Understanding Resilience and Preventing and Treating PTSD

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Resilience is defined as the dynamic ability to adapt successfully in the face of adversity, trauma, or significant threat. Some of the key early studies of resilience were observational studies in children. They were followed by research in adults, studies testing interventions to promote resilience in different populations, and a recent upsurge of studies on the underlying genomic and neurobiological mechanisms. Neural and molecular studies in preclinical models of resilience are also increasingly identifying active stress adaptations in resilient animals. Knowledge gained from animal and human studies of resilience can be harnessed to develop new preventive interventions to enhance resilience in at-risk populations. Further, treatment interventions focused on enhancing potentially modifiable protective factors that are consistently linked to psychological resilience can enrich currently available treatment interventions for individuals with posttraumatic stress disorder (PTSD). Translating our expanding knowledge of the neurobiology of resilience additionally promises to yield novel therapeutic strategies for treating this disabling condition. This review summarizes the vast field of resilience research spanning genomic, psychosocial, and neurobiological levels, and discusses how findings have led and can lead to new preventive and treatment interventions for PTSD.

Keywords: neurobiology, prevention, PTSD, resilience, treatment

THE STUDY OF RESILIENCE

Resilience is broadly defined as the dynamic ability to adapt successfully in the face of adversity, trauma, or significant threat. Resilience is complex and might be best conceptualized on a continuum, with the potential for it to change across an individual’s lifespan. Some of the key early studies of resilience were conducted in the 1970s in children at risk for psychopathology stemming from diverse risk factors, including parental serious mental illness or having been raised in an orphanage, and also in identified subgroups of such children who nevertheless showed normative development. A vast range of subsequent studies in children and later in adults characterized key psychosocial factors associated with resilience, including the importance of a positive bond with a primary caregiver during development, as well as emotion regulation, cognitive flexibility, perceptions of purpose and control, and the availability of social support for resilience across the lifespan, among other factors reviewed below.

Resilience research gradually progressed from descriptive studies to investigating how to promote resilience in different populations, with longitudinal studies emerging more recently. In the last decade, studies have increasingly focused on understanding the mechanisms underlying resilience at various phenotypic levels and their interaction, incorporating genomic, psychosocial, and neurobiological perspectives.

While recent developments in the study of resilience are exciting, much remains to be discovered and understood. The present review is not meant to be exhaustive; it summarizes progress in resilience research, with a special focus on resilience in the face of psychologically traumatic experiences, and on the prevention and treatment of posttraumatic stress disorder (PTSD).

GENOMICS

The heritability component for PTSD has been estimated at 30% to 40%; trauma severity and frequency significantly influence PTSD risk. Earlier twin studies were followed by candidate gene studies, which identified several gene × environment interactions modifying risk for PTSD. The best example of an extensively studied candidate gene is the one coding for FKBP5, a chaperone protein that reduces glucocorticoid receptor (GR) sensitivity to circulating cortisol. A set of FKBP5 haplotypes has been found to modify risk for PTSD in adults in interaction with the severity of childhood trauma. FKBP5 is only one of several genes found to affect resilience or risk for PTSD, including genes related to the hypothalamic-pituitary-adrenal (HPA) axis, monoamines (e.g., serotonin transporter and dopaminergic system genes), and neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF] gene), among many others, including inflammatory-response genes. More recently, large-scale research collaboration led by the Psychiatric...
Genomics Consortium–Posttraumatic Stress Disorder group (PGC-PTSD) has made it possible to achieve large sample sizes for conducting genome-wide association studies (GWASs). The largest multiethnic GWAS in PTSD, including over 20,000 samples from 11 studies, has recently found a shared genetic risk between PTSD and schizophrenia, and possible shared risk with bipolar and major depressive disorders. Ongoing collaborations will make it possible to achieve the larger sample sizes needed to identify genetic risk for PTSD at the genome-wide level.

Over the past decade it has become evident that other influences beyond genetic sequence are central to gene expression and function. Epigenetic modifications affecting the structure of chromatin (how tightly DNA is wound around histones)—for example, via DNA methylation and histone methylation or acetylation—can facilitate or limit the accessibility of transcription factors to genes, thus enhancing or suppressing gene expression. Epigenetic modifications often occur in response to environmental exposures, especially during early development, ultimately enhancing resilience or vulnerability to stress and trauma into adulthood. In the earliest demonstration of epigenetic changes during early development in rodents, Michael Meaney and collaborators found lower methylation of the GR promoter region in the hippocampus in offspring of high licking, grooming, and arched-back nursing dams—which was associated with higher GR expression and lower anxiety-like behaviors and HPA-axis activation in the offspring, thus resulting in enhanced resilience. These studies and many others have contributed to our understanding of the mechanisms underlying the influence of early-life environment on resilience into adulthood via epigenetic mechanisms.

Of note, some of the same genetic variations that increase the risk for mental illness upon exposure to early adversity also appear to enhance psychosocial function in positive and supportive developmental environments, possibly mediating the degree of individual sensitivity to environmental influences in general. Increasingly sophisticated studies in animal models are elucidating molecular mechanisms underlying resilient phenotypes and have discovered genotype × epigenetic × environment interactions. Further, some molecular adaptations have been uniquely identified in resilient phenotypes and are absent in more vulnerable animals. New epigenome-wide analyses are emerging from collaborative studies in humans.

**DEVELOPMENTAL YEARS**

Psychological factors identified in studies of resilient children include higher cognitive and executive functioning, advanced maturity, rapid response to danger, and positive relationships with peers, among others. While a comprehensive review of this important topic is beyond the scope of the present review, both early adversity and mitigating environmental factors have been consistently shown to affect the development of stress response systems, brain structure and function, and consequently psychological and behavioral responses to stress into adulthood. In particular, caregiving quality and family stability have been shown to promote resilience following exposure to early-life adversity by regulating emotional and neurobiological development, highlighting clear opportunities for preventive interventions for high-risk youth. When trauma occurs during development, the timing and duration of exposure to adversity is key, as is the timing of preventive interventions. Because of heightened brain plasticity, infancy and adolescence are developmental periods that are especially sensitive to both trauma exposure and positive interventions.

