**Supplemental Text Box 2**

**Parasympathetic Innervation of the Heart**

In humans, the parasympathetic innervation of the heart involves vagal preganglionic neurons from two topographical locations: neurons lying in the nucleus ambiguous (NA) and neurons lying in the dorsal motor nucleus (DMN).1–3 The NA neurons, located in close proximity to neurons involved in respiration, modulate heart function on a second-by-second basis in synchrony with the respiratory cycle.2,3 Under resting conditions, these respiration-related NA neurons are maximally activated, resulting in high cardiac vagal tone and a comparatively low heart rate.4 When a mammal is confronted with a challenge, vagal tone is withdrawn, which increases both the heart rate and cardiac output. If further activation is required, the sympathetic system is activated, and heart rate and cardiac output increase still further. The second subpopulation of cardiac vagal preganglionic neurons—non-respiration-related neurons from the DMN—are intermittently active only.1,5 In the context of threat, as in the initiation of the defense cascade, the amygdala, paraventricular nucleus of the hypothalamus, and ventrolateral periaqueductal gray activate the DMN and set in motion a range of defensive functions in the heart and gut.6–8 Among other things, activation of the DMN neurons causes a drastic reduction in heart rate (Armour JA, personal communication, 2011),1,9 a central feature of orienting responses, freezing, tonic immobility, and collapsed immobility.

Although the topographical distribution of the functionally different subpopulations of cardiac vagal neurons is largely agreed on,1,3 two factors—the existence of vagal neurons between the NA and DMN in the dog (Armour JA, personal communication, 2011)3,5 and the modulation of esophageal tone in synchrony with respiration10—suggest complex functional interactions between the NA and DMN. In other words, although the main text of the article presents the NA and DMN as functionally distinct, some functional overlap, as yet undetermined, appears likely. Other issues that remain unresolved between different researchers are the phylogenetic development of the NA and whether cardiac fibers from the DMN are unmyelinated (vs. NA fibers, which are myelinated).1,11 Although these details are important from an anatomy and a research perspective, they are not important for understanding the clinical consequences of the defense cascade. What is important from a clinical perspective is that the NA and DMN include functionally different subpopulations of cardiac vagal neurons; the existence of these subpopulations allows for models that can explain drastic reductions in heart rate, via the DMN, that occur in the defense cascade.

The interactions between sympathetic and parasympathetic inputs to the heart are complex, and current models remain largely hypothetical. Differences in theory and in the associated neurophysiological models are a matter of ongoing discussion.1,11 In general, however, it is accepted that in mind-body states characterized by calm, vagal activity is dominant. In mind-body states involving either preparation for action or states of action, sympathetic activation occurs in tandem with withdrawal of NA vagal activity.1,12,13 Once the challenge has passed, activation of NA vagal efferents—with parallel inhibition of sympathetic influences—allows the individual to return to a state of calm. During freezing, sympathetic activation coexists with vagal activation.14 During tonic and collapsed immobility, it is hypothesized that the activity of DMN vagal fibers to the heart is triggered when activity by the NA vagal fibers to the heart is withdrawn.1 The issue of concurrent sympathetic activation during tonic immobility—whether it is partially inhibited or simply overridden—is a matter of contention and may differ between species.15,16 During collapsed immobility, bradycardia-induced cerebral hypoxia results in a temporary disruption to a broad range of cerebral functions.

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