Neurobiology of Stress and Anxiety

Anxiety is a normal emotional and neurophysiological reaction to a perceived threat, and serves the purpose of preparing one to "freeze, take flight, or fight." Such a reaction is obviously an appropriate and even adaptive survival mechanism in the presence of actual threats, allowing one both to escape the current threat and to avoid future ones through conditioned fear learning. When the reaction occurs in the absence of a realistic threat, however—whether because the threat itself is unlikely or because harm from the perceived threat is unlikely—then it serves no useful purpose and instead can significantly disrupt one's ability to function, thus constituting an anxiety disorder.

There are several anxiety disorders, as defined in the *Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR*, each with distinct characteristics, criteria, and symptoms, but all sharing the common core symptoms of excessive fear and worry. The neurobiological circuits underlying these core symptoms may thus be involved in all anxiety disorders, with the different phenotypes reflecting not unique circuitry but rather divergent malfunctioning within those circuits.

This chapter covers the neurobiology of normal fear and worry and how genetic and environmental factors may interact to affect these circuits and increase risk for psychiatric illnesses such as posttraumatic stress disorders (PTSD), which is the focus of this book.

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SECTION ONE

The Core Symptoms of Anxiety Disorders: Fear and Worry

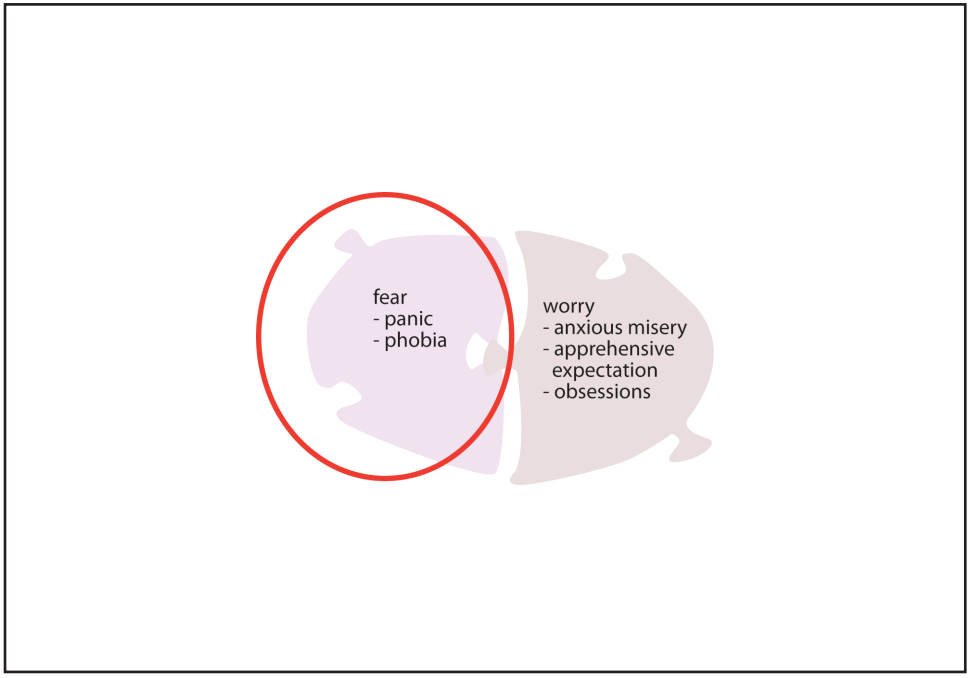

FIGURE 1.1. The two core symptoms shared by all anxiety disorders are anxiety or fear coupled with some form of worry. The circuitry mediating these two features is different, and will be addressed in turn, beginning with anxiety/fear.

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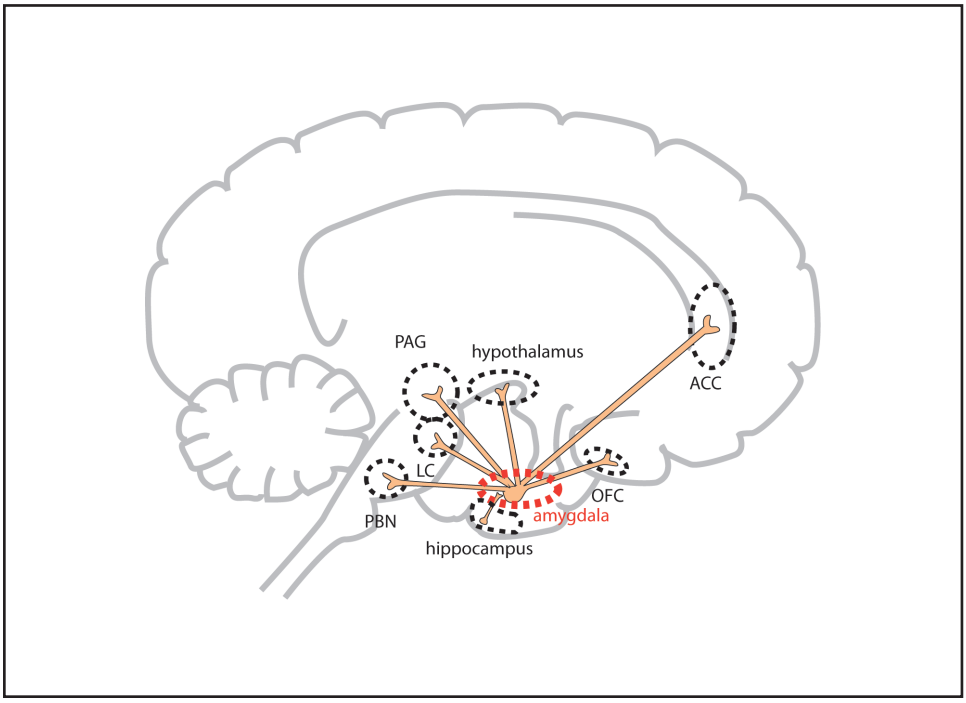

PAG: periaqueductal grey. LC: locus coeruleus. PBN: parabrachial nucleus. OFC: orbitofrontal cortex. ACC: anterior cingulate cortex.

FIGURE 1.2. Anxiety is a state that encompasses both an internal "feeling" of fear and the physiological expression of that fear. Although separate circuits mediate these different aspects of anxiety, they share in common a central role of the amygdala, an almond-shaped limbic structure with widespread reciprocal connections with both higher and lower brain regions. As shown in Figures 1.3 through 1.9, the amygdala both regulates and is regulated by these other brain regions in order to produce (or suppress) a fear response.

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Fear vs. Anxiety

TABLE 1.1.

