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Review article

The hierarchical basis of neurovisceral integration

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ABSTRACT

The neurovisceral integration (NVI) model was originally proposed to account for observed relationships between peripheral physiology, cognitive performance, and emotional/physical health. This model has also garnered a considerable amount of empirical support, largely from studies examining cardiac vagal control. However, recent advances in functional neuroanatomy, and in computational neuroscience, have yet to be incorporated into the NVI model. Here we present an updated/expanded version of the NVI model that incorporates these advances. Based on a review of studies of structural/functional anatomy, we first describe an eight-level hierarchy of nervous system structures, and the contribution that each level plausibly makes to vagal control. Second, we review recent work on a class of computational models of brain function known as "predictive coding" models. We illustrate how the computational dynamics of these models, when implemented within our proposed vagal control hierarchy, can increase understanding of the relationship between vagal control and both cognitive performance and emotional/physical health. We conclude by discussing novel implications of this updated NVI model for future research.

Contents

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1. Introduction

There is now very compelling evidence that parasympathetic or vagal tone – often measured using the high frequency component of heart rate variability (HRV) – is associated with a variety of psychological and behavioral variables on the one hand, and a variety of health outcomes on the other. With regard to psychological/behavioral variables, there now exist several replicated findings suggesting that higher HRV is associated with greater capacity for emotion regulation (Appelhans and Luecken, 2006; Butler et al., 2006; Ingjaldsson et al., 2003; Lane, 2008; Melzig et al., 2009; Ruiz-Padial et al., 2003; Thayer and Brosschot, 2005) and with greater performance on several cognitive tasks involving attention, working memory, and inhibitory control (Hansen et al., 2009, 2004, 2003; Johnsen et al., 2003; Saus et al., 2006; Thayer et al., 2005). With regard to health outcomes, higher HRV has also been associated with better glucose regulation, better hypothalamic-adrenal-pituitary (HPA) axis function, reduced inflammation, and reduced risk for stroke, cardiovascular disease, and all-cause mortality (Brosschot et al., 2007; Liao et al., 2002; Thayer and Fischer, 2009; Thayer and Lane, 2007; Thayer and Sternberg, 2006); lower HRV has also been associated with affective disorders such as depression and anxiety (Gorman and Sloan, 2000; Kemp and Quintana, 2013; Kemp et al., 2012, 2010). As is true of most correlational findings in mind-body medicine, the demonstration of mechanisms mediating these observed relationships can potentially extend both understanding and practical utility. One such attempt at mechanistically explaining the HRV-related findings highlighted above is the "neurovisceral integration" (NVI) model (Thayer and Lane, 2000), which represents an integrative effort to combine current knowledge about the relationship between mental states, autonomic function, and health outcomes into a single framework centered on a network of reciprocally connected brain regions called the "central autonomic network" (CAN; Benarroch, 1993). This model was first presented in 2000; it was then updated in 2009 by reviewing new evidence supporting the original proposal and providing an updated characterization of the multiple circuits linking the heart and brain (Thayer and Lane, 2009).

A primary goal of the current paper is to extend the original model further by providing additional specificity and detail. This appears important because previous presentations of the NVI model have been somewhat vague about the specific neuroanatomical loci involved in vagal tone regulation. For example, many separable network regions have previously been grouped together, and the functions of each of these different regions have not been thoroughly specified. Moreover, the way these different regions interact has not been fully addressed. This paper therefore aims to fill that gap and present an updated model of how the different brain regions implicated in vagal regulation work together. This update is informed by more recent studies on brain-HRV interactions, as well as by more general developments in computational neuroscience. In particular, we will suggest below that recent developments in neuroscience may allow for a more detailed characterization of the multi-level control architecture that allows for adaptively coordinated cognitive, affective, autonomic, and behavioral responses. Before doing so, however, it is important to review current knowledge of the general structural anatomy relevant to vagal control, and to review where gaining increased understanding of function may be important.

2. A gap between understanding of structure and function

In earlier presentations of the NVI model, the CAN (Benarroch, 1993) was described as being made up of several regions. These included the anterior cingulate cortex (ACC), the anterior (AI) and posterior (PI) insula, the ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC), the amygdala, the bed nucleus of the stria terminalis (BNST), the hypothalamus, the periaqueductal gray (PAG), the parabrachial nucleus (PBN), the nucleus of the solitary tract (NTS), the nucleus ambiguus (NA), the dorsal motor nucleus of the vagus (DMNV), the noradrenergic locus coeruleus (LC), and the rostral (RVLM) and caudal (CVLM) ventrolateral medulla (among others). The primary output of the CAN was described as occurring via preganglionic sympathetic and parasympathetic neurons, which innervate the heart through both stellate ganglia and the vagus nerve. The integrated effects of these different signal pathways, when they reach the sino-atrial (SA) node of the heart, were also described as the proximal factor determining HRV. Given that the CAN also receives a large amount of afferent information from both the body and the external world – allowing for context-specific cardiac regulation – it was argued that HRV can be understood as an important index of the level of integration between the peripheral autonomic and central nervous systems. Further, because the timescale for changes in sympathetic tone is relatively slow compared to that of parasympathetic tone (on the order of seconds vs. milliseconds; Saul, 1990), it was argued that faster, moment-to-moment adjustments in autonomic function (e.g., as in cognitive/affective contexts) primarily reflect the addition or withdrawal of vagal influence.

The overarching structure of the CAN described above has been supported by retrograde viral staining studies of parasympathetic cardiac regulation in both rodents and primates (Chuang et al., 2004; Ter Horst and Postema, 1997); these studies provide evidence of (1) structural connections between the ventricular myocardium and vagal motor neurons, and (2) connections between those vagal motor neurons and a series of hierarchically organized higher-order control neurons in a number of brain regions. These include brainstem regions (i.e., the DMNV, NA, NTS, area postrema, LC, and PBN), higher subcortical regions (i.e., PAG, hypothalamus, amygdala, and BNST), and cortical regions (i.e., ACC, insula, and frontal cortex). More recently, retrograde viral staining studies have also provided evidence of structural connections between sympathetic effector organs and (1) visceromotor, (2) skeletomotor, and (3) higher prefrontal cortical regions involved in cognition and affect (Dum et al., 2016). As stated above, however, although the NVI model proposed that the regions listed above form a distributed control network, allowing for the integration of cognitive, affective, attentional, and autonomic information to guide adaptive goal-directed behavior, a detailed account of this network architecture (and the different functions of the regions involved) was not provided.

