Biological Psychiatry: Celebrating 50 Years

Review

Neurobiology of Resilience: Interface Between Mind and Body

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ABSTRACT

Stress-related neuropsychiatric disorders, such as major depressive disorder and posttraumatic stress disorder, exact enormous socioeconomic and individual consequences. Resilience, the process of adaptation in the face of adversity, is an important concept that is enabling the field to understand individual differences in stress responses, with the hope of harnessing this information for the development of novel therapeutics that mimic the body's natural resilience mechanisms. This review provides an update on the current state of research of the neurobiological mechanisms of stress resilience. We focus on physiological and transcriptional adaptations of specific brain circuits, the role of cellular and humoral factors of the immune system, the gut microbiota, and changes at the interface between the brain and the periphery, the blood-brain barrier. We propose viewing resilience as a process that requires the integration of multiple central and peripheral systems and that elucidating the underlying neurobiological mechanisms will ultimately lead to novel therapeutic options.

Keywords: Blood-brain barrier, Gut microbiota, Inflammation, Major depressive disorder, Mesolimbic reward circuit, Posttraumatic stress disorder, Resilience, Stress

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Psychosocial stress is part of our everyday life—e.g., being bullied at school or work or the recent loss of a close relative—and many people experience physical or sexual abuse. However, it is also intuitive that individual reactions to similar traumatic events can be different. These range from lifelong disabling mental disorders to relatively moderate acute stress reactions or even a strengthening effect that protects one from future traumas. The topic of this review is stress resilience, defined here based on the American Psychological Association's definition as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress" (1).

Our aim is to provide an update on the current state of research of the neurobiological mechanisms of stress resilience, focusing on literature that has specifically investigated resilience in preclinical rodent models that are relevant to major depressive disorder (MDD) and posttraumatic stress disorder (PTSD).

STRESS, RESILIENCE, AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

An adequate reaction of the body to acute threats is a crucial mechanism to adapt to environmental changes that occur in different developmental stages throughout life. The autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis play a key role in orchestrating the body's reaction to threats (2). Upon danger, the hypothalamus secretes corticotropin-releasing hormone, which via the pituitary hormone adrenocorticotropin induces the production of cortisol from the adrenal cortex. Parallel activation of the sympathetic nervous system leads to effects on several peripheral organs, including the release of epinephrine from the adrenal medulla. These responses mediate the necessary acute "fight-or-flight" reaction (3,4). On the other hand, stress of an extreme nature or of a prolonged duration is among the most important risk factors for many diseases, including neuropsychiatric disorders such as MDD and PTSD (5,6). An informative conceptualization of this continuum between adaptive and maladaptive stress was introduced with the terms allostasis and allostatic load. While allostasis refers to the adaptive processes that maintain homeostasis, the term allostatic load describes the cumulative burden of adaptations that result when the involved systems fail to shut off after the stressor has subsided or when these systems do not respond adequately (7,8). Responses to similar stressors are strikingly distinct across individuals, and the first scientific attention drawn to resilience as a phenomenon of adaptation in the context of risk or adversity took place in the 1970s (9). It was soon established that resilience is a common phenomenon rather than an extraordinary process (10). Over the years, several factors have been linked to resilience, including a strong social support network and intrinsic behavioral traits, such as optimism (11,12). Individual coping strategies (13) are particularly relevant to resilience and can be classified into two categories. The first category is active coping responses, which are intentional efforts of the subject aimed at minimizing the physical, psychological, or social harm of a stressor and that are associated with actual or perceived control over the stressor (14). Such coping is considered to lead to changes facilitating an adaptive, resilient response (14). The second category, passive coping, includes mechanisms

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such as avoidance or helplessness and is associated with increased vulnerability (15,16).

RODENT MODELS OF SUSCEPTIBILITY AND RESILIENCE

The neurobiological mechanisms underlying resilience have long been difficult to uncover, primarily because creating significant adversity in humans in controlled experimental settings is impossible and because the exploration of molecular and circuit brain mechanisms in humans remains limited. Over the past decade, advances in preclinical animal stress models that uncover individual differences in stress reactivity have allowed detailed neurobiological characterization of the precise mechanisms of stress vulnerability versus resilience (14,17). One of the first animal models demonstrated to separate susceptible and resilient phenotypes is learned helplessness (LH) (18,19). However, there are considerable shortcomings in the validity of the LH procedure to depression-like behaviors, including that the depression-like behaviors only last a few days and the fact that that in some strains acute administration of an antidepressant is sufficient to reverse LH behavior (19). In addition, Nasca *et al.* (20) showed individual differences in response to both chronic unpredictable stress and restraint stress, with some mice exhibiting resilience to the development of depression- and anxiety-related behaviors.

