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Review

# Neural Mechanisms of Stress Resilience and Vulnerability

Tamara B. Franklin,[1] Bechara J. Saab,[2] and Isabelle M. Mansuy[2,*]
[1]EMBL Monterotondo, Adriano Buzzati-Traverso Campus, IT-00015 Monterotondo, Italy
[2]Brain Research Institute, Medical Faculty of the University Zürich and Department of Health Science and Technology, Swiss Federal Institute of Technology, Neuroscience Center Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland
*Correspondence: mansuy@hifo.uzh.ch
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Exposure to stressful events can be differently perceived by individuals and can have persistent sequelae depending on the level of stress resilience or vulnerability of each person. The neural processes that underlie such clinically and socially important differences reside in the anatomical, functional, and molecular connectivity of the brain. Recent work has provided novel insight into some of the involved biological mechanisms that promises to help prevent and treat stress-related disorders. In this review, we focus on causal and mechanistic evidence implicating altered functions and connectivity of the neuroendocrine system, and of hippocampal, cortical, reward, and serotonergic circuits in the establishment and the maintenance of stress resilience and vulnerability. We also touch upon recent findings suggesting a role for epigenetic mechanisms and neurogenesis in these processes and briefly discuss promising avenues of future investigation.

## Introduction

### *Stress Resilience and Vulnerability*

Stress is classically defined as a condition that seriously perturbs the physiological and psychological balance of an individual (Tables 1 and 2). Stress-related psychopathologies such as major depressive disorder (MDD), anxiety, conduct disorders, and posttraumatic stress disorder (PTSD) perturb behavioral, cognitive, and social domains and exacerbate one's reactivity to stressful events. Traumatic stress, however, does not affect everyone similarly. While susceptible individuals poorly adapt to stressors and express inappropriate responses that can become persistent states of stress, resilient individuals can perceive adversity as minimally threatening and develop adaptive physiological and psychological responses (Del Giudice et al., 2011). Such stark difference in individual resilience/vulnerability occurs across age, sex, and culture. The underlying mechanisms are known to depend on a combination of genetic and nongenetic factors that interact in complex and consequential ways but these mechanisms remain not fully understood.

### *Coping Strategies*

Coping strategies are essential to minimize the impact of stress and determine the degree of resilience or susceptibility. Coping is active when an individual tries to deal with a challenge, faces fears, participates in problem solving, and seeks social support. It also engages optimism and positive reassessment of aversive experiences that can produce long-term resilience. In contrast, passive coping involves denial, avoidance of conflicts, suppression of emotions, and behavioral disengagement. It is maladaptive and provides only short-term resilience to stress (Sherrer, 2011).

Coping style varies between individuals and situations and influences how the neuroendocrine and neuroimmunological systems are activated in response to stress (Zozulya et al., 2008). It also plays a central role in determining whether stress-related disorders develop or not. For example, the use of passive coping is often a characteristic of MDD and PTSD patients (Taylor and Stanton, 2007). The biological basis of stress response and coping strategies is not clearly defined, and its understanding is essential for a better comprehension of the etiology of these disorders. Animal models have been instrumental in this respect and, like humans, animals use coping strategies when faced to stress. Thus, rodents can express both active coping, manifested by defensive/aggressive behaviors, fight and exploratory activity, and passive coping, manifested by submission, freezing, and immobility. These behaviors can be reliably measured as reflecting stress responses and can be used as models of stress in humans.

This review outlines some of the mechanisms underlying stress resilience and vulnerability and describes current knowledge about the way these mechanisms are established at a behavioral, cellular, and molecular level. As the general topic of stress vulnerability and resilience is quite expansive, we have chosen to focus on select themes. As such, although the influence of early life stress on developmental processes is of interest, in this review, we particularly emphasize findings that highlight some of the consequences of stress on adult plasticity and behavior, particularly those which may provide converging causal mechanistic insights, with the aim of limiting the broad scope of this topic to manageable number of themes. We first describe animal models used to study the mechanisms of stress resilience and vulnerability and delineate their major characteristics. We then discuss causal and mechanistic findings involving signaling pathways and connectivity in specific neural structures and molecular components and also reflect on findings implicating epigenetic mechanisms and adult neurogenesis in these processes. We then conclude with future perspectives and a general discussion of the utility of these findings in driving medical research.

**Table 1. Definitions**

| | |
|---|---|
| Stress | Activation of a stress response, a stressful stimulus itself, and/or the consequences of a stressful experience. |
| Stressor | Stimulus or event that challenges the organism with a potential threat and that induces a physiological and behavioral response. Unpredictability is a reinforcing factor, and a stressor that is unexpected, cannot be controlled or avoided, and has uncertain consequences is more severe. Unpredictable stressors are distinguished from stimuli that vary expectedly such as seasonal shifts that homeostatically increase stress axis activity. |
| Stress response | Mobilizes resources from metabolic, cardiovascular, autonomic, immune, and CNS to adapt to stimulus. Comprised of activation, recovery and adaptation. Rapid activation by stress is followed by quick recovery, except after traumatic events (e.g., combat, life-threatening accident, assault). Such events can lead to chronic stress that engages long-term adaptive coping mechanisms. These mechanisms can become maladaptive and increase vulnerability to stress-related psychophathology (e.g., PTSD). |
| Basic stress physiology | Stress hormones and neuropeptides include CRH, urocortins, ACTH, glucocorticoids, vasopressin, endorphins, and neurotransmitters such as adrenaline. CRH acts through CRH receptor 1 (CRHR1) and to a lesser extent CRHR2 (Refojo and Holsboer, 2009). Urocortin 2 and 3, CRH-related peptides, preferentially bind to CRHR2. CRHR1 is predominant in PFC, hippocampus, PVN, anterior pituitary, and BLA. CRHR2 is abundant in the ventromedial hypothalamus, DRN, and medial amygdala (Steckler and Holsboer, 1999). CRH-CRHR1 is involved in stress response initiation and urocortin-CRHR2 system in termination. CRHRs are linked to intracellular Gs/adenylyl cyclase-dependent and MAPK signaling. |
| Actions of glucocorticoids | Upon entering the brain, glucocorticoids (GC) rapidly increase stress reactions, then contain these reactions to facilitate recovery, while promoting behavioral adaptation. Moderate and controlled GC levels mediate normal cellular functions, while low or excessively high levels cause dysfunction. GCs act via mineralocorticoid (MR) and glucocorticoid (GR) receptors. MRs are involved in stress appraisal and response onset, while GRs facilitate response termination and the establishment of coping strategies. MR/GR imbalance is associated with stress vulnerability and related pathologies (De Kloet et al., 1998). Chronically elevated GC compromise neuronal survival and plasticity, neurotrophic factor expression, chemoresistance to oxidative stress, and promote inflammatory cascades. |

## The Use of Animal Models to Study Stress Resilience and Vulnerability

Behavioral studies in rodents have demonstrated that environmental manipulations at different stages of life can have profound and lasting consequences on stress vulnerability and resilience. Here, we describe some of the major manipulations and paradigms developed in animals during development or adulthood, their primary features and use, and their relevance to human.

### *Environmental Manipulations in Early Life*

The prenatal and postnatal milieu in mammals strongly influence development, and if compromised can severely alter physiological, behavioral, and cognitive functions in young and adult individuals. In rodents, prenatal insults such as maternal stress during gestation, or pathogenic immunological activation increase the risk for neurodevelopmental and brain disorders during postnatal and adult life (Howerton and Bale, 2012; Laloux et al., 2012). Prenatal stress affects the hypothalamic-pituitary-adrenal (HPA) axis, with a severity that depends on the gestational stage of stress exposure, and the sex of the animal. The underlying mechanisms involve complex interactions between the maternal hormonal milieu, the placenta, and the developing fetus.