Instead, the original NVI model appealed to the dynamical systems (DS) perspective to provide an abstract mathematical language for understanding the complex functional dynamics of the CAN (Thayer and Lane, 2000). The DS perspective abstractly con-

ceptualizes an organism as a complex set of parallel reverberating circuits that interact in a coordinated (loosely coupled) manner, and that can be described with a particular set of mathematical concepts. Specifically, it was suggested that an evolving cognitive/emotional response in the CAN could be understood as a trajectory through a high-dimensional state-space (e.g., in which each dimension might describe the possible state values of a particular CAN region). Given this formalism, movement through the CAN state-space could be guided by a small set of modulatory influences on the network that acted as control parameters. Further, given a set of such modulatory influences, some points in this state-space (called "attractor basins") could have relatively greater stability than others, and these points could be identified with stable cognitive/emotional states of the organism. This theoretical set-up allowed the NVI's suggestion, for example, that affective disorders might be viewed as arising from dysfunctional state-space topographies that facilitate an individual getting "stuck" in particularly strong attractor states (e.g., particular feeling states or behavior patterns), and therefore unable to shift into a state representing a more adaptive emotional/behavioral response to the current situation (Friedman and Thayer, 1998; Thayer and Friedman, 1997). Although this abstract way of characterizing CAN dynamics was useful, in the present paper we have sought to expand on the model further by providing more concrete detail regarding particular brain regions of the CAN and how they may interact to support vagal control.

More specifically, the broad idea we develop in what follows is that this network is organized hierarchically such that lower levels mainly integrate current afferent information from the body in order to regulate energy expenditure in response to *present* metabolic needs. In contrast, higher levels of the hierarchy integrate a wider range of information (e.g., from exteroceptive perception and memory) in order to regulate energy expenditure in response to *both present and expected future* metabolic needs (e.g., as in the context of a long-term cognitive or social/emotional goal). This general organizational structure is sensible when one considers how higher level functions can asymmetrically depend upon lower level functions. For example, before one can worry about meeting longer timescale needs like friendship and procreation, it is required that present metabolic resources are kept at appropriate levels. Meeting such basic needs requires mechanisms that detect when resources (e.g., water, glucose) are approaching low levels, and that adjust energy expenditure and behavior in ways that would be expected to remedy this. Such mechanisms must therefore be in place before one can reliably adjust energy expenditure in the body for higher-level cognitive/emotional purposes.

After such lower-level circuits are secure, higher-levels can mobilize metabolic resources by modulating the outputs of these lower-level mechanisms. Consider, for example, the function of neural mechanisms involved in emotion generation (EG). EG can be understood to involve a system of "situational appraisal mechanisms" (SAMs) that jointly function 1) to determine the extent to which needs, goals, and desires are met or not met when interacting with the environment and 2) to trigger an appropriate emotional reaction in response. This emotional reaction can in turn be understood to modulate an organism's internal state across multiple dimensions, including influences on thought, attention, perception, memory, and action selection, as well as the autonomic, endocrine, and immune system adjustments needed to support these changes (including cardiac control adjustments). In this way, whenever one's longer timescale emotional needs are not being met (e.g., when deviations from adaptive equilibrium states are predicted in response to perceived threat or loss), involuntary reactions can be triggered that alter bodily function, cognition, and behavior in a manner that is predicted to promote a return of physiological variables to more stable, adaptive state values. However, such involuntary emotional reactions can often be triggered by fairly simple perceptual cues (e.g., Whalen et al., 2004), and they may not always be sensitive to important aspects of a larger social context. In addition, therefore, in order to successfully navigate the relatively large social groups and idiosyncratic cultural environments that characterize human life, a flexible, context-sensitive regulatory system involving yet higher levels of control would also be required to enable individuals to adjust automatic emotional responses in adaptive ways. For example, it is often better for achieving one's long-term goals to voluntarily regulate (rather than express) either affectionate or hostile feelings in the workplace. While one cannot typically abolish such automatic feelings voluntarily, humans do appear capable of learning both effortful and habit-like strategies for either indirectly decreasing their intensity or inhibiting their behavioral expression (Buhle et al., 2014; Gross, 1998; Gyurak et al., 2011). Such regulatory strategies would also be expected to have important modulatory influences across many levels of control, including influences on cardiac activity.

A key question, therefore, is how to understand the organizational architecture of these different functions, from the most basic to the most complex. In what follows we will suggest that the NVI model should be extended to include a multi-level neural network architecture involving several neurovisceral integration loops, and that their function can be characterized similarly to a multi-step group decision process. To outline the details of such processes, in the following section we will first review current knowledge of the nature of many of the specific structural connections between the CAN regions described above, and how this may relate to regional function. Given our focus on HRV, we will adopt cardiac function as our example case of autonomic control, and use this to highlight different levels of sensory integration and associated regulation within this network.[1] After reviewing these levels, in Section 4 we will then review recent progress on computational models of neural function. These models specifically address the need for the brain to predict the need for metabolic resources in advance, and thus to mobilize these resources in time to successfully meet the expected needs of both short and long timescale challenges. This will allow us to describe an updated NVI model in section 5 that includes the inter-level dynamics of information processing, and that can more fully account for the known relationships between higher HRV and better physical health, emotion regulation, and cognitive control.

3. The multi-level structure/function of vagal control

Each of the hierarchical levels described below is involved in vagal control via participation in the generation, integration, or expression of vagal influence. In the sections below we provide evidence of participation in vagal control as well as evidence of the functions of the structures at each level and how the range and complexity of functions increases at each level of the hierarchy. A fundamental principle of the organization we describe is that new types of information are integrated at each level, and, as a result, each level is more flexibly recruited to modify vagal tone than the level below. Therefore, the highest (and most flexibly recruited) levels we describe will play much more prominent roles in regulating vagal output in some contexts relative to others.

[1] Many of the levels we describe below have also been discussed to some extent in previous work (Smith and Lane, 2015). However, the extended NVI model we describe proposes novel/expanded ways of understanding the functions of, and interactions between, these levels. Unlike previous work, it is also not restricted to the domain of emotion, but instead considers cognition-related changes in vagal control as well.

3.1. Level 1: intra-cardiac control

At the lowest levels of cardiac control, it is well established that the peripheral nervous system makes use of multiple somatic and visceral reflex pathways, including cross-organ reflex pathways and even intra-cardiac reflex pathways (Longhurst, 2011; Strominger et al., 2012). Intrinsic cardiac ganglia, for example, consist of neurons that function as efferent neuronal relays (under the control of medullary and spinal cord [adrenergic] nuclei) and also engage in local cardiocentric reflexes (Armour, 2004). These intrinsic ganglia are considered to be complex structures that have additional functions beyond simply serving as vagal relay stations, and they are capable of responding to chemical, mechanical, and electrophysiological stimuli. For example, intrinsic cardiac ganglia neurons coordinate regional cardiac responses, which also involve pathways serving interactions with intra-thoracic local circuit neurons, dorsal root ganglia neurons, and with cardiac afferent neurons that sense 1) regional mechanical deformations, 2) the composition of the local chemical milieu, or 3) both (Armour and Ardell, 2004; Wake and Brack, 2016; Shivkumar et al., 2016). Finally, there are two major types of cardiac motor neurons at the lowest level – cholinergic (vagal) and adrenergic (sympathetic) – that are known to exert opposing effects on the heart.

