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Individual differences in stress susceptibility and stress inhibitory mechanisms

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Many individuals experience stressful life events, but only a minority develops stress-related pathologies including mental disorders such as depression or anxiety disorders. Such individual differences in stress vulnerability are based on alterations in neural circuits/mechanisms designed to properly tune and terminate stress responses. Recent studies in animal models combining behavioral, molecular, functional imaging and optogenetic techniques reveal maladaptive, dysregulated gene expression and impaired stress-neurocircuit function across multiple brain regions as sources of individual stress-vulnerability. In this review, we focus on novel findings providing evidence for a critical role of stress-inhibitory neural pathways in individual stress-susceptibility. Moreover, we highlight candidate genetic, epigenetic and biochemical factors that characterize vulnerability and may drive maladaptive processes in these stress-inhibitory circuits, as well as at the level of the hypothalamic-pituitary-adrenal (HPA) axis. Finally, possible therapeutic implications of these findings are discussed, also in relation to new candidate risk factors that serve as biomarkers for the prediction of phenotypes vulnerable to develop stress-related syndromes. A better understanding of neurobiological mediators underlying individual stress-susceptibility would be a significant step forward to identify novel prevention and treatment strategies for stress-related disorders.

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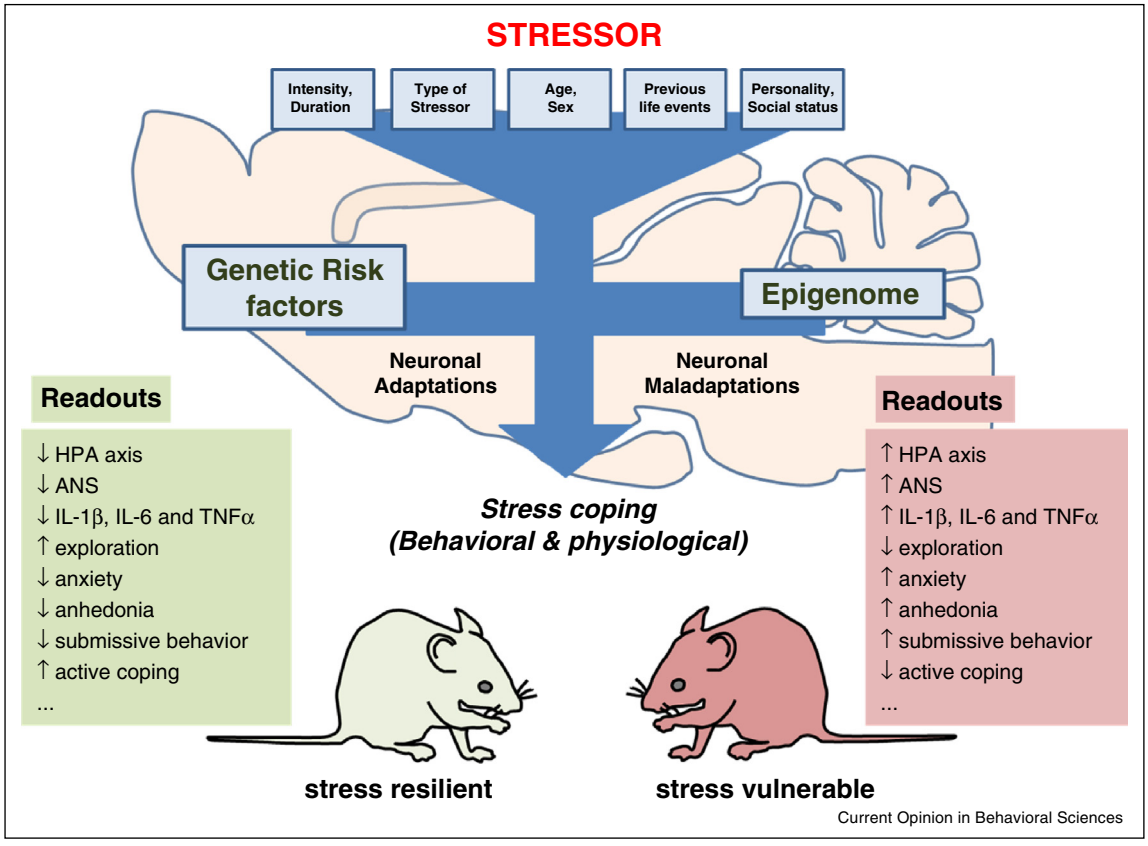
Introduction

It is well recognized that individuals exhibit considerable variability in behavioral and physiological responses to stressors. Physiological stress responses, which are designed to produce stress adaptation and maintain homeostasis (allostasis), are mediated through output of hormones via the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS) and interaction with mediators of immune and metabolic systems [1••]. While normally protective, these stress response mechanisms can be severely damaging when dysregulated and fail to cease after termination of stressor exposure. Individual stress sensitivity and reactivity is thus important in the etiology and maintenance of pathologies for which excessive stress impact is a risk factor including cardiovascular, metabolic and immunological diseases as well as stress-related psychopathologies such as depression, anxiety, substance abuse and personality disorders. Indeed, individuals that display particular behavioral and physiological stress-related characteristics due to genetic and epigenetic alterations and are termed susceptible/vulnerable (Figure 1) have been found to be affected by certain stress-related diseases [2,3], while resilience mechanisms protect from these consequences [4,5] (Figure 1). These alterations can be inborn/inherited and/or acquired. Underlining the importance of research in this field, individual differences in response to threat and loss is listed in the Research Domain Criteria (RDoC) matrix developed by the National Institutes of Mental Health (NIMH) as a strategy to guide research on mechanisms of psychopathology [6].

