2013). Similarly, according to the 'match-mismatch' hypothesis, animals subjected to stressors during early life may perform better and thus have a better survival advantage if their future environment matches that encountered in early life (Schmidt, 2011). This hypothesis has been validated by multiple studies that demonstrate that animals exposed to early stressors of low maternal care, maternal separation or postnatal novelty exposure perform better in stressful but not emotionally neutral learning tasks (Champagne et al., 2008; Suri et al., 2013). Mild adolescent stressors including single tailshock or social isolation show improved hippocampal-dependent spatial memory when tested in adulthood on inherently stressful learning tasks such as the MWM (Frisone et al., 2002; Avital and Richter-Levine, 2005; Uysal et al., 2012). Juvenile stress exposure also results in improved performance on episodic fear memory tasks (Reich et al., 2013). Though when present in a severe form the enhancement in fear learning accompanied by an inability to extinguish aversive memories denotes a PTSD-like phenotype, in its milder forms it likely represents a potentially adaptive alteration. These specific improvements in stress-associated tasks and fear-related learning are possible indicators of an early life reprogramming of circuits which enables potentiated encoding or retention of emotionally relevant information that facilitates future survival in adverse contexts. The improved stress-associated learning in early stress animals also likely involves enhanced arousal and attention to emotionally salient cues. Indeed, key arousal circuitry such as locus coeruleus neurons exhibits higher tonic firing rates in MS animals, and these changes may underlie the differential behavioral reactivity (Swinny et al., 2010). Strikingly, the adaptive effects of early life stress appear to be transmitted transgenerationally with the progeny of animals subjected to maternal separation combined with unpredictable maternal stress exhibiting enhanced behavioral flexibility and improved goal directed behavior (Gapp et al., 2014).

The mild early stress-induced adaptive consequences on stress-associated cognitive behavior are accompanied by corresponding changes in synaptic plasticity in the hippocampus. Animals born to low maternal care giving mothers exhibit impaired hippocampal LTP under low corticosterone conditions, but strikingly improved LTP under conditions of high corticosterone (Champagne et al., 2008; Oomen et al., 2010). Mild elevations in postnatal corticosterone (Macrì et al., 2009), hippocampal cellular changes (Uysal et al., 2012; Suri et al., 2013) and enhanced trophic factor expression (Uysal et al., 2012; Suri et al., 2013) have been thought to contribute to the adaptive effects of early and juvenile stress on hippocampus-dependent cognitive function.

Exposure to mild stressors in early postnatal and juvenile life has recently been linked to a decline in anxiety and depressive behavior. Rodents exposed to novelty stress during postnatal life and primates subjected to mild social stress during adolescence demonstrate enhanced social recognition (Tang et al., 2003), social coping and improved neuroendocrine response to stress (Tang et al., 2006; Lee et al., 2014). Further, anxiolytic and antidepressant effects of adolescent mild stress (acute exposure to predator odor, mild complex stressors and chronic predictable mild stress) have also been noted (Miura et al., 2011; Oztan et al., 2011; Suo et al., 2013).

The adaptive behavioral effects of postnatal and adolescent stressors are accompanied by molecular and cellular alterations, thus providing an insight into their mechanistic underpinnings. The improvement in stress coping in primate models of adolescent stress is accompanied by an increase in GR expression in the anterior cingulate cortex but not the hippocampus (Lee et al., 2014), suggesting enhanced feedback regulation of the HPA axis (reviewed in Jankord and Herman, 2008) in these animals. Adolescently stressed animals that exhibit enhanced behavioral and physiological coping to adult defeat episodes (Buwalda et al., 2013) concomitantly show increased supra pyramidal-mossy fiber and mossy fiber terminal field volumes (Oztan et al., 2011) indicating dynamic hippocampal circuit changes. The results of these recent studies challenge the prevailing notion that adverse early

life experience is deterministic for future psychopathology, and provide support for a more nuanced perspective on the role of early life environment in shaping adult behavior.

To summarize, our review indicates that stressor experience can evoke changes at the molecular, cellular, synaptic and structural level along a continuum, with putative adaptive and maladaptive consequences emerging based on the nature of stressor, timing of exposure, controllability and predictability of stress, life history and the context in which stress effects are tested. On reviewing the existent literature, it is tempting to parcellate stressor effects into end states that are either protective or damaging. However, current studies do not allow us to reach such a conclusion about the stress-elicited effects and behavioral states. Rather, we believe that these results confirm the notion that stress experience serves to alter the manner in which we buffer life events proving to be beneficial or harmful based on the nature of future life events we encounter.

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