**Supplemental Text Box 6**

**Summary of Overlapping Emotion-Regulation Systems Within Which the Circuits of the Amygdala, Hypothalamus, and Periaqueductal Gray Circuits Are Embedded**

**THE PREFRONTAL CORTEX–HIPPOCAMPUS–AMYGDALA SYSTEM**

The medial regions of the prefrontal cortex (PFC)—the ventromedial PFC, orbitofrontal cortex, dorsomedial PFC—and anterior cingulate cortex (ACC) are implicated in the control of emotional behaviors.1–4 The PFC is involved in top-down inhibition of the amygdala, hypothalamus, and periaqueductal gray (PAG), the modulation of emotional face and body expressions through the cranial nerves (nos. V, VII, IX, X, and XI), and cortico-striato-thalamic loops.5,6 In humans, the lateral regions of the PFC (the dorsolateral and ventrolateral PFC), which are principally involved in higher executive functions, are the most recent phylogenetic addition to the affect-regulating system. Lateral regions of the PFC come on line—and work together with the ventromedial PFC—when individuals utilize conscious emotion-regulation strategies.2,3,7,8 The hippocampus is also part of this system and is crucial to context association in memory formation9 and modulation of the hypothalamic-pituitary-adrenal (HPA) axis.10–12 It projects to the amygdala and can exert top-down modulation of the amygdala in the context of new learning.13 More recently, some researchers have extended this emotion-regulation system to include the cingulate cortex, insulae, parahippocampal gyri, and HPA axis.8,14–16

**THE AUTONOMIC NERVOUS SYSTEM**

The autonomic nervous system is involved in regulating the internal milieu—to maintain it (homeostasis) or to adjust it to specific behaviors such as exercise or defense responses (to real or expected dangers). Because of the latter, efferent (or motor) fibers of the autonomic nervous system contribute to the visceral expression of emotions. On the sensory side, afferent fibers that regulate the autonomic nervous system also contribute to interoception, the subjective experience of body state. Early writers conceptualized the autonomic system primarily as a motor-output system to the viscera: visceral motor fibers innervated smooth muscle in the viscera,17,18 whereas the somatic motor fibers innervated skeletal muscle. Later, it became apparent that autonomic nerves carried a large percentage of afferent fibers (e.g., 80%–90% of the vagal nerve and 50% of the splanchnic nerve) and not just efferent fibers.19 The term *visceral afferents* was used to refer to sensory fibers that carry information from the viscera about the body’s internal state, and the term *somatic afferents* to refer to those fibers that carry information from the skin and muscle about the external environment. More recent, “functional” models conceptualize the autonomic system as a complex body-brain-body feedback system, with central representations on multiple levels.5,20–26 Accordingly, the brain is informed about the state of the body via afferent signals from all body tissues—exteroceptive and interoceptive—and in response to this information, the brain coordinates integrative programs for maintaining the body’s internal environment and implements these programs by parallel activation of the autonomic efferent system, the HPA axis, and the somatomotor system.23,26

As noted above, contemporary models of the autonomic system are functional in character. Functional models attempt to describe overarching regulation functions that build upon, but also expand beyond, the neural substrate that makes up the autonomic system per se. Such models synthesize, condense, and bring a sense of coherence to large bodies of complex information, with the consequence that some detail may be lost. Despite these limitations, the autonomic system is a key neural system involved in homeostasis and interoception27 and in emotion regulation and expression; using a functional account to understand it is especially useful in clinical practice. Likewise for the other emotion-regulation systems discussed here.

**The Sympathetic Branch**

The sympathetic branch of the autonomic nervous system originates from preganglionic motor neurons located in the thoracic cord. These sympathetic preganglionic neurons exit the spinal cord with spinal nerves and relay in the para- and pre-vertebral sympathetic ganglia17 or directly in the adrenal medulla (where they cause the secretion of adrenalin/noradrenaline into the blood). Postganglionic sympathetic fibers supply smooth muscles in the heart, lungs, intestines, other viscera, brown fat, and immune cells throughout the body, where they release noradrenaline to produce catabolic responses, usually associated with an increase in arousal.

