Review

Biological Psychiatry: Celebrating 50 Years

The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span

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ABSTRACT

Recent scientific and technological advances have brought us closer to being able to apply a true biopsychosocial approach to the study of resilience in humans. Decades of research have identified a range of psychosocial protective factors in the face of stress and trauma. Progress in resilience research is now advancing our understanding of the biology underlying these protective factors at multiple phenotypic levels, including stress response systems, neural circuitry function, and immune responses, in interaction with genetic factors. It is becoming clear that resilience involves active and unique biological processes that buffer the organism against the impact of stress, not simply involve a reversal of pathological mechanisms. Here, we provide an overview of recent progress in the field, highlighting key psychosocial milestones and accompanying biological changes during development, and into adulthood and old age. Continued advances in our understanding of psychological, social, and biological determinants of resilience will contribute to the development of novel interventions and help optimize the type and timing of intervention for those most at risk, resulting in a possible new framework for enhancing resilience across the life span.

Keywords: Biopsychosocial, Human, Interventions, Life span, Neurobiology, Resilience

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Resilience is a complex and dynamic process, broadly defined as the ability to adapt successfully to adversity, stressful life events, significant threat, or trauma. It is best conceptualized as a continuum, with potential for change across the life span (1). Studies have repeatedly shown that severity and frequency of exposure to stress matter. Resilient outcomes are less likely in the face of severe adversity. This is especially true of trauma or neglect during childhood, when biological stress response systems are under development (2,3), and of chronic adversity (4). Additionally, risk factors commonly co-occur and accumulate over time, and higher cumulative risk generally predicts worse outcomes (5–8). Yet even at the most severe exposure levels, it is often possible to identify individuals who recover from stress, managing to lead meaningful lives, or find "relative resilience" to severe adversity.

Recent studies have begun to show that resilience is an "active process," not simply involving a reversal of pathological mechanisms (9,10). The present review will focus on the biology of human resilience during development and across the life span, introducing advances in the field and providing illustrative examples of research findings. Scientific and technological progress in recent decades has enabled a more integrative biopsychosocial approach to the study of resilience in humans (see Figure 1). Interdisciplinary collaboration involving animal, translational, and human studies promises to yield novel interventions to enhance resilience (11).

GENETICS AND GENOMICS OF RESILIENCE

Studies of the heritability of resilience have only recently begun to emerge. For example, a longitudinal study in 7500 adult twins modeled resilience as the difference between actual and predicted internalizing symptom severity, based on number of experienced life stressors. Resilience was found to have moderate heritability and was equally influenced by genetic and environmental factors (12). Other twin studies have focused on the heritability of trait resilience, or on psychological and behavioral traits associated with resilience (13,14). Candidate gene studies have identified protective variants in genes modulating the norepinephrine stress response (15) or influencing amygdala and hippocampal activation to threat (16). A few studies have examined candidate genes and resilience in childhood maltreatment (CT) survivors, including children (17–19) and adults (20). A rare study in older adults examined multiple candidate genes and optimism and trait resilience (21).

Increasing evidence suggests that certain gene variants confer heightened sensitivity to the environment, so that the same gene variants that increase risk in the face of adversity might confer advantages in positive environments (22–25). This appears to carry over to preventive interventions in children and adolescents exposed to adversity. Some randomized controlled trials (RCTs) of preventive interventions against externalizing and against alcohol and drug use problems, have shown benefits in risk allele carriers but not noncarriers (26–28).

Only one genome-wide association study (GWAS) of psychological resilience has been published (29). The rise of publicly available genetic datasets has made it possible to conduct large GWASs of psychological, behavioral, and biological factors linked to resilience, including a GWAS of social

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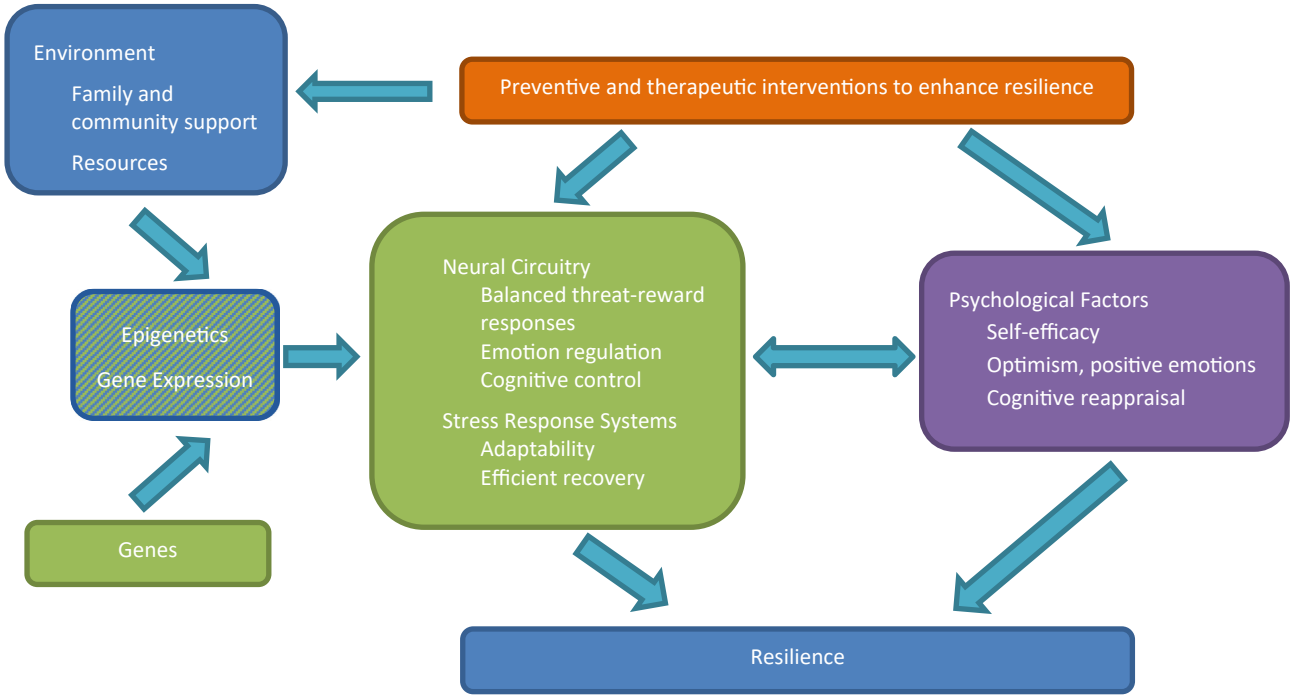

Figure 1. Biopsychosocial model of resilience. Genes interact with environmental influences to shape the function of neural circuitry and stress response systems, especially during development. Environmental influences additionally exert a lasting impact on neural and stress response system function through epigenetic modifications affecting gene expression. At the core of resilience are stress responses that are sufficient but not excessive, as well as rapid and efficient psychobiological recovery following stress exposure. At the neural level, appropriate activation of brain regions mediating threat appraisal, efficient emotion regulation circuitry function, and neural adaptability to changing environmental contingencies support accurate appraisal of stressful contexts and adaptive coping. Additionally, brain circuitry function subserving reward responses and cognitive control underlie key psychological factors associated with resilience, including optimism and the capacity for cognitive reappraisal. Accumulating evidence suggests that preventive and therapeutic interventions at different phenotypic levels have the potential to enhance resilience. Examples include interventions targeting psychological factors (e.g., practicing cognitive reappraisal), family/social factors (e.g., parenting interventions, youth development programs, social engagement), brain circuitry function (e.g., computer-based cognitive-emotional training, electroencephalographic neurofeedback), and brain/stress response system function (e.g., ketamine administration).

interaction and isolation utilizing UK Biobank data (30) and a GWAS meta-analysis of subjective well-being (31). Another GWAS identified genetic and psychosocial factors associated with hippocampal volume, known to be protective against stress-related psychiatric disorders (32).