3.2. Level 2: coordinated cardiovascular control

The primary example of this second level is the *arterial baroreflex* (or baroreceptor reflex; Jänig, 2008), which coordinates cardiac output with blood pressure (BP). A primary function of the cardiovascular system is to maintain optimal arterial blood pressure and to provide adequate blood flow to the brain, the heart, and other vital organs. In response to environmental demands, blood pressure and the distribution of blood flow throughout the body are finely tuned by an intricate system that includes this reflex. Baroreceptors are principally stretch-pressure receptors. Cardiopulmonary baroreceptors are located in the cardiac atria, ventricles, and pulmonary vasculature, whereas arterial baroreceptors are mainly located in the aortic arch and carotid sinus. BP sensitive neurons also innervate the right carotid artery-right subclavian artery junction and coronary arteries; these contribute to a separate branch of the baroreflex, the *coronary artery baroreflex*, which modulates vascular resistance and peripheral sympathetic nerve activity, but unlike the arterial baroreceptor reflex, has little effect on heart rate (Chapleau, 2012).

The baroreceptor reflex involves lower brainstem nuclei, such as the NA, the DMNV, and the NTS. These nuclei detect organ-specific visceral activity via afferent sympathetic and parasympathetic nerve pathways, and use this information in homeostatic, reflex-like regulation of autonomic tone. Baroreceptor afferents relay information to the NTS, which modulates outputs to excitatory projections to vagal motor neurons, and inhibitory influences on nuclei controlling spinal sympathetic neurons (Benarroch, 2008). More specifically, the NTS receives information from blood pressure-sensitive baroreceptors within the carotid sinus and aortic arch (Jänig, 2008); increased baroreceptor activity then initiates a response within specific NTS neurons – which indirectly inhibit the RVLM – resulting in decreased sympathetic tone, and therefore a decrease in blood pressure. NTS neurons further influence parasympathetically innervated nuclei, such as the NA and the DMNV. The resulting increases in vagal tone can then lead to coordinated decreases in heart rate.

The baroreceptor reflex is implicated both in short- and long-term setting of heart and vasomotor activity, and thus is potentially relevant in the development of essential hypertension (Hesse et al., 2007). As a main source of cardiovascular autonomic regulation, decreases in baroreflex function are strongly associated with several cardiovascular diseases, being a powerful predictor of adverse clinical outcomes (Guyenet, 2006; La Rovere et al., 1998). The function of the baroreflex, though dually innervated, is largely under parasympathetic control and the various indices of baroreflex function correlate with vagally-mediated HRV (Benarroch, 2008; Duschek and Reyes del Paso, 2007), although it's prognostic significance is independent of vagally-mediated HRV (La Rovere et al., 1998).

When BP increases, the baroreflex increases vagal cardiac activity (increasing inter-beat interval, IBI), and inhibits efferent α-adrenergic outflow to the vasculature (producing vasodilatation), and β_1-adrenergic activity to the myocardium (lowering stroke volume, SV). The opposite reflex changes are elicited when BP decreases, thus buffering BP oscillations (Benarroch, 2008; Reyes del Paso et al., 1996). Consistent with these reflex effects, three closed-loop control branches can be identified in the baroreflex: the cardiac (influencing IBI), vascular (influencing vasomotor tone) and myocardial (influencing SV). Through negative feedback loops in response to BP changes, the vascular branch modulates vasomotor tone (i.e., blood vessel diameter); the myocardial branch controls inotropic-related sympathetic outflow to the ventricle (i.e., blood ejected from the heart in each beat or force of contraction, SV); and the cardiac branch modulates chronotropic influences (i.e., IBI). Several indices of baroreflex function have been suggested and defined (Duschek and Reyes del Paso, 2007; Parati et al., 2000). Baroreflex *sensitivity* (BRS) refers to the magnitude of reflex changes in heart rate (or vasomotor tone or contractility) following fluctuations in blood pressure. Baroreflex *effectiveness* refers to the relative frequency in which the reflex heart rate (or vasomotor or contractility) changes respond to fluctuations in blood pressure and the baroreflex *power* refers to the reflex changes in a specific time period (see Duschek & Reyes del Paso, 2007, for a detailed account of these different indices.). The inverse relationship between HRV and BP variability is an example of an important physiological regulation strategy known as *heterostasis* (Davis, 1958), where variability in one system (HRV in this case) is associated with stability in another system (BP in this case). Thus an examination of the baroreflex provides a case study for understanding a mode of physiological regulation that has been suggested to be more prevalent and relevant than homeostasis (Davis, 1958).

3.3. Level 3: coordinated cross-organ system control

The third level of control involves similar lower brainstem nuclei as level 2, such as the NA, the DMNV, and the NTS. However, beyond detecting and using organ-specific visceral activity to ensure homeostatic, reflex-like regulation of single organ systems, these regions are also responsible for coordination and regulation across organ systems. Using the arterial baroreceptor reflex as an example: unlike at level 2, additional pathways allow baroreceptor-mediated activity in the NTS to use afferent cardiovascular information to trigger coordinated changes in other organ systems (e.g., changes in respiration). Other examples of coordinated cross-organ reactions include the impact of arterial baroreceptors on cerebral autoregulation (Talman et al., 1994; Tzeng et al., 2010) and renal autoregulation (Pires et al., 2002).

These lower brainstem nuclei therefore provide an added level of control over peripheral cross-organ reflexes that extends beyond the cardiovascular system. Related mechanisms for homeostatic control in these brainstem nuclei are also present both within and across other organ systems (Jänig, 2008), potentially allowing the integration of a wider range of organ-specific information in the regulation of peripheral reflex arcs. For example, the NTS is also known to participate in glucose and immune regulation (Solomon et al., 2006; Thayer et al., 2011), where such systems are under tonic inhibition from the vagus nerve. In fact, the known organotopic

organization of the NTS could, in principle, allow it to alter such functions (e.g., increase inflammation, alter glucose metabolism) in a region-/organ-specific manner, by temporarily withdrawing this inhibitory vagal influence along organ-specific efferent pathways.