Of note, exposure to manageable, nontraumatic stressful events during development might actually enhance resilience. This phenomenon, termed stress inoculation, was initially reported in young monkeys exposed to weekly short maternal separations over ten weeks. Despite behavioral and biological evidence of acute stress during separations, by the age of three the animals showed more adaptive behaviors and biological stress responses over time, as well as larger ventromedial prefrontal cortex (PFC) volume, a brain region subserving emotion regulation and fear extinction. Learning to cope with stress has been linked to expression of specific genes in brain regions involved in learning and emotion regulation. In humans, an individual’s perceived degree of control over a stressor is known to be of key significance, and exposure to manageable stress levels is thought to enhance resilience to future stressors.

**PSYCHOSOCIAL FACTORS IN ADULTHOOD**

Some of the most widely replicated and potentially modifiable protective factors linked to psychological resilience include emotion regulation, cognitive flexibility and reappraisal, positive emotions, and the ability to harness social support. Emotion regulation has been linked to greater executive function, broadly defined as the ability to plan and complete a task, and required for quick and effective responses to threat, which is crucial for survival and well-being. Effective implicit (automatic) emotion regulation involves top-down cortical regulation of subcortical fear-processing structures, and supports cognitive flexibility (the ability to adapt one’s thinking to face new situations), cognitive control and adaptive (or constructive) coping. Cognitive reappraisal is a conscious (explicit) emotion-regulation strategy employed by resilient individuals; it involves noticing negative thoughts and replacing them with a more positive perspective. Positive reappraisal has also been linked to lower anxiety symptoms in trauma-exposed individuals and is a central component of cognitive-behavioral therapy (CBT) for individuals with PTSD.

Dispositional positive affect, characteristic of resilient individuals, has been linked to greater social connectedness, psychological well-being, constructive problem solving, and adaptive coping with stress. Positive emotions enhance resilience and promote broader associative thinking (the opposite of rumination), thus supporting active coping with stress. Positive emotions have also been found to decrease autonomic arousal and facilitate efficient cardiovascular...
recovery following stress exposure,\textsuperscript{51} and to protect against the negative impact of stress on general health.\textsuperscript{45,52} The capacity to experience positive emotions is closely linked to reward responsiveness.\textsuperscript{48,49,53} Positive affect and reward play a central role in modulating cognitive control and maximizing executive function, crucial for effective responses to threat.\textsuperscript{41,54}

The availability of social support and the ability to establish and nurture a supportive social network have repeatedly been linked to resilience.\textsuperscript{55} High levels of social support reported by resilient individuals function as a safety net in stressful situations,\textsuperscript{9,56} including in military and war settings.\textsuperscript{57} Conversely, low social support and low social integration have been identified as strong risk factors for PTSD.\textsuperscript{58,59} Further, individuals with PTSD commonly report that their lives lack social integration, which has been identified as a strong risk factor for PTSD.\textsuperscript{58,59} Further, individuals with PTSD commonly experience difficulties with interpersonal relationships and intimacy, partially explained by impairments in social cognition,\textsuperscript{60–62} and decreased sensitivity to positive social stimuli.\textsuperscript{63} A focus on increasing social support and engagement with others is of key importance in treating individuals with PTSD.

A range of other psychosocial factors has been linked to resilience. Higher coping self-efficacy, the perception that one is able to manage or recover from a stressful event, has been linked to positive adjustment and lower PTSD symptoms after trauma exposure.\textsuperscript{64,65} Related constructs include a sense of control or mastery over stressors—found to be associated with lower perceived threat and physiological responses to stress—and the ability to face one’s fears.\textsuperscript{66,67} In addition, active coping has been found to support resilience, whereas avoidant coping is linked to PTSD.\textsuperscript{68–70} The last decade has also witnessed a growing interest in mindfulness, the ability to focus one’s awareness on the present moment, while noticing, observing, and describing sensations, thoughts, and feelings, as a protective factor associated with better physical and mental health.\textsuperscript{71,72} Additionally, a solid sense of purpose and the ability to find meaning in the face of challenges might facilitate emotional recovery from negative experiences.\textsuperscript{73} It is known that traumatic experiences can shatter a person’s assumptions about safety and predictability, also affecting their sense of purpose in life.\textsuperscript{70,74} The ability to make sense of a traumatic experience—meaning making—has been recognized as important to psychological recovery in treating PTSD.\textsuperscript{75}

**NEUROBIOLOGY**

Biological responses to stress involve complex adaptive systems of interrelated hormones, neurotransmitters, and neuropeptides acting in concert. Resilience is understood to depend on the efficient activation and termination of the stress response. Notably, key resilience factors, such as cognitive reappraisal and positive emotions, may buffer against the deleterious effects of trauma and adversity. Habitual cognitive reappraisal has been linked to lower levels of reported anger and physiologic arousal in healthy adults,\textsuperscript{76} and positive emotions have also been found to decrease autonomic arousal and facilitate efficient cardiovascular recovery following stress exposure,\textsuperscript{51} protecting individuals against the negative impact of stress on general health.\textsuperscript{45,51}

The HPA axis and locus coeruleus–norepinephrine (LC-NE) system are key components of the stress response system, enabling the organism to react and adapt in the face of stress. Early-life stress is known to affect “HPA-axis programming”\textsuperscript{80} and has been linked to chronically elevated corticotropin-releasing hormone (CRH) levels, resulting in decreased resilience to subsequent exposure to adversity and trauma.\textsuperscript{77} In addition, the dopaminergic system, known to mediate reward responses, is increasingly understood to play a role in regulating fear learning and anxiety by acting as a “brake” on fear responses.\textsuperscript{78} The “threshold” beyond which the capacity to adapt is taxed differs for each individual and might also differ across the lifespan.\textsuperscript{55} Interaction between genetic makeup, early-life environment, and the timing, intensity, and chronicity of stress and trauma exposure can result in the development of PTSD and other stress-related disorders.

