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Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders

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Abstract

Stress responses entail neuroendocrine, autonomic, and behavioral changes to promote effective coping with real or perceived threats to one's safety. While these responses are critical for the survival of the individual, adverse effects of repeated exposure to stress are widely known to have deleterious effects on health. Thus, a considerable effort in the search for treatments to stress-related CNS disorders necessitates unraveling the brain mechanisms responsible for adaptation under acute conditions and their perturbations following chronic stress exposure. This paper is based upon a symposium from the 2014 International Behavioral Neuroscience Meeting, summarizing some recent advances in understanding the effects of stress on adaptive and maladaptive responses subserved by limbic forebrain networks. An important theme highlighted in this review is that the same networks mediating neuroendocrine, autonomic, and behavioral processes during adaptive coping also comprise targets of the effects of repeated stress exposure in the development of maladaptive states. Where possible, reference is made to the similarity of neurobiological substrates and effects observed following repeated exposure to stress in laboratory animals and the clinical features of stress-related disorders in humans.

INTRODUCTION

One of the major limitations in stress research related to disease etiology is the difficulty in distinguishing between what are considered as adaptive versus maladaptive coping mechanisms. Characterization of each of these can be a matter of perspective and context (Herman, 2013). Stress responses promote survival by helping organisms meet the demands of a variety of acute challenges in the short-term (Huether, 1996; Levine and Ursin, 1991;

McEwen, 2004; Ursin and Olff, 1993), yet they are also linked with impaired functioning and the development of pathology under repeated activation or extended conditions (Chrousos, 2000; Mann, 1999; McEwen, 2000; Pasternac and Talajic, 1991; Paykel, 1976; Shively et al., 2009; Vanitallie, 2002). One popular formulation of maladaptation is allostatic load, and refers to the cumulative effects or "costs" generated following repeated stress exposure on multiple physiologic systems (Brindley and Rolland, 1989; McEwen and Stellar, 1993). In a similar vein, stress responses can also be thought of as representative of the recruitment of a global response systems (i.e., neuroendocrine, autonomic, and behavioral) to any threat, real or perceived, that overwhelms selective homeostatic systems (Day, 2005). In this framework, the prolonged induction of stress responses in the face of repeated challenges are unable to prevent the adverse consequences associated with the breakdown of specific homeostatic systems. Over time, the cumulative effects of chronic stress are linked to a variety of adverse health consequences, such as hypertension, atherosclerosis, metabolic syndrome, diabetes, infertility, immunosuppression, osteoporosis, psychopathologies, and even neurodegenerative diseases.

The physiological response to stress entails activation of sympathoadrenal, (i.e., “fight-or-flight”) and hypothalamo-pituitary-adrenal (HPA) systems. Over the years, glucocorticoids (cortisol in primates, corticosterone in rodents), the end-products of HPA axis output, have taken center stage as primary mediators of stress-related disorders (Herman, 2013; McEwen, 2004). Under acute conditions, glucocorticoids redirect metabolism for increased energy demands, bias the response properties of other physiological systems, and promote cognitive adjustments associated with adaptive responses to environmentally salient experiences. Importantly, in the aftermath of a stressful experience, adrenocortical hormones help to restore HPA functioning to pre-stress levels via receptor mediated negative feedback. Nevertheless, heightened or prolonged glucocorticoid levels such as during chronic stress exposure are known to be predictive of, and contribute to, the development of various disease states (Aguilera, 1994; Post, 1992; Post and Weiss, 1998; Ursin, 2014).

Differential responsiveness of stress systems are also influenced by early-life experience, hereditary factors, and stress history, and have been shown to predict susceptibility to neuropsychiatric and somatic diseases in humans (Biondi and Picardi, 1999; Claessens et al., 2011; Dickerson and Kemeny, 2004; McEwen and Stellar, 1993; Reiss et al., 2013). Robust sex differences in the prevalence of stress-related psychiatric disorders highlight the role of gonadal steroids in differentially altering stress responses and susceptibility under repeated conditions (Kessler, 2003; Kessler et al., 1993; Kessler et al., 1995; Ter Horst et al., 2009; Weissman et al., 1993). Taken together, elucidating the neural mechanisms of stress responses, their alterations under chronic conditions, individual or population differences influencing these processes, and how these factors influence susceptibility for psychiatric illness, has been a dauntingly complex undertaking for stress neurobiologists. Nevertheless, significant progress has been made in laying the groundwork for understanding these issues, and this review will summarize the current state of knowledge and some recent developments from a basic research perspective.

STRESS AND LIMBIC NETWORK PLASTICITY

Stress triggers autonomic, endocrine, and behavioral responses regulated by multiple brain circuits and neurochemical systems (Cullinan et al., 1995; Dallman, 2000; Dayas et al., 2001; Herman and Cullinan, 1997; Herman et al., 2003; Joels et al., 2012; Li and Sawchenko, 1998; Radley and Sawchenko, 2011). Whereas, physiological stressors involve more targeted challenges that overwhelm selective homeostatic systems, such as hemorrhage, hypoxia, or immunogenic stimuli, emotional (a.k.a., psychogenic, psychological, processive) stressors require interpretation by exteroceptive sensory modalities and integration with distinct cognitive (comparison with past experience) and affective (positive or negative valence) information processing systems in the brain (Dayas et al., 2001; Herman and Cullinan, 1997; Sawchenko et al., 2000). Commonly employed animal models of emotional stress are restraint, footshock, noise, and social defeat. Whereas each class of stressor enlists brainstem and hypothalamic effectors for activation of the sympathoadrenal and HPA axis output, emotional stressors manifest widespread activation in the limbic forebrain, and correspond to a broad array of behavioral changes (e.g., vigilance, fear) that help to facilitate adaptive coping as required by the specific environmental demand (Campeau and Watson, 1997; Cullinan et al., 1995; Dayas et al., 2001; Li and Sawchenko, 1998). Emotional stressors are further distinguished by their capacity to induce long-term alterations in limbic forebrain networks that are associated with cognitive and affective symptoms in stress-related disorders.