Another set of important structures at the level of cross-organ control are the circumventricular organs (CVOs), which are specialized locations of contact between the central nervous system and the internal milieu of the body that lack a typical blood-brain-barrier. CVOs include the area postrema (adjacent to the medulla), the organum vasculosum of the lamina terminalis (OVLT; within the wall of the third ventricle), and the subfornical organ (SFO; within the lamina terminalis) (see Benarroch, 2011). Neurons in these structures are reliably influenced by a range of circulating chemical indicators of cardiovascular and metabolic status, serum osmolarity, levels of sodium and calcium, and the presence of various toxic substances; when activated, these structures may also influence various homeostatic regulatory functions and behaviors (e.g., those associated with sodium intake, thirst, and vomiting) through connectivity with each other, and with the cingulate cortex, hypothalamus, amygdala, and multiple autonomic brainstem nuclei including the PAG, NTS, and PBN (Benarroch, 2011; Mimee et al., 2013).

3.4. Level 4: coordinated skeletal-motor, visceral-motor, and endocrine control

The fourth level represents the first stage at which coordinated visceromotor and skeletomotor control may converge. This level of control in the CAN involves groups of neurons within the hypothalamus and periacqueductal gray (PAG) that have bidirectional connections with the lower brainstem nuclei discussed above. With regard to the former, this was first suggested by early decortication experiments demonstrating that coordinated emotional expressions are abolished by hypothalamic, but not cortical, lesions (Bard, 1934, 1929, 1928; Cannon and Britton, 1925; Cannon, 1929); more recent work has also confirmed that hypothalamic circuits (including a range of distinct hypothalamic nuclei) are capable of triggering coordinated autonomic, endocrine, and behavioral reactions – associated with phenomena such as thermoregulation, hunger, thirst, sex drive, aggression and sleep (Morrison and Nakamura, 2011; Saper, 2002; Sternson, 2013). The hypothalamus has also long been known to have both "pressor" and "depressor" regions, which respectively increase sympathetic and parasympathetic influence when stimulated (Allen and Cechetto, 1993, 1992).

The PAG has similarly been associated with the coordinated production of different physiological/behavioral response patterns (Bandler and Shipley, 1994; Satpute et al., 2013). For example, PAG stimulation reliably evokes the behavioral freezing reaction associated with threat and fear (Brandão et al., 2008). Stimulation of either the PAG or the lateral hypothalamus can also produce the classic "defense reaction," which includes increases in heart rate, regional changes in vasoconstriction and vasodilation, and multiple organ-specific activation changes that are often adaptive in threatening "fight-or-flight" circumstances (Arthur et al., 1991; Morrison, 2001; Schadt and Hasser, 2001). Similar to the hypothalamus, the PAG is also known to be divided into dorsal (pressor) and ventrolateral (depressor) columnar regions, which are known to mediate increases in sympathetic and vagal tone, respectively (Behbehani, 1995).

An important insight, however, is that the hypothalamus has a very large number of direct and indirect "upward" projections to the entire cerebral cortex as well (Rempel-Clower and Barbas, 1998; Risold et al., 1997; Swanson, 2000). In fact, it appears to be one of the largest sources of input to cortex aside from the thalamus, including projections to the MPFC/ACC, insula, lateral PFC, and to primary sensory cortices. It also has strong projections to the amygdala and to cholinergic and GABAergic basal forebrain (BF) nuclei (e.g., the nucleus basalis/substantia innominata), which each themselves project strongly to cortex. Thus, the hypothalamus is well positioned to initiate very broad influences on both higher (e.g., cortical) and lower (e.g., brainstem) levels of control. Major projections are also received by the hypothalamus from regions of the hippocampal formation, amygdala, insula, and prefrontal cortex (largely from medial/orbital sectors).

3.5. Level 5: coordinated control of stimulus-driven somatic, visceral, and cognitive/attentional responses

The key structures exerting a further influence over vagal processing at the next level of control are the amygdala and the basal forebrain. For example, in a recent meta-analysis (Thayer et al., 2012), amygdala responses were found to be consistently associated with HRV across several studies. Through its efferent outputs in the central-medial nuclei, the amygdala is also known to have a downward influence on a wide range of subcortical regions, including the hypothalamic nuclei, the PAG, and the brainstem nuclei discussed above (LeDoux, 2012, 1996; Pessoa and Adolphs, 2010). In addition, the amygdala is known to play an important role in the detection of "significant" stimuli, such as those that are novel and/or relevant to one's current needs/concerns (Blackford et al., 2010; Brosch and Sander, 2013; LaBar et al., 2001; Ranganath and Rainer, 2003; Schwartz et al., 2003); thus, the above mentioned efferent outputs are thought to allow such stimuli to initiate specific coordinated autonomic/behavioral responses via this amygdalar influence on lower-level structures. This allows the amygdala to serve as an important low-level mechanism for generating coordinated bodily emotional responses.

Aside from these downward influences, however, the amygdala is highly connected structurally to the entire cortex as well (Barbas, 1995; Petrovich et al., 2001; Swanson, 2003; Young et al., 1994). Its connections with all sensory cortices (Sah et al., 2003), as well as with higher association cortices (Amaral et al., 1992; Young et al., 1994), appear to facilitate automatic attention to "emotional" (i.e., novel, concern-relevant) stimuli (Vuilleumier and Huang, 2009). However, the amygdala also has bidirectional structural connectivity with medial/orbital as well as lateral PFC (Amaral and Price, 1984; Ghashghaei et al., 2007); measures of functional connectivity between amygdala and MPFC have previously been associated with HRV as well (Sakaki et al., 2016). While direct structural connections with lateral PFC are weaker, it is estimated that 90% of PFC can be influenced by the amygdala through only 1 intermediate synapse (Averbeck and Seo, 2008). These bilateral prefrontal connections allow the amygdala to have a strong upward influence on cortical regions involved in higher cognitive/attentional processes, but can also allow prefrontal regions to modulate amygdala reactivity via downward pathways (e.g., Comte et al., 2014; Davis and Whalen, 2001; Gupta et al., 2011; Kim et al., 2011; Mitchell and Greening, 2011; Peck and Salzman, 2014; Pessoa and Adolphs, 2010; Pessoa, 2008). Thus, in addition to coordinated autonomic/behavioral control, the amygdala also appears capable of generating the cognitive/attentional changes associated with an emotional response.