Other key neuropeptide and neurotransmitter signaling systems include neuropeptide Y (NPY), BDNF, endocannabinoid, oxytocin, and glutamatergic/gamma-aminobutyric acid (GABA)ergic systems. Higher levels of plasma NPY, an anxiolytic neuropeptide thought to counteract the effects of CRH in the amygdala, hippocampus, and hypothalamus,\textsuperscript{79} were found to correlate with better performance during rigorous military training in a study of highly resilient Special Forces soldiers.\textsuperscript{80} Studies in individuals with PTSD have reported alterations in plasma and cerebrospinal fluid NPY levels.\textsuperscript{81} BDNF, a neuropeptide that promotes hippocampal and PFC function,\textsuperscript{82} was found to be differentially expressed in the nucleus accumbens (a key reward region in the brain) of resilient mice after exposure to chronic social-defeat stress, an animal model of stress-related psychopathology. Resilient mice have been found to upregulate KCNQ potassium channels within the ventral tegmental area, ultimately preventing heightened BDNF signaling within the nucleus accumbens;\textsuperscript{83} these findings have led to a new randomized, controlled trial (RCT) in humans, currently under way. Animal studies are increasingly identifying such neuroplastic changes at the molecular level within fear and reward centers, constituting active adaptations in resilient animals.\textsuperscript{23}

Chronic stress has been shown to induce changes in glutamate-system function, associated with synaptic atrophy in the hippocampus and PFC in animal models, an effect that is rapidly reversed by administration of N-methyl-D-aspartate (NDMA) glutamate receptor antagonist ketamine.\textsuperscript{83} Oxytocin, a neuropeptide that promotes social attachment, is also involved in attenuation of the fear response.\textsuperscript{84} Endocannabinoid signaling regulates stress responses, including attenuating stress-induced activation of the HPA axis, and possibly mediating stress controllability.\textsuperscript{85,86} The development of novel treatment interventions targeting these and other signaling systems is the focus of active ongoing research, discussed below.
THE IMMUNE SYSTEM
The immune system has reciprocal communication with the HPA axis and has been increasingly implicated in stress and resilience. Following stress, glucocorticoids regulate the immune response by inhibiting production of pro-inflammatory cytokines (e.g., interleukin-6 [IL-6]). In turn, cytokines in the brain and circulating cytokines activate the HPA axis. Immune-system mediators have also been shown to play a role in adult neurogenesis, learning, and memory. Several studies in individuals with PTSD have found evidence of altered immune function, including elevated C-reactive protein (CRP), with one study linking CRP polymorphisms to PTSD symptomatology. A meta-analysis found that PTSD is associated with increased inflammatory biomarkers, although psychotropic medication use and comorbid depression were significant moderating factors. A recent study in Gulf War veterans found alterations in peripheral inflammatory activity associated with both reduced hippocampal volume and higher PTSD symptom severity.

Compared to individuals with current PTSD, recent studies have reported lower plasma levels of pro-inflammatory IL-6 as well as CRP in women recovered from PTSD (comparable to levels in nontraumatized controls), and higher levels of anti-inflammatory IL-10 in resilient individuals. Additional evidence suggests that psychosocial factors consistently associated with resilience, such as higher perceived sense of mastery, and a composite self-report measure of social engagement, awareness of self and others, meaning in life, and physical health behaviors might mitigate systemic inflammation in the face of significant lifetime exposure to trauma and adversity. Dispositional positive affect, a psychosocial factor associated with resilience, has also been linked to lower levels of inflammatory cytokines. While preliminary, these results indicate that more resilient individuals might have more adaptive immune-system function.

In a recent, elegant study employing variations of the social-stress paradigm in mice—an animal model of resilience—peripheral immune-system differences measured before exposure to social stress were found to predict resilience and also, in additional experiments involving depletion of IL-6 from leukocytes, to promote resilience. These interesting findings suggest potential novel avenues for the treatment of PTSD—in particular, ones aimed at reducing peripheral inflammation.

NEURAL CIRCUITRY
Research on the neurocircuitry of fear has advanced greatly in recent decades, delineating the roles of the amygdala, hippocampus, and ventromedial PFC in mediating conditioning, reconsolidation, and extinction.

Individuals suffering from PTSD experience significant distress when exposed to trauma reminders, “overgeneralizing” the original fear cues to other similar cues in their environment, which also trigger fear responses. Of particular relevance for PTSD, recent studies have shown that memory is dynamic instead of fixed. Each time a stored memory is reactivated, it can be strengthened or weakened, and potentially updated with new information afforded by experience. These changes, associated with induction of brain plasticity, represent opportunities for modifying the meaning, centrality, or emotional valence of traumatic memories.

New research continues to uncover the surprising degree of plasticity of the human brain, enabling ongoing development of novel interventions to “train” or strengthen specific brain circuits known to function abnormally in individuals with stress-related psychopathology. Of note, neuroimaging studies to date have primarily focused on individuals with PTSD, with less emphasis on resilient, trauma-exposed comparison groups. Further, incorporating a third, healthy control group with no or low exposure to trauma is essential to the design of resilience studies, as it helps to identify factors specific to the resilient or vulnerable groups, and also the common effects of trauma exposure in both exposed groups.