Postnatal stress is also detrimental, in particular in early infancy which is a critical period during which the offspring almost entirely depends on parents or caregivers. Because paternal upraising is marginal, rodent pups fully rely on their mother and are markedly affected by any change in the quality, quantity, and reliability of maternal care. While high level of active maternal behaviors such as licking-grooming and nursing has beneficial effects throughout life and in adulthood, low level can lead to depressive-like symptoms, anxiety, and altered cognitive and social behaviors (Myers-Schulz and Koenigs, 2012; Figure 1A). Likewise in humans, maternal/caregiver attachment, reliable and safe environment in childhood are favorable and predispose individuals to stress resilience (Jaffee, 2007) while neglect, physical/sexual abuse, or traumatic events

**Table 2. Stress Models**

| | |
|---|---|
| Allostatic load model | Cumulative cost of continual adaptation to repeated predictable stress (McEwen and Wingfield, 2003; Sterling and Eyer, 1988). Allostasis is an active process that maintains physiological and behavioral stability during change. When insufficient or poorly organized, it can induce delayed arrest of the stress response and lead to allostatic overload. When acting optimally or beyond need, it can promote adaptive coping and resilience. Resilience is the ability of an organism to respond to environmental stressors by recruitment and efficient termination of allostatic responses (Karatsoreos and McEwen, 2011). |
| Reactive scope model | Complementary model that captures additional aspects of stress like the notion of reactive/predictive allostasis or differences in stress response across context, systems, and species (Romero et al., 2009). Integrates the coordinated involvement of behavioral, cognitive, and social domains across development and considers neural circuits and molecular pathways beyond the stress pathway (Kim et al., 2011). |

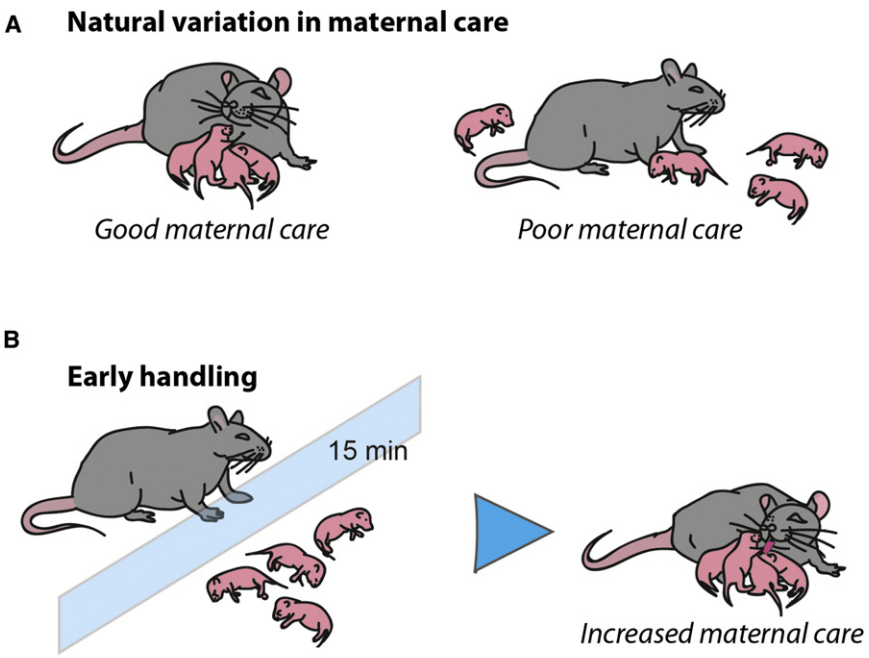


**Figure 1. Experimental Paradigms Based on Maternal Care Used to Study Stress in Rodents**

(A) Rat and mouse dams display natural variation in maternal behaviors. "Good" mothers (left) provide high level of active maternal care such as licking/grooming, arched-back and blanket nursing, and nest building. "Poor" mothers (right) provide low level of these behaviors. Maternal behaviors are determinant for stress responsiveness later in life.

(B) Early handling involves brief separation (up to 15 min) of mother and pups. When reunited, dams provide more care, which favors resilience in pups when adult.

(C) Maternal separation or deprivation paradigms involve longer periods of separation, classically 3 to 24 hr applied once (1 × 24 hr, "deprivation"), or daily during the first postnatal week(s) ("chronic separation"). Separation can be predictable (same time each day) or unpredictable and may be combined with maternal stress. Maternal separation or deprivation perturbs the continuity of maternal care and causes stress to the pups. Unpredictable separation is more disturbing, and induces disorganized and unreliable maternal behaviors when chronic.

increase the risk for mood, affective, and conduct disorders later in life (Dietz et al., 2011; Hulme, 2011). Changes in maternal care can occur naturally due to individual variability in motherhood but can also be induced experimentally using specific manipulations in rodents.

*Early Handling Models*. Early handling is a simple paradigm that consists in subjecting pups to short periods of separation from their mother during the first week(s) of life (Figure 1B). This manipulation decreases overall stress responsiveness and favors a rapid surge and return to baseline of glucocorticoids immediately after stress (Cirulli et al., 2003; Meaney et al., 1996). Such fast adaptive response minimizes the risk of damage to the nervous system due to prolonged glucocorticoids exposure. It also reduces anxiety and enhances exploratory activity across life (Levine, 1957; Weinberg et al., 1978). Early handling also has beneficial effects in primates. In squirrel monkey, a species that strongly relies on maternal attachment, brief and intermittent maternal withdrawal renders infants more adventurous and less anxious when adults and diminishes stress-induced activation of the HPA axis (Lyons et al., 2000, 2010b).

Early handling mediates its effects differently in rodents and primates. In rodents, it increases active maternal behaviors, which reduces HPA axis activity and can elicit stress resilience in the offspring when adult (Meaney et al., 1996; Pryce et al., 2001). Such "maternal mediation" effects operate through maternal influence (Grant et al., 2009) and can have multiple sources ("maternal modulation" model [Tang et al., 2012]). In contrast, in squirrel monkey, maternal care does not predict stress responsiveness of the offspring later in life, but it is the stress experienced by the infant itself that favors resilience. In such "stress inoculation" model, brief challenges in early life are believed to elicit a form of resistance that persists through adulthood and involves the use of coping strategies (Lyons and Parker, 2007). Clinical studies in human support this model and have linked mild controllable challenges in childhood with improved response to adversity later in life (Bonanno and Mancini, 2008; Tang et al., 2012).

*Maternal Separation/Deprivation Models*. In contrast to brief handling, extended periods of maternal separation during postnatal life can persistently interfere with neurochemical, hormonal, and behavioral responses and induce stress vulnerability (Figure 1C). In rodents, 3 hr of daily separation from birth to 2 weeks postnatal can result in depressive-like behaviors upon re-exposure to stress later in life (Franklin et al., 2011; Uchida et al., 2010). Maternal separation can have a strong or mild impact depending on its duration, frequency, and predictability. Long, chronic, and unpredictable separation has more profound and persistent effects than predictable separation, because it