An important aim is to reveal involved brain areas and circuitries as well as biological mechanisms including genetic/epigenetic alterations leading to such differences in stress processing. For example, individual differences in diurnal HPA axis rhythms and responsiveness to challenging situations have been found to be partially determined by genetic factors [7••,8]. Indeed, candidate gene and genome-wide association studies have linked common genetic variations within the HPA axis cascade to individual differences in diurnal and stress-evoked HPA axis function [8,9]. In most cases, however, an interaction of these genetic variants with stress exposure (particularly when early in life and/or chronic/traumatic) is necessary to shape stress-vulnerable phenotypes (Figure 2) and convey vulnerability to stress-related physical and mental health disorders via epigenetic mechanisms such as DNA methylation and hydroxymethylation, as well as histone modifications [10–12]. Thus, environmental insults can act via direct effects of glucocorticoids (see below) on gene transcription, as well as via recruitment of epigenetic mechanisms leading to activation or repression of genetic factors affecting neural circuit processing and resulting

Figure 1



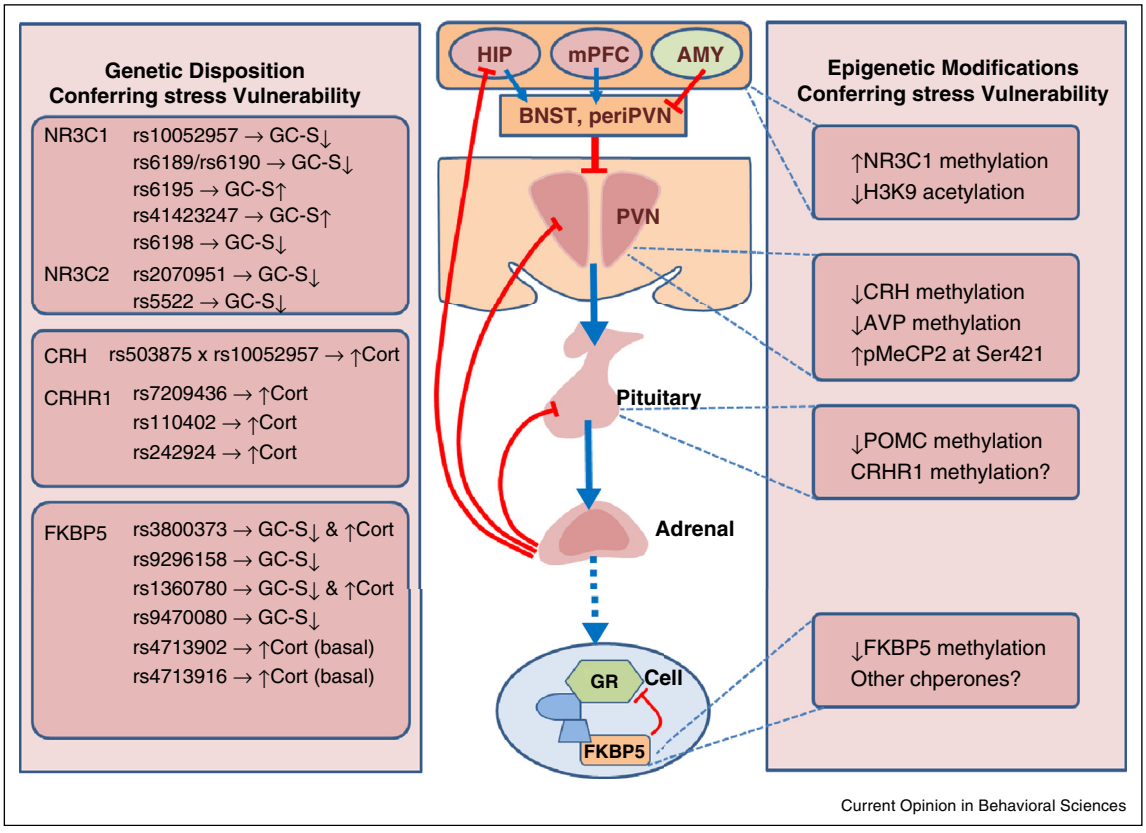
Schematic illustration of how gene x environment interactions produce stress-vulnerable or stress-resilient phenotype, respectively genetic background can enhance vulnerability to stressful life events and early-life history including stress experiences can, in turn, change the genetic profile through epigenetic mechanisms. The interaction of these factors leads to maladaptive or adaptive molecular and cellular changes in the brain that determine whether the organism is susceptible or resilient to stressors in adulthood. Stress vulnerable individuals are often characterized by increased stress sensitivity and/or reactivity reflected by several physiological and behavioral readouts (see red box) compared to resilient individuals (green box) (for review see [4,5,22]). ANS, autonomic nervous system; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; TNF, tumor necrosis factor.

ultimately in enhanced stress vulnerability [1••]. Fortunately, susceptibility pathways matured through adverse gene x-environment interactions can still be modulated later in life [4,5], e.g. by targeted behavioral interventions combined with drugs that facilitate treatment efficacy by supporting plasticity mechanisms [13,14]. In this review, we focus on neural mechanisms that are associated with differences in stress-susceptibility, in particular regulatory mechanisms that are directly or indirectly associated with the neuroendocrine stress axis. Accordingly, we provide evidence of an aberrant stress response system in vulnerable individuals that is characterized by exaggerated stress sensitivity and/or deficient ability to balance or cease stress responses. In particular, we highlight novel results assessing anatomical and functional evidence for a critical role of alterations in stress-inhibitory neural pathways in individual stress-susceptibility.