Beyond the genetic code, epigenetic changes stemming from environmental influences, most importantly during development, are associated with differential stress resilience (6). A series of studies of the *FKBP5* gene constitute a well-known example, identifying genotype × epigenetic × environment (childhood trauma) interactions conferring differential susceptibility to trauma into adulthood (33). Candidate gene methylation studies are beginning to include children: for example, a recent study of prefrontal cortex (PFC) connectivity in maltreated children (34). Epigenome-wide studies focused on resilience have yet to be published.

DEVELOPMENTAL YEARS: EARLY CHILDHOOD TO ADOLESCENCE

Childhood is a critical period for the development of stress response systems and brain circuity mediating emotion regulation (2,35). Human studies have documented the lasting impact of uncontrollable childhood trauma and neglect on stress response systems, brain morphology, and neural circuitry function (3,36). The impact of stress during development greatly depends on its timing and duration, reflected in differential epigenetic changes across the genome (6). Early adversity might also accelerate maturation of emotion neural circuits, with potential consequences into adulthood (37–39). Chronic stress among youths, such as poverty, may also increase allostatic load and epigenetic aging and heighten risk for mood and anxiety disorders and cardiometabolic and immune-related conditions (40).

Infancy and adolescence are two key periods of heightened brain plasticity and increased sensitivity to the environment, including both adverse and nurturing circumstances (2,41). Beginning in infancy, the establishment of a solid bond with a caregiver is of primary importance as a powerful stress buffer. Maternal sensitivity toward 6-month-old infants was found to be associated with lower hypothalamic-pituitary-adrenal (HPA) axis and sympathetic responses to stress (42). In 18-month-old infants, secure attachment with a parent present during stress exposure (e.g., a loud toy) prevented increases in salivary cortisol (43). In another study, parenting quality assessed by observing mothers and their 3-year-old children predicted differential connectivity in reward and emotion regulation circuitry by 11 years of age (44). Maternal

presence has also been found to buffer fear-potentiated startle in 8- to 10-year-old children but not in early adolescents, suggesting that the period of brain plasticity for learning threat and safety occurs earlier in childhood (45). Similarly, in an experimental study, the presence of a parent while preparing for the Trier Social Stress Test prevented increases in cortisol in 9- to 10-year-olds but no longer acted as a stress buffer in 15- to 16-year-olds (43).

Studies in children who demonstrate more resilient outcomes despite exposure to early trauma have identified key psychosocial factors that promote resilience, most significantly the establishment of a solid bond with a competent caregiver and family stability (46–48). Parenting/caregiving that enhances resilience provides a loving and supportive environment that protects the child from overwhelming stress, but also ensures ample opportunities to explore, master challenges, and learn from failure. Such "good enough" parenting fosters the development of skills in the child that are important for successful negotiation of later stress and adversity.

Adolescence is a period of transition, during which youths gradually achieve increasing independence and learn about the social world without the close presence of a caregiver. Some parents who are highly skilled at parenting their young child may not have the flexibility to adjust their parenting style as their child reaches adolescence. This may result in an overprotected adolescent who fails to develop sufficient skills to successfully meet challenges and grow from adversity. Despite increasing independence, family support and stability remain extremely important during this period (40).

Additionally, because adult levels of cognitive capacity are achieved significantly earlier than socioemotional maturity, the resulting imbalance can impact decision making into the second decade of life, increasing risk for impulsivity and risky behavior (49). Established protective factors in this context include greater executive function, capacity for self-regulation, and self-efficacy (46,48). During adolescence, positive relationships with peers are also key promoters of resilience in youths exposed to adverse childhood family environments (50). As adolescents learn to navigate their social environment, social ability, genetic makeup, and daily experiences with others all interact to influence brain maturation (51). Further, access to positive role models is thought to be particularly important during adolescence (52,53).

Few biological studies have focused on children or adolescents who have demonstrated resilience to adversity or trauma. A study in school-age children from low-income families examined HPA axis function in children with and without a history of maltreatment. Maltreated children with high resilience scores showed an atypical daytime rise in salivary dehydroepiandrosterone, but additional studies are needed (54). An ongoing longitudinal study in school-age children from lower socioeconomic backgrounds, the Families and Childhood Transitions Study, includes assessment of family environment, measures of HPA axis and immune function, and neuroimaging (55).

Of note, psychologically resilient African American youths from lower socioeconomic backgrounds have shown evidence of higher allostatic load, poorer cardiometabolic health, and accelerated epigenetic aging as they transitioned into early adulthood, suggesting that in this context psychological resilience and self-control might come at a cost to general health (40). Importantly, interventions to enhance supportive parenting during childhood were found to be protective in this setting, lessening inflammation and epigenetic aging and preventing reduced hippocampal and amygdala volumes by young adulthood (40,56).

Stress Inoculation

The degree of control that animals and humans experience over stressors, particularly during development, plays an important role in later vulnerability or resilience to stress. Animal studies have consistently found that repeated exposure to uncontrollable stress can have a detrimental effect on developing brain structure and function (57–59). In contrast, in a well-known series of experimental studies in young monkeys, early exposure to manageable stress—referred to as "stress inoculation"—resulted in enhanced arousal regulation and resilience via PFC adaptations (60). More indirect evidence exists in humans. For example, in a study of cumulative adversity in 9- to 16-year-olds, children with moderate adversity exposure showed more robust cortisol responses than both unexposed and highly exposed children (61). A few studies in adults also suggest that having experienced moderate life adversity might be steeling (62–64).

RESILIENCE IN ADULTHOOD AND OLDER AGE

A rich body of research has identified psychosocial factors contributing to resilience in adulthood, including greater emotion regulation, executive function, dispositional optimism, active coping, cognitive reappraisal, and social support (52,65,66). Other studies have identified the role of religion, meaning-making, and a sense of purpose (52,67,68). Many of these protective factors are interlinked. For example, better automatic emotion regulation, involving activation of the anterior cingulate cortex (ACC) and ventromedial PFC (vmPFC), is associated with greater executive function, required to mount effective responses to threat (46,69,70). Higher emotion regulation capacity also supports cognitive flexibility in challenging situations (71,72). Cognitive reappraisal, an emotion regulation strategy involving reinterpreting the meaning of a situation, activates brain regions mediating cognitive control (dorsomedial PFC, dorsolateral PFC, and ventrolateral PFC) and modulates amygdala activation (73). Positive emotions also support resilience by promoting broader associative thinking and adaptive coping (74–76). In one study, dispositional optimism was found to correlate with rostral ACC activation in individuals instructed to imagine future positive events (77). Dispositional optimism is associated with greater social support and is consistently linked to psychological well-being and better health (52,78). Social support, a key protective factor, can take many forms—from family support to mentorship to community networks—and should be considered a primary component of interventions to enhance resilience (52,79–81).

At the core of resilience are stress responses that are sufficient but not excessive, as well as rapid and efficient psychobiological recovery following stress (82,83). Trait resilience has been shown to correlate with positive emotionality and faster recovery of cardiovascular reactivity after stress (84).

While HPA axis dysregulation and enhanced locus coeruleus–norepinephrine system function have been consistently demonstrated in individuals with stress-related psychiatric disorders, additional research is needed in resilient individuals (85,86). Physical exercise can also help buffer the impact of stress by increasing positive mood and neural plasticity in dopaminergic brain reward circuits (87).

Stress response systems beyond the HPA axis and locus coeruleus–norepinephrine system have been primarily studied in adults. Endocannabinoid signaling is closely coupled with HPA axis signaling, modulating the stress response and facilitating recovery from stress (88). Endocannabinoids might play a key role in regulating vmPFC circuitry during controllable stress, with potential implications for resilience (89). Other key signaling systems include neuropeptide Y (NPY), glutamatergic, brain-derived neurotrophic factor, and oxytocin systems. In an early study of resilient Special Forces soldiers, higher plasma NPY levels correlated with better performance during a rigorous military training exercise (90). More recent evidence suggests that the dopamine system, involved in reward responses, may act as a "brake" in fear response termination (91).