Neuroimaging studies have identified automatic (implicit) emotion regulation as a core dysfunction in stress-related disorders, including PTSD, accomplished through top-down regulation of amygdala activation by the ventral anterior cingulate cortex (ACC). For example, in an functional magnetic resonance imaging (fMRI) study, trauma-exposed individuals without PTSD (more resilient), compared to the PTSD group, exhibited significantly higher rostral ACC activation during an emotional conflict (incongruent) contrast while performing an implicit emotional-interference task. Another series of neuroimaging studies has focused on neural circuits underlying effortful (explicit) emotion regulation in healthy volunteers and psychiatric populations, involving conscious attempts to modulate the intensity of emotional responses. In fMRI studies, resilient women with a history of sexual assault demonstrated higher prefrontal activation than the control group with PTSD during explicit cognitive reappraisal of aversive images, and veterans with PTSD, compared to combat-exposed controls, showed reduced dorsolateral PFC activation during cognitive reappraisal of aversive images. Positive appraisal style and positive reappraisal are of particular interest as coping strategies associated with resilience. A recent neuroimaging study found that positive reappraisal ability, or “finding positive meaning in negative experiences,” is associated with enhanced connectivity between the ventromedial PFC and the amygdala, striatum, and dorsal PFC, regions subserving reward valuation. Further, cognitive reappraisal has also been linked to lower amygdala and higher prefrontal/parietal activation in response to negative stimuli.

The neurocircuitry of reward has been implicated in other studies of resilience and PTSD. Self-reported positive emotions have been found to correlate with neural responsiveness to reward in fMRI studies of patient and nonpatient samples. In behavioral studies, individuals with PTSD reported lower reward anticipation and lower satisfaction when rewarded, and exhibited avoidance of positive affective (i.e., rewarding) stimuli during performance of an approach-avoidance task. Neuroimaging studies have
further documented reward-related circuit abnormalities—for example, in the nucleus accumbens and medial PFC—in individuals with full and subthreshold PTSD,125–128 and have reported a link between PTSD symptom increase after exposure to stressful military service and decreased response to reward in the nucleus accumbens in a longitudinal study of healthy soldiers.129 Stress-induced reward-system dysregulation is thought to increase vulnerability to stress-related disorders49,53—an observation that has been further supported by candidate-gene studies.130,131 Further, imbalanced neural responses to risk and reward might constitute a biomarker of stress vulnerability.129

Although resilient individuals are thought to possess “robust” neural reward circuitry function, to date only one neuroimaging study, with a small sample size, has examined neural circuits of reward in highly resilient individuals (Special Forces soldiers), compared to civilian controls (n = 11 per group), while performing a monetary incentive delay task.132 Interestingly, while civilians showed greater right subgenual PFC and ventral striatum activation during reward anticipation, the Special Forces soldiers showed no differential activation in reward-processing regions between the high-reward and no-reward conditions. A longitudinal fMRI study in a sample of 200 nonpatient, student volunteers found positive affect when facing stressful life events.49 Addicional activation in reward-processing regions between the anticipation, the Special Forces soldiers showed no difference in reward-processing regions between the high-reward and no-reward conditions. A longitudinal fMRI study in a sample of 200 nonpatient, student volunteers found an interaction between ventral striatal reactivity to positive feedback and recent stressful life events in predicting self-reported state-positive emotions, supporting a protective effect of higher reward-related neural responses against reductions in positive affect when facing stressful life events.49 Additional neuroimaging studies of reward circuitry and brain function underlying other psychological factors central to resilience are needed, including social cognition and connectedness with others.133

As reviewed above, the study of resilience incorporates multiple levels of inquiry, including research on genetic determinants, gene × environment interactions, gene expression, functional differences observed across multiple integrated stress response systems, and psychosocial characteristics observed in resilient individuals. Emerging neuroimaging and genome-wide studies promise to advance our understanding of the neurobiology of resilience, with the ultimate goal of developing novel intervention strategies to enhance resilience. Additionally, research on resilience-based interventions is essential to clarify potential mechanisms underlying adaptive responses to stress and trauma, and to broaden the range of available preventive and treatment approaches for trauma-exposed individuals.

ENHANCING RESILIENCE I: DEVELOPMENTAL RESILIENCE-BASED INTERVENTIONS

Without early intervention, childhood adversity can significantly increase an individual’s risk for developing mental and physical health disorders, including PTSD and depression.134–136 The developmental period is marked by increased plasticity and heightened responsiveness to resilience-based prevention and intervention efforts, reviewed below and summarized in Table 1.

Caregiver and Family-Based Interventions

Protective factors identified in studies of resilience during development have been incorporated into the design of youth-based interventions. Given the centrality of positive caregiving as a buffering factor during development,136 many intervention paradigms for high-risk youth focus on improving parenting skills and attachment patterns, strengthening family bonds, and enhancing caregiver responsiveness.137,138,139 Three interventions that have targeted parenting skills to enhance resilience include Multidimensional Treatment Foster Care for Preschoolers (MTFC-P),137 Attachment and Biobehavioral Catch-Up (ABC),138,139 and Kids’ Club and Mom’s Empowerment.140,141 Each of these programs targets specific aspects of parenting skills. For example, Multidimensional Treatment Foster Care for Preschoolers, designed for foster care children aged three to six years, centers on bolstering supportive caregiving and positive-parenting skills, such as responding consistently and contingently to positive and negative behaviors.137 The ABC program, designed for foster care children, aims to improve attachment patterns and regulatory capacity in young children by instructing caregivers to be highly responsive and sensitive in their interactions with them through recognizing the children’s needs, reducing the frequency of frightening parental behaviors, and addressing the parent’s own issues.138,139 Both interventions have been shown to improve attachment security and to normalize cortisol patterns in children.136,139,140,152 Finally, Kids’ Club and Mom’s Empowerment, an intervention for mothers and children exposed to intimate partner violence, has also demonstrated significant improvements in positive parenting.140,141