	DESCRIPTION	ANATOMICAL LOCALIZATION
fear	Short-term, stimulus-specific response	Basolateral, central, and medial nuclei of amygdala
anxiety	Sustained response influencing behavior after the stimulus is removed	Basolateral amygdala projections to bed nucleus of stria terminalis

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The Amygdala and the Feeling of Fear

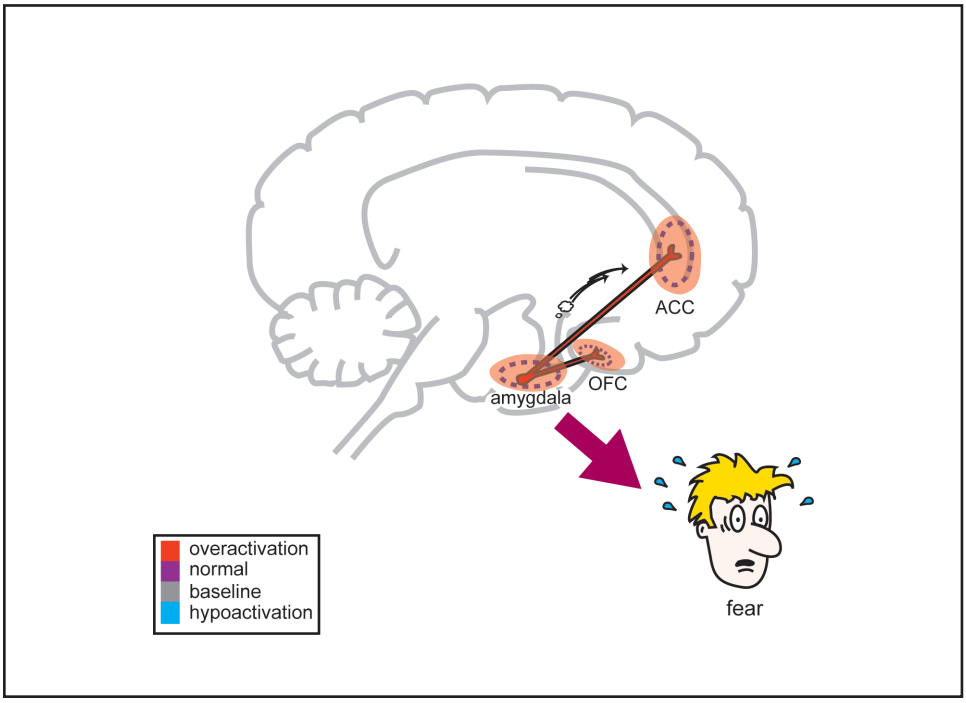

FIGURE 1.3. The emotional aspect of fear is regulated by connections between the amygdala and key areas of the prefrontal cortex, specifically the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC).

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The Amygdala and the Physiology of Fear:
Autonomic Output

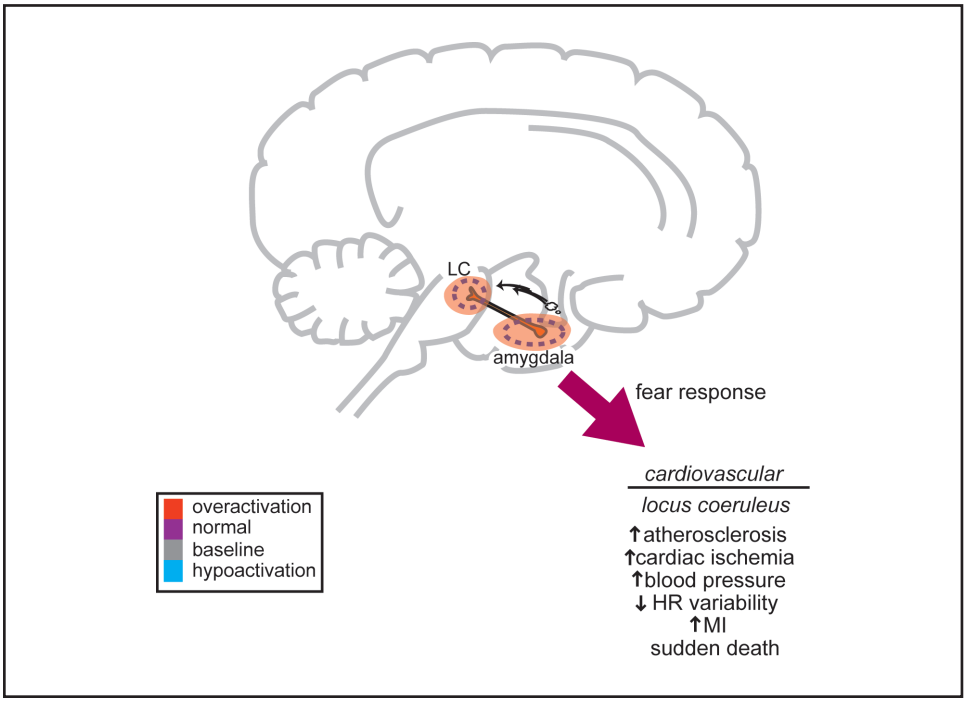

FIGURE 1.4. The physiological reaction to a fearful stimulus involves activation of multiple systems, including the autonomic system, as shown here. Activation of this system is regulated by connections between the amygdala and the locus coeruleus (LC), and leads to an increase in heart rate (HR) and blood pressure that is necessary for a fight/flight reaction.

Although acute activation of the autonomic nervous system is important for survival in response to real threats, chronic activation as part of an anxiety disorder can lead to increased risk of cardiovascular issues such as atherosclerosis, cardiac ischemia, hypertension, myocardial infarction (MI), or even sudden death.

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The Amygdala and the Physiology of Fear:
Endocrine Output

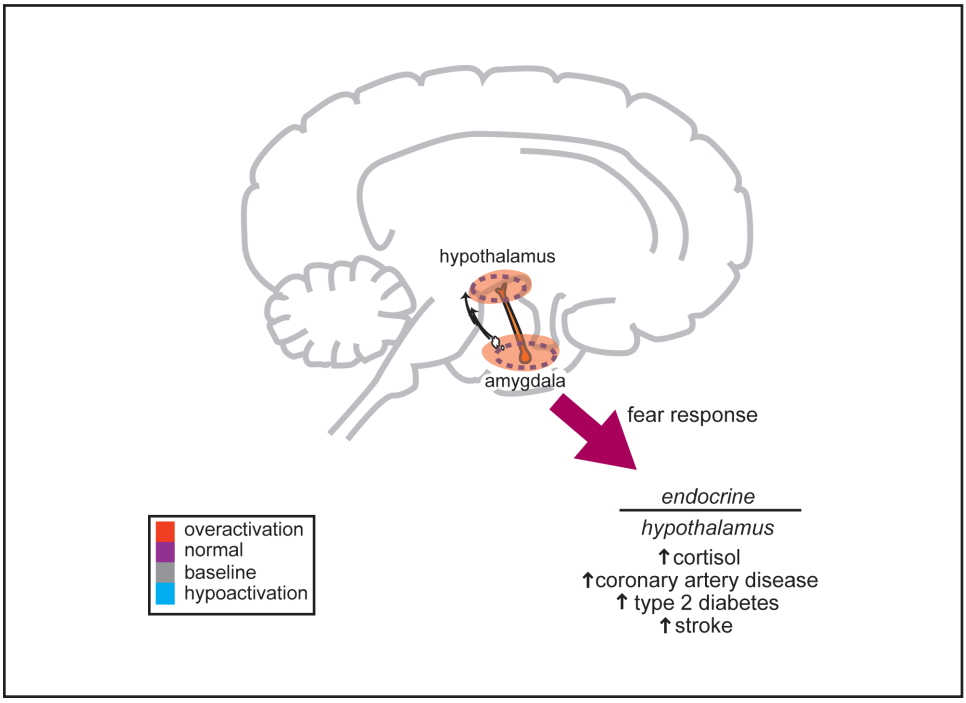

FIGURE 1.5. The hypothalamic pituitary adrenal (HPA) axis is responsible for endocrine output during the fear/stress response, and is regulated by the amygdala via reciprocal connections with the hypothalamus. During acute stress, such as exposure to a fearful stimulus, HPA activation increases the release of glucocorticoids such as cortisol, but only for a short time, until the perceived danger is gone. An abnormal stress response may occur due to chronic, unrelenting stress and/or due to stress during critical developmental periods, and can be associated with increased rates of medical complications such as coronary artery disease, type 2 diabetes, and stroke.