The glutamate system is also an active focus of research, as ketamine—an *N*-methyl-D aspartate glutamate receptor antagonist shown to rapidly reverse hippocampal and PFC synaptic atrophy caused by chronic stress in animals (92)—has demonstrated efficacy for treatment-resistant depression (93,94) and initial promise for posttraumatic stress disorder (PTSD) treatment (95). Recent years have also seen increasing interest in the immune system, known to have reciprocal communication with the HPA axis. Initial studies suggest that resilience is associated with lower systemic inflammation (96), and that psychosocial factors associated with resilience mitigate the impact of stress on systemic inflammation (97–99).

Less is known about the biology of resilience in older age. How HPA axis function changes with age and relates to resilience in older adults is insufficiently understood (100). Older adults have typically been exposed to a greater number of traumas and losses. For some, the accumulation of traumas may leave them sensitized to future stressors, while for others, a long history of learning how to cope successfully with stress has had a stress-inoculating effect. Successful aging has been linked to greater social connectedness, greater purpose in life, fewer cognitive problems, and better health (101). With age, PFC neurons become less stress resilient owing to a loss of plasticity (102). Reductions in ventrolateral PFC and dorsomedial PFC activation in older adults were found to be associated with lower cognitive reappraisal success at decreasing unpleasant emotions but, surprisingly, greater success at increasing unpleasant emotions (103). These findings might partially explain older adults' greater reliance on acceptance and toleration of negative affect, in contrast to younger adults' greater use of active problem solving (104).

NEUROIMAGING STUDIES

Key interconnected brain regions involved in emotion regulation include the amygdala, hippocampus, ACC, and vmPFC, forming integrated parallel circuits. Subcortical brain regions, including limbic and reward systems, develop earlier than areas of the PFC, which plays a central role in executive function and resilience (49). While extensive neuroimaging research has identified neural abnormalities underpinning PTSD symptomatology (105), studies of particular relevance to resilience are growing in number. These include studies examining neural correlates of psychological traits linked to resilience, studies of high trait resilience, and studies of trauma-exposed resilient individuals.

Among studies of trauma survivors, the definition of resilience and type and timing of adverse life events vary widely. Cross-sectional neuroimaging studies usually define resilience as absence of psychopathology in trauma survivors, and include both symptomatic trauma-exposed and unexposed control groups, essential to disentangling trauma exposure effects. In this review, examples of relevant structural and functional neuroimaging studies are organized by developmental phase.

Studies in Children and Adolescents

Published neuroimaging studies of resilience in children are rare. In a functional magnetic resonance imaging (fMRI) study of urban children and adolescents ranging in adversity exposure, differential dynamic resting-state functional connectivity among key cognitive networks was associated with higher trait resilience, thought to reflect higher top-down control (106). The ongoing longitudinal Families and Childhood Transitions Study of community children, mentioned above, includes structural MRI and fMRI, and will examine how family environment impacts brain development and risk for mental illness in children ranging in adversity exposure (55).

Larger studies of resilience to stressful life events in adolescence, conducted by the IMAGEN Consortium, have been recently published. In these structural MRI studies, resilience, modeled as high adversity with high competence and no mental health problems, was associated with larger gray matter volumes in right prefrontal structures (107) and higher fractional anisotropy in the anterior corpus callosum (108). Of note, while not focused on psychological resilience, a recent fMRI study of over 200 urban youths 12 to 14 years of age is an excellent model for future resilience studies. In this study, higher central executive network resting-state functional connectivity was found to be protective against the impact on cardiometabolic health of living in high-crime neighborhoods (109).

Studies in Adults

We begin with studies examining the neural underpinnings of psychological traits known to be associated with resilience, including cognitive reappraisal and positive emotionality. Widely studied, cognitive reappraisal has been found to engage PFC regions involved in cognitive control (73). Findings suggest that habitual use of cognitive reappraisal as a coping strategy reduces emotional reactivity to negative stimuli. In an fMRI study of healthy women, higher habitual reappraisal was found to correlate with lower amygdala reactivity to fearful and angry faces, as well as higher activation of emotion regulation regions including dorsomedial PFC (110). In another study of university students, habitual reappraisal was associated with higher dorsolateral PFC activation during performance of a

"cold" executive control task, which in turn appeared to buffer the impact of stressful life events on mood and anxiety symptoms (111). Another common characteristic of resilient individuals is positive emotionality, thought to be mediated by reward responsiveness (112,113). Among student volunteers in an fMRI study, for participants with higher (but not lower) reactivity to positive feedback in the ventral striatum, greater recent life stress was not associated with lower positive affect. This illustrates the potential stress-buffering role of hearty reward circuitry responsiveness (114).

Other neuroimaging studies have centered on individuals with high trait resilience, assessed with self-report scales, examining neural responses to negative stimuli. In one study, young adult healthy volunteers with high trait resilience showed faster insula activation recovery when anticipating a possible negative picture that turned out to be neutral, suggesting higher adaptability of emotional circuitry to changing contingencies (115). In another study of trainee firefighters prior to any trauma exposure, higher trait resilience correlated with greater right amygdala and left orbitofrontal cortex activation to a trauma script (116). In this study, higher activation of brain structures important for assessing threat and guiding purposeful behavior in resilient firefighters might reflect greater ability to mobilize "appropriate emotional resources" necessary for adaptive coping (116).

Using a different definition of resilience, other studies have examined neural function in trauma survivors who did not develop psychopathology. To date, few cross-sectional studies have included all three groups—trauma-exposed resilient and symptomatic groups, and an unexposed control group. Studies also differ by trauma timing and type and by neuroimaging method. Intriguing novel findings have come from recent studies in CT survivors. A recent study including both late adolescent and young adult CT survivors examined brain networks with diffusion tensor imaging and tractography. While resilient and symptomatic CT survivors did not differ in global network architecture, resilient survivors demonstrated lower nodal efficiency in the right amygdala and 8 other nodes, suggesting that lower ability of these nodes to communicate with the network might represent a compensatory mechanism underlying resilience (117). Another study of CT survivors in their late 20s to early 30s used fMRI to examine task-based amygdala connectivity while participants viewed emotional faces. Adult adaptive functioning assessed over a range of domains was associated with amygdala connectivity to frontal and parietal regions, irrespective of CT history status (118).

A handful of studies of resilient trauma survivors have focused on trauma types sustained during adulthood. Findings from a well-known structural MRI study of male monozygotic twin pairs in their early 50s, differing by combat exposure and by outcome among those exposed (PTSD vs. resilience), suggest that larger hippocampi might confer resilience to trauma (119). A different MRI study in male veterans found higher resting-state functional connectivity between the rostral ACC and precentral/middle frontal gyrus in the resilient group, compared with both PTSD and unexposed control groups (120). In a small but intriguing fMRI study of reward responses in highly resilient middle-aged Special Forces soldiers, civilian control subjects showed higher activation of reward circuitry regions during anticipation of high versus no reward, but soldiers showed no such difference, suggesting a "sturdy" reward system (121).

To our knowledge, only one neuroimaging study in resilient female sexual assault survivors compared with symptomatic and unexposed control subjects has been published. Unlike paradigms examining passive responses to negative stimuli, study participants were asked to deliberately enhance emotional responses to negative pictures. Resilient assault survivors unexpectedly demonstrated higher ability to deliberately enhance their emotional responses, associated with higher PFC activation (122). The ability to appraise negative contexts accurately is thought to be important for resilience and might involve the capacity to tolerate triggered emotions. In contrast to excessively positive or negative appraisals, accurate appraisal of negative situations is necessary to mount an appropriate response to danger (123).