In addition to targeting positive and responsive caregiving to enhance resilience, a “family resilience framework” highlights three domains of family functioning to be addressed in resilience-oriented family intervention programs: communication processes, organizational patterns, and belief systems.153 For example, FOCUS, a brief intervention for families coping with traumatic exposures and loss, has been administered nationally to military families and has been implemented in community, clinical, and school settings.142 FOCUS utilizes core psychosocial resilience factors such as meaning making, problem solving, and social support to promote family resilience.142 The program has resulted in decreased distress and symptomatic behaviors in parents and children, and increased children’s prosocial behaviors and families’ resilience processes.143

School-Based Interventions

School-based programs to enhance resilience represent an opportunity to bolster support in the child’s natural social networks.154–156 These programs also capitalize on well-known psychosocial factors to enhance resilience, such as cognitive reappraisal, defined above as a conscious emotion-regulation strategy that involves noticing negative thoughts and replacing
them with a more positive perspective. Bounce Back, a 10-session CBT intervention for trauma-exposed children in elementary school, was shown to significantly reduce PTSD, depression, and anxiety symptoms compared to a delayed intervention condition. Notably, the intervention was also successfully delivered by school-based therapists, demonstrating its potential for more widespread scalability. School-based intervention programs have also begun to adopt mindfulness-based stress reduction (MBSR) to improve mental health and reduce stress in high-risk youth populations. In a small RCT of MBSR for seventh- and eighth-grade males in a low-income urban area, participants receiving this intervention showed improved coping skills compared to those who received a health education program. A review noted that since 2005, at least 14 studies of school-based intervention programs have directly trained students in mindfulness, with associated improvements in several resilience-related domains, such as emotion regulation, academic skills, and social skills, and decreases in anxiety and stress.

Table 1: Examples of Resilience-Boosting Interventions for Children and Adolescents

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Program example</th>
<th>Population</th>
<th>Intervention summary</th>
<th>Resilience factors targeted</th>
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</thead>
<tbody>
<tr>
<td>Caregiver- and family-based</td>
<td>Multidimensional Treatment Foster Care</td>
<td>Foster preschool children and foster</td>
<td>Children’s playgroup</td>
<td>Supportive and consistent parenting</td>
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<td></td>
<td>for Preschoolers137</td>
<td>caregiver(s)</td>
<td>Facilitate school readiness (supplemented by individual behavioral sessions)</td>
<td>Attachment security</td>
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<tr>
<td></td>
<td>Therapist administered</td>
<td></td>
<td></td>
<td>Parent stress levels</td>
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<tr>
<td></td>
<td>Attachement and Biobehavioral Catch-Up</td>
<td>Foster preschool children and foster</td>
<td>10 weekly, in-home sessions</td>
<td>Attachment security</td>
</tr>
<tr>
<td></td>
<td>38,139</td>
<td>caregiver(s)</td>
<td></td>
<td>Sensitive caregiving</td>
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<tr>
<td></td>
<td>Therapist administered</td>
<td>Child protective services involved</td>
<td></td>
<td>Children's regulatory capacity</td>
</tr>
<tr>
<td></td>
<td>Kids' Club and Mom’s Empowerment140,141</td>
<td>School-age children and their mothers</td>
<td>10-session program over 5 weeks</td>
<td>Social competence</td>
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<tr>
<td></td>
<td>Therapist administered</td>
<td>exposed to intimate partner violence</td>
<td>Group format (separate groups for mothers and children)</td>
<td>Facing fears</td>
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<tr>
<td></td>
<td>FOCUS142,143</td>
<td>Families coping with traumatic exposures</td>
<td>Narrative sharing process</td>
<td>Social and emotional adjustment for mothers</td>
</tr>
<tr>
<td></td>
<td>Therapist administered</td>
<td>and loss; military families; families with chronic illnesses</td>
<td>Strengths-based approach</td>
<td>Parenting skills</td>
</tr>
<tr>
<td></td>
<td>Bounce Back144</td>
<td>Multicultural school-age children</td>
<td>10 sessions</td>
<td>Cognitive-reappraisal skills</td>
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<td></td>
<td>School-based therapist delivered</td>
<td>exposed to traumatic events</td>
<td>CBT-based</td>
<td></td>
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<td>Mindfulness-based stress reduction145</td>
<td>7th- and 8th-grade males in a low-income</td>
<td>Structured program of mindfulness instruction</td>
<td>Coping skills, emotion awareness</td>
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<td></td>
<td>Trained instructor delivered</td>
<td>urban area</td>
<td></td>
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<tr>
<td>Community-based</td>
<td>Positive Youth Development146,147</td>
<td>High-risk and general community youth</td>
<td>Five Cs: competence, confidence, character, connection, caring</td>
<td>Individual strengths, positive adult-youth relationships, self-regulation skills</td>
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<td></td>
<td>Trained mentors</td>
<td></td>
<td>Engage youth in community (prosocial approach)</td>
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<tr>
<td></td>
<td>Communities That Care148–150</td>
<td>High-risk and general community youth</td>
<td>Prevent adolescent behavior and health problems (e.g., drug abuse prevention)</td>
<td>Family management styles, social support, and academic engagement</td>
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<tr>
<td></td>
<td>Trained mentors</td>
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</table>

CBT, cognitive-behavioral therapy; PTSD, posttraumatic stress disorder.
School-based psychosocial interventions have been studied in children with PTSD symptoms, but few have measured resilience as an outcome beyond symptom reduction. One program for war-exposed children focused on enhancing social and peer support. In this teacher-delivered intervention, participating children showed reduction in PTSD symptoms and greater adaptive functioning.\(^{156}\) A separate study of Sri Lankan children utilized a quasi-RCT design for students aged 9 to 15 years with high tsunami exposure. Compared to a waitlist control group, students in the active condition (focused on cognitive-behavioral skills, meditation, and processing traumatic experiences) had not only decreased PTSD and depressive symptoms but also increased hopefulness.\(^ {159}\)