Readouts of inter-individual variability in stress-reactivity

Inter-individual variability in the stress response has been assessed using different readouts (Figure 1). The primary symptoms of increased stress-reactivity include elevated stress hormone levels and an overreaction of the autonomic nervous system [15,16•]. Mechanisms for autonomic hyper-responsiveness to stress have been linked with gene polymorphisms, for example, the alpha adrenergic 2 receptor gene [17]. Stress-associated autonomic dysregulation has clinical significance and contributes to cardiovascular pathologies, amongst others [18]. Individual differences in the behavioral response to aversive and threating situations can be seen across many species including rodents and humans [19••]. The behavioral pattern that seems to emerge consistently is that some individuals respond to challenging situations with more offensive, aggressive and impulsive behavior, whereas

Figure 2



Selected genetic variations and epigenetic modifications associated with altered hypothalamic-pituitary-adrenal (HPA) axis regulation conferring stress vulnerability. Individual differences in HPA axis functionality are determined by genetic variants (left box) and epigenetic modifications (right box) of genes coding for glucocorticoid (GC) receptor (GR; NR3C1) and mineralocorticoid receptors (MR; NR3C2), as well as other components of the HPA axis cascade (CRH, CRHR1, AVP, POMC). To strengthen the relevance of these changes to HPA axis regulation, we focused here only on studies with clear measures of HPA readouts from healthy humans and excluded deliberately patient studies (for a review on such data see e.g. [8]). Single nucleotide polymorphisms (SNPs) related to changes in HPA axis reactivity are primarily localized in GR, MR and FKBP5 genes. Reduced or impaired GR and MR function, for example, reduced glucocorticoid sensitivity (GC-S ↓) or glucocorticoid hypersensitivity (GC-S ↑) and associated altered feedback inhibition via GCs (red lines) has been suggested to underlie HPA axis dysfunctions (hyperactivity or hypoactivity) in stress susceptible individuals. Epigenetic mechanisms such as DNA methylation and histone modifications have been shown to modulate gene expression at different levels of the HPA axis and in different brain areas (right box) regulating HPA axis and implicated in shaping stress-vulnerable phenotypes (for review see [11,12]). AMY, amygdala; AVP, arginine vasopressin; BNST, bed nucleus of stria terminalis; CRH, corticotropin releasing hormone; CRHR1, CRH1 receptor; GC-S, glucocorticoid sensitivity; GR, glucocorticoid receptor; HIP, hippocampus; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; periPVN, perinuclear PVN area; POMC, Proopiomelanocortin; PVN, paraventricular nucleus.

others appear to avoid such situations, behaving more cautiously and fearfully. These different coping styles have been described as proactive versus passive/reactive, which seems to be of relevance for differences in disease susceptibility [19••]. Other common behavioral readouts in stress-susceptible animals are listed in Figure 1 [20]. For instance, if rats or mice exposed to chronic social stress, experienced defeat produces specific behaviors in susceptible individuals that resemble symptoms of humans with affective disorders, such as anhedonia, social avoidance, despair and/or anxiety. This behavioral susceptibility has also been investigated in several other stress models such as the chronic mild stress model or learned helplessness [21]. In addition to behavioral variability, consistent individual differences have been observed in various physiological stress responses including cardiovascular parameters such as increased blood pressure and heart rate [15,18], responses of the immune system, indexed by levels of pro/anti-inflammatory mediators such as cytokines (for detailed review see [22] and the HPA axis, indexed typically by stress hormone levels including adrenocorticotropic hormone (ACTH) and glucocorticoids [16•,23]).

Animal models of variability in stress-reactivity

One strategy to generate animal models of variability in stress-reactivity is to compare common inbred rat or mouse strains that differ in their behavioral and/or neuroendocrine responsiveness to stress (Table 1).

Table 1

Neurobiological changes related to altered HPA axis function in stress susceptible animals

	Tissue	Effect	Animal Model	References
Central markers				
GR mRNA	HIP	↓	F344 versus LEW rats	[24]
	v+dHIP	↑	HR versus LR mice	[30]
GR binding	Pituitary	↓	RLA versus RHA rats	[27]
	BLA	↑	HR versus LR mice	[30]
MR mRNA	HIP, pituitary	↓	F344 versus LEW rats	[24]
MR binding	HIP	↓	RLA versus RHA rats	[27]
CRH mRNA	PVN	↑	CD1 mice (CSD)	[36]
	PVN	↑	RLA versus RHA rats	[34]
CRHR1 mRNA	Pituitary	↑	HR versus LR mice	[31•]
	Pituitary	↑	HR versus LR mice	[30]
	BLA	↑	HR versus LR mice	[30]
CRHR1 IH	Pituitary	↑	RLA versus RHA rats	[35]
AVP mRNA	PVN	↑	RLA versus RHA rats; HAB versus LAB rats	[27,28]
AVP *release*	PVN	↑	HAB versus LAB rats	[28]
AVP1b mRNA	Pituitary	↑	HR versus LR mice	[30]
POMC mRNA	Pituitary	↑	HR versus LR mice	[30]
11HSD1 mRNA	Pituitary, PFC, HIP	↑	F344 versus LEW rats	[24]
FKBP5 mRNA	v+dHIP	↑	HR versus LR mice	[30]
BDNF mRNA	HIP, PFC	↓	C57BL/6J mice (CMS)	[65]
	NAc, VTA	↑	C57BL/6J mice (CSD)	[26••]
Peripheral markers				
ACTH	Plasma	↑	HR versus LR mice	[30]
CORT	Plasma	↑	HR versus LR mice	[30]
adrenal weights	Adrenals	↑	HR versus LR mice	[30]
CORT (Dex-suppress)	Plasma	↓	RLA versus RHA rats	[35]
CORT (Dex/CRH-test)	Plasma	↓	HAB versus LAB rats; RLA versus RHA rats	[28,35]