Despite the above mentioned amygdala-PFC connections, some of these amygdalar functions may also be indirectly mediated by its projections to the BF. The BF is known to be the origin of both cholinergic and GABAergic projections to the entire cortex (Mesulam, 2000), as well as to the hippocampus and amygdala (Mesulam et al., 1992; Zaborszky et al., 1999). It is also known that, via the influence of these output pathways, the BF functions to enhance alertness, selective attention, and cortical plasticity (Dykes, 1997; Kilgard and Merzenich, 1998; Sarter and Bruno, 1999; Weinberger, 2003). For example, bilateral BF-amygdala interactions are impli-

cated in multiple aspects of attentional processing (Holland, 2007; Maddux et al., 2007), and the BF has also been shown to improve signal-to-noise ratios (i.e., reduced variability) in neural responses within cortical sensory systems (Goard and Dan, 2009). Interestingly, there appears to be a gradient such that the most dense BF projections are received in agranular cortical regions (such as the ACC, AI, and OFC), which have themselves been identified in the retrograde tracer studies of cardiac control described above (Chuang et al., 2004; Ter Horst and Postema, 1997). Further, these same cortical regions that receive the largest BF projections also send back the most projections to it (Zaborszky, 2002), allowing for many parallel circuit loops to form between the BF and these different regions. Finally, in addition to the amygdala, it is worth highlighting that other major projections to the BF arise from the hypothalamus as well as multiple brainstem nuclei (including midbrain dopamine neurons and LC noradrenergic neurons), which in turn may serve important functions. For example, in addition to it's classical role in modulating wakefulness, the LC has been suggested to convey a "warning signal" to the entire forebrain, in part via its influence on the BF (e.g., in response to potentially threatening stimuli; Zaborszky et al., 1999). When considering the many studies that now link higher HRV to better performance in cognitive, attentional, and emotion-related tasks (Appelhans and Luecken, 2006; Butler et al., 2006; Hansen et al., 2009, 2004, 2003; Ingjaldsson et al., 2003; Johnsen et al., 2003; Lane, 2008; Melzig et al., 2009; Ruiz-Padial et al., 2003; Saus et al., 2006; Thayer and Brosschot, 2005; Thayer et al., 2005), the fact that vagal regulation, detection of emotional stimuli, and attentional control appear to interact in these level 5 structures suggests that it is likely at this level (and those levels above it) that the mechanisms explaining the HRV-performance relationship will be found.

3.6. *Level 6: regulation based on perceptual representation of one's current somatic/visceral state*

Two conceptually distinct levels of control that are higher in the neuraxis than the amygdala and BF can also be identified. These levels are the first to include cortical regions. They involve overlapping regions of the insula, somatosensory cortex, ACC, PCC, and the OFC/MPFC. The first of these two levels (level 6) can be understood to involve regulation of lower levels of the hierarchy based on cortical perceptual representations of one's current somatic/visceral state – primarily involving regions of the insula, cingulate, and somatosensory cortex. The second of these two levels (level 7) instead involves regulation of lower hierarchical levels based on conceptual interpretations of the meaning of perceptual input (from the body as well as other sensory systems) based on past experience – and involves the cortical regions making up the "default mode network" (Barrett and Satpute, 2013; Buckner et al., 2008), including (among others) the MPFC, ACC, PCC, and medial and lateral temporal lobe regions associated with declarative memory. There is considerable spatial overlap between these two levels when considering gross cortical anatomy. However, despite this spatial overlap, there is good evidence suggesting that these regions play different roles in different cortical networks, subserving perception and conceptualization respectively (reviewed in Barrett and Satpute, 2013). It is on this basis that we propose more than one level of processing within these broad cortical regions.

The first structure we will review is the insula, which plays a primary role in level 6 processing. While the insula is often discussed as a visceral-sensory structure (Craig, 2002), it is also believed to play a visceromotor role (Augustine, 1996). Descending projections to the hypothalamus and parabrachial nucleus, for example, arise from both the AI and PI (Saper and Loewy, 1980), and stimulation of both of these regions has been shown to influence a range of sympathetic and parasympathetic responses (Cechetto and Chen, 1990; Yasui et al., 1991). With regard to interoception, afferent signals from the viscera are first received in the PI (which, similar to the NTS, is also topographically organized with respect to the viscera), and then conveyed to the AI via the mid-insula, leading to higher and higher levels of internal body state representation that can be used in a variety of ways (Craig, 2009, 2002). The AI, for example, is known to be engaged by a wide range of perceptual, cognitive, and affective tasks (Craig, 2009), and has been identified as one of the most functionally diverse cortical regions in large-scale functional analyses (Anderson et al., 2013). Interestingly, however, cardiac interoception appears to also involve non-viscerosensory pathways that terminate in primary/secondary somatosensory cortex (Gray et al., 2007; Hassanpour et al., 2016; Kern et al., 2013; Khalsa et al., 2009; Pollatos et al., 2016, 2005). This suggests that "level 6" control over cardiac function is likely informed by somatosensory signals as well. Thus, insula and somatosensory cortex representations of the state of the whole body are likely both of central importance to many aspects of vagal control, and may also make important contributions to cognitive and behavioral control.

One of the main regions the insula interacts with is the cingulate gyrus, which represents a highly complex structure including roughly 40 separable sub-regions (Vogt, 2009). The cingulate also appears to have the most extensive descending projection system of any cortical structure (Vogt and Vogt, 2009), including projections to the amygdala, hypothalamus, PAG, parabrachial nucleus, and NTS (Vogt and Derbyshire, 2009). Consistent with a visceromotor role, stimulation of numerous sites in the cingulate has been found to produce effects on a range of sympathetic, parasympathetic, and endocrine mechanisms (Vogt, 2009); however, the cingulate also receives direct projections from the NTS and other visceral-sensory nuclei (e.g., nociceptive nuclei), which suggests an afferent processing role as well (Vogt et al., 2009). Functionally, the ACC in particular has been most closely linked to AI function in representing/regulating bodily states (i.e., "level 6" functions; Medford and Critchley, 2010). However, it has also been implicated in functions informed by conceptualization, such as volitional action selection, emotion, and several executive functions (Barrett and Satpute, 2013; Etkin et al., 2011; Etkin et al., 2006; Silvetti et al., 2014). The PCC, in contrast, has been more strongly associated with long-term memory and conceptualization-related processes as part of the default mode network (e.g., Barrett and Satpute, 2013; Li et al., 2014), and is therefore more primarily involved in "level 7" control.

The OFC represents an additional, highly related area for cortical control of CAN output. This region has been structurally divided into two networks: the "orbital" and "medial" networks (Carmichael and Price, 1996). The orbital network appears to receive and integrate sensory information, especially in relation to the rewarding properties of food; in contrast, the medial network is much more heavily connected to the ACC, MPFC, hypothalamus, and related visceral control regions (Ongur and Price, 2000). It also receives few sensory inputs (relative to the orbital network), and, via hypothalamic nuclei, appears capable of influencing autonomic control down to the level of spinal cord nuclei (Barbas et al., 2003). Thus, the medial OFC network appears considerably more important than the orbital network with respect to modulating vagal output. Due to its proximity to, and overlap with, MPFC default mode regions, we suggest the OFC is perhaps best understood as a structure that plays a role in both levels 6 and 7. This is because certain sub-regions within it appear to represent viscerally relevant perceptual information, while others appear to regulate vagal output based on a conceptualized understanding of current sensory input.