Finally, emerging longitudinal studies hold special promise for the study of resilience. For example, in a sample of young college students, lower baseline amygdala reactivity to threat was identified as a biomarker of resilience to stressful life events prospectively assessed for at least 1 year (124). In a study of Israeli soldiers using a different, combat-relevant threat-related paradigm, lower amygdala reactivity predeployment predicted lower PTSD symptom levels postdeployment, as did greater increase in hippocampal-vmPFC functional coupling from pre- to postdeployment (125). Of note, greater hippocampal-vmPFC functional coupling had previously been linked to greater extinction recall in healthy volunteers, a capacity thought to promote resilience (126). Findings from a different study of soldiers scanned before and after military service suggest that maintaining a balance between threat and reward responses postexposure supports resilience (127).

In summary, neuroimaging studies of resilience are still limited in number and differ widely in design and focus. Initial findings suggest that lower activation of threat appraisal regions and higher activation of prefrontal regions involved in implicit emotion regulation during automatic threat-processing might support resilience. Resilience also appears to involve higher neural adaptability to changing contingencies and more effective mobilization of neural-emotional resources for adaptive coping. Additionally, effective activation of dorsolateral PFC regions involved in cognitive control and executive function supports emotion regulation. Finally, novel findings suggest that resilience to early trauma might involve compensatory reduced communication between certain nodes (e.g., amygdala) and the network. A growing number of studies in large cohorts, combining multimodal neuroimaging, clinical measures, and genetics (128), should serve as a model for future studies of resilience.

RESILIENCE-ENHANCING INTERVENTIONS

As the brain continues to reorganize throughout the life span, resilience-enhancing interventions can be informed by our evolving knowledge of psychobiological changes at each stage of development (see Table 1).

Psychosocial and Cognitive Interventions

During early childhood, interventions focused on enhancing parenting skills and family stability are critical for high-risk

Table 1. Resilience Throughout the Life Span

Developmental Stage	Emotional Brain	Key Risk Factors	Key Protective Factors	Examples of Resilience-Enhancing Interventions
Childhood	Subcortical development (3,41)	Childhood trauma and neglect Poverty	Solid bond with caregiver (42–48) Family stability (48) Ample resources (132)	Early parenting and family interventions (40,56,129–131) Provision of resources (132)
Adolescence	Subcortical-cortical development (49)	Weaker executive function/ self-control Poor self-efficacy Poor social skills Low parental support	Strong executive function (46,48,109) Self-efficacy (46,48) Positive relationships with peers (50,51) Mastering challenges (52) Family support and stability (40,48) Role models (53)	Family and community interventions (40,56) School-based interventions (133) Positive development programs (133,134) Resiliency programs (135,136)
Adulthood	Cortical development reaches maturity by young adulthood (49)	Poor self-efficacy Weaker executive function Low social support	Emotion regulation capacity, executive function (71,72) Optimism/positive emotions (74–77) Habitual cognitive reappraisal (110,111) Active coping (52) Meaning and purpose (52) Social support (79–81) Role models (52)	Hardiness training (137) Preparedness training (138,139) Cognitive behavioral therapies (52) Attention and cognitive emotional training (140–142)
Older Age	Reduced prefrontal cortex stress resilience (102)	Poor health Impaired cognition Low social support	Intact cognition (101) Acceptance (104) Social support (143,146)	Cognitive remediation (143) Social engagement (143,146) Physical exercise (144,145)

Resilience at each stage is influenced by genetics and gene × environment interactions (see text, Genetics and Genomics of Resilience).

children. Described earlier, RCTs of interventions to enhance parenting quality in poor rural families have demonstrated positive outcomes at multiple phenotypic levels (40,56). In studies of foster children, interventions focused on helping parents recognize children's needs, respond consistently to children's behaviors, and reduce their own frightening responses were found to be associated with improved attachment security and normalization of cortisol patterns in the children (129,130). A family-oriented brief intervention for families experiencing trauma or loss that incorporates three resilience domains—problem-solving, meaning-making, and social support—was found to increase children's prosocial behaviors and decrease distress in both parents and children from military and civilian families (131). Additionally, provision of resources to poor families to promote child development might be most beneficial during early childhood (132).

In adolescence, school- and community-based interventions designed to master challenges unique to this period, including promoting peer relationships, child-adult bonds, self-efficacy. and prosocial behaviors, have shown promising results (133,134). Successful outcomes have included increased resilience and reduced depressive symptoms, substance abuse, and risk-taking behaviors in high-risk youths. The Penn Resiliency Program has been effective in preventing depression and anxiety in adolescents by teaching cognitive reappraisal and enhancing coping strategies and social skills (135,136).

Among resilience intervention studies conducted in adults, interventions aimed at enhancing a person's sense of control, coping skills, and resources can reduce appraisal of stressful situations as threatening, as in hardiness training (137). Preparedness training interventions for first responders and military personnel focus on enhancing coping skills, cognitive reappraisal, and support-seeking (138,139). Well-established cognitive behavioral therapies for anxiety and depression center on practicing cognitive reappraisal. New potential interventions are emerging from our growing understanding of brain circuitry function. Novel computer-based approaches under investigation include attentional bias modification for PTSD prevention (140,141) and cognitive emotional training for the treatment of major depressive disorder (142).

Fewer studies have investigated interventions aimed at promoting successful aging and resilience in older adults. Strategies including physical exercise, cognitive remediation, and social engagement have shown benefits (143). In a recent RCT, sedentary older adults randomized to 8 weeks of yoga showed improved working memory compared with a stretching control condition, mediated by reductions in perceived stress and cortisol responses (144). In another RCT, aerobic exercise training increased hippocampal volume and memory (145). The potential resilience-enhancing effects of age-friendly communities, in which older adults are valued as active participants and provided with necessary support services, deserves to be formally studied (146). Additionally, key questions for translational stress researchers include whether plasticity of prefrontal neurons can be maintained as we age, and whether a "window of plasticity" can be reopened in adulthood and older age (102).

Neurobiological Interventions

Collaborations among translational researchers promise to yield new resilience-enhancing interventions. Investigational pharmacotherapies based on resilience research include intranasal NPY administration for the treatment of PTSD. In a rodent model of PTSD, prophylactic intranasal NPY

administration mitigated the development of PTSD-like symptoms and prevented stressor-induced changes in the locus coeruleus (147,148). In another example of translational research, the identification of a unique molecular adaptation in resilient mice led to a proof-of-concept clinical trial of a KCNQ-type potassium channel opener for depression in humans, with promising effects on depressive symptoms and functional connectivity in brain reward regions (11). Mentioned earlier, the glutamate *N*-methyl-D aspartate receptor antagonist ketamine, shown to increase prefrontal global connectivity in depressed patients (149), has demonstrated efficacy for treatment-resistant depression (93,94) and initial promise for PTSD treatment (95). New research aims to capitalize on ketamine-induced plasticity to enhance the efficacy of psychotherapeutic interventions (150). Further, in animal studies, ketamine was found to reduce learned fear after foot-shock administration and prevent the development of depressive-like symptoms following chronic social defeat stress when administered prophylactically 1 week prior (151).

Other RCTs have administered pharmacologic agents shortly after trauma exposure in attempts at secondary prevention of PTSD in adult samples, including the β-blocker propranolol, with insufficient results to date (152); hydrocortisone (153,154); and intranasal oxytocin (155). Further study of these and other potential secondary prevention and treatment interventions is necessary. Based on knowledge of brain circuitry function, a recent study tested a different type of preventive intervention in healthy soldiers participating in stressful military training. In this study, soldiers learned to reduce amygdala activation with real-time electroencephalography neurofeedback, resulting in improved emotion regulation and increased amygdala-vmPFC connectivity (156). Additional research will determine whether this intervention can enhance resilience after deployment.