Another widely used rodent stress model that distinguishes susceptible and resilient phenotypes with greater etiological validity is repeated social defeat stress (RSDS) (17,21). Over a period of usually 10 days, a rat or mouse is repeatedly subordinated by a dominant animal; for example, a C57BL/6 mouse is defeated by a larger, more aggressive CD1 mouse (22,23). Importantly, despite undergoing the same stress, individual mice and rats (even from inbred strains) display different behaviors. While susceptible mice are characterized by alterations in behaviors with high face validity to MDD, such as social avoidance and anhedonia (measured by the preferences of a sweet-tasting solution over water), resilient mice do not show these changes and display behaviors similar to control mice (24). Until recently, one major limitation of this model was that it could only be applied in male C57BL/6 mice (25), primarily because innate aggression of male toward female mice is limited—although female social defeat has been validated in a different mouse species (26). From a translational perspective, male and female patients differ not only in the prevalence of stress-related neuropsychiatric disorders but also in their clinical presentations (27,28). Therefore, it is a major recent advance that two female mouse models, both based on the defeat stress paradigm, have been developed for C57BL/6 mice: Harris *et al.* (29) proposed a model in which male urine is applied to females to induce CD1 males to attack them. Another paradigm uses a DREADD (designer receptor exclusively activated by designer drugs) approach, where the induction of aggression in male CD1 mice toward female C57BL/6 mice is achieved by activation of the ventromedial hypothalamus (30). Similar to social defeat in males, both stress models lead to different stress responses, with some female mice being susceptible and others being resilient (29,30). These models provide important tools to further elucidate the neurobiological mechanisms underlying sex-specific differences and commonalities in stress responses that are relevant to affective disorders [see Bale and Epperson (31) for review].

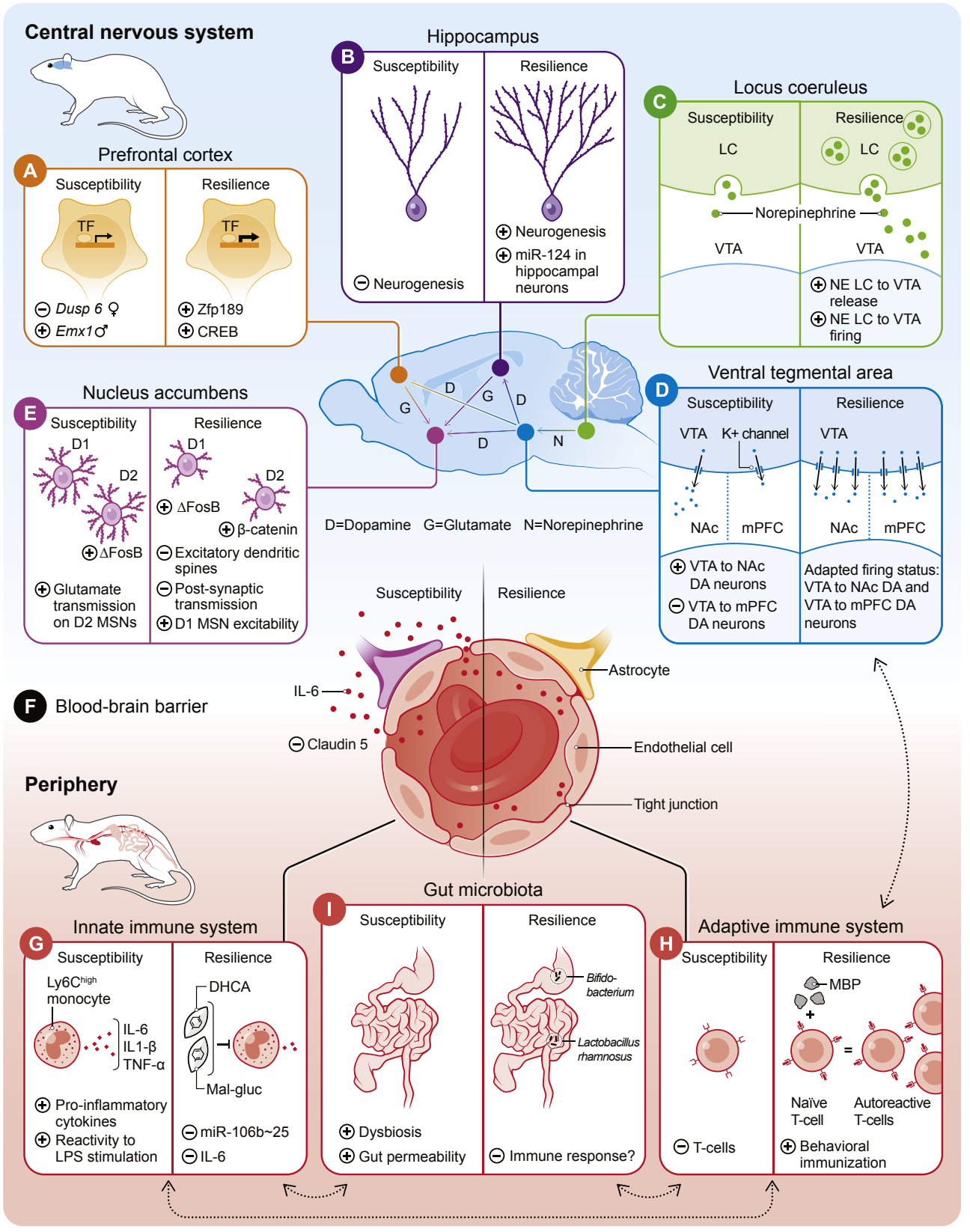
Given that adversity experienced in childhood and during adolescence can profoundly impact individual trajectories, early-life stress animal models are of great importance (32). Several established rodent early-life stress paradigms exist, with maternal separation and reduced bedding material being the most commonly used (33). Interestingly, the relation between the extent of stress exposure and stress response is not linear. While no/low and high levels of stress have a negative effect on performance, moderate exposure to stress can promote active coping responses and therefore have pro-resilient effects. If pups experience maternal deprivation for a long period, they show a higher susceptibility to subsequent stressors in adult life, HPA axis hyperactivity, and altered glucocorticoid responses (34,35). However, if stress exposure is less severe, it can have pro-resilient effects, a process termed stress inoculation. Rat pups that are exposed to postnatal handling, a moderate early-life stress, display lower plasma levels of corticotropin-releasing hormone and an attenuated stress-induced increase in plasma corticosterone compared with both rats that were left undisturbed and those that were severely stressed as pups (36). In addition, certain behavioral traits that manifest in early life are associated with outcomes in later life. Rats that showed less exploratory behavior of a novel environment in early life had a shorter life span than their more exploratory conspecifics (37).