Sympathetic outflow—that is, the level of activity in sympathetic preganglionic neurons—is regulated by two types of input, one spinal and the other supraspinal (see virus study by Westerhaus and Loewy [2001]).26 *Spinal inputs* come from neurons located in lamina 1 of the dorsal horn of the spinal cord, and those neurons relay sensory information carried by small-diameter A-delta and C-afferent fibers. These sensory fibers are of visceral and somatic origin, and many originate from nociceptors, mechanical or chemical. It is through the connections in the spinal cord that they activate basic spinal sympathetic reflexes. *Supraspinal* inputs come from premotor sympathetic (or pre-sympathetic) centers located in the brain stem and hypothalamus. These pre-sympathetic centers are responsible for more integrated sympathetic reflexes because they can integrate lamina-1 inputs (ascending via the spinothalamic tract) with inputs from two additional relays of visceral and somatic afferents located in the brain stem: the nucleus of the solitary tract (more visceral input from thorax and abdomen ascending with the vagus nerve) and the spinal trigeminal nucleus (somatic input from the face and head), respectively. Pre-sympathetic centers are, in turn, regulated by higher structures located in the forebrain, including the insular cortex, medial PFC/ACC, ventromedial temporal lobe, ventral hippocampal regions, and amygdala.28–30 They, too, are modulated by sensory information ascending from lamina 1, the nucleus of the solitary tract, and the spinal trigeminal nucleus. This visceral and somatic spinal and supraspinal “lamina-1 type” sensory information is relayed by brain stem centers such as the parabrachial nuclei and PAG to the posterior ventromedial nucleus of the thalamus and, finally, to the insula, where the higher-order representations of this input allows for subjective experience of body state.20,21 According to Craig,20,21 it is the anterior portion of the right insula that specifically receives this “lamina-1 type” visceral and somatic sensory input. Because these sensory inputs activate sympathetic outflow, a convenient way of referring to them could be *pro-sympathetic afferents*. Craig uses the term *sympathetic afferents* to describe this input, but this terminology may lead to confusion because, anatomically speaking, there are no such sympathetic afferents, and visceral sensory nerves that travel in splanchnic nerves with efferent sympathetic fibers represent only one portion of the sensory information reaching the right anterior insula.

**The Parasympathetic Branch**

The parasympathetic branch of the autonomic nervous system regroups all the other autonomic nerves whose efferent fibers do not relay in pre- or para-vertebral ganglia. The ganglia in which these efferent fibers relay are located further away, close to the target organ. Parasympathetic efferent fibers are found in cranial nerves III, VII, IX, and X (oculomotor, facial, glossopharyngeal, and vagal nerves) and in sacral nerves. The two main sets of parasympathetic nerves are the two vagal nerves, which supply the thorax and abdomen, and the sacral nerves, which supply the pelvic organs. The preganglionic parasympathetic neurons of the vagal nerve are located in the lower brain stem (dorsal motor nucleus of the vagus and nucleus ambiguous). Those of the sacral nerves are in the sacral spinal cord. The preganglionic parasympathetic neurons of the vagal nerve are regulated by visceral and somatic sensory afferents originating from the nucleus of the solitary tract and spinal trigeminal nucleus, and those of the sacral serves are regulated by inputs from lamina 1 of the spinal cord. The descending modulation of parasympathetic preganglionic neurons by premotor centers, such as Barrington’s nucleus, is not as well understood as that of sympathetic preganglionic neurons, but the modulation originates in large part from the same cortical and subcortical centers that modulate sympathetic outflow—that is, the insular cortex, the medial PFC/ACC, the dorsomedial/dorsolateral PFC, middle temporal cortices, cerebellum, hippocampal regions, and amygdala.24,31–33

Activation of vagal efferents tend to produce effects that in opposition to those of sympathetic efferents—that is, the effects are anabolic, energy conserving, and usually associated with a decrease in arousal. The effect of sacral parasympathetic efferents is more complex and not necessarily in opposition to those of sympathetic efferents.

The vagus nerve contains visceral afferents that make an important contribution to the regulation of vagus efferent fibers. Some will have vagal efferents and produce the vagal effects as described above. Other “pro-vagal” inputs—of visceral and somatic origin and relayed by the spinal trigeminal nucleus and the dorsal horn of the spinal cord (including lamina 1)—may also produce the same type of effects. These pro-vagal afferents are antagonistic to the pro-sympathetic afferents described above. They ascend via the same relays (parabrachial nuclei, PAG, posterior ventromedial nucleus of thalamus) but appear to have a different representation in the insula cortex—this time in the left anterior insular cortex, according to Craig.20 The two types of afferents are responsible for interoception. How we feel depends on the balance of inputs between the left and right insulae.

**The Autonomic System as a Complementary/Dual-Control System**

In organs that receive both sympathetic and parasympathetic innervation, the two systems have complementary actions that can be either synergistic or antagonistic (e.g., control of the genitals vs. heart rate, respectively). Overall, the sympathetic system has a catabolic effect, causes the release and expenditure of energy, and is associated with arousal, whereas the parasympathetic system has an anabolic effect, increases saving and storing of energy, and is associated with rest. Working in tandem, the sympathetic and parasympathetic systems produce a continuous stream of signals that maintain homeostasis on a second-by-second basis. In the context of threat, the two systems generate other patterns of activation—namely, defensive programs that serve to defend the stability of the internal environment and to prepare the body for appropriate action.5,23,26