Brain regions: BLA, basolateral amygdala; HIP, hippocampus (dorsal + ventral); NAc, nucleus accumbens; PFC, prefrontal cortex; PVN, paraventricular nucleus; VTA, ventral tegmental area.
Animal models: CMS, chronic mild stress (stress-susceptible versus resilient individuals); CSC, chronic social defeat (stress-susceptible versus resilient individuals); Fisher 344 (F344) versus Lewis (LEW) rats; High anxiety (HAB) versus low anxiety-related behavior (LAB) breeding line; High (HR) versus low stress reactivity (LR) breeding line; Roman-low-avoidance (RLA) versus Roman-high-avoidance (RHA) breeding line.

For instance, Fisher-344 rats show a stress-hypersensitive phenotype indicated by symptoms of enhanced emotionality and anhedonia while other strains such as Lewis rats are typically less responsive to stress [24]. Similar strain differences were also found in mice, where strains such as BALB/c were considered more vulnerable to stress than C57BL/6 [25]. Interestingly, inter-individual variability in susceptibility to stress has been observed even within inbred strains. For example, C57BL6/J mice subjected to chronic social defeat can be separated into susceptible and unsusceptible individuals based on their social interaction scores [26••]. These data show that inbreeding and associated genetic selection does not eliminate inter-individual variations in stress-reactivity und supports the idea that stress-susceptibility is caused by a combination of genetic and non-genetic factors (see below and Figures 1 and 2). A further strategy is to selectively breed animals that show certain characteristics of stress-susceptibility. There are several well-characterized examples (see [20] for a review): For instance, the outbred Roman high avoidance (RHA) and Roman low avoidance (RLA) rats were obtained by genetic selection on the basis of their performance in a two-way active avoidance task. Notably, RLA rats show increased stress responses (e.g. increased ACTH and corticosterone levels) and adopt a more passive coping style when confronted with a novel environment compared to their RHA counterparts [27]. Similarly, rats selected for high anxiety-related behavior (HAB) show passive stress-coping, higher stress hormone secretion to mild stress and PVN hyperactivity to various stressors as compared to their low anxiety (LAB) counterparts [28,29]. Also mice with high versus low stress-reactivity were obtained by selectively breeding according to hyper-reactivity (high reactivity, HR) or a hypo-reactivity (low reactivity, LR) of the HPA axis to a standardized, moderate restraint stress [30]. HR but not LR mice show lasting consequences of early-life stress (e.g. dysregulated behavioral and neuroendocrinological stress-coping), supporting the concept that in individuals that are genetically predisposed for increased stress reactivity, early-life adversity can enhance the probability to develop psychopathology [31•], which is even more accentuated when 3 factors (1) genetic susceptibility; (2) early-life priming; (3) acute stress triggers come together ('three hit concept of vulnerability') [32].

Neurobiological correlates associated with stress-susceptibility: alterations at the level of the HPA axis

Activation of the HPA axis represents a hallmark of the physiological stress reaction as HPA axis changes are triggered by almost all varieties of stressors studied so far, both in animals and humans [16•]. Although large parts of the brain are directly or indirectly involved in regulating the overall stress response, specific areas of the brain (in particular hypothalamus, but also extrahypothalmic areas including hippocampus, amygdala (AMY), bed nucleus of stria terminalis (BNST), prefrontal cortex (PFC)) have critical, distinct roles in orchestrating stress mechanisms [1••,33]. Various neuroanatomical, neurochemical or molecular mechanisms have been found to be involved in mediating individual differences in stress-reactivity [2].

A number of changes in stress-susceptible individuals have been observed in HPA axis functions (Figure 2). Increased HPA axis reactivity and associated excessive glucocorticoid levels are linked to an increased risk of developing stress-related psychopathology such as depression [7••] (note: also the opposite, HPA hypoactivity, is related to psychopathologies such as atypical depression and posttraumatic stress disorder [2]). The regulation of the HPA axis is highly complex with the paraventricular nucleus (PVN) as a key regulatory brain site where corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) neurons are localized. These neurons project to the median eminence, where the neurosecretory nerve terminals release their respective hormones at the primary capillary plexus of the hypophyseal portal system. At the anterior pituitary gland they stimulate ACTH secretion, which in turn leads to peripheral glucocorticoid release from the adrenal glands. HPA axis reactivity is regulated to a large extent by feedback mechanisms (Figure 2) mediated by glucocorticoids acting on the two brain corticosteroid receptors, the lower-affinity glucocorticoid receptor (GR) and the high-affinity mineralocorticoid receptor (MR) (see below). Dysfunction in these homeostatic mechanisms produces differences in stress processing and susceptibility.