Decades of research have investigated the importance of the HPA axis in psychosocial stress and indeed led to potential clinically applicable biomarkers, e.g., neuropeptide Y or dehydroepiandrosterone (38,39). Nevertheless, progress in the development of novel therapeutics, including the generation of resilience-promoting drugs that directly target the HPA axis, stands in no relation to the vast number of preclinical findings that exist, making more effective translational research a high priority.

CENTRAL NERVOUS SYSTEM MECHANISMS OF RESILIENCE

Hippocampal Neurogenesis

The hippocampus is important in mediating responses to stress. Both mineralocorticoid and glucocorticoid receptors are vastly expressed in the hippocampus, making it a region that is highly responsive to activation of the HPA axis (40,41). The dentate gyrus of the hippocampus is capable of generating functional neurons from adult neural precursors, a process called adult neurogenesis (42). Stress and glucocorticoid release decrease adult hippocampal neurogenesis, a process that is reversed by treatment with some but not all antidepressants (43,44). The findings regarding the role of adult hippocampal neurogenesis in mediating RSDS-induced susceptibility versus resilience, however, are inconsistent. Lagace *et al.* (45) showed that compared with resilient and control mice, 4 weeks after the defeat susceptible mice display enhanced survival of dentate gyrus neurons that were produced 24 hours after but not those produced before defeat stress. Irradiation-induced ablation of neurogenesis led to pro-