**Community-Based Interventions**

Another hallmark of preventive interventions for youth is an emphasis on identifying and developing positive individual strengths, such as the Positive Youth Development (PYD) programs centered on the “5 Cs” of competence, confidence, connection, character, and caring, in addition to emphasizing strong bonds with adults.\(^ {147,160}\) The 4-H study, a PYD evaluation project, followed 1700 fifth-grade children participating in community youth-development programs and examined their developmental trajectories throughout the second decade of life.\(^ {147}\) The Communities That Care (CTC) effort, a different program developed to prevent adolescent problem behavior, including substance abuse, guides communities to select, test, and implement effective preventive interventions addressing high-risk children.\(^ {148,149}\) The CTC model is now being adapted for community child-maltreatment prevention.\(^ {150}\)

Psychosocial interventions for youth in juvenile justice services, also at heightened risk for PTSD, are increasingly recognized as critical services for this population.\(^ {161}\) Trauma-Adapted Multidimensional Treatment Foster Care is a behavioral intervention that targets adaptive social support (e.g., engagement in prosocial activities and decreased contact with antisocial peers) and a positive relationship with a caregiving adult. In RCTs, this program has been shown to reduce delinquent behaviors and mental health problems.\(^ {162–164}\)

**ENHANCING RESILIENCE II: RESILIENCE-BASED INTERVENTIONS FOR ADULTS**

**Pre-trauma Training and Other Preventive Approaches**

Preparedness training for occupational groups frequently exposed to potentially traumatic situations (e.g., first responders, military personnel) aims to bolster resilience through targeting specific skills (e.g., firefighting) and stress-management skills (e.g., relaxation training, cognitive reframing), and are thought to work through enhanced coping self-efficacy and a heightened sense of control.\(^ {165,166}\) Examples of preparedness training include Stress Inoculation Training (SIT) pre-deployment for military personnel\(^ {167}\) and the Mental Agility and Psychological Strength (MAPS) training program for first responders in Western Australia,\(^ {168}\) both centering on psychoeducation about stress control, coping skills, cognitive restructuring, and support seeking.

Hardiness training similarly focuses on enhancing a sense of control by teaching attitudes and skills that reduce threat perception, help reframe stressful situations as opportunities for growth, and enhance coping abilities.\(^ {169}\) Hardiness, which incorporates coping self-efficacy, meaning making, and cognitive reframing, has been linked to decreased PTSD symptoms in deployed soldiers.\(^ {170}\) Recent resilience-training programs for soldiers have focused on meaning making and personal strengths.\(^ {171,172}\) A different approach, designed to enhance performance under stress and aligned with the concept of stress inoculation, involves extremely taxing captivity-simulation exercises employed as preparedness training for soldiers.\(^ {180,173}\)

Mindfulness programs have also been investigated as preventive strategies for trauma-exposed adults. Mindfulness-Based Resilience Training (MBRT) for first responders aims to reduce negative health outcomes and enhance resilience. In a pilot study for law enforcement officers, MBRT improved sleep quality and reduced burnout levels, perceived stress, and fatigue.\(^ {174}\) In secondary analyses, increased resilience partially mediated the effect of increases in mindfulness on decreased levels of burnout.\(^ {175}\) Mindful Awareness and Resilience Skills Training (MARST), a program designed for foster care workers and family support counselors, aims to increase resilience by focusing on mindfulness, positive cognitive-reappraisal skills, and awareness of positive emotions.\(^ {176,177}\)

A novel preventive intervention that originated from the study of neurocognitive mechanisms—attention-bias modification training (ABMT)—is based on observations that in stressful environments, resilient soldiers focus attention on threats, whereas a tendency to direct attention away from threat might be associated with greater risk for PTSD.\(^ {178}\) In an RCT with soldiers, ABMT designed to enhance attention to threat, when administered pre-deployment or immediately prior to combat, mitigated combined risk of PTSD and the development of depressive symptoms after combat exposure.\(^ {179}\) A very different approach—administering a pharmacologic agent prior to trauma exposure to prevent or mitigate stress-related symptoms—might now be within reach. For example, the NMDA glutamate receptor antagonist ketamine has recently been shown to induce stress resilience in rodents when administered one to two weeks prior to stress exposure, suggesting possible applications for occupational groups with high exposure to potentially traumatic events.\(^ {180,181}\)

**Early Post-trauma Interventions**

Many years after discouraging results from earlier psychological debriefing studies,\(^ {182}\) a recent upsurge of research on preventive interventions administered shortly after a traumatic event has aimed to prevent the development of PTSD symptoms.\(^ {183}\) A brief video intervention focusing on coping strategies for women survivors of sexual assault, administered within 72 hours of the assault, was associated with lower PTSD symptoms both six weeks and six months later, primarily in...
women with a prior history of rape. A separate approach utilizing a modified exposure therapy paradigm in the emergency department hours after trauma exposure was found to mitigate the emergence of PTSD reactions, particularly in rape victims. Using a combined genotype risk score, those at higher genetic risk for PTSD who did not receive the intervention had higher PTSD symptom levels.

There is also an active interest in developing early pharmacologic interventions to help prevent or mitigate first onset of PTSD symptoms after trauma exposure. In studies to date, the beta-adrenergic blocker propranolol administered shortly after trauma to try to prevent initial consolidation of traumatic memories failed to reduce PTSD incidence but did attenuate physiological responses. Studies of pharmacologic agents showing promise for the secondary prevention of PTSD include RCTs of hydrocortisone administration (thought to enhance synaptic plasticity), and naturalistic studies of morphine administration, and intranasal oxytocin studies. Preclinical studies have also identified NPY as a promising agent, as it has consistently shown to attenuate stress responses and, more recently (in animal models), the development of PTSD-like symptoms. Further research is needed before early secondary prevention can be implemented in clinical practice.

