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The Science of Resilience: Implications for the Prevention and Treatment of Depression

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Despite these important new leads, there is unfortunately still no consensus about a bona fide genetic mouse model of depression, with a well-replicated, multifaceted phenotype and strong pharmacological validity, at par, for instance, with those used for the study neurodegenerative disorders. This could reflect the unique complexities of MDD etiology and phenomenology, but may also derive, to a certain extent, from our lack of concerted efforts to homogenize behavioral paradigms and methodologies across laboratories. This is a likely cause for the frequent lack of replication of Gene × Environment effects and an issue that will become increasingly important as studies of epigenetic mechanisms in models of depression become more common (*59*). Another critical lack of consensus is related to the time course of antidepressant responses in animal models: Although a delayed response requiring weeks of treatment might simulate the clinical effects of current antidepressants, this question needs reconsideration given the emergence of the potential fast and long-lasting antidepressant effects of ketamine and derivatives (*14*). There is a need to determine how the doses of drugs administered to animals relate to their clinical effects for future discoveries, because brain or blood levels of drugs necessary for the engagement of target effects are rarely reported in animal studies. Although a large number of patients remain resistant to current treatments, there is little consensus on how to develop animal models for these subpopulations.

Conclusion

Neuroscience may not hold all the keys to a public health issue as complex as depression. However, the tremendous advances made over the past few decades continue to hold the promise that a better understanding may ultimately ease suffering and erase stigma. Animal models are pivotal in this effort to translate basic progress into better care. The brief overview proposed here suggests that, although it seems unlikely that any one model will ever recapitulate this heterogeneous illness in its entirety, many current paradigms are yielding key neurobiological insights relevant to behavioral dimensions and affective constructs in humans. A challenge remains to understand how these dimensions integrate in the context of pathology. A second challenge will be to effectively align variables measured in animals with those assessed in genetic studies or during the various phases of development of novel antidepressants. Translational medicine is a two-way bridge. Preclinical research needs to inform clinical trials and diagnosis, but the reverse is also true. Without a consensus about what depression is and how to more reliably and specifically measure it, rapid progress seems unlikely. Thus, it is critical to keep in mind the conceptual, methodological, and organizational factors that cause the field of depression therapeutics to remain at least one step behind in the pursuit of valid animal models.

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PERSPECTIVE

The Science of Resilience: Implications for the Prevention and Treatment of Depression

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Human responses to stress and trauma vary widely. Some people develop trauma-related psychological disorders, such as posttraumatic stress disorder (PTSD) and depression; others develop mild to moderate psychological symptoms that resolve rapidly; still others report no new psychological symptoms in response to traumatic stress. Individual variability in how animals and humans respond to stress and trauma depends on numerous genetic, developmental, cognitive, psychological, and neurobiological risk and protective factors.

Resilience to stress is a complex multidimensional construct. Although there is no one universally accepted definition of resilience, it is generally understood as the ability to bounce back from hardship and trauma. The American Psychological Association defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of threat" (*1*).

Genetic factors play an important role in an individual's response to stress and trauma (*2*). Twin studies have estimated an overall heritability of posttraumatic stress disorder (PTSD) ranging from 32 to 38%, and DNA studies have found that regulation of the stress response is affected by genetically mediated differences in reactivity of the sympathetic nervous system (SNS) (e.g., polymorphism of the alpha-2C adrenergic receptor gene), the hypothalamic-pituitary-adrenal axis (HPA axis) [e.g., functional variants of brain mineralocorticoid, glucocorticoid and corticotropin-releasing hormone (CRH) receptor genes], neuropeptide Y (NPY), and the serotonin system, among others.

The best-studied gene-environment interaction involves a naturally occurring variation in the promoter of the human serotonin transporter gene (*5-HTTLPR*) (*3*, *4*). The short allele of *5-HTTLPR* and a single base substitution in the long form of *5-HTTLPR* are associated with decreased serotonin transporter availability and a resulting lower reuptake of serotonin from synaptic clefts. It appears that these lower-expressing alleles may be specifically associated with an increased risk of depression following exposure to childhood maltreatment (*5*). It has been proposed that the mechanism underlying the gene-environment interaction between the serotonin transporter gene and stress may involve alteration in the critical amygdala–ventromedial prefrontal cortex (PFC) and dorsal raphe circuitry that is similar to that observed in depressed patients (*6*).