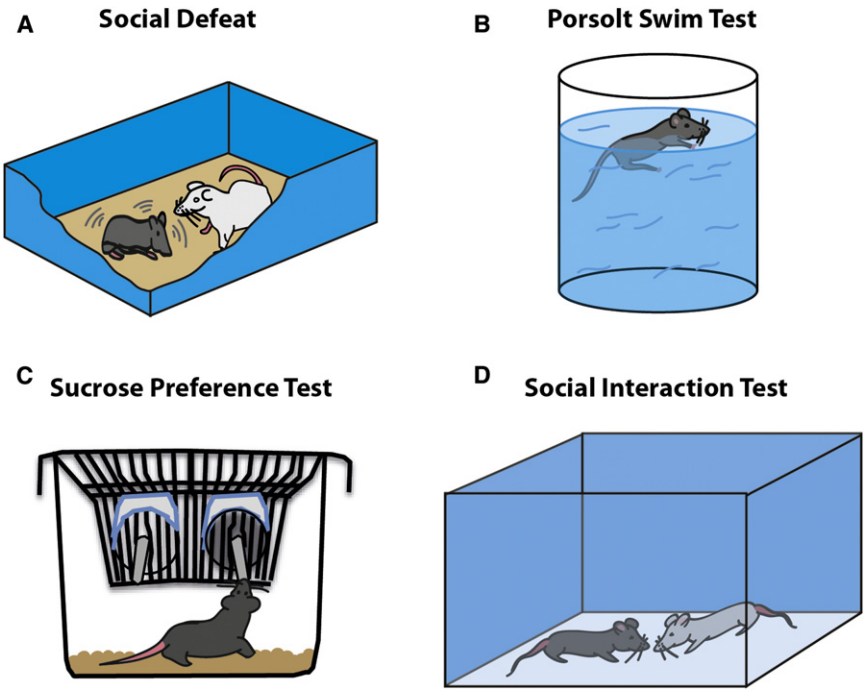


**Figure 2. Behavioral Paradigms Used to Induce or Test Stress in Rodents**

(A) Social defeat consists in exposing a male mouse or rat to an aggressive, dominant conspecific, the "aggressor" (same or different strain selected for high aggressiveness), 5–10 min daily for 1–2 weeks. Repeated attacks, confrontations, and defeat by the aggressor induce subordination, social avoidance, and depressive- and anxiety-like behaviors in the defeated animal.

(B–D) Tasks to evaluate behavioral responses to stress. (B) In the Porsolt swim test, an animal is placed in a small basin of cold water for a few minutes. The time spent in escape-directed behaviors like active swimming versus helpless behaviors like passive floating is a measure of depressive-like behaviors. This test can also be used to induce stress. (C) In the sucrose preference test, an animal can drink from a bottle of water or a bottle of sucrose. A reduction in natural sucrose preference reflects anhedonia, a trait of depression. (D) In the social interaction test, an animal is placed in a novel arena with an unfamiliar peer for direct contact or contact through a barrier. The time spent investigating the peer reflects sociability. Reduced interaction indicates social anxiety and withdrawal. This test is often used following social defeat.

cannot be anticipated and compensated for (Enthoven et al., 2008). Nonetheless in some conditions, maternal separation can also be beneficial and promote stress resilience later in life. In Wistar rats, prolonged separation (6 hr) can lower emotional response and risk assessment and decrease anxiety in adverse conditions in adults (Roman et al., 2006). Likewise, in mice, pups exposed to chronic unpredictable separation combined with maternal stress develop some resilience to social stress when adult (Franklin et al., 2011), similar to the stress inoculation model. Although opposite, these effects can be reconciled by a "cumulative and mismatch" stress model which predicts that major stress in both early and adult life can cumulate and exacerbate susceptibility, while adversity restricted to early life can trigger the acquisition of stable active coping strategies (Daskalakis et al., 2012; Nederhof and Schmidt, 2011). What ultimately determines whether early stress leads to adaptive or maladaptive responses remains, however, unclear.

### *Environmental Manipulations during Adulthood*

Stress in adulthood can also be detrimental, especially when recurrent (Joëls et al., 2007). In rodents, chronic stress can be induced by multiple manipulations such as daily corticosterone administration or repeated physical restraint (Buynitsky and Mostofsky, 2009). While these models can be useful to evaluate therapeutic treatments, they have limited construct validity because they use a single invariant stressor that elicits habituation (García et al., 2000). More relatable paradigms can be used that combine physical and psychological stressors (i.e., damp bedding, brief food or water deprivation, white noise) repeatedly for several weeks (chronic mild stress paradigm). Such paradigms cause multiple signs of stress-like passive coping, anhedonia, and reduced grooming and self-care, which are characteristics of MDD (Griebel et al., 2002; Katz, 1982; Kompagne et al., 2008). Stronger stressors such as restraint, cold/warm exposure, swim stress, and shaking/cage rotation, applied unpredictably to prevent habituation, or challenges involving aspects of hierarchy, defeat, and inescapable aggression in males (Figure 2A) can also be used. These manipulations have good construct validity, and the depressive phenotypes they elicit can be reversed by chronic but not acute antidepressant treatment. Moreover, they also reproduce the variability in response observed in humans since submissive behaviors and social avoidance occur in only about 50%–60% of animals (Krishnan et al., 2007; Strekalova et al., 2004). The long-term effects of these manipulations can be assessed using different behavioral tasks (Figures 2B–2D).

## Neural Circuits Implicated in Stress Resilience and Vulnerability

The anatomical and functional connectivity of the brain is an important determinant of the degree of stress resilience or vulnerability in an individual. Below, we outline recent findings describing the implication of the neuroendocrine system, the hippocampus, the medial prefrontal cortex (mPFC), reward circuits, and dorsal raphe nucleus (DRN) projections in stress resilience and susceptibility and summarize causal and mechanistic evidence for their involvement. Although the amygdala is a key structure for stress responses, its role in stress vulnerability and resilience will not be covered, and we refer the reader to the extensive existing literature on the subject (Davidson and McEwen, 2012; Kim et al., 2011; Mahan and Ressler, 2012).

### *The Neuroendocrine System*

*Differential Activity of the HPA Axis in Stress Resilience and Vulnerability*. The HPA axis is a highly adaptive neuroendocrine