Central nervous system
Hippocampus
B
Susceptibility
Resilience
⊖ Neurogenesis
⊕ Neurogenesis
⊕ miR-124 in hippocampal neurons
Locus coeruleus
C
Susceptibility
Resilience
LC
LC
Norepinephrine
VTA
VTA
⊕ NE LC to VTA release
⊕ NE LC to VTA firing
Prefrontal cortex
A
Susceptibility
Resilience
TF
TF
⊖ Dusp 6 ♀
⊕ Emx1♂
⊕ Zfp189
⊕ CREB
G
D
G
D
D
N
D=Dopamine G=Glutamate N=Norepinephrine
Ventral tegmental area
D
Susceptibility
Resilience
VTA
K+ channel
VTA
NAc
mPFC
NAc
mPFC
⊕ VTA to NAc DA neurons
⊖ VTA to mPFC DA neurons
Adapted firing status: VTA to NAc DA and VTA to mPFC DA neurons
Nucleus accumbens
E
Susceptibility
Resilience
D1
D2
D1
D2
⊕ ΔFosB
⊕ ΔFosB
⊕ β-catenin
⊕ Glutamate transmission on D2 MSNs
⊖ Excitatory dendritic spines
⊖ Post-synaptic transmission
⊕ D1 MSN excitability
Susceptibility
Resilience
IL-6
⊖ Claudin 5
Astrocyte
Endothelial cell
Tight junction
F Blood-brain barrier
Periphery
Gut microbiota
I
Susceptibility
Resilience
Bifido-bacterium
Lactobacillus rhamnosus
⊕ Dysbiosis
⊕ Gut permeability
⊖ Immune response?
Innate immune system
G
Susceptibility
Resilience
Ly6C^high monocyte
IL-6
IL1-β
TNF-α
DHCA
Mal-gluc
⊕ Pro-inflammatory cytokines
⊕ Reactivity to LPS stimulation
⊖ miR-106b~25
⊖ IL-6
Adaptive immune system
H
Susceptibility
Resilience
MBP
Naïve T-cell
Autoreactive T-cells
⊖ T-cells
⊕ Behavioral immunization

resilient behaviors. Lagace *et al.* (45) suggested that this compensatory enhancement in hippocampal neurogenesis is related to the maladaptive stress response (45). In contrast, a recent study reported that increasing hippocampal neurogenesis promotes resilience to social defeat stress (Figure 1B) (46). Anacker *et al.* (46) used a gain-of-function model, where deletion of the proapoptotic gene *Bax* from adult neural stem cells was sufficient to increase hippocampal neurogenesis, and showed that this manipulation protects from social defeat–induced social avoidance and anxiety-like behaviors. Anacker *et al.* (46) also describe a population of stress-responsive cells that are inhibited by adult-born neurons and suggested that direct silencing of these cells confers resilience to stress (46).

Ventral Tegmental Area Dopamine Neurons

The mesolimbic dopamine (DA) pathway is a key reward circuit in which DA neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), hippocampus, prefrontal cortex (PFC), and other forebrain regions (47). Neurons of the VTA release DA in response to both rewarding and aversive stimuli, and different stressors can differentially influence the dopaminergic neurons of the VTA (48–50). One of the key findings of this circuit is that stress-susceptible mice show increased firing of DA neurons projecting from the VTA to the NAc, whereas projections from the VTA to the medial PFC display the opposite (Figure 1D) (49). Interestingly, resilient mice display control-level firing activity in both of the aforementioned circuits (51,52). Further supporting the role of the VTA in actively mediating resilience are data from gene expression studies in which significantly more genes were regulated in the VTA and NAc in resilient compared with susceptible mice (24). Particularly interesting is the fact that microarray data revealed upregulation of four distinct potassium (K^+) channel subunits in the VTA of resilient mice only (Figure 1D) (24). These findings suggest that K^+ channels may play an active functional role in driving the higher firing of VTA DA neurons back to normal levels in resilient mice, indicating that resilience represents a physiological state distinct from control mediated by a host of resilience-promoting mechanisms. It is known that RSDS increases the excitatory I_h current in VTA DA neurons of susceptible mice, and induces even greater increases in I_h in these neurons of resilient mice (51,53,54). Further studies showed that local infusion of hyperpolarization-activated cyclic nucleotide–gated channel inhibitors into the VTA rapidly normalized social avoidance in susceptible mice (51,53). This finding suggests that the force that drives the pathological higher firing exists in resilient mice, but that additional compensative ionic mechanisms such as K^+ channel induction could drive the higher firing back to normal levels in resilient mice as stated above. In addition, measuring K^+ currents revealed a selective increase in resilient mice (51). Among these voltage-gated K^+ currents, KCNQ subtype of K^+ channels plays a key role in regulating the firing activity of VTA DA neurons, and pharmacologically enhancing KCNQ channels showed significant antidepressant-like effects in the RSDS model (51). Informed by these preclinical results, a recent study reported that a 10-week treatment with a nonselective KCNQ channel opener, ezogabine, decreased depressive symptoms in patients with MDD, an effect that is associated with changes of ventral striatal connectivity as a function of clinical improvement (55).