CONCLUSIONS

While knowledge of the biology of human resilience is accumulating, the field is still new. Wide differences across studies—in definition and assessment of resilience, study population (including age), design and methods, and trauma type and timing—preclude any firm conclusions. More research is needed, especially studies in children and adolescents including preventive interventions, longitudinal studies, and collaborative studies with large sample sizes. Despite these limitations, a body of knowledge is gradually accumulating on the psychobiology of resilience across developmental cohorts. In particular, a number of innovative intervention studies in high-risk populations have begun to demonstrate the beneficial impact of optimizing timing and type of intervention. These exciting and novel findings, stemming from research collaborations across disciplines, are generating a possible new framework of opportunities for enhancing resilience across the life span.

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DSC is a named co-inventor on patents filed by the Icahn School of Medicine at Mount Sinai (ISMMS) relating to the treatment for treatment-resistant depression, suicidal ideation, and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc., and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), DSC is entitled to a portion of the payments received by the ISMMS. As SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, DSC, will be entitled to additional payments, beyond those already received, under the license agreement. DSC is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. ISMMS has entered into a licensing agreement with Click Therapeutics, Inc., and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, DSC has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. DSC is a named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered neuropeptide Y for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. DSC and AF are named co-inventors on a patent application in the United States, and several issued patents outside the United States filed by the ISMMS related to the use of ketamine for the treatment of posttraumatic stress disorder. This intellectual property has not been licensed. SMS and DSC have received royalties from a book published by Cambridge University Press, *Resilience: The Science of Mastering Life's Greatest Challenges*. SF-T reports no biomedical financial interests or potential conflicts of interest.

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REFERENCES

1. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R (2014): Resilience definitions, theory, and challenges: Interdisciplinary perspectives. Eur J Psychotraumatol 5:25338.
2. Gee DG, Casey BJ (2015): The impact of developmental timing for stress and recovery. Neurobiol Stress 1:184–194.
3. VanTieghem MR, Tottenham N (2018): Neurobiological programming of early life stress: Functional development of amygdala-prefrontal circuitry and vulnerability for stress-related psychopathology. Curr Top Behav Neurosci 38:117–136.
4. Hobfoll SE, Mancini AD, Hall BJ, Canetti D, Bonanno GA (2011): The limits of resilience: Distress following chronic political violence among Palestinians. Soc Sci Med 72:1400–1408.
5. Masten AS (2014): Ordinary Magic: Resilience in Development. New York: The Guilford Press.
6. Burns SB, Szyszkowicz JK, Luheshi GN, Lutz PE, Turecki G (2018): Plasticity of the epigenome during early-life stress. Semin Cell Dev Biol 77:115–132.
7. Kessler RC, McLaughlin KA, Koenen KC, Petukhova M, Hill ED, Consortium WHOWMHS (2012): The importance of secondary trauma exposure for post-disaster mental disorder. Epidemiol Psychiatr Sci 21:35–45.

8. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, *et al.* (2010): Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 67:113–123.
9. Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, *et al.* (2014): Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 344: 313–319.
10. Friedman AK, Juarez B, Ku SM, Zhang H, Calizo RC, Walsh JJ, *et al.* (2016): KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. Nat Commun 7:11671.
11. Tan A, Costi S, Morris LS, Van Dam NT, Kautz M, Whitton AE, *et al.* (2018): Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder [published online ahead of print Nov 1]. Mol Psychiatry.
12. Amstadter AB, Myers JM, Kendler KS (2014): Psychiatric resilience: Longitudinal twin study. Br J Psychiatry 205:275–280.
13. Wolf EJ, Miller MW, Sullivan DR, Amstadter AB, Mitchell KS, Goldberg J, *et al.* (2018): A classical twin study of PTSD symptoms and resilience: Evidence for a single spectrum of vulnerability to traumatic stress. Depress Anxiety 35:132–139.
14. Rushton JP (2004): Genetic and environmental contributions to prosocial attitudes: A twin study of social responsibility. Proc Biol Sci 271:2583–2585.
15. Neumeister A, Charney DS, Belfer I, Geraci M, Holmes C, Sharabi Y, *et al.* (2005): Sympathoneural and adrenomedullary functional effects of alpha2C-adrenoreceptor gene polymorphism in healthy humans. Pharmacogenet Genomics 15:143–149.
16. Zhou Z, Zhu G, Hariri AR, Enoch MA, Scott D, Sinha R, *et al.* (2008): Genetic variation in human NPY expression affects stress response and emotion. Nature 452:997–1001.
17. Cicchetti D, Rogosch FA (2012): Gene x Environment interaction and resilience: Effects of child maltreatment and serotonin, corticotropin releasing hormone, dopamine, and oxytocin genes. Dev Psychopathol 24:411–427.
18. Cicchetti D, Rogosch FA, Sturge-Apple ML (2007): Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds. Dev Psychopathol 19:1161–1180.
19. Malhi GS, Das P, Outhred T, Dobson-Stone C, Irwin L, Gessler D, *et al.* (2019): Effect of stress gene-by-environment interactions on hippocampal volumes and cortisol secretion in adolescent girls. Aust N Z J Psychiatry 53:316–325.
20. Liberzon I, King AP, Ressler KJ, Almli LM, Zhang P, Ma ST, *et al.* (2014): Interaction of the ADRB2 gene polymorphism with childhood trauma in predicting adult symptoms of posttraumatic stress disorder. JAMA Psychiatry 71:1174–1182.
21. Rana BK, Darst BF, Bloss C, Shih PA, Depp C, Nievergelt CM, *et al.* (2014): Candidate SNP associations of optimism and resilience in older adults: Exploratory study of 935 community-dwelling adults. Am J Geriatr Psychiatry 22:997–1006.e5.
22. Belsky J (2016): The differential susceptibility hypothesis: Sensitivity to the environment for better and for worse. JAMA Pediatr 170: 321–322.
23. Belsky J, Hartman S (2014): Gene-environment interaction in evolutionary perspective: Differential susceptibility to environmental influences. World Psychiatry 13:87–89.
24. Hankin BL, Nederhof E, Oppenheimer CW, Jenness J, Young JF, Abela JR, *et al.* (2011): Differential susceptibility in youth: Evidence that 5-HTTLPR x positive parenting is associated with positive affect 'for better and worse. Transl Psychiatry 1:e44.
25. Borelli JL, Smiley PA, Rasmussen HF, Gomez A, Seaman LC, Nurmi EL (2017): Interactive effects of attachment and FKBP5 genotype on school-aged children's emotion regulation and depressive symptoms. Behav Brain Res 325:278–289.
26. Albert D, Belsky DW, Crowley DM, Latendresse SJ, Aliev F, Riley B, *et al.* (2015): Can genetics predict response to complex behavioral interventions? Evidence from a genetic analysis of the fast track randomized control trial. J Policy Anal Manage 34:497–518.
27. Brody GH, Yu T, Beach SR (2015): A differential susceptibility analysis reveals the "who and how" about adolescents' responses to preventive interventions: Tests of first- and second-generation Gene x Intervention hypotheses. Dev Psychopathol 27:37–49.
28. Brody GH, Chen YF, Beach SR (2013): Differential susceptibility to prevention: GABAergic, dopaminergic, and multilocus effects. J Child Psychol Psychiatry 54:863–871.
29. Stein MB, Choi KW, Jain S, Campbell-Sills L, Chen CY, Gelernter J, *et al.* (2019): Genome-wide analyses of psychological resilience in U. S. Army soldiers. Am J Med Genet B Neuropsychiat Gent 180: 310–319.
30. Day FR, Ong KK, Perry JRB (2018): Elucidating the genetic basis of social interaction and isolation. Nat Commun 9:2457.
31. Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, *et al.* (2016): Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 48:624–633.
32. Janowitz D, Schwahn C, Borchardt U, Wittfeld K, Schulz A, Barnow S, *et al.* (2014): Genetic, psychosocial and clinical factors associated with hippocampal volume in the general population. Transl Psychiatry 4:e465.
33. Klengel T, Binder EB (2015): FKBP5 allele-specific epigenetic modification in gene by environment interaction. Neuropsychopharmacology 40:244–246.
34. Kaufman J, Wymbs NF, Montalvo-Ortiz JL, Orr C, Albaugh MD, Althoff R, *et al.* (2018): Methylation in OTX2 and related genes, maltreatment, and depression in children. Neuropsychopharmacology 43:2204–2211.
35. van Bodegom M, Homberg JR, Henckens M (2017): Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. Front Cell Neurosci 11:87.
36. Teicher MH, Samson JA (2016): Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry 57:241–266.
37. Callaghan BL, Tottenham N (2016): The stress acceleration hypothesis: Effects of early-life adversity on emotion circuits and behavior. Curr Opin Behav Sci 7:76–81.
38. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, *et al.* (2013): Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 110:15638–15643.
39. Fareri DS, Gabard-Durnam L, Goff B, Flannery J, Gee DG, Lumian DS, *et al.* (2017): Altered ventral striatal-medial prefrontal cortex resting-state connectivity mediates adolescent social problems after early institutional care. Dev Psychopathol 29:1865–1876.
40. Brody GH, Yu T, Beach SR (2016): Resilience to adversity and the early origins of disease. Dev Psychopathol 28:1347–1365.
41. Tottenham N (2014): The importance of early experiences for neuro-affective development. Curr Top Behav Neurosci 16:109–129.
42. Bosquet Enlow M, King L, Schreier HM, Howard JM, Rosenfield D, Ritz T, *et al.* (2014): Maternal sensitivity and infant autonomic and endocrine stress responses. Early Hum Dev 90:377–385.
43. Gunnar MR, Hostinar CE (2015): The social buffering of the hypothalamic-pituitary-adrenocortical axis in humans: Developmental and experiential determinants. Soc Neurosci 10:479–488.
44. Kopala-Sibley DC, Cyr M, Finsaas MC, Orawe J, Huang A, Tottenham N, Klein DN (2018): Early childhood parenting predicts late childhood brain functional connectivity during emotion perception and reward processing [published online ahead of print Aug 13]. Child Dev.
45. van Rooij SJ, Cross D, Stevens JS, Vance LA, Kim YJ, Bradley B, *et al.* (2017): Maternal buffering of fear-potentiated startle in children and adolescents with trauma exposure. Soc Neurosci 12:22–31.
46. Sapienza JK, Masten AS (2011): Understanding and promoting resilience in children and youth. Curr Opin Psychiatry 24:267–273.