The HPA axis is often regarded as the canonical stress response system (Munck et al., 1984; Selye, 1980). Early investigations into glucocorticoid functions arose from observations that their receptors are widely expressed and distributed in the entire body and brain, and are especially enriched in many of the limbic forebrain networks involved in the genesis of stress responses (Gerlach and McEwen, 1972; McEwen et al., 1986; McEwen et al., 1968; Sapolsky et al., 1983b). Evidence from animal studies and post mortem brains of patients that suffered from mood disorders show decreases in density and/or expression levels of corticosteroid receptors throughout the limbic forebrain (Alt et al., 2010; de Kloet, 1987; Furay et al., 2008; Klok et al., 2011; Matsubara et al., 2006; Patel et al., 2008; Perlman et al., 2004; Sapolsky et al., 1983a; Sapolsky et al., 1984b). This diminished sensitivity to glucocorticoids is likely to impair the capacity of these networks to optimally respond to subsequent challenges for promoting cognitive and affective adjustments for adaptation. Alterations in the forebrain distribution of this receptor population also disrupts negative feedback regulation of HPA axis (Dallman and Jones, 1973; de Kloet, 1987; Keller-Wood and Dallman, 1984; Sapolsky et al., 1984a), and underlies HPA axis abnormalities in major depression and post-traumatic stress disorder (PTSD; (de Kloet et al., 2005; Holsboer, 2000; Mason et al., 1986; Mathew et al., 2008; Pariante and Miller, 2001; Pariante et al., 1995; Strohle and Holsboer, 2003; Yehuda, 2002)). Below, we shall highlight the involvement of several key forebrain regions - amygdala, hippocampus, and prefrontal cortex that are implicated in the modulation of stress responses, with specific reference to how neuroplasticity in these networks may contribute to maladaptive changes.

Amygdala

The amygdaloid complex is implicated in a wide array of behavioral, autonomic, and neuroendocrine responses relevant to stress, such as aversive learning, associative fear conditioning, and anxiety (Allen and Allen, 1974a; Davis, 1992; LeDoux, 2000; Loewy, 1991; McGaugh, 2002; Ressler, 2010; Shekhar et al., 2003). Information flow through the amygdala is generally considered to begin by afferent input into the lateral amygdala, and through several intrinsic pathways in the basolateral complex (BLA) before relaying to central nucleus (CeA), which provides the principal source of extrinsic connections with behavioral, autonomic and endocrine effector systems (Pitkänen and Amaral, 1998; Pitkänen et al., 1997; Pitkanen et al., 1995). The amygdala exhibits the capacity to facilitate most of these functions under both acute and chronic stress conditions, and in some instances may even show augmentation or sensitization following repeated stress exposure. These experimental data are consistent with human imaging studies showing increased amygdaloid volume (Frodl et al., 2002; Lange and Irle, 2004; Lupien et al., 2011; Shin and Liberzon, 2010; Weber et al., 2013) and functional activity (Breiter et al., 1996; Drevets et al., 1992; Siegle et al., 2002; Thomas et al., 2001) in individuals suffering from depression or anxiety disorders, and suggest that its dysfunction or hyperactivity may be a key contributor in the pathogenesis of anxiety disorders, PTSD, and related symptomatologies in other types of mental illnesses.

Under acute conditions, stress-induced HPA activation is generally facilitated or attenuated by CeA stimulation or lesions, respectively (Allen and Allen, 1974b; Beaulieu et al., 1986; Carter et al., 2004; Prewitt and Herman, 1994, 1997; Van de Kar et al., 1991; Prewitt and Herman, 1994; cf. Prewitt et al., 1997; Carter et al., 2004). The circuitry accounting for how stress-stimulatory influences from the amygdala reach HPA-effector neurons in the paraventricular hypothalamic nucleus (PVH) remains to be tested, it likely involves disynaptic relays via components of the bed nuclei of the stria terminalis (Sun et al., 1991; Tsubouchi et al., 2007). Amygdala activation following acute stress exposure is also critically important for memory consolidation (Roozendaal and McGaugh, 1997; Wolff et al., 2014), and may be enhanced by a variety of neurochemicals, most notably corticosteroids and brainstem aminergic inputs into BLA (McGaugh, 2002; Roozendaal et al., 2009; Roozendaal and McGaugh, 2011). These effects are produced via widespread activation of the limbic forebrain brought about by the extensive and divergent projection systems emanating from BLA, although the specific neural circuits likely depend on the particular type of learning or memory systems undergoing modulation (McGaugh, 2006).

Evidence from *in vitro* and *in vivo* physiological studies suggests that amygdala responses following acute stressors are also excitatory, although some studies suggest inhibitory effects (Buffalari and Grace, 2007; Chen and Sara, 2007; Correll et al., 2005; Garcia et al., 1998; Kavushansky and Richter-Levin, 2006; Kavushansky et al., 2006; Pelletier et al., 2005; Shors, 1999; Vouimba et al., 2006; Vouimba et al., 2004). Direct manipulations of corticosteroid or noradrenergic receptors within BLA mimics some of the excitatory effects observed in acute stress studies, via the induction of high-voltage activated calcium currents (Karst et al., 2002; Liebmann et al., 2008), reducing $GABA_A$ receptor mediated currents (Duvarci and Pare, 2007) and increasing the amplitude and frequency of AMPA receptor-

mediated responses (Karst et al., 2010; Liebmann et al., 2009). Nevertheless, contrasting patterns of amygdala activation is likely accounted for by differences in the recording methodologies and the fact that there is a substantial degree of intrinsic processing within this region. For instance, the application of optogenetic techniques to this problem have generally verified that activation of BLA promotes anxiety-like responses in rodents, whereas stimulation of BLA-projecting inputs into CeA were observed to reduce these behaviors (Tye et al., 2011). Moreover, both BLA and CeA contain heterogeneous intrinsic subpopulations of interneurons that differentially modulate adaptive behavioral responses (Ciocchi et al., 2010; Haubensak et al., 2010; Wolff et al., 2014). Collectively, these studies highlight the fact that amygdala activation of autonomic, endocrine, and behavioral outputs are mediated via intrinsic disinhibitory mechanisms within BLA and CeA.

The amygdala plays a similar role in modulating these same response systems following repeated stress exposure, albeit typically to a greater degree than under acute conditions. Many of these sensitizing actions can be understood in terms of the apparent anabolic effects produced by repeated stress exposure on amygdala plasticity and activity. Interestingly, these anabolic-like effects of amygdala functioning have yet to be reconciled with the fact that the increased metabolic demands associated with prolonged glucocorticoid exposure are mostly catabolic in nature. Increases in intrinsic BLA neural electrotonic properties (larger membrane resistance and time constants) and excitability have been observed *in vivo* following repeated restraint stress (Rosenkranz et al., 2010; Zhang and Rosenkranz, 2012). Enhanced excitatory synaptic drive into BLA principal neurons has also been reported after repeated restraint (Padival et al., 2013), which is simultaneously associated with reductions in tonic GABAergic control (Liu et al., 2014; Suvrathan et al., 2014) and increased expression and activation of NMDA receptors (Mozhui et al., 2010; Suvrathan et al., 2014). Indeed, whereas amygdala excitability under acute conditions involves a larger AMPA receptor-mediated component (Karst et al., 2010; Liebmann et al., 2009), sustained activity following chronic stress appears more closely associated with NMDA receptor functioning (Mozhui et al., 2010; Suvrathan et al., 2014).