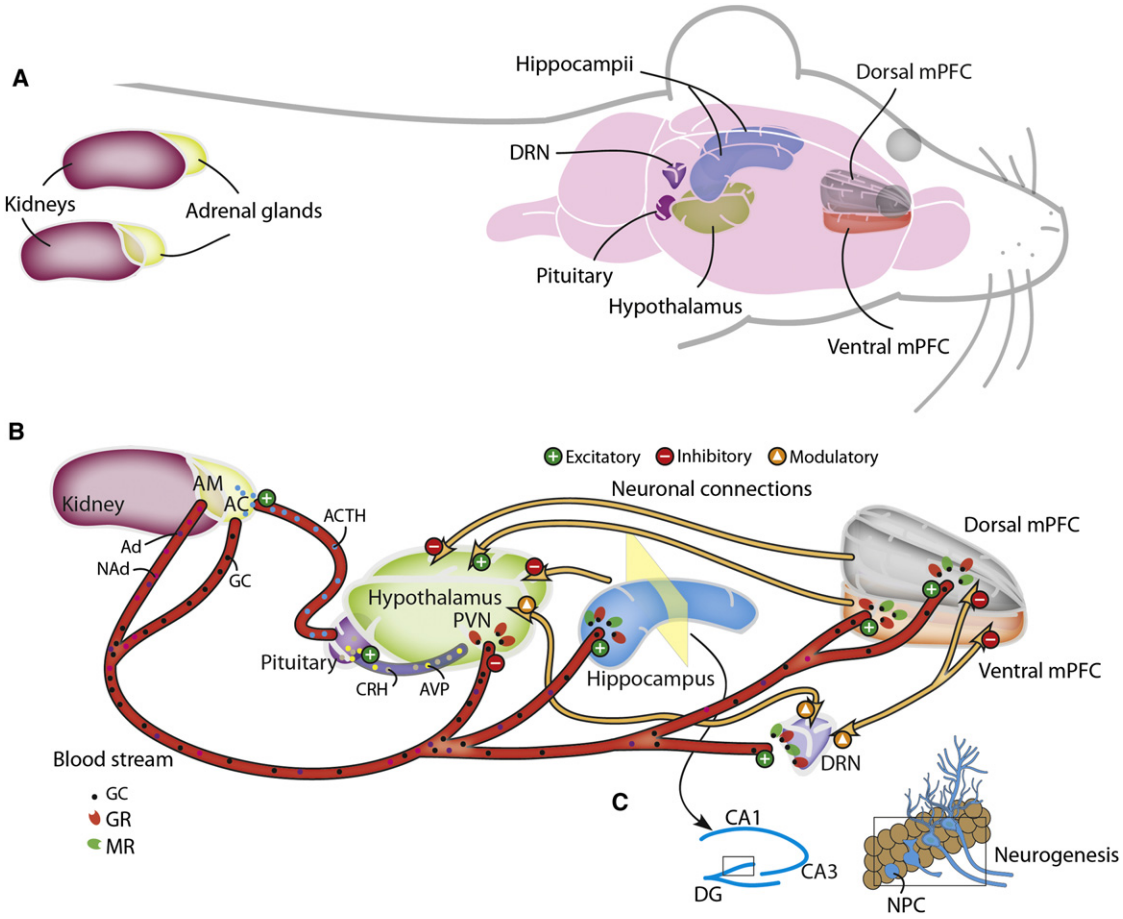


**Figure 3. Anatomical and Functional Arrangement of the HPA Axis and Associated Structures**

(A) Major components of the HPA axis and connected brain structures.

(B) Connections between the hypothalamus, pituitary, and adrenal glands in the HPA axis, and hippocampus, mPFC, and DRN. Activation of the HPA axis is initiated by stimulation of neurons in the medial parvocellular region of the paraventricular nucleus (PVN) of the hypothalamus and secretion of corticotropin-releasing hormone (CRH, or corticotropin-releasing factor, CRF) and arginine vasopressin (AVP) that amplifies the effect of CRH, in the portal vein. The pituitary gland secretes adrenocorticotropic hormone (ACTH), initiating the release of glucocorticoids (GC) from the adrenal cortex (AC), and adrenaline (Ad) and noradrenaline (NAd) from the adrenal medulla (AM) into the blood stream. This cascade is transient, and upon termination or removal of the stimulus, the HPA axis returns to a baseline state by the action of several negative feedback loops. In these loops, GC act directly to shut down the response of the hypothalamus and pituitary, and the release of CRH then ACTH, and indirectly by activating glucocorticoid receptors (GRs) in the hippocampus and frontal cortex, that project back to the hypothalamus. GC also activate mineralocorticoid receptors (MRs), and the coordinated action of GRs and MRs regulates stress response. The hypothalamus and mPFC have reciprocal projections with the dorsal raphe nucleus (DRN). Neurogenesis occurs in the dentate gyrus and yields new neurons from neural progenitor cells (NPCs). Plus and minus signs indicate positive and negative regulation, respectively; triangles indicate modulation that can be inhibitory or excitatory.

system strongly implicated in stress resilience and vulnerability. In rodents and humans, its functions are highly variable both within and between individuals. This variability is associated with differential response to stress (Figure 3). In Sprague-Dawley rats, males with altered HPA axis habituation and signs of CRH hypersecretion, such as low level of pituitary CRH1 receptors and blunted ACTH response to physical restraint, most quickly adopt a submissive posture when subjected to chronic social defeat (about 42%). In contrast, males with good HPA axis habituation, reduced CRH efficacy, and lower corticosterone release develop proactive resisting behaviors (Wood et al., 2010). Consistently, depleting CRH in the PVN using a short interfering RNA viral vector can attenuate social avoidance following social defeat (Elliott et al., 2010), suggesting a critical role for CRH in stress susceptibility.

Differential HPA axis activity is also linked to sexual dimorphism in stress susceptibility. In rodents, the increased vulnerability of females to stress correlates with higher CRH in PVN and stronger and prolonged secretion of ACTH and corticosterone (Dalla et al., 2011). Sex differences in response to stress are also associated with increased sensitivity of CRH target neurons. In rats, CRH signaling in locus coerulus (LC) neurons, which provide the major source of noradrenaline (NAd) and regulate emotional arousal, is higher in females. This is due to compromised trafficking and internalization of CRH receptors in dendrites, possibly because CRH phosphorylation is altered (Bangasser et al., 2010). LC CRH receptors also have increased coupling to Gs and are more active in females, rendering CRH-receptive neurons more sensitive to low level of CRH and less adaptable to high level that heightens stress susceptibility. This

sex bias in response to stress is reminiscent to observations in human (Kirschbaum et al., 1999). Thus, several stress-related disorders are more prevalent in women than men; for example 31% of women but only 19% of men develop PTSD after a major trauma (Young and Korszun, 2010), even if both experience comparable stressors during their lifetime. This dimorphism is in part mediated by the sex steroids estrogens and testosterone that oppositely regulate ACTH and corticosterone secretion (increase and attenuate, respectively) and by differences in the neural circuitry controlling ACTH.

*Alterations in HPA Axis Components during Early Life*. HPA axis development is strongly influenced by external factors in early life, and in particular by maternal environment. In the brain, the HPA axis progressively matures and is in a transitory state during postnatal days 4–14 in rodents. This stress hyporesponsive period (SHRP) is characterized by low and stable circulating level of corticosterone and reduced sensitivity to stressors. Maternal care regulates the SHRP and exerts a tonic inhibitory control on the HPA axis (Claessens et al., 2011). In pups, active maternal behaviors, such as licking/grooming and arched-back nursing during the first weeks of life, reduce the HPA axis responsiveness and stress susceptibility, diminish CRH mRNA expression in PVN neurons, and increase glucocorticoid feedback sensitivity and GR mRNA expression in the hippocampus (Liu et al., 1997; Plotsky and Meaney, 1993). These changes directly correlate with the level of care (Wilkinson et al., 2009) and, therefore, may in part underlie natural interindividual differences in HPA axis activity and sex-dependent stress susceptibility (perhaps due to sex discrimination in maternal care (Richmond and Sachs, 1984)).

Poor or perturbed maternal care, resulting from maternal separation or stress, disrupts the SHRP, activates the HPA axis, and lowers the threshold of corticosterone secretion in response to mild stressors or exogenous ACTH. These potentially pathological responses can however be rapidly desensitized when separation is prolonged and repeated, due to HPA axis habituation. However, despite this habituation, the neuroendocrine system is maintained alert and can respond to unexpected stressors, such as exposure to an unfamiliar environment (Enthoven et al., 2008). The dissociation between habituation to a predictable chronic stress, and stimulation by an unpredictable acute stress reflects the astonishing plasticity of the HPA axis that depends on molecular processes in different brain regions. For instance, while GR forebrain overexpression during development alters HPA negative feedback and induces sensitization to acute stress (Hebda-Bauer et al., 2010), GR deficiency in the pituitary induces resilience to chronic social stress in adulthood (Wagner et al., 2011).

Mechanistically, HPA axis (re)programming by maternal care is complex. It involves transcriptional regulation such as changes in binding of the transcriptional repressor neuron-restrictive silencer factor (NRSF) to CRH promoter in hypothalamic neurons (Korosi et al., 2010) and epigenetic mechanisms (McGowan et al., 2011). HPA axis (re)programming also recruits learning mechanisms, such as LC/NAd-dependent pathways that are hyperfunctional in neonates and favor maternal attachment (Landers and Sullivan, 2012). Observations that poor maternal care disrupts the HPA axis in animals are consistent with the link between childhood maltreatment, social adversity, emotional neglect, and lower cortisol in humans (Dietz et al., 2011). It is therefore important to better understand the mechanisms of HPA axis (re)programming. Several brain regions have been causally associated with this process, in particular the hippocampal formation and the mPFC.