The role of the HPA axis in anxiety disorders is discussed in more detail in Figure 1.6 as well as in Figures 2.6 and 2.7.

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The HPA Axis

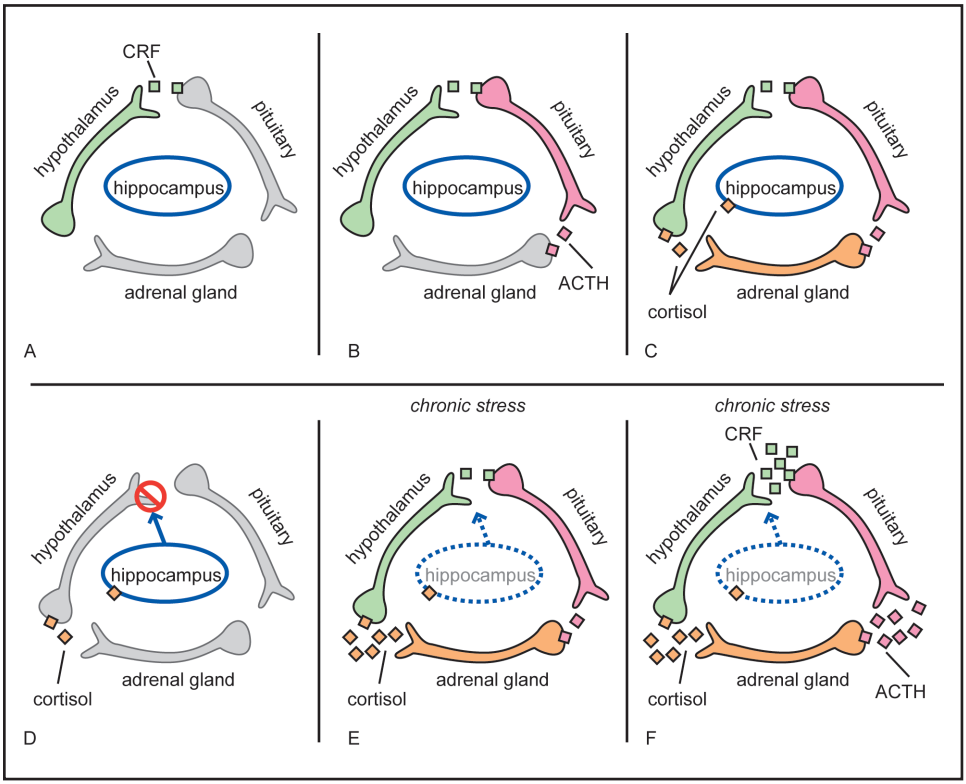

FIGURE 1.6. The central role of the HPA axis in stress processing makes it logical that it would be involved in the risk for anxiety disorders. The normal stress response involves activation of the hypothalamus and a resultant increase in corticotrophin releasing factor (CRF) (A), which in turn stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland (B). ACTH causes glucocorticoid release (cortisol in humans) from the adrenal gland, which binds to receptors in the hypothalamus, pituitary, and hippocampus (C). Glucocorticoid binding in the hypothalamus inhibits CRF release, ending the stress response (D). In addition, the hippocampus plays a role in inhibiting the stress response (D).

In situations of chronic stress, excessive glucocorticoid release may eventually lead to hippocampal atrophy, thus preventing it from inhibiting the HPA axis (E). This could contribute to chronic activation of the HPA axis (F) and increase risk for an anxiety disorder.

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The Amygdala and the Physiology of Fear:
Breathing Output

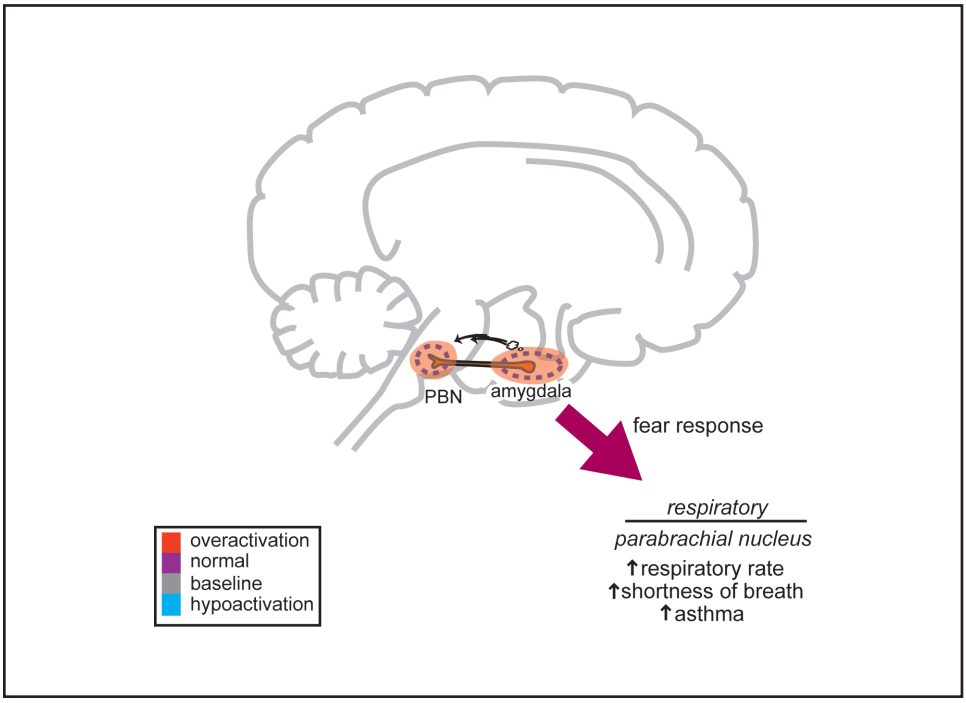

FIGURE 1.7. Increases in respiration rate are also an important part of a fear response and are regulated by connections between the amygdala and the parabrachial nucleus (PBN). However, when excessive activation occurs, this can cause shortness of breath, exacerbation of asthma, or a sense of being smothered—all of which are symptoms of a panic attack.