Studies examining the effects of chronic stress on structural plasticity in the amygdala have identified substantial increases in excitatory synaptic input into BLA principal neurons. Repeated restraint stress in rats increased both dendritic branching and spine density in BLA pyramidal-like neurons (Mitra et al., 2005; Vyas et al., 2002). This neuronal hypertrophy was observed to correspond specifically with a repeated stress regimen resulting in elevated plasma levels of glucocorticoids (Vyas et al., 2002), and subsequent studies have shown that adrenal steroid administration also increases dendritic spine density in BLA neurons (Mitra and Sapolsky, 2008). In fact, increases in spine density in amygdala neurons, whether induced by stress or glucocorticoids as in the aforementioned studies, or as a preexisting genetic condition (Adamec et al., 2012), are each linked with increased anxiety-like behaviors. In addition to glucocorticoids, tissue plasminogen activator enzyme, corticotropin-releasing hormone (CRH) and brain derived neurotrophic factor have also been implicated in stress-related structural plasticity in the amygdala, and recent evidence suggests that epigenetic mechanisms may mediated their induction (for reviews, see (Bennett and Lagopoulos, 2014; Gray et al., 2013; Maddox et al., 2013; McEwen et al.,

2012). Differential susceptibility of mice to display anxiety-like behaviors has also been linked to epigenetic marks on the CRHR1 receptor gene promoter region (Sotnikov et al., 2014).

Collectively, the evidence suggest that durable increases in amygdala plasticity may be initiated by, and maintained long after the abatement of stress exposure. These studies help to envisage how structural and functional alterations in the amygdala could play an important role in the sequelae of events initiated by stress, that, while adaptive for survival (i.e., heightened vigilance and arousal, enhancement of aversive memories to harmful stimuli and contexts), may also lead to anxiety and states of hypervigilance that are maladaptive.

Hippocampal Formation

Over the past several decades, the hippocampus has been the quintessential limbic region implicated in stress regulation. Attention was first directed to this, when autoradiographic evidence revealed prominent steroid binding in hippocampal cell layers, relative to other limbic regions (McEwen, 1994; McEwen et al., 1969). Since then, numerous studies have shown that the hippocampal formation has the capacity to inhibit the HPA axis under both basal and stress conditions, is a prominent site for glucocorticoid receptor-mediated feedback, and is essential for restoring glucocorticoids to baseline levels following the cessation of stress ((Herman et al., 1992; Herman, 1992; Herman et al., 1995b; Herman et al., 1989; Jacobson and Sapolsky, 1991; Sapolsky et al., 1984a) cf.(Tuvnes et al., 2003)). The circuitry accounting for how hippocampal influences are regulated over HPA effectors in PVH has been anatomically characterized (Cullinan et al., 1993), and functionally, is relayed in part via extrinsic projections from the ventral subiculum that project to GABAergic neurons in the anterior division of the bed nucleus of the stria terminalis, and in turn, to PVH (Radley and Sawchenko, 2011)(see Box 1).

Both acute and repeated stress are associated with the disruption of hippocampal memory functions in many species (Conrad, 2008; Conrad et al., 1996; Kim and Diamond, 2002; Luine et al., 1994; McLaughlin et al., 2007; Sousa et al., 2000; Venero et al., 2002), and can be recapitulated by increasing glucocorticoid levels (Bodnoff et al., 1995; Dachir et al., 1993; Luine et al., 1993; McLay et al., 1998). By contrast, there is also evidence that hippocampal-dependent functions may be promoted by acute stress exposure (McGaugh, 2006; Shors and Servatius, 1997; Shors et al., 1992), although these examples tend to involve emotionally salient forms of learning that have a strong amygdala component associated with them. Rapid effects of glucocorticoid on physiological plasticity are relayed via non-genomic steroid receptors, that are probably localized on or near post-synaptic membranes in hippocampal neurons (Joels et al., 2012; Johnson et al., 2005; Karst et al., 2005). Although the precise mechanisms have yet to be clarified (for review, see (Groeneweg et al., 2011)), glucocorticoids may rapidly alter neuronal excitability to enhance responsiveness to contextually relevant information. During chronic stress, long-term increases in glucocorticoids impair both structural and functional plasticity in the hippocampus (Conrad, 2008; Herman et al., 1995a; McEwen, 2001, 2004; McLaughlin et al., 2009; Mizoguchi et al., 2003; Roozendaal and McGaugh, 2011; Sapolsky et al., 1985;

Vaher et al., 1994; Vyas et al., 2002; Young et al., 1990). These structural alterations are most prominently featured by dendritic retraction and spine loss in CA3, and to a lesser extent, CA1 pyramidal neurons (Magariños et al., 1997; Sandi et al., 2003; Sapolsky et al., 1985; Sousa et al., 2000; Stewart et al., 2005; Vyas et al., 2002; Watanabe et al., 1992). These findings parallel human neuroimaging studies reporting reduced hippocampal volumes in individuals suffering from stress-related disorders (Bremner, 1999, 2002; Lindauer et al., 2006; Lupien et al., 2007; Sheline et al., 2003; Sheline et al., 1996; cf. Fink, 2011).

One unique feature of the hippocampal formation is its ability to undergo neuronal replacement throughout the lifespan of rodents and primates (Eriksson et al., 1998; Gould et al., 1999a; Kaplan and Bell, 1983). Neurogenesis is reliably decreased by exposure to glucocorticoids following a variety of repeated stress paradigms (Gould et al., 1992; Gould et al., 1997; Mirescu et al., 2004; Pham et al., 2003; Tanapat et al., 2001). Newly-generated granule neurons are known to migrate into the granule cell layer, extend axons to their appropriate targets in CA3 and become functionally integrated into the hippocampal network. Evidence supports a role for the survival of these newly-generated neurons in certain forms of hippocampal-dependent learning (Cameron et al., 1993; Gould et al., 1999b; Hastings and Gould, 1999; Markakis and Gage, 1999; Shors et al., 2001; Shors et al., 2002; van Praag et al., 2002), and HPA restraining influences during chronic stress exposure (Snyder et al., 2011).

A number of parallels have been identified between results obtained from animal studies of repeated stress and observations made in clinically depressed, PTSD and Cushing's syndrome patients (Conrad, 2008). A large proportion of these patients show hippocampal volume reductions, hippocampal-based cognitive impairments and abnormal glucocorticoid secretory properties (Bremner, 2002; Dalgleish et al., 2007; Gurvits et al., 1996; Karl et al., 2006; Rigucci et al., 2010; Sheline et al., 2003; Sheline et al., 1996; Starkman et al., 1992; Starkman et al., 2001). Impaired glucocorticoid receptor-mediated feedback has been widely documented in individuals suffering from major depressive illness (Carroll et al., 1976; Holsboer, 1983; Young et al., 2004). Some evidence supports the idea that normalization of circulating glucocorticoid levels leads to an amelioration of hippocampal volumetric cognitive impairments (Bourdeau et al., 2005; Starkman et al., 1999; Starkman et al., 2003; Starkman et al., 1986). However, many inconsistencies linger in the human literature with respect to the association of stress, hippocampal volume and cognitive functions (Fink, 2011; Lindauer et al., 2006; Pederson et al., 2004; Stein et al., 1999). Difficulties with generalizing laboratory animal studies to clinical populations derive from determining the direction of causality between glucocorticoid secretion during stress exposure and adverse effects of these stress hormones that alter hippocampal plasticity. Another difficulty entails the fact that individual differences in hippocampal structure may predict vulnerability to stress and related disorders (Conrad, 2008; McLaughlin et al., 2009).