Developmental risk and protective factors have an enormous impact on brain development and on shaping neural circuits that regulate future responses to stress and adversity. Repeated episodes of uncontrollable or overwhelming stress during infancy and childhood, such as child abuse, can lead to "learned helplessness" and can cause exaggerated emotional, behavioral, SNS, and HPA-axis responsiveness to future stressors, even into adulthood (*2*, *7*, *8*).

On the other hand, mild-to-moderate stressors that are controlled and mastered can have a "steeling" or stress-inoculating effect, where the child develops an adaptive stress response and becomes more resilient than normal to the negative effects of future stressors. In animal studies, early experiences with successful behavioral control over stressful events induce neuroplasticity in the PFC, which appears to protect the animal from some of the negative effects of future uncontrollable stress. An enriched environment and consistency of supportive maternal care provide an atmosphere that fosters exposure to novelty and the mastering of challenges. Negative and positive neurobiological and behavioral consequences of parental care can even be transmitted across generations, possibly through epigenetic mechanisms (*9*).

In addition to genetic and developmental factors, numerous neurobiological factors and systems mediate and/or moderate resilience to stress, including an HPA axis that is well modulated by dehydroepiandrosterone, NPY, and other regulators of CRH activity; a SNS that responds effectively to stress and provocation, but that returns to baseline rapidly secondary to regulation by NPY and galanin; a mesocorticolimbic dopaminergic-mediated reward system that is durable and that maintains positive emotions and/or optimism in the face of acute and chronic stress; functional hippocampi that adequately inhibit the HPA-axis response to stress and that have the ability to differentiate dangerous versus safe environments; robust PFC executive functioning and capacity to inhibit and regulate limbic, emotional, and behavioral reactivity to stress; and well-modulated amygdala activity that does not over- or underreact to external or internal stimuli (*2*).

Psychosocial factors that have been associated with resilience include positive emotion and optimism, loving caretakers and sturdy role models, a history of mastering challenges, cognitive flexibility including the ability to cognitively reframe adversity in a more positive light, the ability to regulate emotions, high coping self-efficacy, strong social support, disciplined focus on skill development, altruism, commitment to a valued cause or purpose, capacity to extract meaning from adverse situations, support from religion and spirituality, attention to health and good cardiovascular fitness, and the capacity to rapidly recover from stress (*10*).

Utilization of these resilience-promoting factors can be beneficial throughout the life span. Most research has shown that older adults tend to be more stress-resilient than younger adults. Potential contributing factors include prior experience with trauma and stress inoculation, more mature and effective coping styles, greater acceptance of and tolerance for negative affect, and better regulation of emotions. In older adults, resilience has been associated with social connectedness, curiosity, spiritual grounding, and wisdom (*11*).

Resilience-Informed Strategies and Interventions for Prevention and Treatment of Depression

How can what we currently know about resilience be applied to the prevention and treatment of depression? There are several areas that have been studied.

Genetics and environment. Research in genetics and epigentics suggests that putative vulnerability genes or "risk alleles" operate in a dynamic interplay with the environment and that resilience may be promoted, in some cases, by changing the biological and/or psychosocial environment (*12*). For example, in a study of maltreated children, positive social support appeared to protect against depression, even in children having the short allele of the serotonin transporter gene (*13*).

Child rearing. To protect against learned helplessness and depression, as well as to promote resilience, it is critical to provide children with a supportive and loving environment that fosters healthy attachment, protects them from repeated experiences of uncontrollable stress, and provides them with ample opportunities to master life challenges. Such mastery can contribute to stress inoculation with reduced overall reactivity to future stressors and enhanced mastery of future challenges. Classes in effective parenting might help to provide a resilience- promoting child-rearing environment and to reduce transgenerational transmission of stress vulnerability.

Social support. Low levels of social support have been associated with depression, PTSD, and medical morbidity, whereas high levels of social support have been positively associated with active problem-focused coping, sense of control and predictability in life, self-esteem, motivation, optimism, enhanced immune function, dampened neuroendocrine and cardiovascular responses to stress, resilience, and lower levels of depression. Interventions that teach children and adults the skills needed to improve social competence and to construct and maintain supportive social networks are likely to enhance resilience and to decrease rates of stress-related depression. Social-emotional training programs for children, which focus on enhancing executive function and prosocial behavior, have shown promise in strengthening social skills, social networks, and academic performance (*7*).

