**Supplemental Text Box 1**

**The Neurobiology of Arousal**

The defense cascade starts with an increase in the level of arousal, when the danger or potential danger is first identified. Arousal is not just an increase in alertness. It includes bodily changes and a move away from homeostasis. The most important changes are autonomic and are mediated by an increase in sympathetic outflow. Heart rate goes up, and vascular resistance increases in the gut, muscles, and skin, raising perfusion pressure and blood flow to the brain and the heart. Increased blood flow to the muscles will occur later, once skeletal muscles become active (e.g., via flight or fight). Temperature increases, and digestive activity, including intestinal peristalsis, stops. Respiration and skeletal muscle tone also both increase. Postural muscles are affected first (to raise the body and stabilize it), followed by limb muscles—although at this stage no actual movement has occurred. In brief, all muscles, both smooth and striated, are toned up. The mind is awake, and the body is prepared.

The brain region most important for the expression of arousal and the orchestration of the different components of arousal is the dorsal tuberal hypothalamus, which receives top-down projections from the central nucleus of the amygdala1 (see Figure 2 in main text). The dorsal tuberal hypothalamus region has been long known for its role in motivated behaviors and defense.2-5 It also contains the neurons that make the recently discovered peptide orexin (aka hypocretin), whose function is to maintain wakefulness and increase arousal during motivated behavior.6,7 Orexin neurons project to the cortex and thalamus, as well as to premotor centers (autonomic and somatic) and motor neurons, including sympathetic preganglionic neurons.8,9 Orexin receptor antagonists and, in transgenic animals, knockout of the orexin gene promote sleep and relaxation and reduce the cardiovascular response associated with the psychosocial stress response.10,11 Other neurons in the same area—whose neurotransmitter remains to be identified—may also contribute to the control of arousal and to the first stage of the defense cascade.

Activation of the ventral forebrain by the limbic forebrain (including the amygdala) increases cortical arousal—the level of attention and learning—to identify the best strategies to deal with the danger.12 Cortical arousal is also mediated by other parallel pathways such as the locus coeruleus, which is under the control of the orexin neurons of the dorsal hypothalamus and which also receives projections from the amygdala.6,13,14

The human literature has more consistently focused on sustained states of arousal—the generalized stress response and the central role of corticotrophin-releasing hormone (CRH) in the human stress response15,16—because those sustained states are associated with a broad range of psychiatric and physical disorders. Longer-term arousal responses in humans (also known as the “generalized stress response”) appear to be mediated by the bed nucleus of the stria terminalis17 and involve activation of the stress-related peptide CRH, whose role has been extensively described.18 By contrast, the literature on humans has paid little attention to the transient states of arousal that are characteristic of the defense cascade. Consequently, the findings on arousal in animals provide the best-available model for understanding transient arousal in humans: short-duration arousal responses are mediated by projections from the central nucleus of the amygdala to the hypothalamus (see visual representation of arousal in Figure 2). The bed nucleus of the stria terminalis and the amygdala function in parallel to mediate long- and short-term arousal responses, respectively.17 The term *extended amygdala*, often used in discussions of arousal, incorporates both the amygdala proper and the bed nucleus of the stria terminalis.

Arousal responses also involve a concomitant activation of the hypothalamic-pituitary-adrenal axis to facilitate energy consumption: larger pulses of CRH from the hypothalamus, increased levels of adrenocorticotropic hormone from the pituitary, and increased levels of glucocorticoids from the cortex of the adrenals. CRH acts in synergy with the sympathetic nervous system to increase body arousal,9 and glucocorticoids enhance energy metabolism in all tissues of the body.16 The HPA axis is activated by a pathway that runs parallel to the fear circuits of the amygdala, hypothalamus, and periaqueductal gray (not represented on Figures 1 and 2): the central nucleus of the amygdala projects to the bed nucleus of the stria terminalis, which projects to the neuroendocrine zone of the hypothalamus.20,21

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