Prefrontal cortex

The prefrontal cortical regions are implicated in a wide array of complex functions that distinguish human cognitive processes from other species, including cognitive control,

behavioral flexibility, emotional regulation and working memory. The prefrontal cortex (PFC) is anatomically positioned to modulate both amygdala and hippocampal activity, providing a means for top-down regulation of limbic information processing. Moreover, the medial prefrontal cortex (mPFC) exhibits the capacity to modulate endocrine and physiologic adaptive functions during acute challenges. Given these diverse cognitive and homeostatic functions regulated by PFC, it is not surprising that frontal cortical regions have commanded increased interest in recent years for their roles in the maladaptive effects of stress and in stress-related psychopathologies (for reviews, see (Arnsten, 2011; Bremner, 2002; Drevets et al., 1997; Liberzon and Sripada, 2008; Price and Drevets, 2012; Rigucci et al., 2010; Sheline, 2003). An important feature of PFC is the capacity to provide top-down control over homeostatic-like responses during stress exposure, yet it is also a target of the adverse effects of repeated stress. Although it is difficult to pinpoint exactly how this process is initiated, the available evidence suggests a feed-forward cycle whereby repeated stress impairs PFC regulated functions, thereby leading to the further endangerment of cognitive and homeostatic functions subserved by PFC.

Evidence gathered in humans suggests that long-term stress exposure induces deficits in decision-making processes and may lead to reductions in prefrontal volume (Soares et al., 2012). Mild acute stressors have even been found to reliably disrupt working memory functions (Arnsten et al., 2012; Arnsten and Goldman-Rakic, 1998). Similar to the hippocampal formation, morphometric analyses of prefrontal regions in depressed and PTSD patients show volume reductions in anterior cingulate, orbital, medial and ventrolateral subregions of the prefrontal cortex (Li et al., 2010; Salvadore et al., 2011; Weber et al., 2013; Yamasue et al., 2003). Post mortem histological analyses of brains from depressed individuals generally corroborate volumetric data in observing reductions in neuron and glial cell numbers in the same cortical subfields (Cotter et al., 2002; Cotter et al., 2001; Rajkowska et al., 1999; Stockmeier and Rajkowska, 2004). Abnormal prefrontal activity, often in the form of hypoactivity, and diminished executive functioning, are common features of mood and anxiety disorders (Austin et al., 2001; Davidson et al., 2002; Fossati et al., 2002; Matsuo et al., 2003; Merriam et al., 1999; Phan et al., 2006; Rogers et al., 2004). These observations, coupled with an increasing body of evidence from animal studies, implicate the prefrontal cortex as a set of brain structures that are exquisitely sensitive to the effects of environmental stress, such that the modulatory functions on adaptive responses under acute conditions are intricately intertwined with chronic effects that feedback and alter the response properties of these cortical networks.

Acute stress has been shown to induce a relatively consistent diminution in prefrontal processing and related cognitive functions (Arnsten et al., 2012; Arnsten and Goldman-Rakic, 1998). One underlying idea is that the complexity and time demands required for prefrontal cognitive processing exceed the necessity for more immediate responses required for adaptive responding. Experimental results from animal studies of repeated or chronic challenges highlight the same general theme that stress interferes with cognitive flexibility (Birrell and Brown, 2000; Bondi et al., 2010; Bondi et al., 2008; Kim and Ragozzino, 2005; Liston et al., 2006; McAlonan and Brown, 2003; Schoenbaum et al., 2002). Working memory is also sensitive to the effects of stress. Macaque monkeys subjected to acute noise stress demonstrated impairments in a spatial working memory task, whereas several studies

have shown that rats demonstrate a similar type of cognitive impairment following exposure to stressful stimuli (Anderson et al., 2014; Arnsten and Goldman-Rakic, 1998; Hains et al., 2009).

A variety of neurotransmitters and signaling pathways have been shown to underlie prefrontal cognitive alterations during stress, and several examples will be highlighted here. Catecholamine influences in PFC have been demonstrated to play an important role during stress (for review, see Arnsten, 1997). In a series of studies, Arnsten and colleagues have shown that inputs into PFC (dorsolateral area 46 in primates; PL in rodents) activate a cellular cascade in principal neurons, inducing cyclic AMP and increases in protein kinase C signaling, ultimately resulting in dampened neuronal firing patterns and impaired behavioral output (Arnsten, 2009; Arnsten et al., 2012; Hains et al., 2009; Ramos and Arnsten, 2007). Whereas excessive increases in noradrenergic signaling may take the PFC “off-line” to allow for more reflexive responses (Arnsten and Goldman-Rakic, 1998; Radley et al., 2008b), under normal conditions elevations in noradrenergic signaling in PFC promotes cognitive flexibility (Aston-Jones et al., 1999, 2000; Cole and Robbins, 1992; Devauges and Sara, 1990; Page and Lucki, 2002; Ramos and Arnsten, 2007), and may even enhance attentionrelated task processing during periods when heightened vigilance is required (Aston-Jones et al., 1999, 2000). During repeated stress, the relationship between noradrenergic signaling and PFC function appears to be more straightforward, and contributes to the development of prefrontal cognitive deficits (Bondi et al., 2010; Bondi et al., 2008; Jett and Morilak, 2013). Elevated glucocorticoids have also been documented to adversely impact prefrontal-related cognitive functions in a variety of developmental contexts (Gourley et al., 2009; Anderson et al., 2014), and increases in these hormones are likely to play an important role in prefrontal dysfunction following chronic stress exposure (Cerqueira et al., 2007; Dias-Ferreira et al., 2009; Liston et al., 2006). Recent evidence suggests that endocannabinoids may play a countervailing role in limiting glucocorticoid-mediated impairment of prefrontal function (Hill and McEwen, 2010; McLaughlin et al., 2014). However, under repeated stress, decrements in endocannabinoid signaling are also implicated in the exacerbation of glucocorticoid effects.