Cognitive and/or psychological interventions. When individuals believe that the demands of a stressful situation exceed their personal capabilities and external resources, they tend to appraise the situation as a threat and as out of their control, which negatively affects their emotional and behavioral response and increases the likelihood of developing depression. On the other hand, if the individual believes that they have the skills, experience, and resources needed to successfully deal with an adverse situation, they are more likely to appraise the situation as a challenge.

A number of therapeutic approaches have been designed to modify appraisals of threat and adversity (*14*, *15*). These include training in attention control, cognitive reappraisal, and enhancing self-efficacy. Interventions in attention control, such as cognitive control training and mindfulness training, teach individuals how to control where they direct their attention and have shown promise as treatments for depression. Learning

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to selectively attend to positive as well as relevant negative information, while filtering out irrelevant negative information (i.e., consistent with realistic optimism, a pattern that has been associated with resilience), would be particularly helpful for the pessimistic or depressed individual who tends to preferentially focus on, remember, ruminate about, and have difficulty disengaging from negative information. Deficient top-down cognitive control and/or PFC inhibition of subcortical brain regions—such as the amygdala, dorsal raphe nucleus, and habenula—might perpetuate depression through reduced capacity to regulate stress-related emotions and by contributing to negative biases (*8*, *16*).

Cognitive reappraisal, or the ability to cognitively reframe adverse and negative events in a more positive light, is strongly associated with resilience and can moderate the relation between severity of life stress and depression (*14*). It may accomplish this, in part, by attenuating negative emotional and biological stress responses (*7*, *8*, *16*). Interventions that employ training in cognitive reappraisal and that have shown some promise in reducing depression include well-being therapy (*17*), hardiness training (*18*), and Viktor Frankl's logotherapy. Searching for and extracting meaning, purpose, and strength from adversity is an important component of these therapies. Many studies have shown that having a highly valued and meaningful purpose or mission can enhance resilience to stress.

Training in cognitive reappraisal is also a central component of many cognitive-behavioral therapies, which are well-established and effective treatments for depression and PTSD. These therapies typically teach individuals to observe their cognitive and behavioral reactions to stress, to challenge distorted negative appraisals of self and the situation, and to replace distortions with more realistic, accurate, and positive appraisals.

Coping self-efficacy refers to perceived capacity to successfully manage and recover from the demands of a stressful situation. High coping self-efficacy is highly predictive of resilience and adjustment after traumatic stressors such as military combat, motor vehicle accidents, death of a spouse, and natural disasters (*10*, *15*). There are many ways to increase coping self-efficacy. One of the most important involves mastery experiences, where the individual learns the skills needed to successfully manage a stressor and then practices those skills, preferably with feedback, in increasingly challenging situations until he or she has mastered the challenge. Having confidence in one's capacity to deal with stress may increase a sense of control, shift a perceived threat into a perceived challenge, foster active problem-oriented coping, increase motivation and perseverance, modify emotional and neurobiological responses to stressors, and buffer against stress-related psychological disorders such as depression. Training programs designed to enhance mastery and coping self-efficacy in stressful situations are typical of military, police, and firefighter training, as well as outdoor education programs, like Outward Bound.

Neurobiologic interventions. A better understanding of the neurobiology of resilience will hopefully lead to prevention and/or improved treatment for stress-related disorders such as depression and PTSD (*2*). For example, enhancing NPY function, particularly for individuals who do not naturally release sufficient amounts, might boost physiological resilience by helping to maintain the SNS and HPA axis at an optimal level of activation—high enough to respond to danger but not so high as to stimulate excessive fear, anxiety, and depression. Similarly, developing therapeutic agents to contain stress-induced overdrive of CRH, which controls and integrates the body's response to stress, would likely reduce rates of trauma-related psychopathology.

Other mediators of stress resilience that could serve as therapeutic targets for reducing the likelihood of developing stress-related depression include the serotonin, dopamine, noradrenergic, γ-aminobutyric acid, and glutamate systems. For example, antidepressants protect against stress-induced learned helplessness in animals and stimulate the regrowth of hippocampal neurons that have been damaged by stress, and antiadrenergic agents, like propranolol, may have a role in preventing overconsolidation of traumatic memories. It may also be possible to develop pharmacological and/or psychotherapeutic interventions to help regulate neural pathways believed to be critical to resilience, including pathways involved in emotion regulation, attention, positive versus negative outlook, reward and motivation, sensitivity to context, response to fear, learning and memory, adaptive social behaviors, and speed of recovery from stress.