3.7. Level 7: regulation based on conceptualization of sensory input and past experience

This level can be understood to involve the regulation of autonomics (and related subcortical nuclei) by higher cortical regions involved in conceptual recognition, and associated prediction of task demands. A meta-analysis examining brain-HRV interactions has identified the MPFC (including rostral and subgenual ACC regions) as reliably associated with HRV across several studies (Thayer et al., 2012), consistent with previous work suggesting a role for the PFC in monitoring and regulating visceral/bodily functions (Damasio, 1994; Neafsey, 1990). Consistent with the role of MPFC in higher conceptualization processes, however, it is important to highlight that regulation of cardiac activity at this level appears to be influenced by several factors other than afferent bodily input. For example, MPFC and OFC/ACC regions implicated in vagal control are also engaged by factors such as the detection of task errors and response conflict (Etkin et al., 2011, 2006; Silvetti et al., 2014), attention to emotion (Lane et al., 1997; Smith et al., 2014b), self-referential processing (D'Argembeau and Ruby, 2007; Gusnard et al., 2001), and assessing the "affective meaning" of one's current situation (i.e., situational appraisal) via interaction with long-term memory processes in the medial temporal lobe (MTL) (Roy et al., 2012; Wilson et al., 2014). This suggests that all of these factors may further influence expected visceral/metabolic demands and associated visceral-motor adjustments at level 7. For example, the need to reduce error/conflict in a cognitive task, or the recognition that one's situation involves the loss of a loved one, could each lead to the predicted need for visceral-motor (and concomitant cognitive/attentional) adjustments to support expected behavioral demands (e.g., via downward influence on the amygdala; Mitchell and Greening, 2011; Mitchell, 2011).

Each of the aforementioned examples relate to processes occurring on a brief time scale (seconds to minutes). However, as we noted at the beginning, neurovisceral integration and regulation involves short-term (phasic) processes, as well as longer-term (tonic) processes. Structures at this level are uniquely suited to operate across long time scales of function: they function as polymodal higher order association cortices, are near the top of the neural hierarchy, and are presumably buffered from the minutiae of the internal milieu. These regions have been implicated in higher processes occurring across broader time scales, such as long term romantic love (Acevedo et al., 2012), acute grief following the death of offspring (Kersting et al., 2009), and bereavement following the death of a spouse (Gündel et al., 2003). Recent evidence suggests that ACC and other MPFC motor regions (including premotor and supplementary motor cortex) are directly connected to sympathetic effector organs, such as the adrenal medulla (Dum et al., 2016). This provides a potential mechanism by which conceptual processes related to the self can directly impact stress levels over longer time scales, by influencing the release of adrenergic hormones.

Together, therefore, there is considerable evidence that these different cortical regions appear capable of detecting and modulating activity within the lower levels of autonomic control described above, across both brief and prolonged time scales. Despite considerable anatomical overlap, we have distinguished two functionally distinct hierarchical levels, and illustrated how level 6 regulation processes incorporate perceptual representations of one's current bodily state, whereas level 7 regulation processes further incorporate conceptual interpretations of the meaning of both exteroceptive and interoceptive sensory input.

3.8. Level 8: amplifying, maintaining, or suppressing representations based on current goals

The eighth (and final) level of control we propose involves frontal-parietal regions (including regions of dorsal ACC) that are known to selectively amplify/maintain internal representations in a top-down manner (Dehaene, 2014); this "executive control network" (Barrett and Satpute, 2013) is thought to allow goal-relevant information to be consciously held within working memory and freely flow within a core-circuit of highly connected brain regions referred to as "rich-club hubs" (e.g., insula, MPFC, OFC, ACC, PCC, lateral PFC, posterior parietal cortex; Modha and Singh, 2010; van den Heuvel and Sporns, 2011, 2013; van den Heuvel et al., 2008; Zippo et al., 2013). Many of these hub regions are included within the level 6 and 7 structures described above; however, current models (Dehaene, 2014) suggest that top-down amplification/maintenance by frontal-parietal networks can modulate how information flows between these structures, and thus control their ability to "work together" to guide conscious, goal-directed behavior via further information integration processes. To be clear, while any one hub region might be activated unconsciously, when these distinct regions become synchronously active together (allowing the efficient exchange of information; Fries, 2005), they are suggested to form a "global workspace" that allows particular representations to become conscious and enter into strategic, multi-step decision-making processes requiring working memory maintenance and manipulation (Dehaene and Sigman, 2012; Zylberberg et al., 2011, 2010). At this level one can therefore voluntarily hold goal-relevant information in mind, and manipulate that information in strategic ways, allowing core-circuit regions to act as a sort of "top-level committee" in deciding on the best course of action, across short and long term time scales. This is consistent with whole brain connectivity analyses showing that these prefrontal regions primarily receive highly processed/integrated sensory information (Young et al., 1994), which may provide relative insulation from unprocessed sensory inputs and confer greater flexibility in both behavioral responding (Mesulam, 2000) and abstract problem solving (Duncan et al., 1996).

It is important to point out that the frontal-parietal regions we refer to here have traditionally been associated more with cognitive control than with vagal control. While there are several studies that have linked these frontal-parietal regions with cardiac/vagal control (e.g., Ahs et al., 2009; Critchley et al., 2005; Napadow et al., 2008; Smith et al., 2014a; Thayer et al., 2009a; Winkelmann et al., 2016), the major ways that this level of control can regulate vagal output are indirect. For example, by holding a representation of one's situation in working memory, and then reappraising its emotional significance (a form of goal-directed manipulation), one can affect a change in the way that situation is semantically represented/construed. Such changes can then result in different expectations regarding the need for metabolic support, and the state of the viscera can be adjusted accordingly. This model of "indirect" frontal-parietal control of emotion (and associated autonomic arousal) via intermediate manipulation of semantic representations was supported by a recent meta-analysis of emotion regulation studies using cognitive reappraisal strategies (Buhle et al., 2014). This meta-analysis found that, in addition to frontal-parietal regions, such strategies reliably increase activation with lateral temporal cortex areas associated with representing semantic content, and that they also reliably decrease amygdala responses. These processes are typically referred to as voluntary

emotion regulation strategies (Gross, 1998; Ochsner and Gross, 2005, 2007), and they have been repeatedly shown to increase both activity in, and functional connectivity between, frontal-parietal and other rich-club hub regions as well as to influence peripheral autonomic physiology (Banks et al., 2007; Morawetz et al., 2015; Ochsner et al., 2002; Phan et al., 2005; Phillips et al., 2008; Sripada et al., 2014).