The complementary functions of the parasympathetic and sympathetic systems may also be reflected anatomically in the human forebrain.20 According to Craig,20 homeostatic information carried by sympathetic and parasympathetic pathways becomes increasingly lateralized as sympathetic and parasympathetic pathways “progressively activate higher-order homeostatic afferent re-representations in more anterior portions of the human insula.”20(p 567),24,31–33 On this model, “the left anterior insula (AI) is activated predominantly by homeostatic afferents associated with parasympathetic functions, and the right AI is activated predominantly by homeostatic afferents associated with sympathetic functions.”20(p 567) More broadly, this model posits that the left forebrain is associated with predominantly parasympathetic activity—nourishment and energy renewal, safety, positive affect, approach behavior, and group-oriented (positive and affiliative) emotions.20,34 The right forebrain, by contrast, is associated with predominantly sympathetic activity—arousal, danger, negative affect, withdrawal (aversive) behavior, and individual-oriented (survival) emotions.16,20,34–36

Although the model of the autonomic system as a complementary/dual-control system provides a useful overarching framework, some clinical situations require a further level of differentiation. In a more complex version of model discussed above, the parasympathetic system itself has two key subsystems—one that mediates restorative functions, and one that activates defensive programs and works alongside activation of sympathetically mediated defensive programs.37 Important examples of this parasympathetic defensive function can be seen in the parasympathetic afferents that carry nociceptive information,38 in parasympathetically mediated defensive programs in the gut (enteric expulsion programs for vomiting and diarrhea),39,40 and drastic reductions in heart rate mediated by vagal fibers from the dorsal motor nucleus.5

**THE SEROTONERGIC SYSTEM**

Monoaminergic systems and, in particular, the serotonergic system represent another layer for the modulation of information processing in the systems described above. The dorsal raphe nucleus (DRN), the largest serotonergic nucleus, is located on the midline of the brain stem. The DRN projects to many structures— the amygdala (basolateral and central nuclei), bed nucleus of the stria terminalis, PAG, locus coerulus, basal ganglia, and PFC—and receives projections from many of these areas. When serotonergic neurons in the DRN are sensitized in the context of uncontrollable stress, subsequent exposure to mildly stressful stimuli induces excessive activity and, via projections to amygdala-hypothalamic-PAG circuits, triggers anxiety symptoms and passive coping behaviors.41–43 DRN modulation of the amygdala is mediated by serotonin receptors. Serotonin activation enhances activation of fear circuits—particularly those involving passive behaviors such as behavioral immobility, reduction in social exploration, and escape deficits—whereas serotonin antagonism inhibits fear circuits. Regular voluntary exercise and selective serotonin reuptake inhibitors both function to constrain the activity of serotonergic neurons in the DRN.41,44,45 Top-down projections from the medial PFC are thought to modulate the activity of the DRN.

Significant alterations in serotonin metabolism in brain structures—for example, resulting from the activity levels of serotonin-metabolizing enzymes or from the density of receptors in the PFC, striatum, or fear circuits—have been shown to be associated with animals’ predispositions to manifest, or fail to manifest, defensive behaviors.46–51

**REFERENCES**

1. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol 2006;73:61–71.

2. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 2008;13:829,33–57.

3. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol Psychiatry 2006;60:376–82.

4. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. Prog Brain Res 2008;167:151–69.

5. Porges SW. The polyvagal theory: neurophysiological foundations of emotions, attachment, communication, and self-regulation. New York: Norton, 2011.

6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–81.

7. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol 2006;57:27–53.

8. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 2007;164:1476–88.

9. Holland PC, Bouton ME. Hippocampus and context in classical conditioning. Curr Opin Neurobiol 1999;9:195–202.

10. Fendler K, Karmos G, Telegdy G. The effect of hippocampal lesion on pituitary-adrenal function. Acta Physiol Hung 1961;20:293–7.

11. Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 1991;12:118–34.

12. Herman JP, Schafer MK, Young EA, et al. Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo-pituitary-adrenocortical axis. J Neurosci 1989;9:3072–82.

13. Armony JL, LeDoux JE. How the brain processes emotional information. Ann N Y Acad Sci 1997;821:259–70.

14. Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M. Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J Psychiatr Res 2010;44:477–85.

15. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry 2008;63:550–6.

16. King AP, Abelson JL, Britton JC, Phan KL, Taylor SF, Liberzon I. Medial prefrontal cortex and right insula activity predict plasma ACTH response to trauma recall. NeuroImage 2009;47:872–80.

17. Cannon WB. The wisdom of the body. New York: Norton, 1932.

18. Langley JN. The autonomic nervous system: part 1. Cambridge, Eng.: Heffer, 1921.

19. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 2000;85:1–17.

20. Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci 2005;9:566–71.