The NAc and Its Inputs

The NAc integrates dopaminergic projections from the VTA and glutamatergic inputs from the hippocampus, PFC, amygdala, and thalamus and is composed largely of two subtypes of gamma-aminobutyric acidergic medium spiny neurons (MSNs) that express predominantly either DA D_1 or D_2 receptors and play important roles in a host of reward-related behaviors (56–58). Distinct glutamatergic inputs to the NAc allow this region to bidirectionally regulate reward and aversion (59–62), leading to the hypothesis that depression—and by extension resilience—may be due in part to alterations in glutamatergic function within the NAc (63). For example, it was observed that susceptible mice have more excitatory dendritic spines and increased postsynaptic transmission onto NAc MSNs compared with resilient mice (Figure 1E) (64,65). Francis *et al.* (66) expanded upon these initial findings to show increased glutamate transmission specifically on D_2 MSNs of susceptible mice relative to resilient mice (Figure 1E). While there were no changes in excitatory currents in D_1 MSNs after RSDS, Francis *et al.* (66) found an increase in excitability of D_1 MSNs in resilient mice relative to susceptible mice (Figure 1E). Subsequent studies by Khibnik *et al.* (67) suggested that the upregulated amplitude of unitary excitatory postsynaptic currents specifically on mushroom spines of D_1 MSNs could represent an active adaptation enabling the mice to better cope with the effects of social stress. Together, this work points to cell-specific and possibly circuit-specific glutamatergic signaling within the NAc that promotes stress resilience. Given what we know about NAc glutamate signaling in susceptibility versus resilience, it has been suggested that distinct inputs to the NAc may control positive versus negative mood states after chronic stress, contributing to either susceptible or resilient phenotypes. To test this hypothesis, research has used in vivo optogenetic approaches to stimulate or inhibit PFC–NAc, thalamus–NAc, basolateral amygdala–NAc, or ventral subiculum–NAc glutamate pathways in mediating stress responses during social defeat stress (61,62). It was found that

Figure 1. Stress resilience, the process of positive adaptation in the face of psychosocial stress, is a complex process that involves both central and peripheral mechanisms. In the central nervous system, several specific brain regions and circuits are crucial in mediating responses to stress **(A–E)**. In the periphery, cellular and humoral factors of the immune system **(G, H)** and changes in gut microbiota composition **(I)** contribute to the development of resilience. Recently, the blood-brain barrier has been implicated as an additional factor **(F)**. Importantly, these compartments interact extensively with each other. CREB, cyclic adenosine monophosphate–response element binding protein; DA, dopamine; DHCA, dihydrocaffeic acid; IL, interleukin; K^+, potassium; LC, locus coeruleus; LPS, lipopolysaccharide; Mal-gluc, malvidin-3′-O-glucoside; MBP, myelin basic protein; miR, microRNA; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; NAc, nucleus accumbens; NE, norepinephrine; TF, transcription factor; TNF, tumor necrosis factor; VTA, ventral tegmental area; Zfp189, zinc finger protein 189.

stimulation of glutamate inputs from either the thalamus or ventral subiculum potentiates social avoidance after subthreshold social defeat stress. By contrast, the stimulation of PFC–NAc glutamate inputs promotes resilience, but only under specific conditions, and studies to silence these inputs using halorhodopsin have no effect (61,62). This suggests either that PFC neurons promote resilience via collateral pathways or that different stimulation parameters evoke different postsynaptic effects on NAc MSNs. While these findings clearly define the importance of input specificity to NAc neurons in encoding susceptibility versus resilience, we still have a limited understanding of how these inputs differentially activate the NAc. One possibility is that specific inputs are differentially connected to D_1 versus D_2 MSNs or perhaps to gamma-aminobutyric acidergic versus cholinergic interneurons. In vivo tracing studies support this possibility (68); however, functional studies in mouse models of resilience are required to confirm this hypothesis.

The Locus Coeruleus and Its Outputs

There is increasing evidence that the locus coeruleus (LC), a norepinephrine (NE)-producing brainstem nucleus, plays a role in stress susceptibility and resilience (69,70). The LC provides virtually all the NE input throughout the forebrain and also innervates the VTA. Isingrini *et al.* (71) showed that resilient mice display increased NE release from LC neurons that project to the VTA (Figure 1C). In a recent study, Zhang *et al.* (72) reported that resilient but not susceptible mice show increased firing of LC neurons that project to the VTA (Figure 1C) and that mimicking this adaptive change by optogenetic stimulation in stress-susceptible mice promotes resilience. Molecular profiling and pharmacological studies identify α_1- and β_3-adrenergic receptors expressed by VTA DA neurons as being sufficient and necessary to induce resilience, providing an additional potential pharmacological target that now warrants clinical investigation (72).