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The Amygdala and the Behavior of Fear

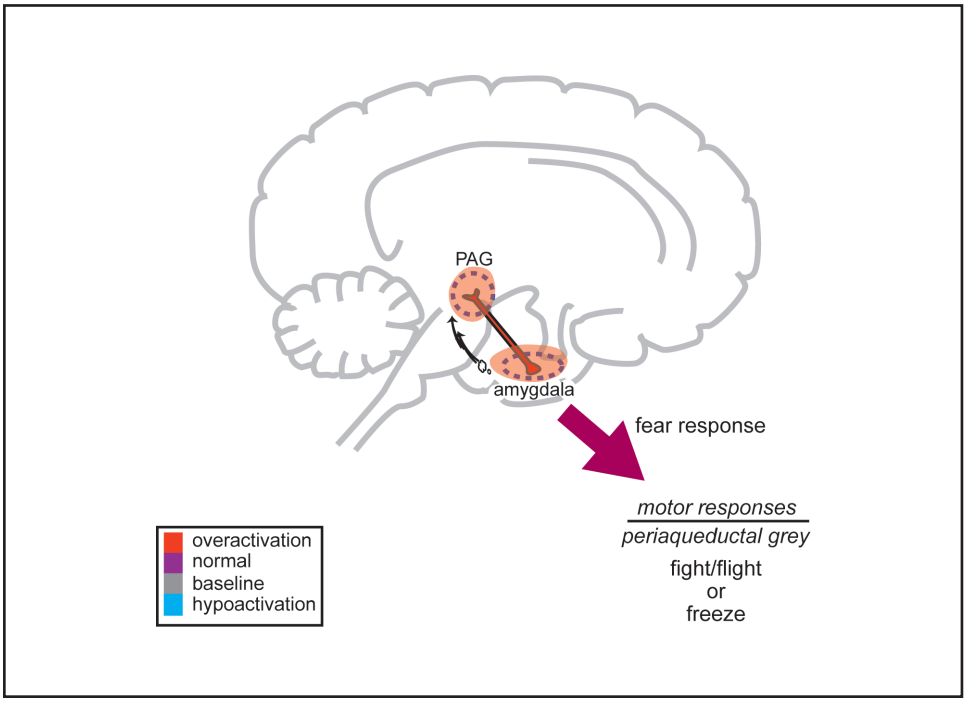

FIGURE 1.8. The emotional and physiological responses to a threat prepare one to take action in order to escape or combat that threat. The actual motor response taken—whether fight, flight, or freeze—is regulated in part through connections between the amygdala and the periaqueductal grey (PAG).

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The Hippocampus:
An Internal Fearmonger

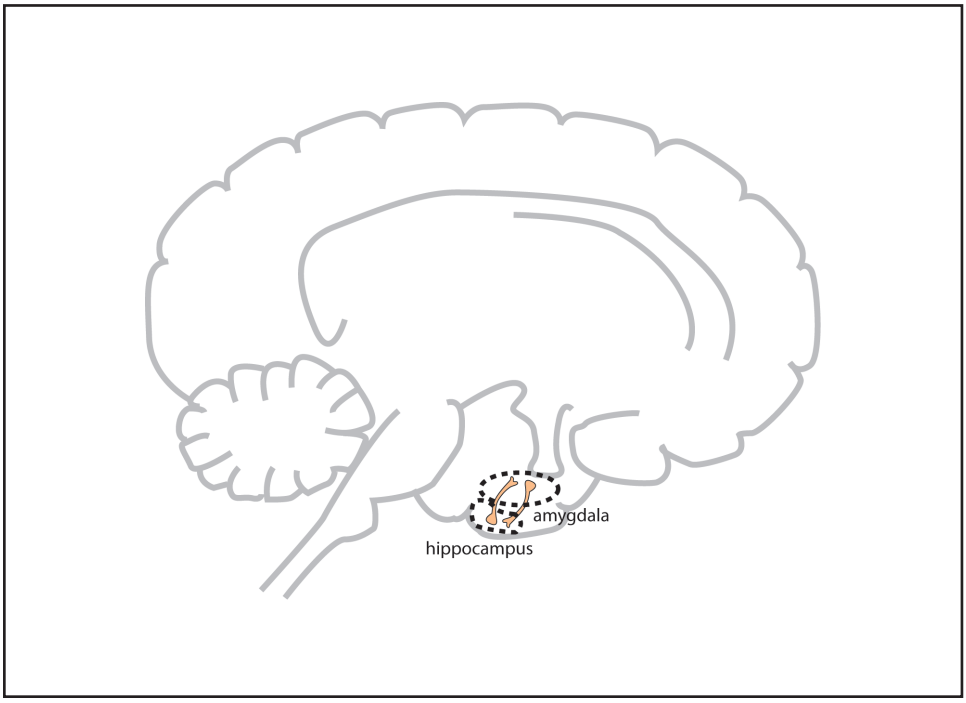

FIGURE 1.9. Anxiety can be triggered not only by an external stimulus but also internally through traumatic memories stored in the hippocampus, which can activate the amygdala and cause it, in turn, to activate other brain regions to generate a fear response. This is known as reexperiencing and is a central feature of posttraumatic stress disorder (PTSD).

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Fear Conditioning

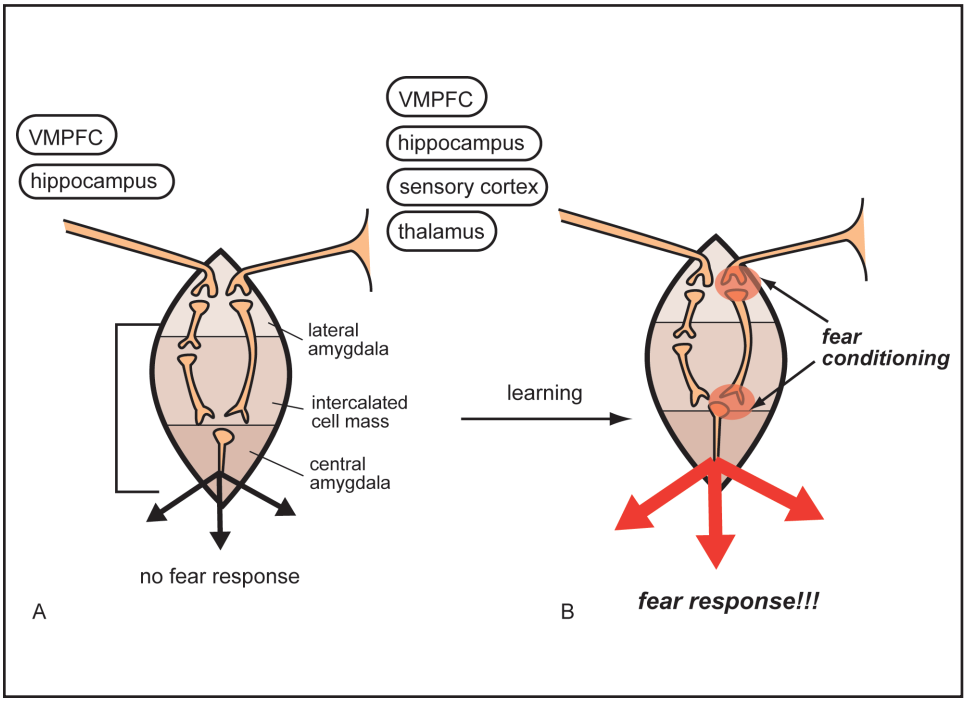

FIGURE 1.10. An important part of the normal fear response is the amygdala's ability to "remember" stimuli associated with the stressor so that it can react more efficiently if the stressor is ever reencountered—a process known as fear conditioning.