In addition to the indirect regulatory processes described above, structural connectivity with the lateral PFC may also allow for more direct interactions with lower levels of the CAN. For example, lateral PFC has strong bidirectional connections with the ACC, medial/orbital PFC, and insula, suggesting this structure has access to representations of bodily feelings and could modify interoceptive perceptual processing in a top-down manner (Averbeck and Seo, 2008; Sporns et al., 2007). These MPFC/ACC structures that lateral PFC is connected with may also partially mediate its ability to regulate amygdala responses as well as HRV (Phillips et al., 2008; Sakaki et al., 2016). Taken together, the evidence reviewed here thus suggests multiple routes by which level 8 structures can play an important role in regulating vagal output; however, because many of these routes are indirect and will only be recruited in particular goal-directed contexts (e.g., those requiring cognitive control of attention, working memory, etc.), they would not be expected to contribute equivalently to vagal control across all types of situations.

4. Computational perspectives on neural function

Having reviewed these different functional levels of control with respect to anatomical pathways, in the present section we will review advances within computational perspectives on neuro-cognitive processes. These advances may shed light on ways that different levels of the CAN exchange information, and how metabolic needs may be predicted in advance of a cognitive/emotional event. In section 5 we will then integrate these recent advances with the detailed structural and functional connections of the CAN described above, and illustrate how such computational approaches can be specifically applied to vagal control.

4.1. The Bayesian brain and predictive coding

The large-scale view of the CAN and related systems described above leaves many questions unanswered about the specific dynamics of information processing. Recent computational perspectives, however, show promise in offering informative links between the large-scale regional functions described above and the smaller-scale interactions between individual neurons within/between specific regions. To begin with, many computational visions of the brain have broadly converged on to what is termed the "Bayesian brain hypothesis" (Knill and Pouget, 2004), which suggests that neural systems are adept at computing and integrating representations of uncertainty (i.e., using probability estimates) in many domains, including perception, attention, action selection, and control of the body. Specifically, neurons across these domains appear to represent probability distributions over region-specific hypotheses, which can then be used in subsequent computational steps that approximate Bayesian inference (Pouget et al., 2000). For example, certain neurons in primary visual cortex can be seen as representing the probability that a contrast edge of a particular orientation is present within part of the visual field (Vinje and Gallant, 2000), and certain neurons in primary motor cortex can be seen as representing the probability of moving a limb in a particular direction (Georgopoulos et al., 1988). This broad perspective also includes proposals for different decision algorithms the brain may use in particular contexts, and how they may probabilistically evaluate expected costs/benefits of different cognitive/behavioral actions (Daw et al., 2005; Dayan and Daw, 2008; Dayan, 2012; Gläscher et al., 2010; Huys and Dayan, 2009). We propose that such perspectives are also applicable to visceromotor control, across the hierarchy of neurovisceral systems described earlier.

More narrowly, however, our focus will be on one particular set of proposals within this literature – those involving "predictive coding" (PC) architectures – that have recently gained considerable support (Bastos et al., 2012; Brown et al., 2011; Clark, 2013; Feldman and Friston, 2010; Friston, 2010, 2005; Friston et al., 2010; Hohwy, 2014). Unlike a passive vision of the brain in which stimuli are identified through "feature detection" processes applied to sensory input, PC models instead portray the brain as continuously attempting to probabilistically predict the pattern of sensory input that will next arrive using downward connections (i.e., axons/synapses passing messages from higher processing levels in the brain toward lower levels near the sensory periphery). These predictions are based on prior probability distributions ("priors") represented within an internal model (formally, a hierarchical generative model) that maps hypotheses regarding interacting "hidden causes" in the world (e.g., "a baseball is moving toward me") to the patterns of sensory input they would be expected to produce. When sensory input deviates from what was predicted, this generates a prediction-error signal that propagates through upward connections into higher processing levels in the brain. These prediction-error signals subsequently prompt revisions to the internal model, until new priors/hypotheses (and associated predictions) are arrived at that minimize this error signal. In this way, the brain's internal model can be continuously updated so as to keep model predictions accurate in its representations of the objects/events present in the external world, including events occurring in the body.

PC models are necessarily multi-level in nature, such that lower-level properties (i.e., those involving regularities at shorter spatiotemporal scales) are represented nearer to the sensory periphery and higher-level properties (i.e., those involving regularities at longer spatiotemporal scales) are represented farther from the sensory periphery. As an example from the visual domain, priors for the edges, colors, and shapes that make up a face would be represented at lower levels whereas priors for facial identity (which would be spatiotemporally invariant across many changes in lower-level properties) would instead be represented at higher levels. As a corresponding example from the visceral domain, priors for heart rate, contractility, and blood pressure patterns during an acute mental stressor (e.g., arithmetic challenge) would be represented at lower levels, whereas priors for one's attitude towards taking math tests would be represented at higher levels. This proposed gradient from lower/concrete to higher/abstract levels of representation allows a tractable means of decomposing the problem of estimating one's current situation into a series of simpler, inter-related questions (e.g., "what edges are present?" "What shapes are present?" etc.) that can be answered via iterative minimization of prediction-error across all levels. Specifically, each level uses its priors to predict the dominant conclusion at the level below, and the prediction-error generated at each level is used to modify priors at the level above. This scheme is consistent with the brain's "centrifugal" pattern of connections (Mesulam, 1998), in which agranular/heteromodal association cortices form a collection of central multi-modal hubs (e.g., the rich-club regions discussed above), and in which connections from these hubs to unimodal sensory cortices nearer the periphery can be depicted as concentric rings. This pattern is hierarchical in that there are "higher" and "lower" regions (i.e., nearer and farther from the innermost ring of hubs); however, this architecture will also allow for

important lateral interactions between representations that are all at the same level (i.e., part of one concentric ring). Further, as discussed below, moment-to-moment changes in the strength of functional interactions between regions (e.g., as a function of attention) will allow different regions/levels to have greater influence on both perception and action in different contexts.

4.2. Predictive coding, motor control, and attention

To illustrate how this can occur, it is important to highlight how the scope of PC models is not limited to perception, but also provides a means of unifying motor control and attention within a single framework. In short, perception, motor control, and attention all fall out of PC models as distinct means of minimizing prediction-error. "Perception" can be seen as a process in which the priors within an internal model are adjusted to minimize error (and thus in which beliefs are adjusted to match sensory input). Motor control can instead be seen as a different strategy for minimizing error (termed "active inference") within the systems serving proprioception and interoception (Friston et al., 2010; Pezzulo et al., 2015; Seth, 2013). In this strategy, the prior expectations in the model are held fixed, and the error signal is used to trigger patterns of muscle contraction (via spinal/peripheral reflex arcs) that bring sensory input into agreement with those expectations. For example, if one had a strong prior for the hypothesis "my right arm is extended," but in fact one's right arm was currently flexed, this would generate a prediction-error signal that could be minimized in multiple ways. First, one could adjust the model so that the prior for "my right arm is flexed" begins to dominate (i.e., perception). Second, however, one could also trigger a pattern of muscle contractions that cause the right arm to extend as predicted (i.e., motor control). Both of these processes minimize sensory prediction-error in different ways, and interestingly, it appears that the major factor which determines which of these processes is selected is attention (Brown et al., 2011).