Resilience-Based Interventions for PTSD
Psychotherapeutic, resilience-based interventions for adults who have developed PTSD aim to enhance social support, positive emotions, physical exercise, emotion regulation, meaning making, and purpose in life. Building upon and utilizing these skills therapeutically may help bolster resilient functioning and posttraumatic growth beyond simple reduction of PTSD symptoms. Further, translating our expanding knowledge of the neurobiology of resilience promises to yield novel therapeutic strategies for treating PTSD (see Text Box 1).

Text Box 1
How Resilience Research Can Benefit PTSD Treatment: Some Examples of Novel and Potential Interventions

Psychotherapy
Social support: Skills Training in Affective and Interpersonal Regulation, promoting social engagement, skills, and functioning
Positive emotions: Incorporating positive mood induction into exposure therapy
Emotion regulation/purpose in life: emotion-regulation therapy, focusing on mindful emotion-regulation skills and on what is meaningful in life to the patient
“Training the brain”
Attention-bias modification training and attention-control training
Cognitive-emotional training
Pharmacotherapy
Pharmacologic augmentation of psychotherapy
Intranasal neuropeptide Y
Intranasal oxytocin
Discovery of novel pharmacological targets in animal models of resilience

Psychosocial and Cognitive-Training Strategies to Enhance Resilience
Numerous studies identifying the buffering effect of social support against stress and trauma have contributed to the development of interventions focused on building social support and relationship skills. Examples include an intervention for veterans with PTSD and their marital partners, incorporating partner-based exercises focused on effective communication, intimacy, and anxiety reduction, and Skills Training in Affective and Interpersonal Regulation, piloted in veterans with military sexual trauma and PTSD. For survivors of sexual assault and intimate partner violence, social support that promotes self-esteem is critical to counter potential negative feedback from their social circle via victim blaming. Of note, in a recent RCT, interpersonal psychotherapy for individuals with PTSD, emphasizing the interpersonal aftermath of trauma, showed similar efficacy as prolonged exposure, the gold-standard treatment.

Other resilience-boosting interventions such as stress inoculation training, mentioned above, incorporate active problem solving, cognitive reappraisal, and relaxation training to assist trauma survivors. In female sexual assault survivors, this approach was associated with reductions in PTSD and depressive symptoms. The Moving Forward program for veterans with PTSD provides training in effective problem solving and emotion regulation, and has been found to yield improvements in social problem solving and resilience measured by the Brief Resilience Scale. Recent studies have also begun to examine the potential of incorporating positive mood induction to increase the effectiveness of exposure therapy interventions.

Meaning-making interventions, which involve integrating a traumatic experience into the survivor’s broader belief system, have also been employed in the treatment of PTSD. Originally developed by Viktor Frankl, logotherapy has been adapted for the treatment of combat-related PTSD, supporting individual strengths and guiding combat survivors in a personal search for meaning and purpose. Narrative-based therapies, such as Skills Training in Affective and Interpersonal Regulation, also incorporate meaning making and the enhancement of emotion regulation and social support. Emotion-regulation therapy, developed to treat individuals with anxiety and depressive disorders, incorporates mindful emotion-regulation skills and a focus on what is, for the patient, meaningful in life, with potential applications for PTSD. Mindfulness, yoga, and meditation, linked to increases in positive affect and improved immune system function, have increasingly been studied as interventions for PTSD. Dialectical behavior therapy, which emphasizes mindfulness-based skills, has been successfully adapted for PTSD, particularly...
for survivors of childhood abuse and for individuals with complex PTSD presentations.221,222 Yoga integrates physical exercise (known to be protective against chronic stress223), is often incorporated into mindfulness and meditation-based paradigms, and has been found to yield improvement in PTSD symptoms, positive affect, and resilience in preliminary studies for PTSD.224,225

The last few years have seen the emergence of cognitive-emotional training interventions, aimed at reducing abnormalities in attention to threat and emotion processing that were identified in earlier cognitive and neuroimaging studies of individuals with stress-related disorders.109,201 Preliminary findings from a study in combat veterans with PTSD suggest that attention-control training, rather than attention-bias modification training, might help normalize attention allocation and improve PTSD symptoms.202 Cognitive-emotional training, another novel intervention with promising initial results in patients with major depression, awaits additional testing in relation to PTSD patients.110

Emerging Pharmacotherapeutic Strategies

Pharmacologic Augmentation of Psychotherapy Gold-standard, evidence-based psychotherapies for PTSD are based on exposure techniques within CBT paradigms. Neuroimaging studies suggest that CBT may reduce PTSD symptoms by decreasing activation of the amygdala and increasing activation of the rostral ACC.226 Increasingly, studies are investigating pharmacological augmentation strategies to enhance the efficacy of exposure-based psychotherapy, thought to work through extinction learning.203 D-cycloserine, a partial agonist at the glycine regulatory site of the NMDA glutamate receptor that was found to enhance fear extinction in preclinical studies, has shown some promise for anxiety and obsessive-compulsive disorders, but results from PTSD studies have not supported the clear efficacy of D-cycloserine for that purpose.227–230 Propranolol, discussed above under secondary prevention, has additionally been tested in conjunction with trauma-memory reactivation in attempts to block or reduce reconsolidation of the trauma memory in individuals with PTSD, with mixed results to date.231–234 Results from preclinical studies suggest the potential utility of other agents in combination with psychotherapeutic intervention for PTSD—including endocannabinoids, estrogen, methylene blue, and histone deacetylase inhibitors—most of which have not yet been studied in humans with this combined approach.203 There is also renewed interest in studying ±3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy, with initial promising results.235,236