Transcriptional and Epigenetic Mechanisms

Transcription factors have been implicated as important mechanisms in mediating environmental influences on the brain (73). As alluded to above, several brain region–specific gene expression studies have indicated that resilience is an active process with the involvement of greater transcriptional activity than stress susceptibility (74,75). Several forms of stress induce ΔFosB, a truncated product of the *FosB* immediate early gene, in specific brain regions, including the NAc (76,77). Interestingly, ΔFosB induction in the NAc after RSDS is cell-type specific. The modest induction of ΔFosB in susceptible mice takes place in D_2 MSNs, whereas the more robust induction in resilient mice is specific to D_1 MSNs (Figure 1E) (78,79). Viral overexpression of ΔFosB in D_1 MSNs promotes a resilient behavioral phenotype and is necessary for the antidepressant action of fluoxetine (78–81). Further supporting its importance, ΔFosB is reduced in postmortem NAc tissue of patients with MDD (78). In addition, β-catenin, a downstream factor of WNT signaling, is highly regulated in the NAc of resilient mice (82). Again, this effect is cell-type specific, because overexpression of β-catenin in D_2- but not D_1-type MSNs induces a pro-resilient phenotype, mediated in part through activation of *Dicer1* and downstream generation of microRNAs (miRNAs) (Figure 1E) (83). In a recent study, Lorsch *et al.* (84) identified in the PFC *Zfp189* as a key hub gene in a resilient-specific gene module. Lorsch *et al.* (84) reported that cyclic adenosine monophosphate-response element binding protein was the strongest predicted upstream regulator of genes within this module and showed that overexpression of *Zfp189* in the PFC promoted resilience (Figure 1A).

The initial findings linking epigenetic alterations and MDD were that broad inhibition of histone deacetylases in several brain regions, including the NAc, hippocampus, and PFC, led to antidepressant-like effects in stressed rodents (85). Additional evidence came from studies suggesting that antidepressant effects of fluoxetine were in part mediated by histone acetylation (86). However, alternative studies have begun to unravel the complex mechanisms of histone modifications and have revealed opposing effects of certain histone deacetylases. For example, RSDS decreased expression of *Hdac5* in the NAc of susceptible mice and chronic imipramine administration increased its expression, therefore suggesting a potential pro-resilient effect (87). Adeno-associated virus–mediated *Hdac2* overexpression in the same brain region protected mice from chronic ultra-mild stress–induced social avoidance (88). These findings suggest that different histone deacetylases regulate different genes to promote susceptibility versus resilience.

DNA methylation is a process during which a methyl group is covalently attached to cytosine (and rarely other nucleotides) and leads generally via hypermethylation of gene promotors to inactivation of gene expression (89). One interesting target relevant to stress susceptibility and resilience is the DNA methyltransferase *DNMT3a*; *DNMT3a* expression is elevated both in the NAc of human MDD patients and in stress-susceptible mice. Interestingly, *Dnmt3a* manipulation seems to have sex-specific effects: overexpression of *Dnmt3a* in the NAc makes both female and male mice susceptible to subthreshold variable stress, while knockout of *Dnmt3a* in the NAc promotes resilience selectively in females (90,91).

Another mechanism of transcriptional regulation takes place through non–protein coding RNAs (92). Recent transcriptional studies have shown that stress leads to brain region–specific changes in miRNA expression (93,94). As an example of the function of miRNAs in promoting resilience, Higuchi *et al.* (95) showed that overexpression of miR-124, an endogenous small, noncoding RNA that represses gene expression post-transcriptionally, confers stress resilience in hippocampal neurons (Figure 1B). Recent advances in molecular methods and gene editing technologies will enable precise cell type–specific manipulation of transcription factors or epigenetic modifications, hopefully further increasing our understanding of the transcriptional and chromatin-based mechanisms of resilience (81,96,97).

PERIPHERAL MECHANISMS OF RESILIENCE

The Innate Immune System

Both preclinical animal models and human studies show that repeated psychosocial stress leads to profound peripheral immunological changes (98,99). Evidence from human studies linking stress vulnerability and resilience to immune alterations

exists at multiple levels: a subset of patients with MDD show elevated levels of several proinflammatory cytokines (100,101), MDD has high comorbidity with chronic inflammatory illnesses such as autoimmune disorders, cardiovascular disorders, or cancer (102–104), and certain anti-inflammatory therapies potentially elicit antidepressant effects (105). Whether traditional antidepressants reduce peripheral cytokine levels remains controversial, with a recent meta-analysis indicating a reduction of levels of interleukin (IL)-1β and possibly IL-6 (106). Interestingly, there is evidence that the rapid-acting antidepressant ketamine reduces levels of proinflammatory cytokines (107,108). However, whether these inflammatory changes are causally linked to antidepressant effects remains unclear.