### Hippocampal Pathways

The hippocampus is one of the major brain areas that exert strong regulatory control over the HPA axis. It is also itself modulated by stress hormones. The hippocampus has direct and indirect polysynaptic connections to the PVN, and it negatively influences the HPA axis via GR-dependent negative feedback (see Figure 3). In rats and humans, hippocampus stimulation decreases glucocorticoid secretion while hippocampal lesion elevates basal glucocorticoid level, especially during the stress recovery phase, which is the most reliant on negative feedback (Jankord and Herman, 2008). Facilitated glutamatergic plasticity in the dentate gyrus (DG) enhances exploratory activity in mice (Saab et al., 2009). In humans, dysfunctions of glutamatergic neurotransmission, maladaptive structural and functional changes in hippocampal circuitry, and decreased hippocampal volume have been associated with stress-related conditions such as MDD. The glutamate hypothesis for depression, for which hippocampus dysfunction is a major component, is well accepted (Sanacora et al., 2012).

*Glutamate and AMPA Receptors*. Both pre- and postsynaptic components of hippocampal glutamatergic neurotransmission are linked to stress responsiveness and HPA axis regulation (Popoli et al., 2012). Extracellular glutamate is sustained after prolonged and repeated stress in rat hippocampus (Fontella et al., 2004), a change that likely involves regulators such as MR (Karst et al., 2005), vesicular glutamate transporters (VGLUTs) that package glutamate in vesicles and glial-glutamate transporters (EAATs) needed for glutamate reuptake. VGLUT1, EAAT2, and vesicular glutamate are increased in dorsal hippocampus following chronic unpredictable stress (Raudensky and Yamamoto, 2007). However, this may depend on the conditions as VGLUT1, EAAT2, and EAAT4 are also decreased in hippocampus and cortex in helpless rats with altered coping abilities (Zink et al., 2010). This suggests different alterations in neuronal and glial glutamate transport/reuptake in basal or stress conditions. Altered gliogenesis, occurring after chronic stress, may also be implicated (Banasr and Duman, 2007).

Postsynaptically, glucocorticoids can modify the expression, trafficking, and functions of hippocampus AMPA and NMDA receptors (AMPARs and NMDARs). AMPAR subunits GluR1 and GluR2 are differentially regulated in the hippocampus in relation to stress vulnerability and resilience. In CD1 mice, an outbred strain with high variability in stress susceptibility, the most vulnerable individuals have fewer GluR1 but more GluR2 than resilient animals in CA1 and DG subregions of the dorsal hippocampus. Higher GluR2, a subunit that limits calcium influx, diminishes AMPAR sensitivity (Schmidt et al., 2010). Consistently, GluR1 knockout mice have altered glutamatergic transmission and depressive-like symptoms (Chourbaji et al., 2008). However, in C57BL/6J mice, which are more resilient, hippocampal GluR1 is lower than in stress-susceptible mice such as DBA/2J (Mozhui et al., 2010). This apparent inconsistency may

be due to differential GluRs trafficking in basal and stress conditions. In vitro application of corticosterone to primary hippocampal neurons indeed favors GluR1/GluR2 lateral diffusion and increases the number of synaptic GluR2-containing AMPARs. The increase is first rapid and initially linked to MRs, then slows down and becomes associated with GRs (Groc et al., 2008; Karst et al., 2005). A causal relationship between glutamate over-release and AMPAR expression or trafficking has however not yet been established. Consistent with the role of AMPARs in synaptic plasticity, hippocampal LTP and LTD are perturbed by stress (Kumar, 2011). Further, the effect of stress on GluRs is in line with early evidence that signaling through AMPARs is impaired in stress-related mood disorders, and that GluR1 alteration can be corrected by chronic antidepressants like imipramine and ketamine (Hashimoto, 2009; Koike et al., 2011). Moreover, ampakine LY451646, an AMPAR potentiator that prevents HPA overactivation, has proresilience and antidepressant effects (Popoli et al., 2012).

*BDNF*. BDNF is another signaling component of stress responses that, in the hippocampus, is both necessary and sufficient for resilience. BDNF mRNA is increased in ventral hippocampus area CA3 in rats resilient to chronic mild stress (Bergström et al., 2008). When overexpressed in the adult DG, it promotes resilience and blocks the anhedonic effect of stress, while its knockdown in young animals elevates corticosterone level, and induces depressive-like behaviors and anhedonia (Taliaz et al., 2010, 2011). Mechanistically, BDNF and glucocorticoid signaling may be linked through the tyrosine kinase receptor TrkB and cortical GRs, which can interact. This interaction is disrupted by binding of glucocorticoids to GRs, which downregulates phospholipase C$\gamma$-dependent pathways and BDNF-mediated neurotransmitter release (Numakawa et al., 2009). Notably, BDNF expression increases when glutamate release is higher, suggesting a dual interaction between BDNF and glutamatergic transmission. Further in PVN, BDNF acts through TrkB-CREB signaling to induce CRH expression (Jeanneteau et al., 2012), suggesting distinct downstream pathways in different brain areas. Besides BDNF, stress responsiveness also implicates other neurotrophic factors. Vascular endothelial growth factor (VEGF), a factor involved in angiogenesis and neuroprotection, is lower in ventral hippocampus area CA3 in susceptible rats (Bergström et al., 2008). Finally, the sustained increase in excitatory synaptic transmission and reduced level of trophic factors in the hippocampus following stress may underlie the dendritic remodeling and volumetric shrinkage associated with stress-related pathologies in animals and humans (Maras and Baram, 2012).

### *mPFC and Projections*

While stress severely affects neurotransmission and neuronal connectivity in the hippocampus, it also has multiple effects in mPFC. Uncontrollable acute stress, even when mild, rapidly and severely perturbs prefrontal functions, and chronic stress alters dendritic organization in prefrontal areas (Arnsten, 2009). But further to being itself influenced by stress, the mPFC also exerts a strong negative control over stress pathways. It represses the HPA axis predominantly through inhibitory projections from the ventral prelimbic (PLC), infralimbic (IC), and anterior cingulate (ACC) cortex that target HPA axis neurons either directly or indirectly through relays in nearby forebrain regions including DRN (Heidbreder and Groenewegen, 2003; see Figure 3). mPFC lesions augment HPA axis response to emotional stress, while intra-mPFC administration of corticosterone attenuates this response (Diorio et al., 1993). In susceptible rodents, neural activity and IEG expression are lower in ventral mPFC following stressors such as social defeat, predator stress, or water submersion (Covington et al., 2010). Clinically depressed patients postmortem have decreased activity in ACC, a region with functional homology to mPFC in rodents (Adamec et al., 2012; Covington et al., 2010). Such hypoactivity is linked to the stress response in animals, because when corrected by optogenetic cortical burst firing, social anxiety and anhedonia after social defeat are reversed (Covington et al., 2010). Notably, mPFC subregions have distinct functional implications for the HPA axis. While PLC dampens ACTH and corticosterone response selectively after restraint stress, IC does so only after a neuroimmunological type of stressor, but not after restraint stress (Radley et al., 2006). This reflects a distinct link between ventral and dorsal mPFC and the HPA axis.