Investigational Pharmacotherapies Currently available medications for treating PTSD are insufficiently effective for many patients.237,238 Though findings from studies of the neurobiology of resilience have suggested potential novel pharmacologic approaches. For example, evidence from studies in resilient Special Forces soldiers and in patients with PTSD, mentioned above, indicates that the anxiolytic neuropeptide NPY might be involved in enhancing resilience.80,239 More recently, in a rodent model of PTSD, intranasal NPY administration immediately prior or following traumatic stress exposure showed protective effects on behavioral, neuroendocrine, and molecular changes.79 Intranasal NPY is currently being investigated as a potential treatment for PTSD.81 The glutamate NMDA receptor antagonist ketamine, shown in animal studies to reverse synaptic atrophy in the PFC stemming from chronic stress,83 has demonstrated efficacy for treatment-resistant depression240 and, more recently—in the first proof-of-concept RCT—for PTSD.241 RCTs of repeated intravenous administration of ketamine over two to four weeks for patients with PTSD are currently under way. Other promising novel pharmacotherapies for PTSD currently under study include intranasal oxytocin administration63,204 and compounds targeting the endocannabinoid system.242,243

Future Directions

Resilience research is blossoming as the field embraces increased interdisciplinary collaboration and translational studies aimed at enhancing preventive efforts, expanding currently available treatments for PTSD, and aiming beyond symptom reduction to boost resilience and coping. Psychosocial factors long known to enhance resilience, such as hardness, coping self-efficacy, social support, cognitive reappraisal, and meaning making, are increasingly incorporated into new intervention designs for children and adults.

Neural and molecular studies in preclinical models of resilience are increasingly identifying active adaptations in resilient animals,25,244 thereby providing valuable insight into potential avenues for novel pharmacological interventions to mitigate the effects of stress and trauma. Additionally, combined genomic and molecular studies, along with new genome-wide studies in large samples of trauma-exposed individuals, will ultimately enable both identification of individuals at high risk for stress-related psychopathology and the development of novel intervention strategies designed for newly identified targets. Key examples of this approach are the studies on the FKBPs5 gene, which discovered genetic × epigenetic × environmental interactions in individuals exposed to childhood trauma, associated with a differential risk for PTSD in adulthood.7 These findings lay the groundwork for the development of FKBP5 antagonists, currently being tested in rodent models of early trauma exposure.245 In the future, it might also be possible to enhance or suppress the expression of specific genes associated with onset or chronicity of PTSD.197

Our advancing understanding of fear conditioning, reconsolidation, and extinction mechanisms emerging from both animal and human studies also has clear translational implications for PTSD—in particular, findings from recent studies demonstrating that memory retrieval can induce brain plasticity.107 Reactivated trauma memories can be “updated” with new information, potentially modifying their meaning or emotional impact on the individual; alternatively, pharmacologic intervention has the potential to block reconsolidation of trauma memories.107 Further, as reviewed above, pharmacologic...
augmentation can potentially enhance extinction learning.\textsuperscript{203} This active area of research is complex and not without risk, especially because pharmacologic intervention can also strengthen trauma memories, depending on the timing of drug administration, mechanism, and emotions elicited during trauma recall.\textsuperscript{203}

Additionally, the development of cognitive-emotional training interventions—based on our growing understanding of neural circuitry subserving attention, perception, and regulation of emotion—holds significant promise for the prevention and treatment of stress-related disorders, including PTSD. A growing number of clinical trials promise to yield novel pharmacological interventions aimed at reducing dysfunction in stress response systems by targeting key neurotransmitter, hormone, and neuropeptide systems as well as immune responses.\textsuperscript{197} New studies also aim to identify a "biomarker panel" for PTSD across the stress response system (including genomic, neuroendocrine, and immune biomarkers) to facilitate the identification of high-risk individuals and the diagnosis of PTSD, and to optimize intervention design.\textsuperscript{246–249}

The extant and rich literature on the consequences of early-life stress, combined with studies of resilience in high-risk children, further emphasizes the importance of early intervention during development with children and adolescents.\textsuperscript{136,250} The type and timing of interventions for children are integral to their effectiveness.\textsuperscript{251} While several interventions for at-risk youth have been investigated in school-aged children and adolescents, wider implementation and studies in very young children at risk remains a critical issue.\textsuperscript{252} Interventions that can be incorporated into children’s ecological environments (e.g., school, communities), such as the PYD and CTC programs mentioned above, may be more feasibly implemented and sustained, have the potential to reach a broader range of children, and represent a promising direction to enhance resilience in children.\textsuperscript{147} Child advocates emphasize the importance of making changes aimed at promoting resilience within systems where children at highest risk reside, such as the child welfare, juvenile justice, and foster care systems.\textsuperscript{253} Several interventions, such as the Multidimensional Treatment Foster Care for Preschoolers and ABC program, have demonstrated success with foster care– and child welfare–involved children.\textsuperscript{137,138}

The development of early screening tools, including psychological and biomarker methods to improve identification of high-risk children, can also help target interventions to enhance resilience.\textsuperscript{254,255} There is a pressing need for brief screening tools that can be easily administered in busy child-service settings (e.g., schools) and also for concerted efforts to educate teachers, nurses, and pediatricians on trauma assessment.\textsuperscript{156} Further, school-based efforts like Bounce Back–based on our growing understanding of psychological resilience—including widely replicated factors such as social support, emotion regulation, adaptive coping, and positive affect and reappraisal—are key to optimizing and developing novel preventive and intervention approaches. A critical goal in the field of resilience is to broaden treatment strategies for individuals with PTSD and other stress-related disorders beyond symptom reduction to bolstering well-being and resilience. New intervention programs for the military and other populations with high trauma exposure are increasingly incorporating mindfulness, meaning making, cognitive reappraisal, and the promotion of adaptive coping. Equally important, the development of new screening and early-identification strategies, along with efforts targeted at optimization, dissemination, and implementation of new interventions, will need to advance alongside the fast-paced growth of preventive and treatment strategies.

Declaration of interest: Dr. Feder is listed as a coinventor on a use patent application of ketamine for treating PTSD.

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