Structural plasticity in PFC is a widely documented phenotype resulting from chronic stress exposure, and provides additional insight into the possible mechanisms accounting for the impairment of prefrontal-related cognitive functions. Morphometric studies in laboratory animals have generally shown regressive structural alterations in pyramidal neurons in multiple PFC subregions in rodents (anterior cingulate, prelimbic, and infralimbic cortices), such as reduced apical dendritic length and branching, and decreases in spine density in the apical dendritic tree (Cook and Wellman, 2004; Liston et al., 2006; Liu and Aghajanian, 2008; Martin and Wellman, 2011; Radley et al., 2005; Radley et al., 2006b; Radley et al., 2008a; Radley et al., 2004; Shansky and Lipps, 2013). Glucocorticoids and their agonists are capable of recapitulating the effects of repeated stress on mPFC structure (Cerqueira et al., 2007; Cook and Wellman, 2004; Wellman, 2001), and interfering with GR receptors may block these structural alterations (Liu and Aghajanian, 2008). Regressive structural plasticity in PL following repeated stress or glucocorticoid exposure has also been correlated with the impairment of prefrontal functioning, and some of these effects may be reversed by protein kinase C inhibition (Anderson et al., 2014; Cerqueira et al., 2005; Dias-Ferreira et al., 2009;

Hains et al., 2009; Liston et al., 2006). With regard to regressive synaptic effects, a subclass of dendritic spines denoted as “thin” (i.e., long neck, small head diameter) have been shown to be particularly vulnerable to the effects of repeated stress, glucocorticoids (Anderson et al., 2014; Bloss et al., 2013; Liston et al., 2013; Liston and Gan, 2011; Radley et al., 2008a), and aging (Anderson et al., 2014; Bloss et al., 2011; Dumitriu et al., 2010). Recent evidence suggests that thin spines play a critical role in maintaining optimal prefrontal network function and working memory (for review, see (Arnsten et al., 2010)). Despite the adverse effects of chronic stress on structural synaptic function in PFC, these alterations have been suggested to provide an adaptive mechanism to restrain adverse glutamatergic influences that would otherwise result in neurotoxicity (Bruno et al., 1993; Holmes and Wellman, 2009; Radley et al., 2008a). If true, then this line of reasoning provides an alternative view that helps to explain the constellation of maladaptive effects of stress on prefrontal functioning; however, more direct evidence for this view has not yet been forthcoming.

PFC is also implicated in the regulation of HPA axis and autonomic functions (Crane et al., 2003; Diorio et al., 1993; Neafsey, 1990; Radley et al., 2006a; Radley et al., 2009; Radley and Sawchenko, 2011; Sullivan and Gratton, 1999; Van Eden and Buijs, 2000). Whereas mPFC effects on these more homeostatic-like responses are generally inhibitory, evidence suggests some differentiation by cortical subfield that also accounts for excitatory modulation of these responses (Radley, 2012; Radley et al., 2006a; Radley et al., 2009). Several recent studies have shown that HPA-inhibitory influences from PFC are mediated by PL, and reach neuroendocrine effector cells in the hypothalamus via a disynaptic relay in aBST ((Radley et al., 2009; Radley and Sawchenko, 2011); see Box 1). Furthermore, pyramidal neurons in PL giving rise to aBST outputs show diminished structural and functional plasticity following chronic stress exposure (Radley et al., 2013). Taken together, these findings underscore that adaptive responses are highly integrative, involving a continuum of multiple cortical projections, in addition to hippocampus-bearing relays to the neuroendocrine hypothalamus. Thus, compromises along any part of this continuum could effectively contribute to maladaptive alterations in HPA axis regulation.

Box 1. Circuit organization providing for limbic forebrain control of the HPA axis

Over the years, attempts to understand top-down inhibitory modulation of stress-induced HPA activation from the limbic forebrain has been complicated by the fact that these influences are likely to be achieved via indirect, or even multisynaptic relays to HPA effector cell groups in PVH. Extrinsic projections from mPFC and hippocampal formation are largely excitatory glutamatergic in nature, implicating a disynaptic GABAergic relay interceding between upstream excitatory forebrain regions and downstream HPA effector cell groups in PVH. Combined pathway tracing and immediate-early gene mapping studies have helped to identify a number of candidate cell groups that could serve as inhibitory relays interfacing between forebrain regulators and PVH (Cullinan et al., 1993; Roland and Sawchenko, 1993; van de Kar and Blair, 1999; Herman et al., 2003), nevertheless, the picture that has emerged is one involving a complex network of higher-order structures interconnected in parallel with PVH.

Work from our laboratory has identified a discrete cluster of GABAergic neurons interposed throughout anterior aspects of the bed nuclei of the stria terminalis (aBST; i.e., within subcommissural, dorsomedial, and fusiform subdivisions of Dong et al., 2001) that forms the missing link in this circuit model (Radley et al., 2009; Radley and Sawchenko, 2011). Our data suggest that stress-inhibitory influences of the mPFC and hippocampal formation are exerted principally via convergence onto the same population of GABAergic neurons, and that these cell groups have the capacity to integrate stress-inhibitory signals from the forebrain (Radley and Sawchenko 2011; Figure 1). This conclusion is based on three lines of evidence: (1) anatomical tracing experiments indicate that extrinsic projections from the hippocampal formation and the mPFC converge onto stress-sensitive, PVH-projecting neurons in the aBST; (2) GABAergic PVH-projecting cell groups in the aBST show diminished functional activation following acute stress in animals bearing excitotoxin lesions of either the hippocampal formation or mPFC; (3) the aBST plays a more prominent inhibitory role than the hippocampal formation over stress-induced increases in plasma corticosterone levels.

There are a number of questions that derive from this work. Is this subpopulation of aBST GABAergic neurons the principal clearinghouse for prefrontal and hippocampal influences? If not, to what extent or under which contexts, are other relays involved? Do other limbic forebrain regions, such as the amygdala, also relay HPA-modulatory influences through these same cell groups? Can neuroplasticity in these pathways help to understand the mechanisms of chronic stress-induced perturbations in endocrine systems? Future studies will help to better understand how stress leads to altered behavioral, physiological and endocrine responses, and how perturbations in key neural pathways leads to maladaptive states.

CAVEATS AND FUTURE CONSIDERATIONS

The preceding implicates several candidate mediators and neural circuits capable of responding in a context- or situation-specific manner to meet the demands of stress. While modifications in these limbic forebrain regions are widely implicated in maladaptive effects following chronic stress, less well understood is the extent to which recruitment patterns within individual network elements are actually required for our survival. Perhaps some level of protection may be afforded by such redundancy, if at all true. However, this might also explain why lesions (i.e. experimental, disease, ageing) of any one limbic structure (or principal afferents) are known to produce widespread and overlapping effects, including those related to mood, metabolic and cardiovascular disorders. Thus, in order to understand or dissociate adaptive from maladaptive responses, incorporating acutely exposed animals in studies of chronic stress is crucial, but all too often remains a neglected comparator.