47. Lind MJ, Brown RC, Sheerin CM, York TP, Myers JM, Kendler KS, *et al.* (2018): Does parenting influence the enduring impact of severe childhood sexual abuse on psychiatric resilience in adulthood? Child Psychiatry Hum Dev 49:33–41.
48. Afifi TO, Macmillan HL (2011): Resilience following child maltreatment: A review of protective factors. Can J Psychiatry 56:266–272.
49. Casey BJ, Heller AS, Gee DG, Cohen AO (2019): Development of the emotional brain. Neurosci Lett 693:29–34.
50. van Harmelen AL, Kievit RA, Ioannidis K, Neufeld S, Jones PB, Bullmore E, *et al.* (2017): Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. Psychol Med 47:2312–2322.
51. Lamblin M, Murawski C, Whittle S, Fornito A (2017): Social connectedness, mental health and the adolescent brain. Neurosci Biobehav Rev 80:57–68.
52. Southwick SM, Charney DS (2018): Resilience: The Science of Mastering Life's Greatest Challenges, 2nd ed. New York: Cambridge University Press.
53. Yancey AK, Grant D, Kurosky S, Kravitz-Wirtz N, Mistry R (2011): Role modeling, risk, and resilience in California adolescents. J Adolesc Health 48:36–43.
54. Cicchetti D, Rogosch FA (2007): Personality, adrenal steroid hormones, and resilience in maltreated children: A multilevel perspective. Dev Psychopathol 19:787–809.
55. Simmons JG, Schwartz OS, Bray K, Deane C, Pozzi E, Richmond S, *et al.* (2017): Study protocol: Families and Childhood Transitions Study (FACTS) - a longitudinal investigation of the role of the family environment in brain development and risk for mental health disorders in community based children. BMC Pediatr 17:153.
56. Brody GH, Gray JC, Yu T, Barton AW, Beach SR, Galvan A, *et al.* (2017): Protective prevention effects on the association of poverty with brain development. JAMA Pediatr 171:46–52.
57. Seligman ME, Maier SF (1967): Failure to escape traumatic shock. J Exp Psychol 74:1–9.
58. Maier SF, Watkins LR (2005): Stressor controllability and learned helplessness: The roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci Biobehav Rev 29:829–841.
59. Lippmann M, Bress A, Nemeroff CB, Plotsky PM, Monteggia LM (2007): Long-term behavioural and molecular alterations associated with maternal separation in rats. Eur J Neurosci 25:3091–3098.
60. Lyons DM, Parker KJ, Schatzberg AF (2010): Animal models of early life stress: Implications for understanding resilience. Dev Psychobiol 52:616–624.
61. Gustafsson PE, Anckarsater H, Lichtenstein P, Nelson N, Gustafsson PA (2010): Does quantity have a quality all its own? Cumulative adversity and up- and down-regulation of circadian salivary cortisol levels in healthy children. Psychoneuroendocrinology 35:1410–1415.
62. Seery MD, Holman EA, Silver RC (2010): Whatever does not kill us: Cumulative lifetime adversity, vulnerability, and resilience. J Pers Soc Psychol 99:1025–1041.
63. Edge MD, Ramel W, Drabant EM, Kuo JR, Parker KJ, Gross JJ (2009): For better or worse? Stress inoculation effects for implicit but not explicit anxiety. Depress Anxiety 26:831–837.
64. Seery MD, Leo RJ, Lupien SP, Kondrak CL, Almonte JL (2013): An upside to adversity?: Moderate cumulative lifetime adversity is associated with resilient responses in the face of controlled stressors. Psychol Sci 24:1181–1189.
65. Southwick SM, Charney DS (2012): The science of resilience: Implications for the prevention and treatment of depression. Science 338:79–82.
66. Horn SR, Feder A (2018): Understanding resilience and preventing and treating PTSD. Harv Rev Psychiatry 26:158–174.
67. Isaacs K, Mota NP, Tsai J, Harpaz-Rotem I, Cook JM, Kirwin PD, *et al.* (2017): Psychological resilience in U.S. military veterans: A 2-year, nationally representative prospective cohort study. J Psychiatr Res 84:301–309.
68. Shen YC, Arkes J, Lester PB (2017): Association between baseline psychological attributes and mental health outcomes after soldiers returned from deployment. BMC Psychol 5:32.
69. Bridgett DJ, Oddi KB, Laake LM, Murdock KW, Bachmann MN (2013): Integrating and differentiating aspects of self-regulation: Effortful control, executive functioning, and links to negative affectivity. Emotion 13:47–63.
70. Etkin A, Buchel C, Gross JJ (2015): The neural bases of emotion regulation. Nat Rev Neurosci 16:693–700.
71. Genet JJ, Siemer M (2011): Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. Cogn Emot 25:380–388.
72. Kent M, Rivers CT, Wrenn G (2015): Goal-directed resilience in training (GRIT): A biopsychosocial model of self-regulation, executive functions, and personal growth (eudaimonia) in evocative contexts of PTSD, obesity, and chronic pain. Behav Sci (Basel) 5:264–304.
73. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, *et al.* (2014): Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. Cereb Cortex 24:2981–2990.
74. Bar M (2009): A cognitive neuroscience hypothesis of mood and depression. Trends Cogn Sci 13:456–463.
75. Ong AD, Bergeman CS, Bisconti TL, Wallace KA (2006): Psychological resilience, positive emotions, and successful adaptation to stress in later life. J Pers Soc Psychol 91:730–749.
76. Carver CS, Scheier MF (2014): Dispositional optimism. Trends Cogn Sci 18:293–299.
77. Sharot T, Riccardi AM, Raio CM, Phelps EA (2007): Neural mechanisms mediating optimism bias. Nature 450:102–105.
78. Boyce WT, Chesterman E (1990): Life events, social support, and cardiovascular reactivity in adolescence. J Dev Behav Pediatr 11:105–111.
79. Pietrzak RH, Feder A, Singh R, Schechter CB, Bromet EJ, Katz CL, *et al.* (2014): Trajectories of PTSD risk and resilience in World Trade Center responders: An 8-year prospective cohort study. Psychol Med 44:205–219.
80. Pietrzak RH, Cook JM (2013): Psychological resilience in older U.S. veterans: Results from the national health and resilience in veterans study. Depress Anxiety 30:432–443.
81. Machisa MT, Christofides N, Jewkes R (2018): Social support factors associated with psychological resilience among women survivors of intimate partner violence in Gauteng, South Africa. Glob Health Action 11:1491114.
82. Averill LA, Averill CL, Kelmendi B, Abdallah CG, Southwick SM (2018): Stress response modulation underlying the psychobiology of resilience. Curr Psychiatry Rep 20:27.
83. Feder A, Nestler EJ, Charney DS (2009): Psychobiology and molecular genetics of resilience. Nat Rev Neurosci 10:446–457.
84. Tugade MM, Fredrickson BL (2004): Resilient individuals use positive emotions to bounce back from negative emotional experiences. J Pers Soc Psychol 86:320–333.
85. Southwick SM, Morgan CA 3rd, Bremner AD, Grillon CG, Krystal JH, Nagy LM, *et al.* (1997): Noradrenergic alterations in posttraumatic stress disorder. Ann N Y Acad Sci 821:125–141.
86. Daskalakis NP, Lehrner A, Yehuda R (2013): Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. Endocrinol Metab Clin North Am 42:503–513.
87. Greenwood BN (2019): The role of dopamine in overcoming aversion with exercise. Brain Res 1713:102–108.
88. Hill MN, Lee FS (2016): Endocannabinoids and stress resilience: Is deficiency sufficient to promote vulnerability? Biol Psychiatry 79:792–793.
89. Worley NB, Hill MN, Christianson JP (2018): Prefrontal endocannabinoids, stress controllability and resilience: A hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 85:180–188.
90. Morgan CA 3rd, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, *et al.* (2000): Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biol Psychiatry 47:902–909.
91. Lee JC, Wang LP, Tsien JZ (2016): Dopamine rebound-excitation theory: Putting brakes on PTSD. Front Psychiatry 7:163.
92. Duman RS (2014): Neurobiology of stress, depression, and rapid acting antidepressants: Remodeling synaptic connections. Depress Anxiety 31:291–296.

93. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV (2015): The promise of ketamine for treatment-resistant depression: Current evidence and future directions. Ann N Y Acad Sci 1345: 47–58.
94. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, *et al.* (2018): Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry 75:139–148.
95. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, *et al.* (2014): Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. JAMA Psychiatry 71:681–688.
96. Teche SP, Rovaris DL, Aguiar BW, Hauck S, Vitola ES, Bau CHD, *et al.* (2017): Resilience to traumatic events related to urban violence and increased IL10 serum levels. Psychiatry Res 250:136–140.
97. Stellar JE, John-Henderson N, Anderson CL, Gordon AM, McNeil GD, Keltner D (2015): Positive affect and markers of inflammation: Discrete positive emotions predict lower levels of inflammatory cytokines. Emotion 15:129–133.
98. Gouin JP, Caldwell W, Woods R, Malarkey WB (2017): Resilience resources moderate the association of adverse childhood experiences with adulthood inflammation. Ann Behav Med 51:782–786.
99. Elliot AJ, Mooney CJ, Infurna FJ, Chapman BP (2017): Associations of lifetime trauma and chronic stress with C-reactive protein in adults ages 50 years and older: Examining the moderating role of perceived control. Psychosom Med 79:622–630.
100. Gaffey AE, Bergeman CS, Clark LA, Wirth MM (2016): Aging and the HPA axis: Stress and resilience in older adults. Neurosci Biobehav Rev 68:928–945.
101. Depp C, Vahia IV, Jeste D (2010): Successful aging: Focus on cognitive and emotional health. Annu Rev Clin Psychol 6:527–550.
102. McEwen BS, Morrison JH (2013): The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79:16–29.
103. Opitz PC, Rauch LC, Terry DP, Urry HL (2012): Prefrontal mediation of age differences in cognitive reappraisal. Neurobiol Aging 33: 645–655.
104. Lamond AJ, Depp CA, Allison M, Langer R, Reichstadt J, Moore DJ, *et al.* (2008): Measurement and predictors of resilience among community-dwelling older women. J Psychiatr Res 43:148–154.
105. Akiki TJ, Averill CL, Abdallah CG (2017): A network-based neurobiological model of PTSD: Evidence from structural and functional neuroimaging studies. Curr Psychiatry Rep 19:81.
106. Iadipaolo AS, Marusak HA, Paulisin SM, Sala-Hamrick K, Crespo LM, Elrahal F, *et al.* (2018): Distinct neural correlates of trait resilience within core neurocognitive networks in at-risk children and adolescents. Neuroimage Clin 20:24–34.
107. Burt KB, Whelan R, Conrod PJ, Banaschewski T, Barker GJ, Bokde AL, *et al.* (2016): Structural brain correlates of adolescent resilience. J Child Psychol Psychiatry 57:1287–1296.
108. Galinowski A, Miranda R, Lemaitre H, Paillere Martinot ML, Artiges E, Vulser H, *et al.* (2015): Resilience and corpus callosum microstructure in adolescence. Psychol Med 45:2285–2294.
109. Miller GE, Chen E, Armstrong CC, Carroll AL, Ozturk S, Rydland KJ, *et al.* (2018): Functional connectivity in central executive network protects youth against cardiometabolic risks linked with neighborhood violence. Proc Natl Acad Sci U S A 115:12063–12068.
110. Drabant EM, McRae K, Manuck SB, Hariri AR, Gross JJ (2009): Individual differences in typical reappraisal use predict amygdala and prefrontal responses. Biol Psychiatry 65:367–373.
111. Scult MA, Knodt AR, Swartz JR, Brigidi BD, Hariri AR (2017): Thinking and feeling: Individual differences in habitual emotion regulation and stress-related mood are associated with prefrontal executive control. Clin Psychol Sci 5:150–157.
112. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, *et al.* (2009): Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry 166:64–73.
113. Corral-Frias NS, Nadel L, Fellous JM, Jacobs WJ (2016): Behavioral and self-reported sensitivity to reward are linked to stress-related differences in positive affect. Psychoneuroendocrinology 66: 205–213.
114. Nikolova YS, Bogdan R, Brigidi BD, Hariri AR (2012): Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. Biol Psychiatry 72:157–163.
115. Waugh CE, Wager TD, Fredrickson BL, Noll DC, Taylor SF (2008): The neural correlates of trait resilience when anticipating and recovering from threat. Soc Cogn Affect Neurosci 3:322–332.
116. Reynaud E, Guedj E, Souville M, Trousselard M, Zendjidjian X, El Khoury-Malhame M, *et al.* (2013): Relationship between emotional experience and resilience: An fMRI study in fire-fighters. Neuropsychologia 51:845–849.
117. Ohashi K, Anderson CM, Bolger EA, Khan A, McGreenery CE, Teicher MH (2019): Susceptibility or resilience to maltreatment can be explained by specific differences in brain network architecture. Biol Psychiatry 85:690–702.
118. Demers LA, McKenzie KJ, Hunt RH, Cicchetti D, Cowell RA, Rogosch FA, *et al.* (2018): Separable effects of childhood maltreatment and adult adaptive functioning on amygdala connectivity during emotion processing. Biol Psychiatry Cogn Neurosci Neuroimaging 3:116–124.
119. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, *et al.* (2002): Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242–1247.
120. Kennis M, Rademaker AR, van Rooij SJ, Kahn RS, Geuze E (2015): Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. Hum Brain Mapp 36:99–109.
121. Vythilingam M, Nelson EE, Scaramozza M, Waldeck T, Hazlett G, Southwick SM, *et al.* (2009): Reward circuitry in resilience to severe trauma: An fMRI investigation of resilient special forces soldiers. Psychiatry Res 172:75–77.
122. New AS, Fan J, Murrough JW, Liu X, Liebman RE, Guise KG, *et al.* (2009): A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. Biol Psychiatry 66:656–664.
123. Southwick SM, Pietrzak RH, Charney DS, Krystal JH (2015): Resilience: The role of accurate appraisal, thresholds, and socio-environmental factors. Behav Brain Sci 38:e122.
124. Swartz JR, Knodt AR, Radtke SR, Hariri AR (2015): A neural biomarker of psychological vulnerability to future life stress. Neuron 85:505–511.
125. Admon R, Lubin G, Stern O, Rosenberg K, Sela L, Ben-Ami H, *et al.* (2009): Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci U S A 106:14120–14125.
126. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007): Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 62:446–454.
127. Admon R, Lubin G, Rosenblatt JD, Stern O, Kahn I, Assaf M, *et al.* (2013): Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. Cereb Cortex 23:28–35.
128. Satterthwaite TD, Connolly JJ, Ruparel K, Calkins ME, Jackson C, Elliott MA, *et al.* (2016): The Philadelphia Neurodevelopmental Cohort: A publicly available resource for the study of normal and abnormal brain development in youth. Neuroimage 124:1115–1119.
129. Fisher PA, Gunnar MR, Dozier M, Bruce J, Pears KC (2006): Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. Ann N Y Acad Sci 1094:215–225.
130. Dozier M, Peloso E, Lindhiem O, Gordon MK, Manni M, Sepulveda S, *et al.* (2006): Preliminary evidence from a randomized clinical trial: Intervention effects on foster children's behavioral and biological regulation. J Soc Issues 62:767–785.
131. Saltzman WR (2016): The FOCUS Family Resilience Program: An innovative family intervention for trauma and loss. Fam Process 55:647–659.