An important feature of the ventral mPFC is its suggested role in the acquisition of stress resilience. Experience-driven resilience is a complex cognitive process involving progressive learning of a coping response. In animals, it can be modeled by exposure to a controllable stressor (tail shock) that can be actively terminated by the animal through running in a wheel, followed by exposure to another but uncontrollable shock in a novel context. The first shock progressively attenuates the escape response induced by the second shock, resulting in "stress immunization." Acquired resilience is long-lasting, protein synthesis-dependent and is mediated by glutamatergic pyramidal cells in ventral mPFC, which act as controllability detectors. These cells project onto GABAergic DRN interneurons and inhibit 5-HT neurons during controllable stress (Amat et al., 2006). During uncontrollable stress, memory of prior controllable experience elicits analogous DRN inhibition and mimics control. Stress resilience can also be acquired by prior exposure to an enriched environment but involves the IC in this case (Lehmann and Herkenham, 2011) and possibly its projections to the hypothalamus, DRN, or amygdala. These projections are distinct from those emerging from PLC and ACC (Vertes, 2004). Finally, some of mPFC-mediated resilience can also result from suppression of activity in the amygdala through reciprocal functional connections (Myers-Schulz and Koenigs, 2012).

### *The Reward Pathway*

In addition to neural circuits in mPFC, circuits classically linked to reward also contribute to stress resilience. Behaviorally, the primary function of reward pathways is to favor goal-directed and motivated behaviors, decisions, positive actions and emotions, and optimism, which are all important traits of resilience. When these pathways are dysfunctional, motivation and drive are affected and mark the appearance of negative behaviors leading to depression (Pizzagalli et al., 2009). The reward circuitry is composed of the mesolimbic dopamine (DA) system, which includes DA neurons in the ventral tegmental area (VTA) projecting to NAc. While some DA neurons in NAc are inactive, others are spontaneously active and release DA differently depending on their firing pattern (Grace and Bunney, 1983).

When firing with an irregular, low-frequency, single spike "tonic" pattern, DA release is tonic, while when firing with a bursting "phasic" pattern, DA is released in large phasic and transient peaks. Irregular firing involves glutamatergic and GABAergic neurons in the ventral subiculum-NAc-ventral pallidum-VTA circuit, and bursting activity is controlled by the pedunculopontine tegmentum and glutamate release (Belujon and Grace, 2011).

The reward system is transcriptionally activated upon stress and different transcriptional programs in NAc and VTA accompany resilience and susceptibility (Krishnan et al., 2007). A prominent marker of proresilience is the transcription factor ΔFosB, a variant of the immediate early gene (IEG) FosB, which is persistently activated by neuronal activity. In NAc, basal ΔFosB expression can predict whether a mouse is resilient or susceptible to social defeat stress. High expression correlates with resilience and low expression with susceptibility (Krishnan et al., 2007). Further, ΔFosB induction in NAc is necessary and sufficient for stress resilience. Its overexpression blocks isolation-induced stress vulnerability and is antidepressant, while its inhibition promotes susceptibility (Vialou et al., 2010b). Once recruited, ΔFosB can regulate multiple downstream genes, in particular GluR2. GluR2 expression increases in medium spiny neurons in resilient mice after chronic social defeat, which shifts the GluR1:GluR2 ratio and thereby lowers neuronal excitability and weakens NAc stimulation by glutamatergic input. Conversely, in susceptible animals, GluR2 expression decreases, and neuronal excitability and NAc (glutamatergic) stimulation increase (Vialou et al., 2010b). Because glutamatergic input to NAc regulates the saliency of rewarding or aversive stimuli, modulating this input can promote or prevent motivated behaviors associated with resilience and susceptibility. These mechanisms in rodents are relevant to the dual model of depression in humans postulating that higher reactivity of limbic emotional circuits but lower reactivity of cognitive circuits and disrupted functional coupling between these circuits underlie major depressive symptoms (Disner et al., 2011). These findings may also explain why in MDD patients, ΔFosB and its targets, GluR2, SCG3, and PCP4, are higher in dorsolateral PFC, a brain region in which hypoactivity is associated with impaired emotional regulation (Teyssier et al., 2011) (although drug treatment in this study may have biased the results). How ΔFosB is regulated in NAc is unclear, but transcriptional changes via the IEG serum response factor (SRF) likely occur. SRF is downregulated in NAc in vulnerable but not resilient animals and in depressed patients (Teyssier et al., 2011; Vialou et al., 2010a). Other transcription factors may also contribute. Finally, besides ΔFosB, BDNF signaling is also increased in NAc following social defeat. In susceptible mice, this is the result of stronger firing of both tonic and bursting DA neurons that project from VTA and negatively correlates with social avoidance behavior. Firing patterns and stress susceptibility can be corrected by chronic treatment with the antidepressant fluoxetine, suggesting that these patterns are important for stress regulation (Cao et al., 2010).

### *Serotonergic Transmission and DRN Projections*

While reward pathways modulate stress reactivity by altering decision making and motivation, other neural pathways, in particular serotonergic circuits, act concomitantly to alter mood and emotions. Indeed, dysregulated serotonergic neurotransmission has long been known to underlie the etiology of stress-induced affective disorders like MDD and anxiety (Stockmeier, 1997), and selective serotonin reuptake inhibitors (SSRIs) are the most efficient treatments to date (Gartside et al., 1995). Serotonergic neurons arise primarily from dorsal and median (MRN) raphe nuclei. While DRN projects to mPFC, lateral septum, amygdala, and striatum, MRN projects to the hippocampus, medial septum, and hypothalamus (Hensler, 2006). The activity of raphe neurons is regulated by negative feedback involving inhibitory metabotropic Gi/Go-coupled somatodendritic 5HT1A autoreceptors (5HT1AR) that limit serotonin release.

While both 5HT1A autoreceptors in raphe and heteroreceptors in projection areas are essential to establish circuits associated with stress reactivity, they play markedly different roles. Elegant experiments in mice demonstrated that a 5HT1A autoreceptor deficiency in adult DRN neurons reduces susceptibility to chronic mild stress and passive coping on the forced swim test, but a deficiency only during development increases anxiety-like behaviors. In contrast, a deficiency in 5HT1A heteroreceptors in projection areas across life leads to depressive-like behaviors without affecting anxiety (Richardson-Jones et al., 2010, 2011). Thus, while both 5HT1A auto- and heteroreceptors are necessary to regulate emotional behaviors, autoreceptors affect anxiety-related circuitry during development and depression-related circuitry in adulthood, and heteroreceptors affect depressive behaviors exclusively. The apparent resilience induced by a lack of autoreceptors in adults and vulnerability induced by a lack of heteroreceptors across life underscore the tight temporal regulation of serotonergic transmission in stress reactivity. These results confirm early studies in human linking 5HT1AR dysfunctions with depression and social anxiety (Savitz et al., 2009).

5HT1ARs are also linked to the effects of maternal care in stress reactivity. In mice, chronic and unpredictable postnatal maternal separation diminishes 5HT1A autoreceptor expression in DRN but not MRN and increases serotonin in DRN projection areas. Heteroreceptor expression is also decreased in DRN target areas like the periaqueductal gray (PAG) and thalamus. This effect is associated with resilience to social defeat and social withdrawal in adult animals and is reversed by the 5HT1AR agonist, 8-OH-DPAT (Franklin et al., 2011). Likewise, unpredictable but not predictable stress in adult rat impairs 5HT1A autoreceptor-mediated DRN inhibition and triggers receptor desensitization (Rozeske et al., 2011). Thus, unpredictable stressors in both early and late life alter 5HT1ARs. The link between 5HT1ARs and the HPA axis is not clear but may involve reciprocal neuronal connections between raphe and hypothalamic nuclei, regulation of 5HT1AR gene by GR through glucocorticoid-response elements in the promoter (Robertson et al., 2005), and/or components like tryptophan hydroxylase 2 required for serotonin metabolism (Tang et al., 2012).