Large variations in individual cortisol release patterns feature prominently in repeated challenge experiments in humans (Kirschbaum et al., 1995; Kudielka and Wust, 2010). As discussed elsewhere, the biological determinants for individual variations are poorly understood, and extensive phenotyping remains essential (Kudielka et al., 2009). Evidence drawn from animal models of chronic stress, nevertheless, continues to shape our understanding of just how disruptive homeostatic threats may be, as well as for identifying

key contributions of different neural substrates. Similar to humans, and depending on the characteristics of stimuli employed in animal models, stressors do not invariably lead to pathology or maladaptive responses (Anisman and Matheson, 2005). Thus, individual differences in resilience, defined as an individual's ability for properly adapting to stress, form an important basis for this variability. Studies exploring this possibility, including models of stressor controllability and repeated homotypic stress (Frank et al., 2013; Grissom and Bhatnagar, 2009; Jaferi and Bhatnagar, 2006; Maier et al., 2006; Maier and Watkins, 2010), for example, show that the reactivity of the HPA axis can readily decline during successive stimulus exposures. This response is thought to be adaptive, insofar as it would limit exposure to circulating glucocorticoids. Moreover, this response does not reflect an exhaustion of the biosynthetic and/or secretory capacity of the HPA axis, nor is it passive. Decrements in neuroendocrine responses are met by global decreases in stress-induced activation of the PVH and its extended circuitries, and various ablation methods (pharmacological, physical, genetic) can reverse the expression of stress HPA axis habituation (Day et al., 2009; Herman, 2013; Masini et al., 2012; Masini et al., 2008; Weinberg et al., 2010)(Box 2). What has emerged from these studies is that similar to chronic stress, the process of stress habituation also requires a sizeable amount of neural substrate. On this point, and if one takes notice, brain regions and/ or neural mechanisms thought to represent antecedents for pathology (in the face of chronic stress) may also be the same as those enlisted during stress HPA axis habituation. Despite the differential effects of uncontrollable and controllable stressors on a variety of experimental endpoints, it is conceivable that these too may share overlapping neurobiological substrates. As discussed elsewhere (De Boer and Koolhaas, 2003; Koolhaas et al., 2010), careful appraisal or analysis of this possibility is requisite for developing better models of individual differences in stress reactivity.

Box 2. Neural mechanisms of stress habituation

An important, and often overlooked aspect of many animal models of repeated stress is the fact that the activity of several systems, including neuroendocrine, behavioral and autonomic responses, tend to decline upon repeated stimulus exposures, a process known as habituation (Armario et al., 1984; Campeau et al., 2002; De Boer et al., 1988; Masini et al., 2008; van Raaij et al., 1997). Work in our laboratory has helped to advance understanding of the neural pathways involved in this process, highlighting the auditory thalamus as an apex responsible for the activation of a several subcortical pathways subserving adaptive responses to repeated audiogenic stress (Campeau et al., 2002). Loud noises are usually associated with danger signals in many species and readily induce HPA, autonomic, and behavioral responses (Bao et al., 1999; Borrell et al., 1980; Campeau and Watson, 1997; De Boer et al., 1989; Gamallo et al., 1992; Henkin and Knigge, 1963; Masini et al., 2008; Overton et al., 1991; Saha et al., 1996; Segal et al., 1989). Although a significant research effort has been devoted to understanding limbic forebrain plasticity following repeated stress exposure, there is a dearth of information available regarding its role in stress habituation. Audiogenic stress affords a significant advantage over other commonly employed paradigms (e.g., social defeat, restraint, footshock) that are multisensory and multimodal, since it provides an opportunity for clarifying how a single sensory modality may come to enlist brain regions encoding stress habituation. In this design, our combined connectivity and functional studies

highlight the posterior hypothalamus as a candidate nodal point for distributing audiogenic information to downstream effectors of HPA, autonomic and behavioral responses (Bailey and Dimicco, 2001; Nyhuis et al., 2010, 2011; Nyhuis et al., 2012) (Figure 2). As the limbic forebrain can gain access to several aspects of this circuitry (and vice versa), this audiogenic model also provides an important entry point for critically examining and affixing changes in PFC and amygdaloid plasticity to adaptive and maladaptive outcomes in neuroendocrine, autonomic and behavioral responses to stress.

Finally, but by no means an end to a large list of candidate factors (Anisman and Matheson, 2005; Anisman and Zacharko, 1990)(Table 1), consideration of sex differences and sex steroid hormone influences is of paramount importance. Males and females would seem to require or develop different neuroendocrine and behavioral coping strategies in response to stress (Babb et al., 2013a, b, 2014; Carvalho-Netto et al., 2011; Mashoodh et al., 2008; McEwen and Milner, 2007; Solomon et al., 2012; ter Horst et al., 2012), which could form a basis for the gender bias in the onset, type and relative risk of different types of disease (Kokras and Dalla, 2014; McCarthy et al., 2012). Manipulating gonadal status in humans and rodents makes clear that androgens and estrogens can potently inhibit and stimulate, respectively, neuroendocrine stress responses, operating on both feed-forward and glucocorticoid-mediated negative feedback regulation of the HPA axis (Goel et al., 2014; Young, 1995). Females express marked variations in stress neuroendocrine and behavioral reactivity in response to cyclic changes in ovarian status, and it is perhaps this variability that deters investigators from including females in their studies. This notion is slightly misdirected, however, as males show circadian variations in testosterone secretion that are as dynamic as the hormonal changes in females (Viau, 2002). Moreover, male rodents show marked changes in testosterone synthesis and release under acute or chronic stress conditions, whereas estrous cyclicity in females remains relatively intact.

Sex steroid hormone receptors are not only distributed within brain regions regulating the gonadal axis, but also within those involving the HPA axis (Bingham et al., 2006; Handa et al., 1994; Handa and Weiser, 2014; Williamson et al., 2005; Williamson and Viau, 2007). These would include the PVH and its extended circuitries, several of the same forebrain regions discussed above, in addition to ascending hindbrain modulators of emotional and somatosensory processing. The onset of depression and anxiety is frequently associated with major disruptions in reproductive endocrine function in females, and in some cases with hypogonadism in males. As previously argued (Rubinow and Schmidt, 2002), changes in gonadal status may not be the root cause of disease onset, but just like glucocorticoid hormones (Bourke et al., 2012; Oitzl et al., 2010; Quinn et al., 2014), may provide a context for understanding how the brain responds to stress. Based on their propensities for directing the HPA axis across all stages of the life span (Gobinath et al., 2014; McCarthy and Arnold, 2011; McCormick et al., 1998; McCormick and Mathews, 2007; Toufexis et al., 2014), as well as other stress response systems, where and how the sex and adrenal steroid hormones intersect in the brain to alter the development of stress habituation remains worthy of pursuit (Bangasser and Valentino, 2012; Goel and Bale, 2009), and promises to explain the bases for both individual and gender based differences in stress-related pathology (Figure 3).