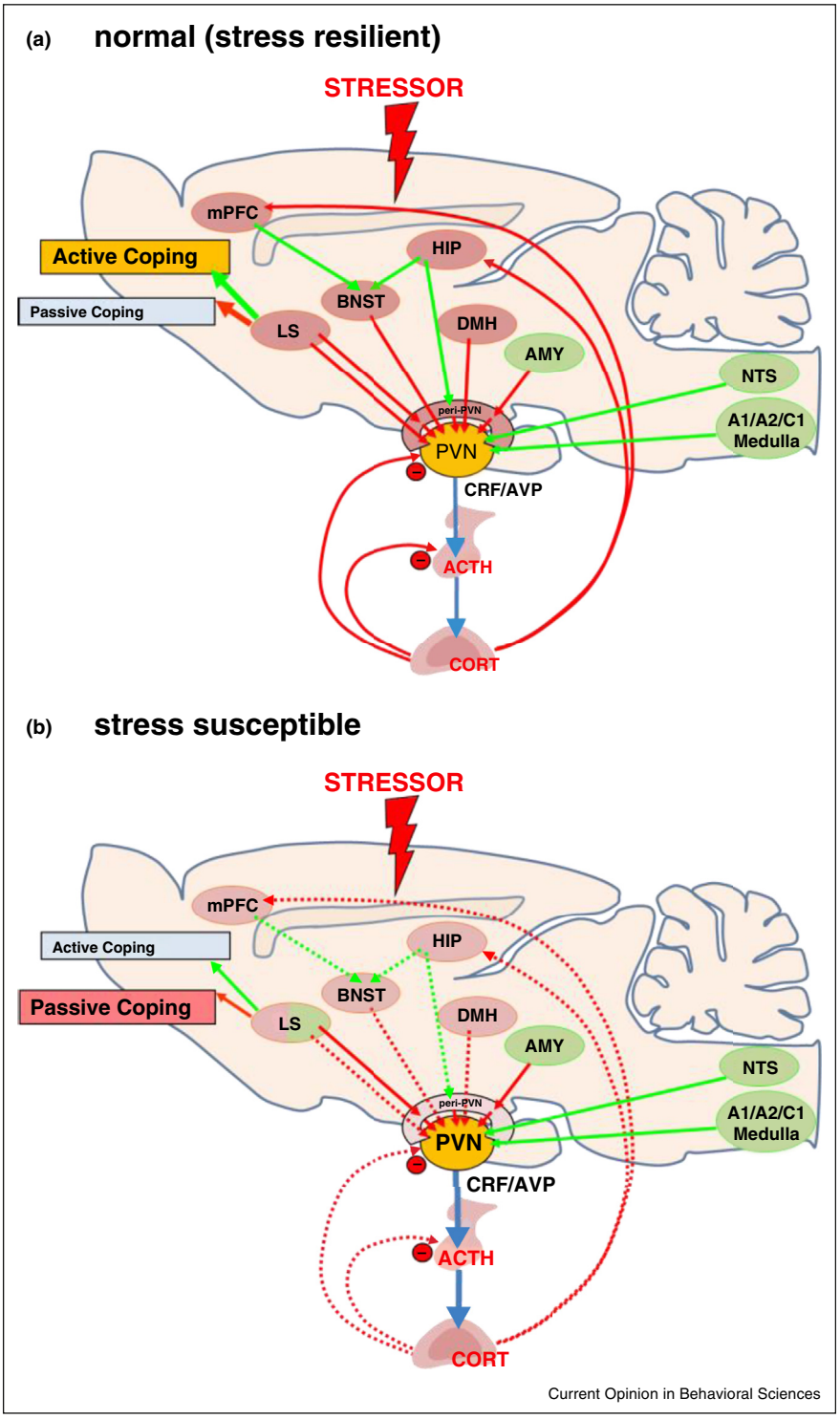
Role of CRH in stress-susceptibility

For instance, associations between altered CRH signaling and differences in behavioral/neuroendocrine stress-reactivity have been demonstrated in the RHA/RLA rats, where higher CRH expression was found in the PVN of stress-susceptible RLA individuals than in RHA counterparts [34]. Moreover, RLA rats show also enhanced pituitary sensitivity to CRH as well as higher CRH R1 receptor (CRHR1) expression in the pituitary [35]. This is in line with previous findings from mice where stress vulnerable individuals had significantly higher baseline CRH mRNA levels compared to resilient and control animals [36]. Notably, increased CRHR1 activity in the pituitary of stress-susceptible animals seems to be accompanied by increased ACTH expression through an upregulation of the POMC gene expression [30]. Interestingly, it has been shown that specific Single nucleotide polymorphisms (SNPs) in outbred CD1 mouse *Crhr1* gene affect the physiological response and recovery of individuals to chronic stress exposure. Mice with a distinct *Crhr1* gene allele (rs27040842 genotype) showed increased C*rhr1* mRNA expression and CRHR1 binding in the anterior pituitary that was associated with a hyper-activated stress-induced HPA axis activity [37]. Together with similar findings of *Crhr1* polymorphism interaction with childhood maltreatment and HPA axis dysfunction in humans [38], these data suggest that naturally occurring genetic variances in the *Crhr1* gene determine stress vulnerability that contributes to the pathogenesis of stress-related disorders [39]. In addition to genetic variances, stress-induced epigenetic modifications of genes for CRH receptors or CRH itself have been shown to be critical factors implicated in individual stress-susceptibility. For instance, in stress-susceptible adult mice, chronic social stress induced long-term demethylation of the CRH gene resulting in increased CRH expression in the PVN, which was associated with an increase in depression-like behavior [40••]. Conversely, stress resilient mice did not show this stress-induced effect on CRH gene induction, nor depressive-like behavior [40••]. Notably, DNA demethylation at the CRH promoter and increased CRH in the PVN of susceptible mice can be reversed by chronic imipramine treatment [40••]. Thus, these data suggest that an up-regulation of CRH system in the PVN is linked to a stress-susceptible phenotype. This finding is of clinical relevance as high levels of CRH have also been found in patients with depression and certain anxiety disorders such as posttraumatic stress disorder [39].