Real-time functional magnetic resonance imaging neurofeedback, mental training exercises, mindfulness meditation, and cognitive reappraisal training are exciting new directions of research that target top-down regulation of specific neural circuits. For example, mindfulness meditation and cognitive reappraisal are believed to exert their adaptive effects on emotion regulation by enhancing PFC regulation of limbic and brainstem systems. It is possible that therapies designed to stimulate and strengthen PFC regulation of emotion will boost confidence in one's ability to gain control of stressful situations (*7*, *8*). To increase resilience and decrease rates of stress-related depression, it will also be important to develop and test interventions that target bottom-up regulation of emotion (*8*).

Improving physical health. Quality of diet, amount of exercise, capacity to relax, and quantity and quality of sleep are important in determining how the body and brain respond to stress (*19*). For example, aerobic exercise has been associated with resilience largely through its

Environmental stressors and genetic predisposition

	Depression risk factors	Therapeutic intervention	Resilience protective factors
Cognitive/behavioral	Weak executive function: weak coping self-efficiency; negative attention bias; cognitive inflexibility	Cognitive behavioral therapy with cognitive reappraisal; positive emotion excercises, coping skill development, and training; well-being therapy	Strong executive function; high coping self-efficacy; positive emotions; realistic optimism; cognitive flexibility
Emotion regulation	Weak regulation (e.g., anhedonia; slow stress recovery)	Mindfulness; training; antidepressant medications	Strong regulation (e.g., delay gratification; rapid stress recovery)
Social	Weak social skills; minimal social network; no resilient role models	Social emotional training; network support treatment	Strong social skills; diverse social network; resilient role models
Physical health	Sleep deprivation; poor cardiovascular fitness; poor nutrition; obesity	Teach sleep hygiene; excercise regimen; improve diet	Strong sleep habits; physically fit; good nutrition
Neurobiology	Dysregulated HPA axis and SNS in response to stress; attenuated prefontal cortical executive function and stress-induced limbic system hyperactivity	Neural circuit training; novel medications (corticotropin-releasing factor, NPY, GABA, glutamate)	Effective regulation of HPA axis and SNS in response to stress; robust prefrontal cortical executive function and capacity to regulate limbic reactivity to stress

effect on reducing anxiety and depression and improving cognition and brain function. Regular aerobic exercise is believed to induce the expression of genes associated with neuroplasticity and neurogenesis, as well as to regulate the HPA-axis response to stress. In some studies, exercise was as effective as antidepressants in treating mild-to-moderate depression and may possibly protect against future episodes of depression (*10*, *19*)

More comprehensive resilience training programs. Although far more research is needed to determine their efficacy, examples of resilience training programs that employ several of the above cognitive behavioral and emotion regulation strategies include hardiness training (*18*), The Penn Resiliency Program (*20*), and the military's Battlemind or Comprehensive Soldier Fitness program (*21*).

Implications. What we currently know about resilience has implications for the prevention and treatment of depression. Risk and protective factors generally have additive and interactive effects so that having multiple genetic, developmental, neurobiological, and/or psychosocial risk factors will increase allostatic load or stress vulnerability, whereas having and enhancing multiple protective factors will increase the likelihood of stress resilience (*19*). Because neuroplasticity is exhibited throughout the life span, many of the stress-protective factors described in this Perspective can be enhanced through practice and training, which make it possible to improve adaptation to stress, increase speed of recovery from stress, and decrease the chances of developing stress-related depression throughout the life span. However, interventions that are initiated early in development are likely to have the greatest impact on future stress resilience, as there appear to be time-limited windows of enhanced neuroplasticity. Nevertheless, recent research suggests that it may be possible to open or reopen windows of neuroplasticity, perhaps with drugs, which might then enhance the efficacy of behavioral interventions (*19*). The study of resilience and its neurobiological underpinnings is a relatively young area of scientific investigation. Similarly, many approaches to enhancing resilience are still in experimental stages. Advances in our understanding of resilience and of its association with depression will come from continued multidisciplinary research on complex interactions between genetic, developmental, neurobiological, and psychosocial risk and protective factors. It is anticipated that this knowledge can then be used to inform the development of evidence-based interventions to mitigate risk for depression and to enhance resilience to stress.

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