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Highlights

- Adaptive and maladaptive processes associated with repeated stress are reviewed
- Amygdala, hippocampus and prefrontal cortex are differentially modulated by stress Adaptive processes associated with habituation to stress are discussed
- Gonadal hormone variations mediate individual differences to stress
- Importance of individual context in characterizing adaptive vs. maladaptive outcome

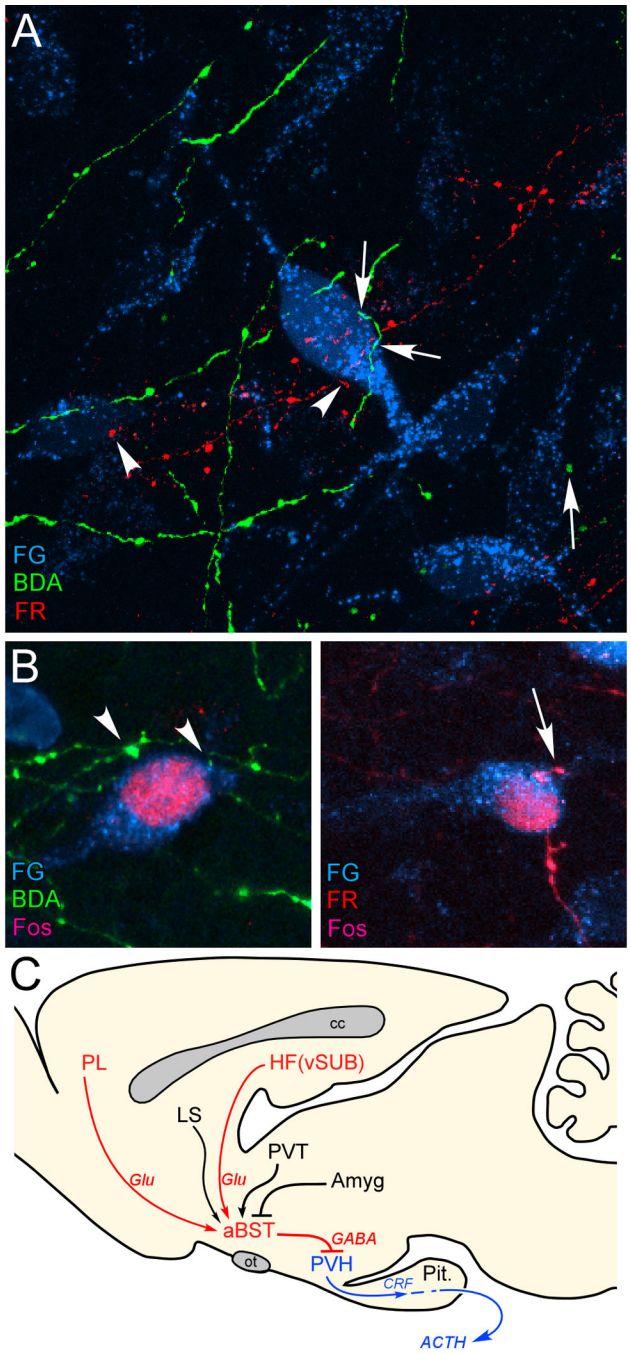

Figure 1.

A: Confluence of labeling in aBST following retrograde tracer injections in PVH (Fluoro-Gold, FG; cyan), and anterograde tracers in PL (biotinylated dextran amine, BDA; green) and vSUB (FluoroRuby, FR; red). Instances of BDA- (arrows) and FR-labeled (arrowhead) terminals make appositions onto single PVH-projecting neurons in aBST, by laser-scanning confocal microscopic analysis. *B:* After a single stress exposure, numerous instances of Fos-labeled nuclei are evident in PVH-projecting neurons containing appositions from BDA- (left) and FR-labeled (right) terminals. *C:* Previous work of ours supports the pathways

highlighted in red, with aBST providing an important source of GABAergic innervation of PVH, and relaying limbic cortical influences. Other forebrain cell groups known to influence HPA output (highlighted in black) also project to aBST, whose integrated output targets PVH directly. Like vSUB and PL, these regions do not provide any appreciable innervation of PVH, but do issue projections to the aBST. ACTH, adrenocorticotropic hormone; Amyg, amygdala; cc, corpus callosum; CRF, corticotropin-releasing factor; Glu, glutamate; HF, hippocampal formation; LS, lateral septum; ot, optic tract; Pit., pituitary gland; PL, prelimbic cortex; PVH, paraventricular nucleus of the hypothalamus; PVT, paraventricular thalamic nucleus; vSUB, ventral subiculum. Data are based upon Radley and Sawchenko (2011).

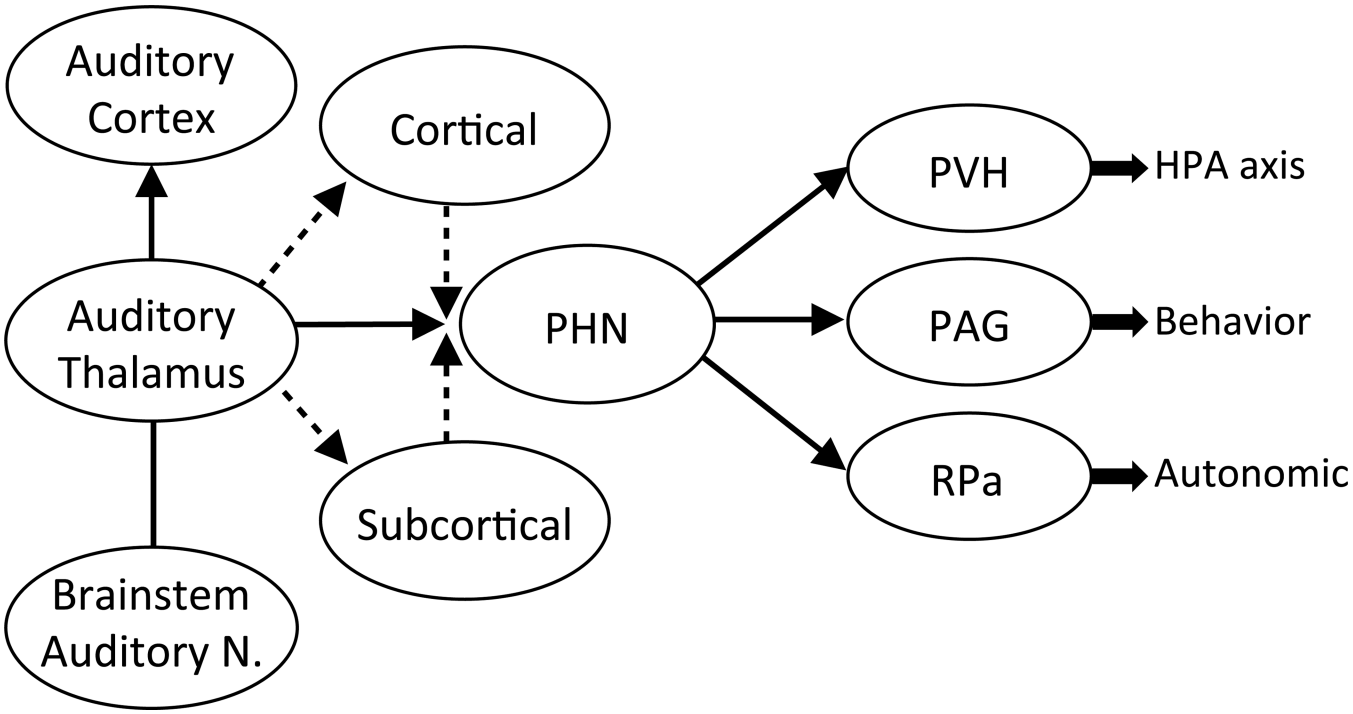

Figure 2.