Neurobiological correlates associated with stress-susceptibility: Role of stress-inhibitory neurocircuitries and associated mechanisms

The critical parvocellular CRH and AVP stress-controlling neurons within the PVN integrate excitatory information arising primarily from the lower brainstem and inhibitory impulses from various cortical and subcortical sources into an appropriate neuroendocrine signal [16•]. Most prominent among the stress-inhibitory pathways are PVN inputs from the hippocampus and medial prefrontal cortex (mPFC) (Figure 3). Lesion studies have shown that inactivation of the hippocampus (particularly its primary ventral output, the ventral subiculum) prolongs HPA axis stress responses whereas electrical stimulation of this region reduces circulating glucocorticoid levels, consistent with an inhibitory role in HPA axis function [16•]. Similarly, mPFC lesions have been shown to delay shut-off of HPA axis responses to a psychogenic stressor (especially the dorsal/prelimbic division whereas the ventral/infralimbic part has opposite function and activates neuroendocrine stress responses [16•]). Both

Figure 3



Schematic representation of neurocircuitries involved in the regulation of stress-induced HPA axis activity. Depicted are functional differences in normal (resilient, **(a)**) and stress-susceptible **(b)** individuals. Excitatory pathways (green) to medial parvocellular PVN neurons arise primarily from brainstem areas (e.g. NTS, medulla), while inhibitory pathways (red) arise from various forebrain regions such as hippocampus (HIP), medial prefrontal cortex (mPFC), dorsomedial hypothalamus (DMH), bed nucleus of the stria terminalis (BNST) or lateral septum (LS). Input from limbic regions may also access the PVN via interaction with local interneurons in the PVN vicinity (peri-PVN). Notably, the amygdala (AMY) exerts a primarily excitatory influence upon HPA axis activity through a GABA-GABA disinhibitory process. Inhibitory information is mediated either via monosynaptic GABAergic pathways (e.g. LS, DMH) or disynaptic glutamate-GABA connections (e.g. mPFC, HIP). Most of these forebrain areas

the hippocampus and mPFC highly express glucocorticoid receptors, and it has been shown that inhibition of stress responses by these forebrain areas is mediated by glucocorticoid feedback [16•,41]. Moreover, there is also evidence for a local rapid feedback inhibition of the HPA axis at the PVN level which is mediated by glucocorticoid-induced endocannabinoids and a retrograde cannabinoid type 1 receptor-mediated suppression of the excitatory synaptic drive to neuroendocrine PVN cells [41]. Of regulatory importance beside steroid feedback is also direct GABAergic input to PVN neurons that arises from different brain areas including neurons scattered in the immediate surroundings of the hypothalamic PVN (perinuclear peri-PVN area) [16•]. In addition to hippocampus and mPFC also selective inactivation of either the BNST, dorsomedial hypothalamus (DMH) or lateral septum (LS) results in enhanced HPA responsiveness to acute stress [16•,42,43•] (note: similar to hippocampus and mPFC in all of these regions subarea-specific effects on HPA axis responses have been described; for detail see [16•]). In addition to HPA axis regulation, inactivation of the LS changes stress coping behavior identifying the LS as a key brain area promoting active stress coping strategies (Figure 3) [43•].

A question that is just beginning to be addressed is to what extent stress-susceptibility is associated with dysregulation in stress-inhibitory pathways. For instance, using immediate early gene expression as marker of neural activity, it was demonstrated that susceptible rats and mice that display enhanced helplessness behavior following inescapable shock show reduced neural activity in stress-inhibitory brain areas such as hippocampus, mPFC and LS [44,45], while resistant animals, which received the same inescapable shock but did not become helpless showed no change in neural activity. Along these lines, reduced c-Fos expression was found selectively in the intermediate part of the LS in stress-susceptible HAB rats as compared to LAB rats suggesting subregional specificity of the LS in stress regulation [29]. However, there is evidence that substrates for both stress-inhibitory and stress-excitatory mechanisms exist within the LS [46••]. Because of space limitations of this review we discuss subregional specificity only for the LS as one representative example. Very recently it has been shown that selective activation of a subset of LS cells identified as CRFR2 positive GABAergic projection neurons targeting the anterior hypothalamus enhanced stress-induced behavioral measures of anxiety and induced an increase of corticosterone levels [46••] via a presumptive di-synaptic disinhibitory connection with the PVN (Figure 3). These data suggest a complex subregion-specific (or even single cell group) correlation between LS activity and stress-susceptible phenotypes. Similarly, mPFC regulation underlying individual differences in stress-related emotional processes was studied. For instance, a correlation was found between individual differences in neural firing of distinct mPFC neurons that are interconnected with the AMY and individual stress vulnerability in chronically stressed mice. The results demonstrate that susceptible mice exhibit lower PFC firing rates and higher AMY coupling to local AMY oscillatory activity than resilient individuals [47]. This is consistent with a recent study demonstrating that stress-induced behavioral abnormalities in susceptible mice exposed to chronic stress are associated with a decreased coordination of rhythmic activity across the PFC-AMY-ventral tegmental area (VTA) network [48]. Direct opto-/chemogenetic stimulation of the PFC-AMY circuitry normalizes activity in the network and restores behavioral function in susceptible [48] or chronic stressed mice [49]. Thus, these findings indicate that a reduced or dysregulated activity in a distinct corticolimbic network of vulnerable animals is associated with impaired stress coping. This is in line with human studies where a hypofunction of the PFC was found to be related to dysregulation of emotion in anxiety or mood disorders [50]. However, further studies are necessary to unravel the precise chemical processes underlying the observed dysregulation of these corticolimbic circuits in stress-susceptible individuals that may be then targeted by therapeutic approaches.