The innate immune system, which represents the first line of host defense during infection, plays an important role in the early recognition and subsequent triggering of a proinflammatory response to invading pathogens (109,110). Similar to the response to pathogens, chronic stress leads to an increase of inflammatory cells, such as Ly6c^{high} monocytes and neutrophils, or of proinflammatory mediators, such as IL-1β, IL-6, and tumor necrosis factor alpha (111,112). The study by Hodes *et al.* (113) was one of the first to investigate differences between stress susceptible and stress resilient phenotypes. After RSDS, resilient mice displayed lower blood levels of IL-6 than susceptible mice (Figure 1G); both neutralizing IL-6 with a systemically administered antibody and depleting IL-6 from bone-derived leukocytes using chimeric mice promoted resilience (113). In addition, predefeat inflammatory markers predicted how mice will respond to RSDS: mice susceptible after RSDS displayed more preexisting circulating leukocytes than resilient mice, and IL-6 release upon stimulation with the bacterial endotoxin lipopolysaccharide correlated negatively with social interaction scores (113). Additional work by Pfau *et al.* (114) investigated the potential role of stress-induced epigenetic regulation of leukocytes by miRNAs. Pfau *et al.* (114) reported that within Ly6C^{high} monocytes of mice exposed to RSDS, several miRNAs were regulated by RSDS, including miR-25-3p, a member of the miR-106b∼25 cluster. Selective knockout of the miR-106b∼25 cluster in peripheral leukocytes promoted behavioral resilience to RSDS (114). Given that Ly6C^{high} monocytes tend to be more inflammatory in nature, it is thought that these cells may be a prominent source of inflammatory molecules after stress and that therapeutic strategies targeting Ly6C^{high} may promote resilience by reducing inflammation. Indeed, systemic administration of the phytochemicals dihydrocaffeic acid and malvidin-3′-O-glucoside promoted stress resilience in mice by decreasing IL-6 release from leukocytes (Figure 1G) (115).

The Adaptive Immune System

The adaptive immune system is involved in the later phase of an infection, where it fights invading pathogens with an immune response characterized by clonal gene rearrangement of antigen-specific receptors on lymphocytes and the formation of an immunological memory (116). Far fewer studies have investigated its main cellular components, B and T lymphocytes (117), in stress responses. One meta-analysis concluded that MDD patients show reduced T cell proportions and a moderate increase in the ratio of CD4/CD8 T cells in blood (118). Rodent studies have indicated a potential neuroprotective or pro-resilient effect of T cells (119). Immunization of rats with modified myelin basic protein before chronic mild stress, which leads to the induction of autoreactive T cells, reduced depressive-like behaviors, such as anhedonia end points and immobility in the forced swim test (Figure 1H) (120). These changes went along with the rescue of chronic mild stress–induced brain-derived neurotrophic factor decrease in the hippocampus (120). Interestingly, recruitment of T cells to the central nervous system correlated positively with stress resilience (121). Lewitus *et al.* (121) showed that T cells infiltrated the choroid plexus, which displayed an increase in intracellular adhesion molecule-1 (121). In addition, mice depleted of lymphocytes (*Rag2*$^{-/-}$) receiving lymphocytes from defeated donors displayed fewer anxiety-like behaviors, reduced proinflammatory cytokine levels, and microglia shifting toward an anti-inflammatory phenotype compared with those receiving no cells or cells from unstressed donors (122). This work suggests that psychosocial stress imprints onto the adaptive immune system, which then influences the outcome of stress exposure. It can be speculated that resilience to psychosocial stress may be promoted via behavioral immunization, where in analogy to traditional vaccination strategies exposure to an attenuated antigen can protect against successive stressful events (Figure 1H) (123,124).

Gut Microbiota

Microbiota refers to the collection of microorganisms in a particular habitat, e.g., the skin or gut (125). The gut microbiota has been implicated in a wide range of physiological processes, including interactions with the host immune system and direct effects on the brain—for example, by production of neuroactive metabolites (126). These pathways, subsumed in the term "microbiota-gut-brain axis," are an important modulator of the body's response to stress (126,127). Several studies reported disturbances in gut microbiota composition in MDD patients compared with healthy control subjects (128,129). In a seminal mouse study, germ-free mice (animals that lack bacterial colonization) displayed increased motor activity and reduced anxiety-like behavior coincident with elevated NE, DA, and serotonin turnover in the striatum (130). Interestingly, it was possible to transfer an "anxious" behavioral phenotype between two mouse strains (BALB/c vs. NIH Swiss mice) via fecal microbiota transfer (131). Additionally, fecal microbiota transplantation of germ-free mice with microbiota derived from MDD patients resulted in increased depression-like behaviors compared with mice colonized with microbiota from healthy control subjects (132). Regarding resilience, a small study reported that oral intake of *Bifidobacterium* significantly increases the number of resilient mice after RSDS compared with vehicle-treated mice (133) (Figure 1I). Treatment with *Lactobacillus rhamnosus* led to decreased RSDS-induced anxiety-like behaviors, prevented deficits in social interaction with conspecifics, and attenuated stress-related activation of dendritic cells while increasing IL-10^{+} regulatory T cells, suggesting a potential resilience-promoting interaction with the immune system (134). However, the mechanisms that link gut dysbiosis to stress susceptibility and resilience-associated immune disturbances remain to be elucidated.