Upon acute exposure to a fearful situation, the lateral amygdala integrates input from several brain regions, including sensory cortex and thalamus, which provide information about stimuli associated with the fearful situation; the hippocampus, which provides memories of related fearful or traumatic experiences; and the ventromedial prefrontal cortex (VMPFC), which may provide mitigating input to suppress a fear response (A). If a fear response is in fact generated, then the amygdala restructures existing synapses to increase the efficiency of glutamatergic neurotransmission in response to future sensory input associated with the feared stimulus (B, represented by increased orange glutamate output and at synapses).

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The Worry Loop

FIGURE 1.11. Figures 1.2 through 1.10 reviewed the circuitry of fear, one of the two core symptoms of all anxiety disorders. The second core symptom, worry, involves different circuitry, as shown in Figure 1.12.

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Worry and Obsessions

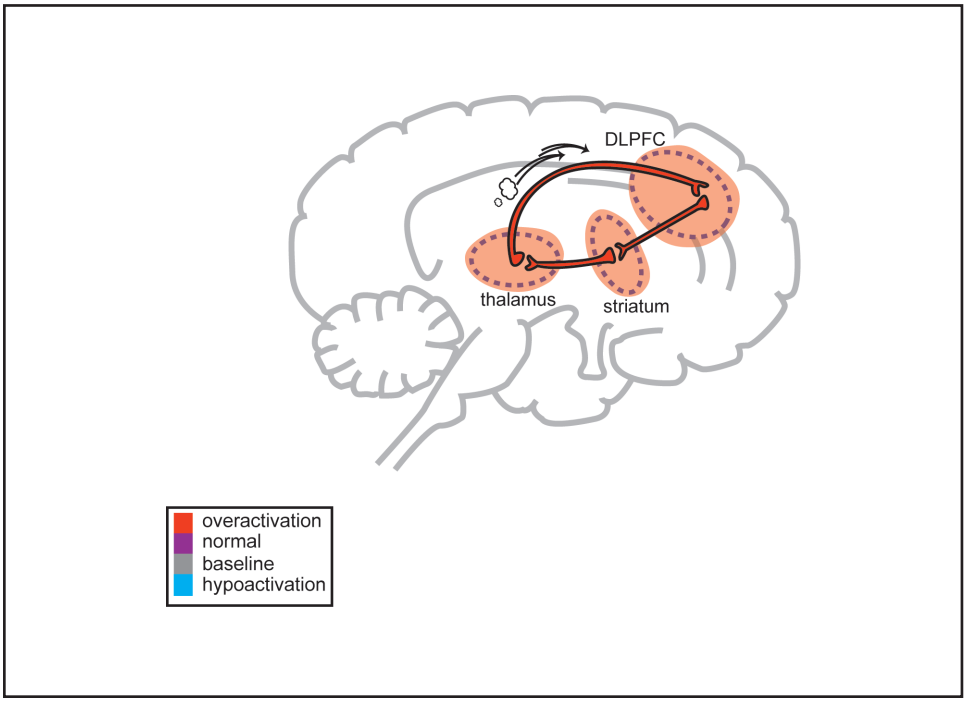

FIGURE 1.12. Worry, which can include apprehensive expectation, catastrophic thinking, and obsessions, is hypothetically linked to cortico-striatal-thalamic-cortical (CSTC) loops. Specifically shown here is a CSTC loop originating and ending in the dorsolateral prefrontal cortex (DLPFC).

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SECTION TWO

The Path to Anxiety Disorders: A Circuit's Story

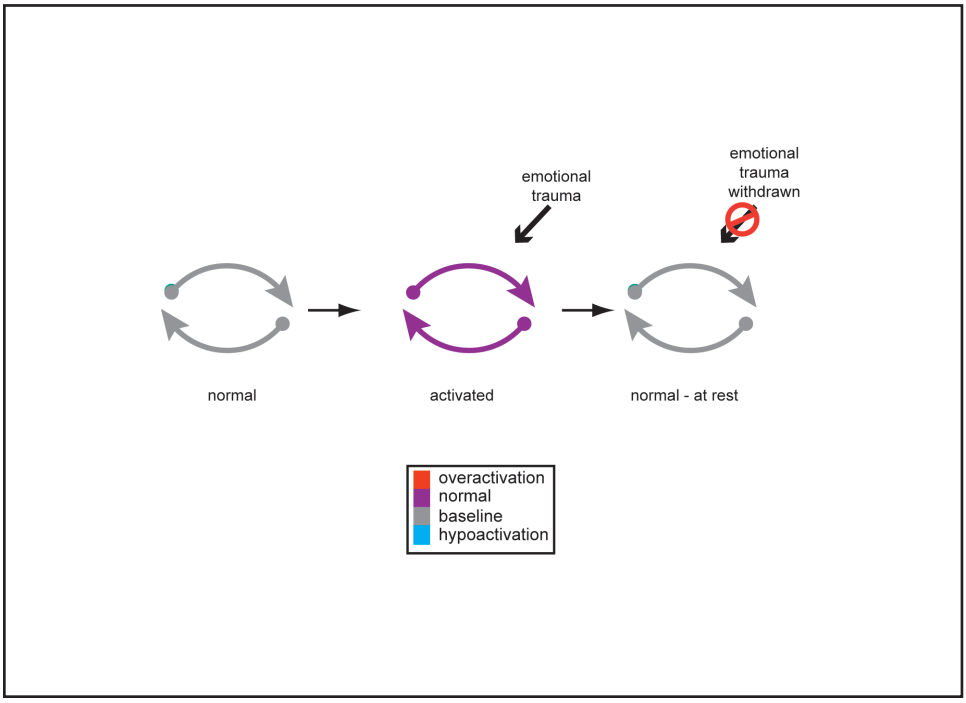

FIGURE 1.13. During acute exposure to stressors, the fear circuits described in Figures 1.3 through 1.9 are activated (middle), thus producing reactions that optimize the chances for survival. Once the trauma is withdrawn, the circuits return to baseline functioning (right). How then might activation of these circuits lead to the pathological symptoms of anxiety disorders?

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Stress Sensitization in Normal Circuits