Role of GR/MR in stress-susceptibility

Changes in corticosteroid signaling due to MR and/or GR variability have been shown to be important sources of inter-individual variability in stress responsiveness (Table 1). For instance, genome-wide expression profiling in rats has shown that differentially expressed genes (in the amygdala and hippocampus) related to GR signaling were associated with individual stress-vulnerability [9]. Notably, the overlap of vulnerability-related and resilience-related genes was found to be very small (<2.4%), indicating that the vulnerability or resilience behavioral constructs were distinct at the transcriptome level. Along these lines, in the RHA/RLA rat model lower GR binding was found at the pituitary level in stress-susceptible RLA individuals compared to stress-resilient RHA animals [35]. GR gene expression has been shown to be modulated by epigenetic modifications relevant to stress vulnerability [12]. For example, increased DNA methylation at a neuron-specific glucocorticoid receptor (NR3C1) promoter (Figure 2), which determines reduced GR expression in the hippocampus was shown to be associated with increased stress-susceptibility and

(Figure 3 Legend Continued) influence HPA axis activity in a subregion-specific manner with both excitatory and inhibitory effects on PVN. For instance, the LS provides additional excitatory input to hypophysiotrophic PVN neurons via GABA-GABA disinhibitory connections. Reduced inhibitory function (dashed lines) in this network brought about by mechanisms outlined in the text and Figures 1 and 2 is considered a main contribution to increased HPA axis activity in stress susceptible animals. (see text and recent reviews [1••,16•]).

increased HPA axis reactivity of animals of a low maternal care group [51••]. These deficits could be reversed by intracerebral administration of the HDAC inhibitor trichostatin A (increases histone acetylation and reduces DNA methylation) [51••]. Thus, these findings indicate that stress-induced epigenetic marks are reversible and there is a capacity for remodeling of epigenetic marks across the lifespan. Interestingly, increased cytosine methylation of the NR3C1 promoter associated with decreased GR mRNA levels were also found in the hippocampus of suicide victims with a history of childhood abuse, compared to suicide victims with no childhood abuse or controls [52]. Collectively, these data provide translational relevance for the results obtained in rodents and suggest common epigenetic mechanisms how early life stress leads to a sensitization of central stress pathways that may lead to an enhanced vulnerability to subsequent stressors and stress-related psychopathologies [12].

In addition, central MRs have been proposed to play a key role in mediating stress vulnerability [53]. The majority of studies indicate that reduced MR functionality or expression is associated with enhanced stress-susceptibility. For instance, in mice exposed to chronic social defeat, stress-susceptible animals showed lower expression of the MR in the hippocampus [36]. Conversely, forebrain MR overexpression localized largely to the hippocampus and cortex, results in decreased anxiety-like behavior and suppressed HPA stress response [54]. As hippocampal MRs are known to exert a tonic inhibitory influence on basal HPA axis activity [53], this finding is in line with the enhanced basal HPA axis tone in stress-susceptible animals [36] and humans with depressive disorders [23]. Notably, human studies have shown that certain haplotypes of *NR3C2*, encoding the MR, that result in gain of function of this receptor, may protect against the consequences of stress exposure, including childhood trauma [55]. Thus, these findings suggest that a reduced MR function or an imbalance between MR and GR function may be a critical risk factor to develop stress-related psychopathologies such as depression [53]. Indeed, lower MR levels in the hippocampus, inferior frontal gyrus and cingulate gyrus have been found in brain tissue from patients with major depressive disorder compared to non-depressed subjects [56].

Importantly, glucocorticoid effects are biphasic and show an inverted U-shaped dose-response curve, which indicates that dysregulated activation of these receptors can lead to maladaptation [57]. As an example, Nasca and coworkers have shown stress-induced upregulation of hippocampal MR expression in stress-susceptible but not resilient mice which mediates a functionally significant (increased levels of anxiety-like and depression-like behavior) suppression of mGlu2 expression [58]. Accordingly, it is proposed that maintenance in glucocorticoid homeostasis and associated balance in MR/GR-mediated effects limit vulnerability to stress-related diseases.