132. Duncan GJ, Magnuson K, Votruba-Drzal E (2014): Boosting family income to promote child development. Future Child 24:99–120.
133. Lerner RM, Lerner JV, Almerigi JB, Theokas C, Phelps E, Gestsdottir S, *et al.* (2005): Positive youth development, participation in community youth development programs, and community contributions of fifth grade adolescents: Findings from the First Wave of the 4-H Study of Positive Youth Development. J Early Adolesc 25: 17–71.
134. Brown EC, Graham JW, Hawkins JD, Arthur MW, Baldwin MM, Oesterle S, *et al.* (2009): Design and analysis of the Community Youth Development Study longitudinal cohort sample. Eval Rev 33:311–334.
135. Gillham JE, Hamilton J, Freres DR, Patton K, Gallop R (2006): Preventing depression among early adolescents in the primary care setting: A randomized controlled study of the Penn Resiliency Program. J Abnorm Child Psychol 34:203–219.
136. Cutuli JJ, Chaplin TM, Gillham JE, Reivich KJ, Seligman ME (2006): Preventing co-occurring depression symptoms in adolescents with conduct problems: The Penn Resiliency Program. Ann N Y Acad Sci 1094:282–286.
137. Escolas SM, Pitts BL, Safer MA, Bartone PT (2013): The protective value of hardiness on military posttraumatic stress symptoms. Mil Psychol 25:116–123.
138. Hourani L, Tueller S, Kizakevich P, Lewis G, Strange L, Weimer B, *et al.* (2016): Toward preventing post-traumatic stress disorder: Development and testing of a pilot predeployment stress inoculation training program. Mil Med 181:1151–1160.
139. Skeffington PM, Rees CS, Mazzucchelli TG, Kane RT (2016): The primary prevention of PTSD in firefighters: Preliminary results of an RCT with 12-month follow-up. PLoS One 11: e0155873.
140. Wald I, Fruchter E, Ginat K, Stolin E, Dagan D, Bliese PD, *et al.* (2016): Selective prevention of combat-related post-traumatic stress disorder using attention bias modification training: A randomized controlled trial. Psychol Med 46:2627–2636.
141. Wald I, Bitton S, Levi O, Zusmanovich S, Fruchter E, Ginat K, *et al.* (2017): Acute delivery of attention bias modification training (ABMT) moderates the association between combat exposure and posttraumatic symptoms: A feasibility study. Biol Psychol 122: 93–97.
142. Iacoviello BM, Wu G, Alvarez E, Huryk K, Collins KA, Murrough JW, *et al.* (2014): Cognitive-emotional training as an intervention for major depressive disorder. Depress Anxiety 31:699–706.
143. Harmell AL, Jeste D, Depp C (2014): Strategies for successful aging: A research update. Curr Psychiatry Rep 16:476.
144. Gothe NP, Keswani RK, McAuley E (2016): Yoga practice improves executive function by attenuating stress levels. Biol Psychol 121:109–116.
145. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, *et al.* (2011): Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 108:3017–3022.
146. Jeste DV, Blazer DG 2nd, Buckwalter KC, Cassidy KK, Fishman L, Gwyther LP, *et al.* (2016): Age-friendly communities initiative: Public health approach to promoting successful aging. Am J Geriatr Psychiatry 24:1158–1170.
147. Sabban EL, Laukova M, Alaluf LG, Olsson E, Serova LI (2015): Locus coeruleus response to single-prolonged stress and early intervention with intranasal neuropeptide Y. J Neurochem 135:975–986.
148. Sabban EL, Alaluf LG, Serova LI (2016): Potential of neuropeptide Y for preventing or treating post-traumatic stress disorder. Neuropeptides 56:19–24.
149. Abdallah CG, Dutta A, Averill CL, McKie S, Akiki TJ, Averill LA, *et al.* (2018): Ketamine, but not the NMDAR antagonist lanicemine, increases prefrontal global connectivity in depressed patients. Chronic Stress (Thousand Oaks) 2:2470547018796102.
150. Wilkinson ST, Wright D, Fasula MK, Fenton L, Griepp M, Ostroff RB, *et al.* (2017): Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. Psychother Psychosom 86:162–167.
151. Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C, *et al.* (2016): Ketamine as a prophylactic against stress-induced depressive-like behavior. Biol Psychiatry 79:776–786.
152. Argolo FC, Cavalcanti-Ribeiro P, Netto LR, Quarantini LC (2015): Prevention of posttraumatic stress disorder with propranolol: A meta-analytic review. J Psychosom Res 79:89–93.
153. Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, *et al.* (2011): High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: Interplay between clinical and animal studies. Eur Neuropsychopharmacol 21:796–809.
154. Delahanty DL, Gabert-Quillen C, Ostrowski SA, Nugent NR, Fischer B, Morris A, *et al.* (2013): The efficacy of initial hydrocortisone administration at preventing posttraumatic distress in adult trauma patients: A randomized trial. CNS Spectr 18:103–111.
155. van Zuiden M, Frijling JL, Nawijn L, Koch SBJ, Goslings JC, Luitse JS, *et al.* (2017): Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: A randomized controlled trial in emergency department patients. Biol Psychiatry 81:1030–1040.
156. Keynan JN, Cohen A, Jackont G, Green N, Goldway N, Davidov A, *et al.* (2019): Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. Nat Hum Behav 3:63–73.