## Epigenetic Mechanisms in Stress Resilience and Vulnerability

Further to specific neural mechanisms and pathways that modulate HPA activity, neurotransmission and signaling, stress resilience, and susceptibility also engage processes at the

chromatin level. These processes involve genetic and epigenetic factors that together, control the expression of genes important for stress regulation.

### Interplay between Genetic and Epigenetic Factors

Decades of research in human genetics based on genome-wide association studies and studies of copy number variations have revealed that complex brain diseases depend on a combination of genetic and environmental factors (Eichler et al., 2010; Wolf and Linden, 2012). Several risk loci for stress susceptibility or resilience have been identified, but epigenetic mechanisms are also now recognized as strong candidates for gene-environment interactions that impact stress responsiveness. Epigenetics is the ensemble of processes that induce mitotically or meiotically heritable changes in gene expression without altering the DNA sequence itself. Epigenetic mechanisms occur primarily at the chromatin, and involve multiple mechanisms including DNA methylation, covalent posttranslational modifications of histones (HPTMs), chromatin folding and attachment to the nuclear matrix, and/or nucleosomes repositioning (likely also noncoding RNAs). These mechanisms can act separately or in synergy to modulate chromatin structure and its accessibility to the transcriptional machinery. Epigenetic mechanisms are highly dynamic and can be influenced by environmental factors such as diet, social/familial settings, and stress. Their dysregulation has been implicated in stress-related neurodevelopmental and psychopathological disorders (Franklin and Mansuy, 2011; Kubota et al., 2012; McEwen et al., 2012).

### Natural Variations in the Epigenetic Profile

HPTMs in the brain are important determinants of stress susceptibility. Resilience to social defeat stress or chronic imipramine treatment in mice is associated with comparable histone 3 (H3) methylation profile in a set of genes in NAc (Wilkinson et al., 2009). Likewise, the histone methyltransferase G9a is reduced in NAc in both susceptible mice and depressed patients brain postmortem, suggesting the involvement of histone methylation in mice and humans. Consistently, G9a reduction in NAc by knockout increases susceptibility to chronic social defeat stress in mice, while viral overexpression after defeat reverses stress-induced behavioral defects (Covington et al., 2011), suggesting a causal link between G9a and stress susceptibility.

An innate predisposition to stress is also associated with epigenetic marks in the brain. In BALB/c, an inbred mouse strain susceptible to stress, H3 acetylation and methylation are regulated differently in NAc after chronic ultramild stress (CUMS) than in C57BL/6J, a resilient strain (Uchida et al., 2011). Acetylation at the glia cell-derived neurotrophic factor (GDNF) promoter, a factor necessary for DA neurons survival and maintenance in striatum, and GDNF expression are decreased in BALB/c mice but increased in C57BL/6J mice after CUMS. In contrast, H3 lysine 27 trimethylation (H3K27me3), a repressive mark, is reduced only in C57BL/6J mice.

Pathways linked to DNA methylation are also differentially regulated in BALB/c and C57BL/6J after CUMS. In both strains, CpG methylation of GDNF promoter and binding of the methyl-DNA binding protein MeCP2 are increased in NAc after stress, but distinct MeCP2 binding partners are recruited. In BALB/c mice, MeCP2 binds to the histone deacetylase 2 (HDAC2) leading to histone deacetylation and GDNF silencing, while in C57Bl/6J mice, it associates with CREB and activates GDNF transcription (Uchida et al., 2011). The repressor and cofactor of KRAB zinc finger, KAP1, is another (indirect) modulator of histone acetylation and methylation involved in stress resilience that regulates specific transcriptional programs. In the adult hippocampus, it increases H3/H4 acetylation and decreases H3K9me3 at promoters of the imprinted genes, Makorin ring finger protein 3 (Mkrn3), and protocadherinβ6 (Pcdhβ6), which alters their expression. Consistently, KAP1 knockout in forebrain neurons promotes stress vulnerability (Jakobsson et al., 2008).

Thus, activating and repressive HPTMs, DNA methylation and chromatin regulators act at multiple loci in a complex and consequential way to induce stress resilience and susceptibility. The functional link among epigenetic marks, gene expression, and stress responses is, however, not straightforward. HPTMs are highly varied and subjected to dynamic crosstalk in the adult brain (Tweedie-Cullen et al., 2012), thus determining their nature and combination will be essential to understand their correlation with gene activity and behavior. Elucidating the mechanisms of interindividual epigenomic variability in relation to stress is also important but is complex, as it may involve genotypic variations in components of the epigenetic machinery (Keane et al., 2011), differences in environmental exposures, or in parental epigenome.

### Evoked Variations in Epigenetic Profile and Their Inheritance

Besides natural variations, epigenetic marks are dynamically influenced by environmental factors. Stress in adulthood differentially modulates DNA methylation at specific genes in relation to stress vulnerability or resilience. CRH promoter is partially demethylated in PVN in susceptible mice showing avoidance after social defeat, which correlates with increased CRH expression (Elliott et al., 2010). Maternal behaviors also persistently alter epigenetic marks. In rat, DNA methylation and H3K9 acetylation are differentially regulated by low and high licking/grooming at multiple genic and intergenic genomic loci, for instance GR in the offspring's hippocampus (McGowan et al., 2011). Perturbed maternal behaviors by chronic unpredictable separation and maternal stress also widely affect methylation in the offspring's brain and cause hypomethylation or hypermethylation of different genes, which alter gene expression. Strikingly, the aberrant methylation is perpetuated across successive generations and is present in the germline of first-generation males and the brain and germline of second-generation progeny. This progeny, but also the following, show multiple stress-related symptoms such as depressive-like behaviors, and social anxiety (Franklin et al., 2011; Franklin et al., 2010; Weiss et al., 2011). Aberrant DNA methylation due to disrupted maternal care thus affects several tissues, can subsist after meiosis in male germ cells, and is transmitted transgenerationally, suggesting a powerful potential means of maintenance and inheritance of the effects of early chronic stress. Like sperm cells, oocytes may also carry epigenetic anomalies resulting from stress exposure since transgenerational inheritance of stress-induced symptoms occur through females independently of maternal care (Weiss et al., 2011). Adult stress can as well lead to transgenerational transmission of some behavioral symptoms, although to a lesser extent probably due to the late exposure to stress (only

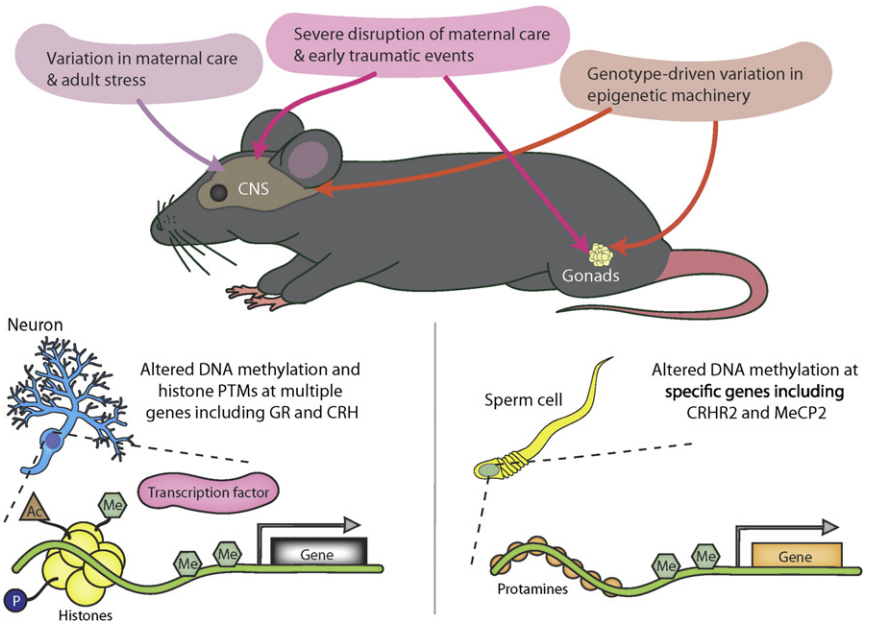


**Figure 4. Epigenetic Processes Associated with Stress Responses**

Schematic representation of the influence of maternal care on the epigenome in the brain and germline. In the brain, DNA methylation and HPTMs, i.e., histone acetylation (Ac), methylation (Me), or phosphorylation (P) modulate chromatin structure and allow transcription factors to be recruited for transcriptional activation of specific genes such as GR and CRH. In sperm cells, DNA methylation marks specific genes for future transcriptional regulation in the developing and adult animal.