Working model of neuroendocrine and autonomic responses following audiogenic stress. In response to repeated loud noise exposure, animals reliably show reduced corticosterone and autonomic responses. Based on previous functional-lesion, connectivity and immediate early gene experiments, audiogenic stress is capable of eliciting neuroendocrine, autonomic and behavioral responses to and through various forebrain, hindbrain and midline thalamic and hypothalamic candidate nuclei. The posterior hypothalamus (PHN) stands out in this regard, based on our current understanding of its functional and anatomical connectivity to HPA effector neurons in the paraventricular hypothalamic nucleus (PVN), as well as the periaqueductal gray (PAG) and the Raphe Pallidus (RPa), important mediators of flight or flight responses and emotional arousal, respectively. Several cortical and subcortical regions known to send reciprocal connections with sensory, motor and limbic-related cortices, have yet to be fully elucidated (dashed lines) in the context of repeat audiogenic stimuli and stress habituation.

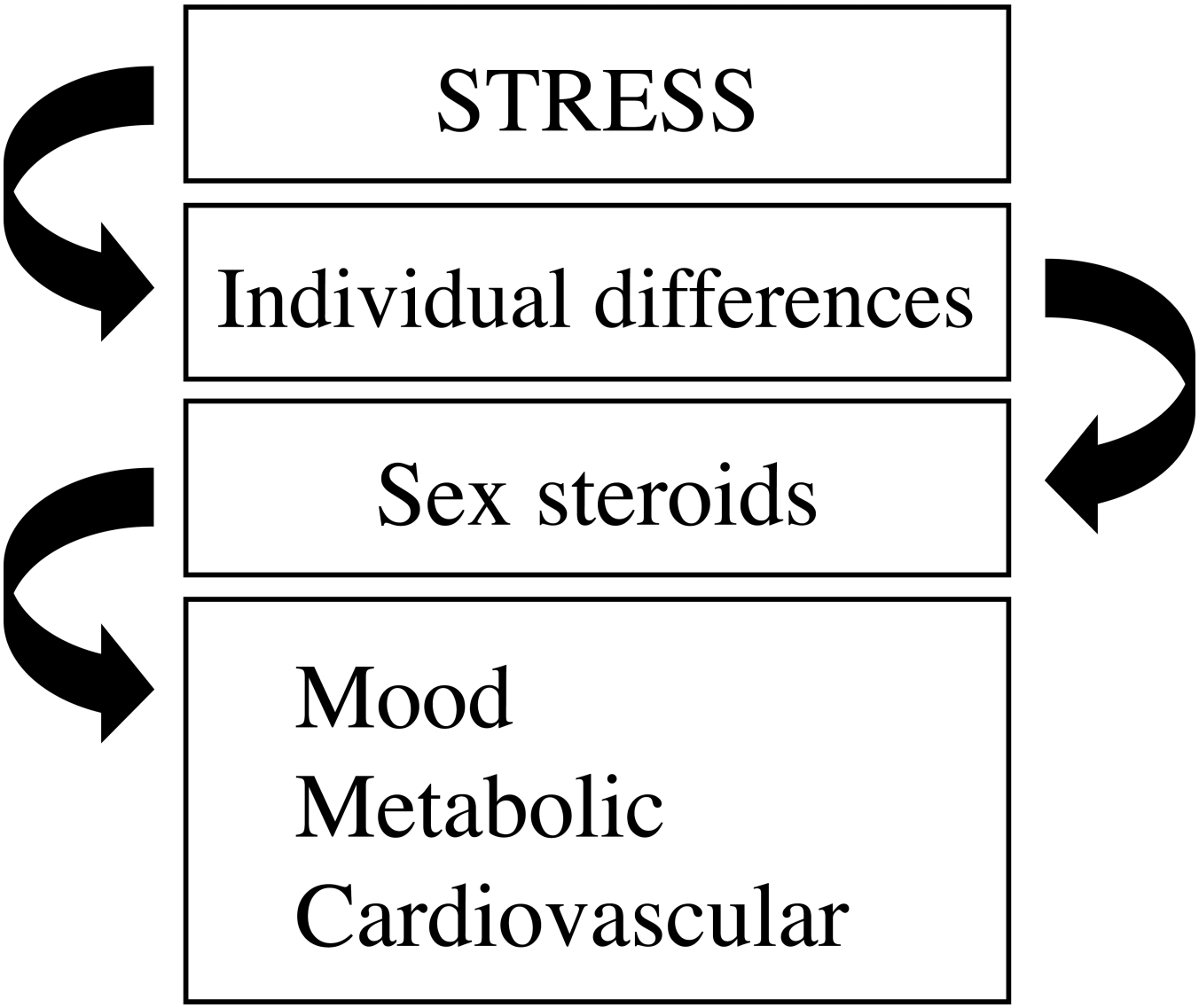

Figure 3.

Schematic to illustrate that the sex steroid hormones (e.g. androgens and estrogens) have an important basis for individual differences in stress reactivity under normal conditions, and under those that produce pathological changes in mood, metabolic and cardiovascular function, for examples. This schematic underscores that the sex steroid hormones can redirect the strength of influence of stress on the body. Note that sex steroid hormone secretion and signaling (as with other factors listed in Table 1) are also themselves subject to homeostatic threat, and in this design can be placed either above or below "individual differences"; implying that relationships between gonadal status and stress can change in a situation- and context-dependent manner.

Table 1

Factors influencing the stress response

Stressor type
Processive (neurogenic or psychogenic)
Systemic (immune insults)
Stressor characteristics
Controllability
Predictability
Ambiguity/uncertainty
Chronicity
Intermittence
Organismic variables
Species
Strain
Age
Sex
Experiential variables
Previous stressor experiences (sensitization)
Early life events (maternal factors, trauma)
Resource characteristics
Personal characteristics
Coping skills
Self-esteem
Self-efficacy
Personality (hardiness, optimism, neuroticism)
Social characteristics
Social support (perceptions)
Attachment (bonding)

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