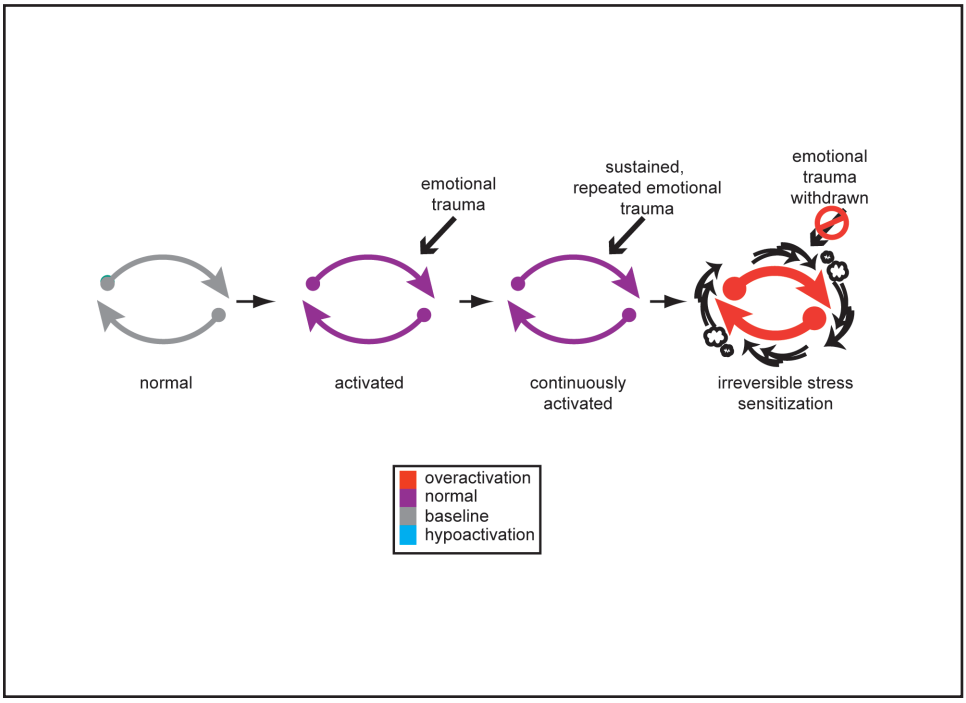

FIGURE 1.14. When circuits are repeatedly stressed and put on overload (middle right), it can lead to a condition known as "stress sensitization," in which circuits not only become overly activated but remain overly activated even when the stressor is withdrawn (right).

A sensitized circuit does not necessarily mean that symptoms will develop, however. Instead, overloading circuits can potentially result in a loss of resilience and development of vulnerability to future stressors. Thus, individuals who have highly stressed and overloaded circuits may be phenotypically normal but have an increased risk for development of future anxiety disorders. This is known as a "presymptomatic" state.

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Progression from Stress Sensitization

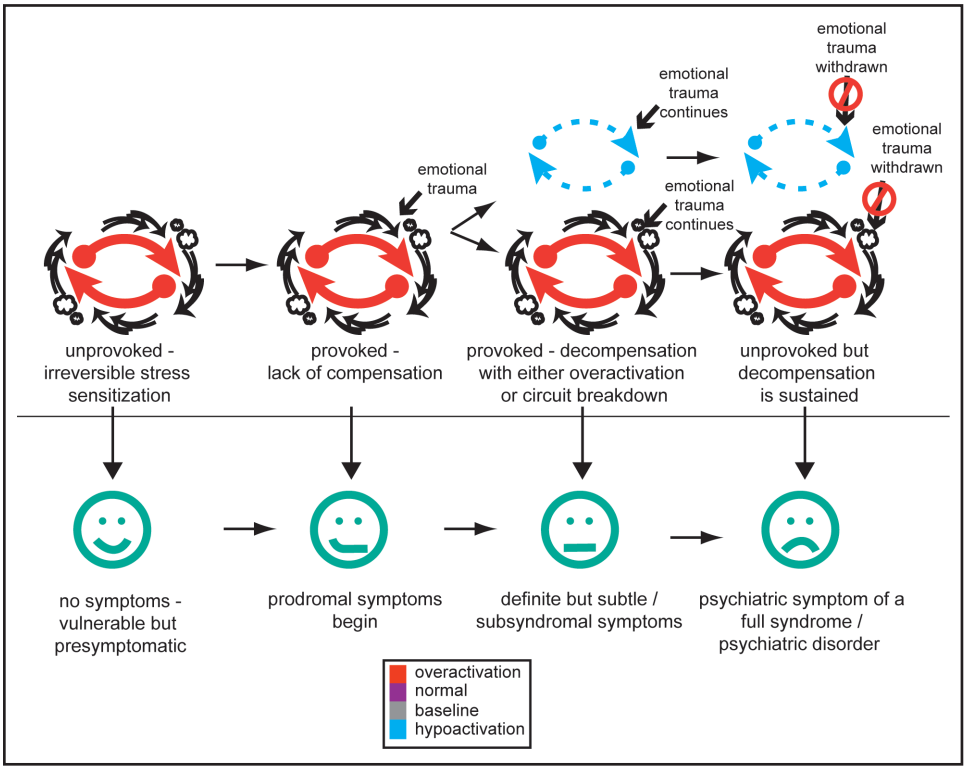

FIGURE 1.15. This figure shows the progression from stress sensitization to psychiatric symptoms. Stress sensitized circuits at rest are shown on the far left. In the absence of additional stressors, these overly activated circuits are clinically silent because they are able to compensate for the excessive activation. However, they are less efficient in their information processing than are normal, nonsensitized circuits. Under additional stress or emotional trauma, stress-sensitized circuits are hypothetically unable to compensate and begin to show signs of breakdown into subtle prodromal symptoms (middle left). With further emotional trauma, these failing circuits either do not compensate when they overly activate or even break down and fail to activate adequately, leading to the development of subsyndromal symptoms (middle right). Finally, with continuing emotional trauma, the malfunctioning circuits break down further; thereafter psychiatric symptoms not only develop but may persist even after withdrawal of the emotional trauma (far right).

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Is All Stress Bad?

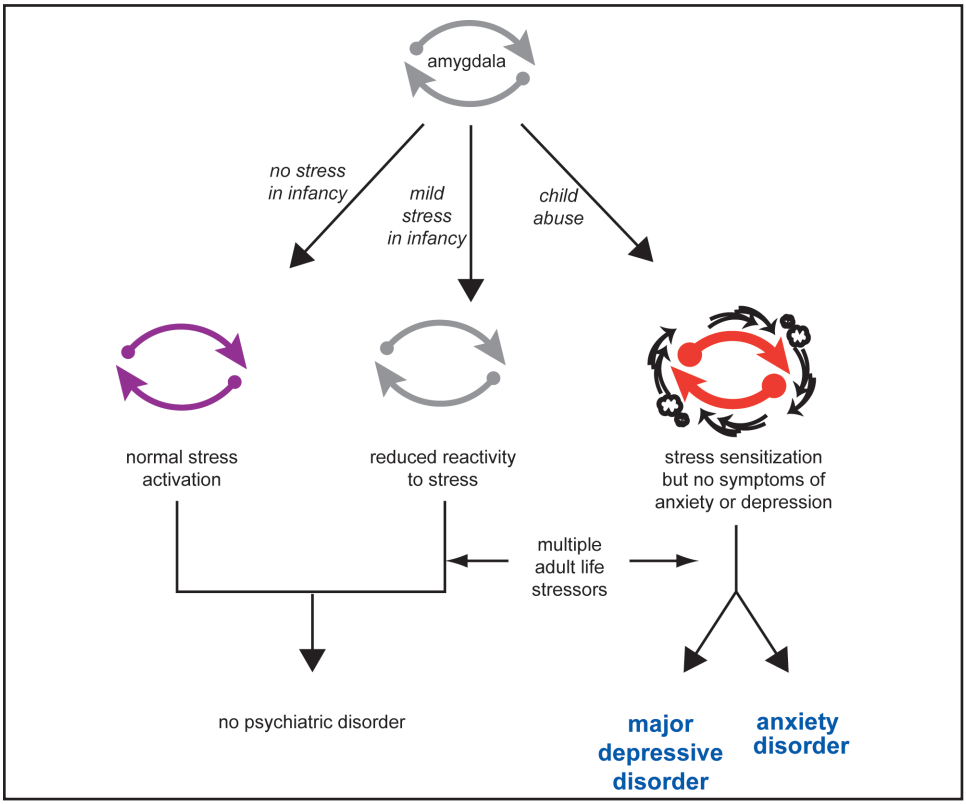

FIGURE 1.16. The experience of life stress can create stress sensitization and consequently increased risk for psychiatric illness, as shown in Figure 1.15. Interestingly, however, the degree of stress seems to make a difference, with only severe or overwhelming stress generally leading to sensitization (far right). In fact, exposure to mild stress in infancy may actually be protective: studies have shown that animals who have experienced mild stress in infancy may be less reactive to future stressors (middle) than animals not previously exposed to stress (left).