21. Craig AD. Interoception and emotion: a neuroanatomical perspective. In: Lewis M, Haviland-Jones JM, Barrett LF, eds. Handbook of emotions. 3rd ed. New York: Guilford, 2010:272–88.

22. Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. Ann N Y Acad Sci 2011;1225:72–82.

23. Janig W, Habler HJ. Specificity in the organization of the autonomic nervous system: a basis for precise neural regulation of homeostatic and protective body functions. Prog Brain Res 2000;122:351–67.

24. Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. NeuroImage 2008;42:169–77.

25. Valentino RJ, Miselis RR, Pavcovich LA. Pontine regulation of pelvic viscera: pharmacological target for pelvic visceral dysfunctions. Trends Pharmacol Sci 1999;20:253–60.

26. Westerhaus MJ, Loewy AD. Central representation of the sympathetic nervous system in the cerebral cortex. Brain Res 2001;903:117–27.

27. Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13:500–5.

28. Saper CB, Loewy AD, Swanson LW, Cowan WM. Direct hypothalamo-autonomic connections. Brain Res 1976;117:305–12.

29. Bittencourt JC, Sawchenko PE. Do centrally administered neuropeptides access cognate receptors?: an analysis in the central corticotropin-releasing factor system. J Neurosci 2000;20:1142–56.

30. Nakamura K, Morrison SF. Central neural circuitry for shivering. Physiol News 2011;85:21–4.

31. Gianaros PJ, Van Der Veen FM, Jennings JR. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. Psychophysiology 2004;41:521–30.

32. Lane RD, Reiman EM, Ahern GL, Thayer JF. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain Cogn 2001;47:97–100.

33. Matthews SC, Paulus MP, Simmons AN, Nelesen RA, Dimsdale JE. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. NeuroImage 2004;22:1151–6.

34. Goldberg E. The wisdom paradox. New York: Gotham, 2006.

35. Hopper JW, Frewen PA, van der Kolk BA, Lanius RA. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. J Trauma Stress 2007;20:713–25.

36. Ahern GL, Sollers JJ, Lane RD, et al. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia 2001;42:912–21.

37. Kozlowska K. Stress, distress, and bodytalk: co-constructing formulations with patients who present with somatic symptoms. Harv Rev Psychiatry 2013;21:314–33.

38. Chen SL, Wu XY, Cao ZJ, et al. Subdiaphragmatic vagal afferent nerves modulate visceral pain. Am J Physiol Gastrointest Liver Physiol 2008;294:G1441–9.

39. Tache Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. J Clin Invest 2007;117:33–40.

40. Wood JD, Alpers DH, Andrews PL. Fundamentals of neurogastroenterology. Gut 1999;45 suppl 2:II6–16.

41. Greenwood BN, Fleshner M. Exercise, stress resistance, and central serotonergic systems. Exerc Sport Sci Rev 2011;39:140–9.

42. Christianson JP, Ragole T, Amat J, et al. 5-hydroxytryptamine 2C receptors in the basolateral amygdala are involved in the expression of anxiety after uncontrollable traumatic stress. Biol Psychiatry 2010;67:339–45.

43. Maier SF, Watkins LR. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci Biobehav Rev 2005;29:829–41.

44. Fleshner M. Physical activity and stress resistance: sympathetic nervous system adaptations prevent stress-induced immunosuppression. Exerc Sport Sci Rev 2005;33:120–6.

45. Fox JH, Hammack SE, Falls WA. Exercise is associated with reduction in the anxiogenic effect of mCPP on acoustic startle. Behav Neurosci 2008;122:943–8.

46. Popova NK. Serotonin in genetically determined types of defensive behavior. Zh Vyssh Nerv Deiat Im I P Pavlova 1997;47:350–7.

47. Popova NK. The role of brain serotonin in the expression of genetically determined defensive behavior. Genetika 2004;40:770–8.

48. Popova NK, Barykina NN, Plyusnina TA, Alekhina TA, Kolpakov VG. Expression of the startle reaction in rats genetically predisposed towards different types of defensive behavior. Neurosci Behav Physiol 2000;30:321–5.

49. Popova NK, Kulikov AV, Avgustinovich DF, Barykina NN. Involvement of striatum serotonergic system in the expression of genetically defined catalepsy. Ross Fiziol Zh Im I M Sechenova 1997;83:66–79.

50. Popova NK, Kulikov AV, Avgustinovich DF, Voitenko NN, Trut LN. Effect of domestication of the silver fox on the main enzymes of serotonin metabolism and serotonin receptors. Genetika 1997;33:370–4.

51. Popova NK, Kulikov AV, Kolpakov VG, Barykina NN, Alekhina TA. Changes in the serotonin system of the brains of rats genetically predisposed to catalepsy. Zh Vyssh Nerv Deiat Im 1985;35:742–6.