Role of FKPB5 in stress-susceptibility

Another possible key factor that may contribute to inter-individual differences in stress-related HPA dysfunctions is FKPB5 (FK506 binding protein 51) a chaperone molecule that is part of the GR complex and decreases its affinity for glucocorticoid binding [59]. When FKPB5 is bound to the GR complex, glucocorticoids bind with lower affinity and nuclear translocation of the receptor is less efficient [59]. Notably, its expression is induced by stress primarily in the ventral hippocampus and prefrontal cortex [60]. Recently, it has been shown that mice selectively bred for extremes in stress-reactivity assessed by HPA axis hyperactivity to restraint stress differ in FKBP5 expression. High responding (HR) mice show higher FKBP5 levels in the hippocampus than low responding mice which lead to an increased GR resistance and decreased feedback efficiency in HR mice [30]. Conversely, mice with a deletion of the FKBP5 gene were less affected by chronic social defeat stress in specific neuroendocrine and behavioral parameters [30]. In humans, genetic variations of FKBP5 predispose individuals to increased sensitivity to psychosocial stress (Figure 2) [59]. The effect of the FKBP5 gene polymorphism as risk factor for developing stress-related psychiatric disorders in adulthood appears to be allele-specific and depends upon epigenetic changes in functional glucocorticoid response elements of FKBP5 as a consequence of childhood trauma exposure [10]. Thus, these results are an excellent example of how stress-induced epigenetic modifications of genes regulating HPA axis activity work in concert with effects of exposure to adverse early life events and genetic polymorphisms to enhance the risk of developing stress-related psychiatric disorders. Collectively, these data propose FKBP5 as an attractive therapeutic target. Experience with recently developed selective FKBP51 inhibitors (SAFit) [61], will show whether this can be a promising new treatment avenue for stress-related disorders.

Role of BDNF in stress-susceptibility

Brain derived neurotrophic factor (BDNF) is involved in dendritic remodeling in stress-related brain areas and has been shown to be an important determinant of stress-susceptibility and resilience in humans and animal models [4]. For instance, mice with a variant BDNF Val66Met polymorphism (associated with HPA axis hyper-reactivity in humans [62] and also found in patients with depression [63]) displayed increased stress vulnerability indicated by HPA axis hyper-reactivity and increased anxiety/depressive-like behavior in response to repeated restraint stress compared to control mice [64]. Moreover, in rodents lower BDNF mRNA and protein levels were found in the hippocampus of stress-susceptible individuals compared to resilient animals [65]. Blockade of hippocampal

BDNF signaling during social defeat sessions in stratified resilient rats has been shown to lead to vulnerability (induction of social avoidance by social defeat), while intrahippocampal infusion of a potent BDNF mimetic and TrkB agonist promoted resilience in vulnerable animals [65]. Similarly, in the learned helplessness animal model lower BDNF levels and reduced spine density were found in the hippocampus (CA3 and dentate gyrus) and mPFC of stress-susceptible helplessness animals compared to control and non-helplessness animals [66•]. Thus, it seems that stress-susceptibility is related to a downregulation of hippocampal and PFC BDNF highlighting low BDNF as a pro-vulnerability factor in specific brain areas. Indeed, this is in line with previous findings demonstrating that knockdown of hippocampal BDNF by RNA interference elevates corticosterone levels and induces behavioral despair (increased depressive-like behaviors) and anhedonia [67], while viral-mediated overexpression of BDNF in the dorsal dentate gyrus prevented these behavioral changes [68]. However, in other stress-associated brain areas such as amygdala (see [1••,2] for review) or the mesolimbic dopaminergic reward circuit including the VTA — nucleus accumbens (NAc) pathway (for comprehensive review see) [3,26••], BDNF can have different or even opposite effects on stress-susceptibility. Obviously, these data underscore the complex, highly region specific effects of BDNF signaling on stress regulation.

Conclusions

The stress response is a highly adapted and balanced process where alterations in regulatory elements can change stress sensitivity and reactivity, resulting in profound consequences for the individual's health. Data reviewed here suggest that differences in stress-reactivity can be attributed at least in part to alterations in distinct neural pathways that regulate and limit the neuroendocrine stress axis. Specifically, rodent studies have shown that stress-susceptible animals display reduced stress-inhibitory function in selected neural circuits localized in corticolimbic areas such as hippocampus, mPFC, BNST and LS. Notably, in these regions, functionally relevant changes in several regulatory elements of the stress axis (e.g. GR/MR ratio, FKBP5 and BDNF levels) have been found in stress-susceptible individuals. Collectively, these alterations contribute to a maladaptive stress response including a dysregulated HPA axis activity through an impairment of negative feedback (e.g. reduced GR expression, reduced GR sensitivity, GR hypersensitivity) and increased hypothalamic and pituitary excitability (e.g. exaggerated CRH/CRHR1 activity) which are key altered parameters of patients with stress-related disorders such as depression and anxiety. Underlining the translational value of these findings, imaging studies have shown reduced activity and/or volume in some of these same areas such as hippocampus and PFC in stress-susceptible human individuals, although such a connection has yet to be firmly established. Further preclinical studies using modern, refined techniques are needed to identify singular pathways that are implicated in such stress inhibition. These have to then be further characterized by complementary techniques such as optogenetics and neurochemical phenotyping revealing the engaged neurotransmitters and receptor systems for possible therapeutic targeting. In summary, these findings may provide a roadmap for future drug discovery efforts to identify agents that restore impaired stress-regulatory functions as novel, rapid and efficacious treatments of stress-related disorders.

Conflict of interest

The authors declare that they have no conflicts of interest to report.

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