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Stress Diathesis Model:
A Tale of Two Influences, Part 1

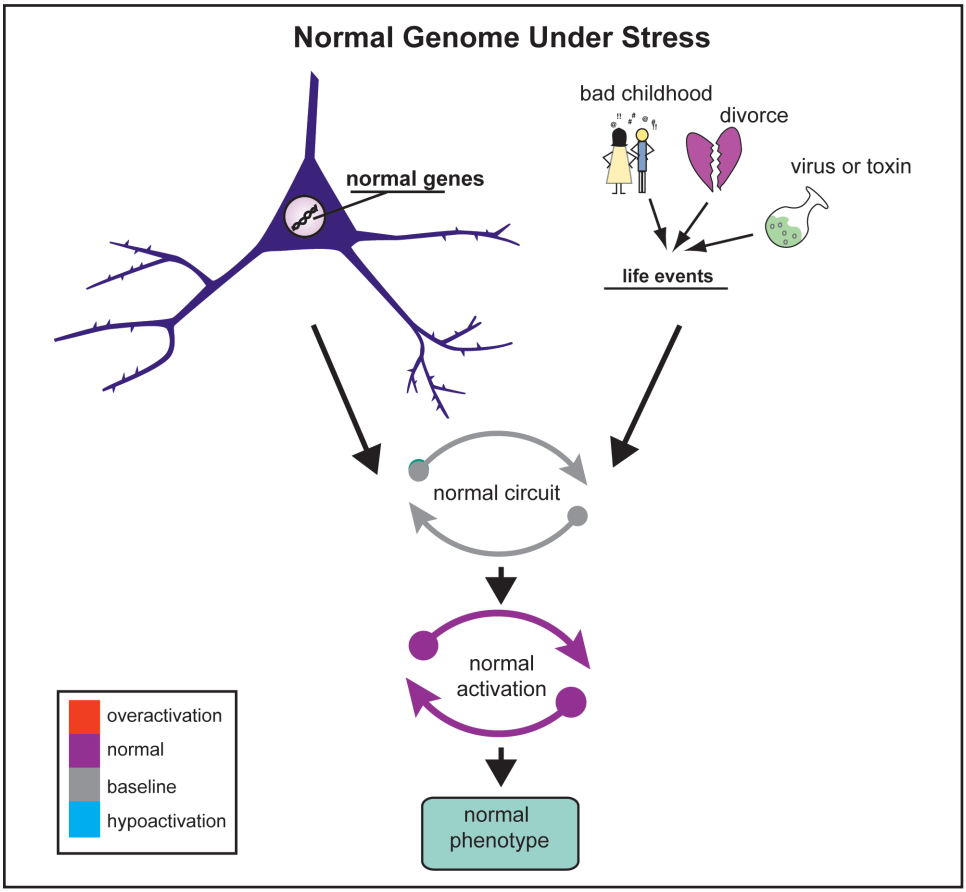

FIGURE 1.17. Exposure to stress isn't the whole story, however. Psychiatric symptoms often develop due both to genetic and environmental influences. This is known as the stress diathesis hypothesis.

Thus, although environmental stressors—such as childhood abuse, divorce, viruses, or toxins—can increase the risk, or diathesis, of developing a mental illness, individuals with a normal genome and thus normal circuits may experience only normal activation of circuits in response to these stressful events. Such individuals would not express a mental illness, exhibiting instead a normal phenotype with no adverse behavioral symptoms.

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Stress Diathesis Model:
A Tale of Two Influences, Part 2

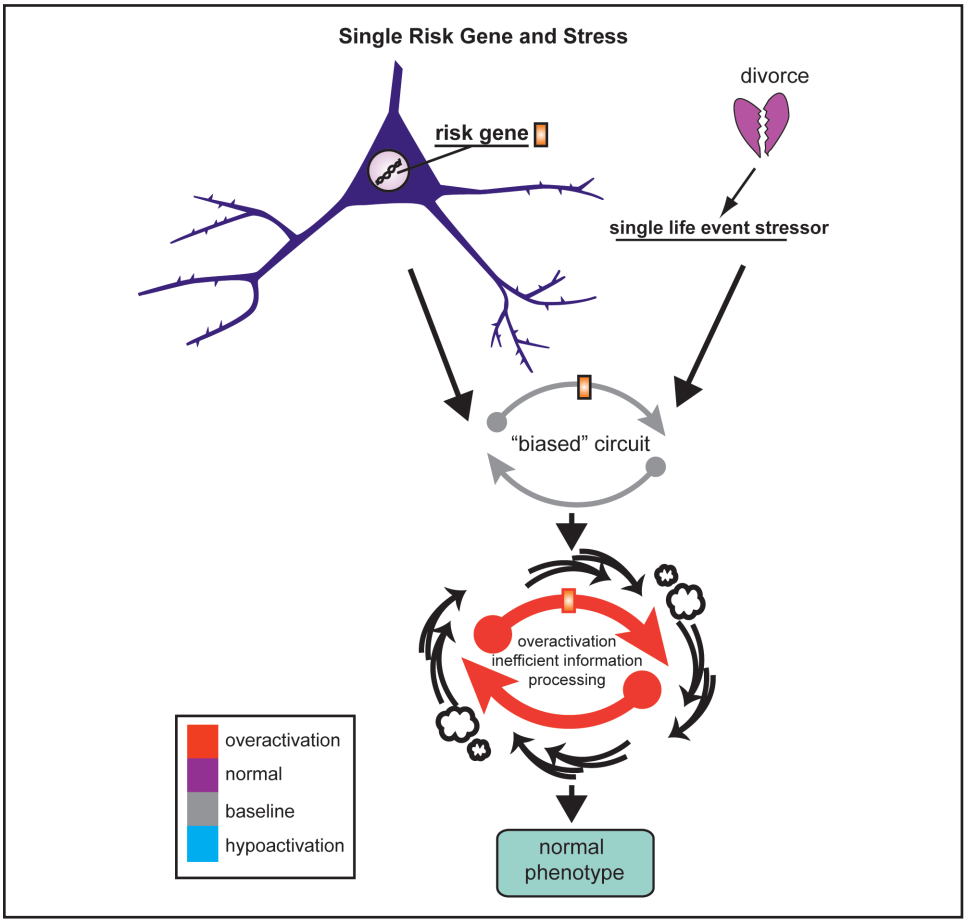

FIGURE 1.18. However, individuals with a risk gene for mental illness may experience inefficient information processing in the "biased" circuit in response to stress, increasing the likelihood of stress sensitization. This does not necessarily mean that behavioral symptoms will ensue. Genetically inefficient information processing may be behaviorally "silent" if it is compensated by overactivation via backup systems. In this case, the individual may still have a normal behavioral phenotype despite having an abnormal biological endophenotype. Thus, abnormal circuit activation may be detectable with functional brain scanning, but clinical interview would reveal no psychiatric symptoms.