The Blood-Brain Barrier

The blood-brain barrier (BBB), composed of brain microvascular endothelial cells, astrocytes, and pericytes, is an important interface between the brain and the systemic circulation (135). Under homeostatic conditions, the BBB tightly controls the communication between these two compartments: cytokines, for example, do not passively diffuse into the brain but are, in a saturable manner, transported actively from the blood to the brain (136). However, studies in humans and rodents under stress conditions have implicated neurovascular impairment in stress responses (137,138). One study revealed that RSDS in mice decreases the endothelial tight junction protein Claudin-5, resulting in a higher permeability to the peripheral cytokine IL-6 (Figure 1F) (139). In this study, viral-mediated downregulation of Claudin-5 promoted greater susceptibility to RSDS. Importantly, Claudin-5 was found to be downregulated in postmortem NAc tissue from MDD patients (139). Another study conducted with rats found that passive coping animals display greater vascular remodeling than active coping animals, with active coping seen as a pro-resilience phenotype (140). Using a murine LH model, Cheng *et al.* (141) showed that BBB permeability increases in the hippocampus of mice after LH induction, and this was maintained in mice with prolonged LH, whereas the BBB permeability had normalized in mice that recovered from LH (141).

Neuroimmune Interactions

A wealth of evidence indicates that stress influences the peripheral immune system, resulting in depression-associated behavioral changes. However, the specific mechanisms are still not well understood. It has been suggested that because RSDS leads to brain region–specific BBB disruption (i.e., increased permeability in the NAc but not in other brain regions), infiltrating cytokines may act directly on these brain regions to affect neuronal function (139). In accordance with this hypothesis, it was recently shown that peripheral IL-6 is necessary for maladaptive synaptic plasticity in the NAc of susceptible mice after RSDS (115). Another interesting possibility is that the central nervous system itself might attract peripheral immune cells, in a region-specific way, to impact brain circuits. A recent study by McKim *et al.* (142) reported that the development of anxiety-like behaviors during stress was dependent on microglial recruitment of IL-1β–producing monocytes, which stimulated brain endothelial IL-1R1 (142). This study adds to the increasing evidence that glial cells, the nonneuronal cells of the nervous system, constitute an important interface between the periphery and neuronal dysfunction (143). While an in-depth discussion of the role of glial cells is beyond the scope of this review, it is important to take into account the regulatory and immune surveillance functions of microglia, the brain-resident macrophages [see Wohleb *et al.* (144) for review]. Different lines of evidence indicate a role of microglia in stress-associated neuropsychiatric disorders. Social defeat stress leads to morphological and functional changes in microglia (145). Postmortem brain analysis in patients that committed suicide showed significant microgliosis (146), and brain translocator protein density, a marker of increased microglial activation, was elevated in MDD patients (147). With regard to resilience, the antibiotic minocycline prevented chronic unpredictable stress induced anhedonia in rats, indicating that manipulations of microglia could be pro-resilient (148). Given that metabolites produced by the gut microbiota can not only influence the immune system but also directly affect glial cells (149) and the BBB (150), the concept of providing resilience via specific modulation of the gut microbiota could provide a promising avenue for novel treatments.

CONCLUSIONS

The societal and individual burden entailed by stress-related neuropsychiatric disorders is immense. Efforts in developing treatments for such disorders have focused on preventing or reversing the damaging effects of stress. Understanding the neurobiological mechanisms that promote resilience to stress in some individuals, but lacking in those who are inherently more susceptible, constitutes a novel, additional important approach in stress biology. Indeed, early clinical studies suggest that inducing mechanisms of natural resilience in depressed humans might be an effective route for antidepressant drug discovery. As shown in this review, the neurobiology of resilience is complex, involving many convergent systems that ultimately affect brain function and behavior. One of the main challenges will be to gain a holistic model of resilience that encompasses both peripheral systems and key circuits in the brain to answer central questions. To address the many open questions in the field, with the goal of developing much-needed therapeutic options, a multidisciplinary, translational approach incorporating multiple levels of analysis of the brain as well as studies of several peripheral organs will be critical.

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