adulthood) (Dietz et al., 2011). Finally, similar to rodents, poor upbringing, abandonment, or child maltreatment in human is associated with widespread methylation defects in blood cells and/or brain (McGowan et al., 2009; Naumova et al., 2012; Tyrka et al., 2012). Likewise, in bonnet macaque females, higher DNA methylation correlates with stress maladaptation. For instance, increased behavioral reactivity due to exposure to unreliable access to food in early life alters methylation at specific loci like serotonin transporter 5HTT in blood (Kinnally et al., 2011).

How epigenetic changes are triggered and maintained in the brain and gametes, and whether they can be reversed are critical questions that need future investigation (Figure 4; Bohacek and Mansuy, 2012). Epigenetic alterations may involve DNA methyltransferases (DNMTs) like DNMT3a, whose mRNA is persistently increased in NAc after chronic social stress (LaPlant et al., 2010) or other DNMTs or DNA methylation regulators. Different mechanisms likely operate in different genes and brain areas as suggested by the occurrence of concomitant hyper- and hypomethylation after stress (Franklin et al., 2010). The causal relationship between DNA methylation/HPTMs and behavioral responses is another critical issue that will need to be resolved.

## Neurogenesis in Stress Resilience and Vulnerability

In addition to molecular mechanisms based on signaling pathways and chromatin remodeling, cellular processes involving neurogenesis have been implicated in stress resilience and vulnerability. Neurogenesis is a process of generation of new neurons that occurs primarily during embryonic and perinatal stages in mammals (Ming and Song, 2011). It persists across life in the adult brain but only in two neurogenic regions: the subgranular zone (SGZ) of the DG and the subventricular zone (SVZ) of lateral ventricles. SGZ generates functional granule neurons from neural progenitor cells (NPCs), while SVZ generates interneurons in the olfactory bulb. In DG, newly produced granule cells incorporate into the hippocampal circuitry; they receive excitatory input mainly from the entorhinal cortex and project to CA3 pyramidal cells. Hippocampal neurogenesis is a dynamic process influenced by environmental and physiological stimuli, and suggested to play a role in stress responses.

Early pioneering work has shown that stress hormones and various forms of stress including prenatal stress, maternal separation, repeated social defeat, immobilization, exposure to predator odor or escapable/inescapable shocks, diminish cell proliferation in DG in adult rodents (Gould et al., 1992; Schoenfeld and Gould, 2012). Although some of these findings could not be confirmed possibly due to divergence in stress paradigms, some causal evidence for a link between neurogenesis and stress responsiveness was provided in animal models with ablated neurogenesis. Blockade of neurogenesis by cranial irradiation, antimitotic agents, such as methylazoxymethanol (MAM) or transgenic expression of an apoptotic protein (i.e., Bax) in NPCs, can prolong glucocorticoid response and induce depressive-like behaviors following traumatic events. However, it can also sometimes increase anxiety after stress but have no effect on depression or even have no effect at all (Petrik et al., 2012; Revest et al., 2009; Saxe et al., 2006; Shors et al., 2002). These differences may reflect inconsistencies in the degree, timing, and location of ablation. However, overall it could be concluded that a lack of neurogenesis alone may not alter stress responsiveness at the time of ablation but rather influence the response to future stressors.

Consistent with the idea that severe stress can be detrimental, but moderate and controllable stress can be beneficial, neurogenesis was shown to be increased by predictable chronic mild stress in rats (Parihar et al., 2011). It is also higher in nonhuman primates who successfully cope with intermittent social stress (Lyons et al., 2010a). Further, the beneficial effect of environmental enrichment on stress-induced depressive symptoms in mice requires neurogenesis (Schloesser et al., 2010), and some antidepressants like fluoxetine can favor neurogenesis (Malberg et al., 2000). However, the therapeutic efficacy of antidepressants can also be retained after neurogenesis abolition (Bessa et al., 2009), questioning the link between antidepressants and neurogenesis. Thus overall, neurogenesis may be part of a resilience repertoire that can be recruited in some

animals, which for instance have high baseline neurogenesis or in which neurogenesis can be effectively activated. Conversely, successful coping may favor neurogenesis and thereby increase the chance for future successful coping.

The mechanisms underlying stress and neurogenesis are not fully understood, but may involve the action of glucocorticoids on cells neighboring newly generated neurons (NPCs themselves do not express MR or GR) (Garcia et al., 2004). Glucocorticoids may also act by increasing glutamatergic transmission through increased glutamate release and NMDA receptor-dependent excitatory input from the entorhinal cortex onto newly generated neurons (Cameron et al., 1995). Glucocorticoids have proapoptotic actions on NPCs and immature neurons in the hippocampus (Yu et al., 2010) and may lead to NPCs depletion. Besides stress hormones, neurotrophic factors like BDNF, VEGF, and insulin-like growth factor 1 (IGF-1), which can promote cell proliferation and differentiation in DG and mediate some of the positive effects of enriched environments, have also been implicated (Fournier and Duman, 2012; Lee and Son, 2009). Neuropeptides released by rewarding social experiences such as endogenous opioids and oxytocin, or the neuromodulator DA may also contribute (Drake et al., 2007; Veena et al., 2011). Finally, serotonergic-dependent mechanisms might be activated since serotonin depletion severely diminishes adult hippocampal neurogenesis (Brezun and Daszuta, 1999; Gould et al., 1992).

## Conclusions

The question of why some people are susceptible to stress, while others are resistant, is fundamental to the understanding, diagnosis, and treatment of stress-associated disorders. It has become clear that multiple neurochemical and neuroanatomical pathways, particularly those related to the HPA axis, react differently to stress in resilient and susceptible individuals. Complex and still undetermined genetic and environmental factors interact and account for these differences. The mechanisms governed by these factors and that underlie the establishment of stress resilience/vulnerability likely act throughout life but may operate differently and affect distinct neural pathways at different stages of development and in adulthood. Animal models of stress-related diseases combining genetic and environmental manipulations will be needed to resolve these issues and gain more causal and mechanistic insights. Innovative approaches such as high-throughput and/or targeted epigenomic analyses (LaSalle, 2011; Peter and Akbarian, 2011) or optogenetic neural activation or silencing (Mei and Zhang, 2012) are expected to help gain new knowledge about the molecular and cellular circuits involved that cannot be obtained with human studies alone. In this respect, a better understanding of epigenome plasticity as it relates to individual variability in the stress response could provide useful insights. In particular, deciphering how psychological factors, diet, metabolic dysfunctions, or neuroinflammation can modulate epigenome plasticity, and identifying the ensemble of genes affected by such plasticity could pave the way for developing epigenetic and pharmacotherapeutic approaches for the potential prevention and treatment of stress-related illnesses (Boks et al., 2012). Finally, the question of the heritability of stress resilience and susceptibility is particularly fascinating and represents another important challenge that will need to be addressed in the future.

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