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Stress Diathesis Model:
A Tale of Two Influences, Part 3

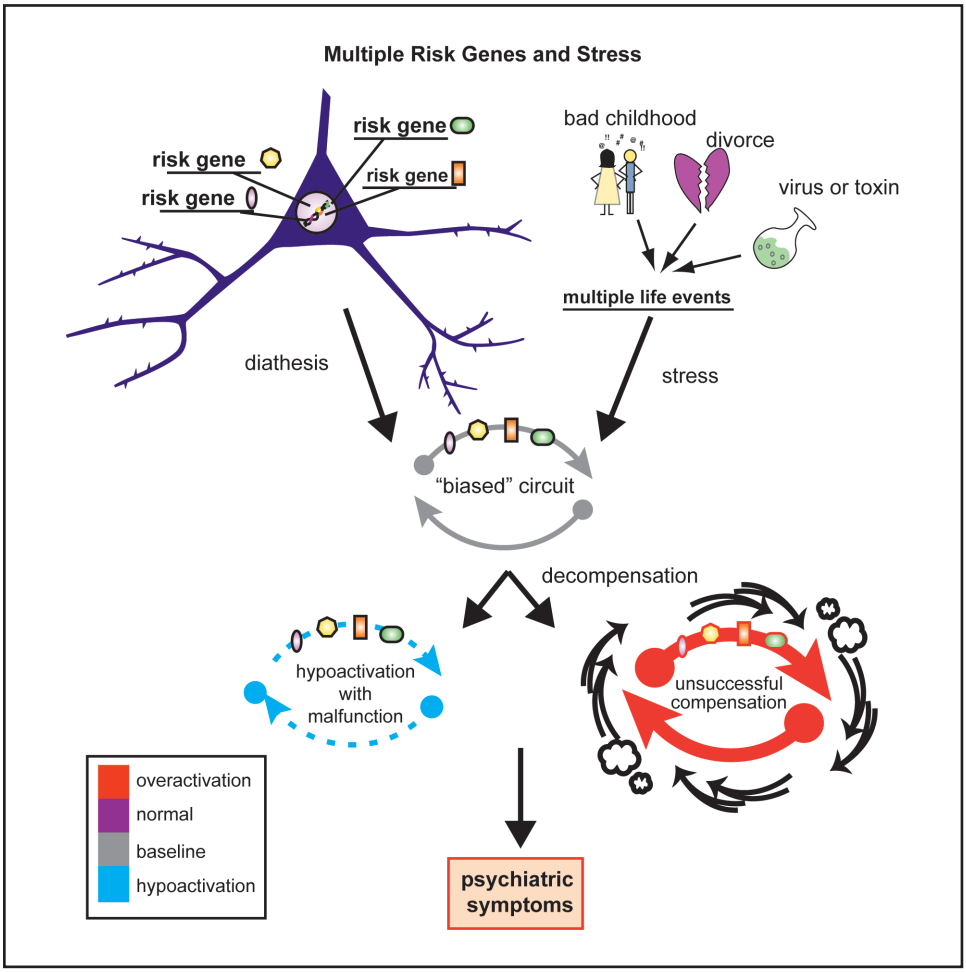

FIGURE 1.19. An individual with multiple stressors and multiple genetic risks may not have sufficient backup mechanisms to compensate for inefficient information processing within a genetically "biased" circuit. The circuit may either be unsuccessfully compensated by overactivation or it may break down and not activate at all. In either case, psychiatric symptoms would be likely to develop.

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An Allegorical View of Stress Diathesis

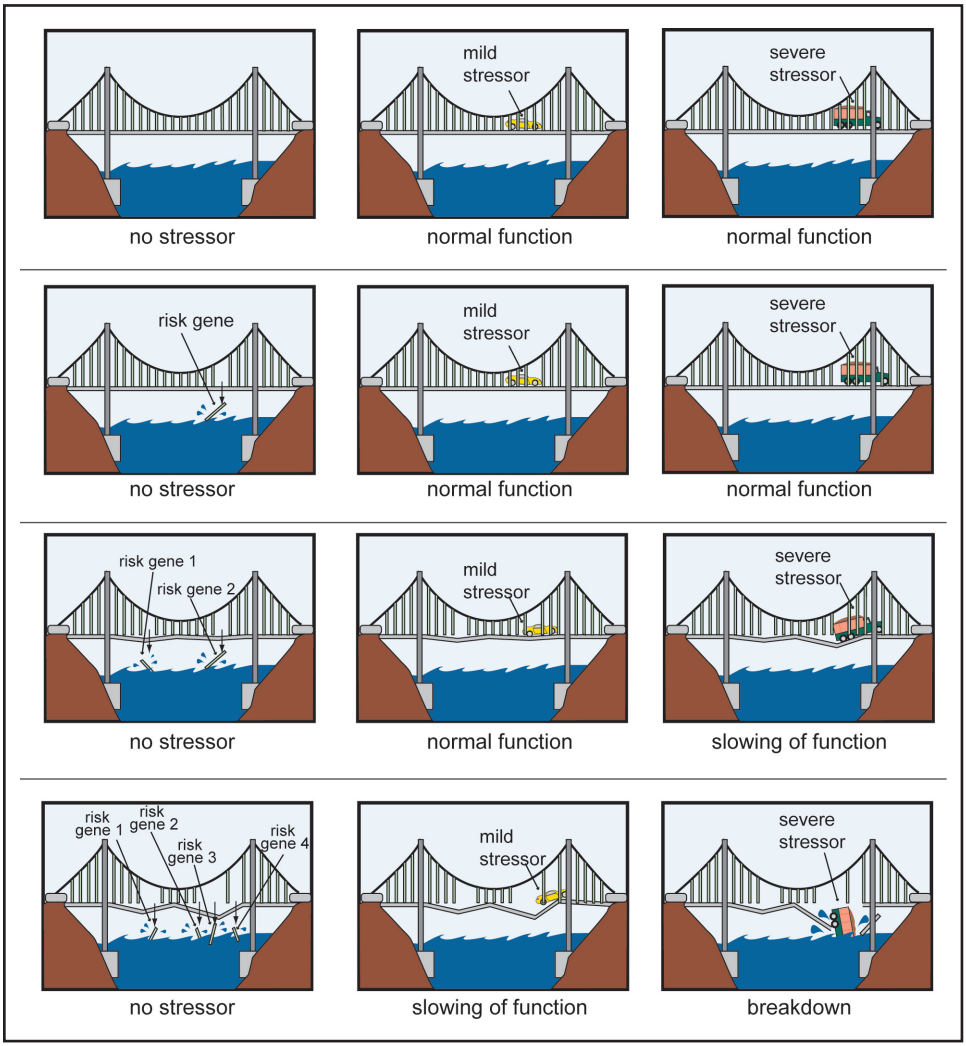

FIGURE 1.20. This representation summarizes the concept of stress diathesis, which was explained in Figures 1.17 through 1.19. Each suspension cable is analogous to a gene, while the vehicles that pass over the bridge represent types of environmental stressors.

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