Attention, in PC models, reflects the need to estimate moment-to-moment changes in the reliability of the sensory input received from different domains (Feldman and Friston, 2010). For example, on a sunny day, visual input will typically be fairly reliable, and this will be reflected in a low amount of variance (or high amount of "precision") in the prediction-error signals this input generates. Given that this is a reliable signal, it makes sense that the influence of such error signals on the priors within the internal model should increase, allowing greater learning in response to high-precision inputs. In contrast, during the dark of night visual inputs will typically become highly unreliable (i.e., they will have high variance/low precision), meaning their influence on the prior beliefs represented within the internal model should decrease. Attention, it is proposed, can be identified as this process of increasing the strength (or "weight") of synaptic connections that are estimated to carry high-precision prediction-error signals, and to decrease the weight of synaptic connections estimated to carry low-precision signals. In this way, learning is preferentially driven by signals estimated to be the most reliable. This process of modulating the weight of particular synaptic connections (based on goal- and context-specific precision estimates) has been suggested to involve a diverse set of mechanisms, including signals from the ACC and posterior parietal cortex, as well as the influence of several neuromodulators (e.g., dopamine, norepinephrine, acetylcholine) (Brown et al., 2011; Feldman and Friston, 2010; Pezzulo et al., 2015). It also provides a direct means of adjusting the strength of the functional interactions between structurally connected regions in a context-specific manner.

4.3. Predictive coding in the context of brain-body interactions

With respect to interoception and proprioception, such attentional mechanisms can also be understood to influence whether a given prediction-error signal is resolved via perception or action. Specifically, recent computational models (Ainley et al., 2016; Barrett and Simmons, 2015; Brown et al., 2011; Pezzulo et al., 2015; Seth and Friston, 2016; Seth, 2013; Stephan et al., 2016) suggest that when proprioceptive/interoceptive predictions are highly weighted at the lowest levels (i.e., those near the sensory periphery), this can cause a change in the set points of reflex arcs, and the error will be minimized through action (i.e., the reflex will bring its effector to the new set point). In contrast, when such proprioceptive/interoceptive predictions are assigned a low precision weighting (i.e., leading the associated proprioceptive/interoceptive prediction-errors to be weighted highly), a perceptual updating strategy will be favored instead. Thus, this highlights an important way in which relative differences in the deployment of interoceptive/proprioceptive attentional mechanisms can – by estimating the context-specific reliability of downward prediction signals and upward prediction-error signals at different hierarchical levels – determine the extent to which the body is controlled by one's expectations – and conversely, the extent to which afferent bodily signals instead govern interoceptive/proprioceptive perception.

Based on this overarching PC framework, Pezzulo et al. (2015) have recently proposed a hierarchical active inference model of how interoceptive/visceral signals can constrain/update the multimodal priors in PFC that act as goal representations, and of how this can in turn lead to adaptive goal-directed behavior capable of maintaining homeostasis over long timescales. As this has clear implications for understanding the relationship between HRV and cognitive/emotional task performance, we conclude this section by reviewing aspects of this model relevant to neurovisceral control. In the following section, we will then integrate these insights with the detailed neuroanatomical considerations reviewed above and illustrate how this can usefully extend the NVI model to incorporate an adaptive multi-level control framework.

In the active inference model described here, the lowest levels of control involve somatic and visceral reflex arcs that use equilibrium points (i.e., set points) to implement closed-loop control. However, as briefly touched upon above, downward prediction signals from proprioceptive and interoceptive neural systems can modify these respective set points in context-specific ways, leading to changes in the activity of either skeletomotor or visceromotor effectors that fulfill these predictions. At lower hierarchical levels, the proprioceptive and interoceptive channels are separated from one another; however, at higher hierarchical levels (e.g., in PFC), interoceptive prediction-error signals can update multimodal priors that include proprioceptive predictions as well. If these updated proprioceptive predictions have high estimated precision, they will then themselves be fulfilled through skeletomotor reflex arcs, leading to behavior that indirectly minimizes interoceptive prediction-error (e.g., as when one eats to reduce a feeling of hunger, or plugs one's nose to reduce a feeling of disgust). This setup allows interoceptive signals to update goals/priors in PFC in a manner leading to the selection of actions that maintain the body's physiological states in an adaptive range. For example, a drop in blood glucose can be understood to lead to a specific prediction-error signal (relative to innate priors for healthy glucose levels), and this error signal can then activate a high-level prior/expectation associated with food-gathering behavior (e.g., one might now "expect" to start making a sandwich). This high-level prior can then convey downward prediction signals to skeletomotor reflex arcs about the sequence of proprioceptive consequences associated with that behavior, and this action sequence would then be fulfilled through successive

bouts of prediction-error minimization (i.e., if it is afforded high precision).

Importantly, Pezzulo et al. (2015) illustrate how different levels of control in this type of hierarchical model can correspond to behavior that has previously been attributed to separate control systems (Daw et al., 2005). First, unconditioned autonomic responses (e.g., salivation in response to food) can be identified with the activation of innate low-level priors that predict a visceral response. Second, conditioned autonomic responses (e.g., salivation in response to a bell) can be identified with the activation of a hierarchically higher (learned) prior that a conditioned stimulus (e.g., a bell) predicts an unconditioned stimulus (e.g., food). Third, "habitual" responses can be understood to involve a yet higher-level prior, where a given stimulus also triggers proprioceptive predictions that are fulfilled through skeletomotor action (e.g., when hearing a bell triggers priors for a button-press behavior that has previously led to receiving food). Finally, at the highest hierarchical level, goal-directed behavior can be understood to involve the engagement (by context-cues) of priors for long sequences of possible behaviors; here the optimal predicted sequence leading to a desired perceptual end-state (e.g., an increase in glucose levels) is selected out of the set of predicted/simulated sequences by assigning these predictions high precision. In summary, each level of control can be understood as a mechanism for contextualizing the contingencies represented at lower levels.

While Pezzulo et al. (2015) do not offer a detailed neuroanatomical basis for these processes, they do suggest broad regional functions. For example, they suggest the highest level (i.e., goal-directed control) is associated with PFC and dorsomedial striatal regions (as well as some potentially supportive cerebellar regions), and that the lowest levels of control involve spinal motor neurons and the peripheral autonomic nervous system. In between these two extremes they suggest there exists a spectrum of levels that progress in graded fashion from more habitual to more goal-directed types of control. This includes "lower" intermediate regions associated with innate and conditioned responses (e.g., premotor/motor cortex, hypothalamus, specific cerebellar and ventral striatal regions) and "higher" intermediate regions associated with instrumental/habitual control (e.g., inferotemporal cortex, AI, supplementary motor area, other cerebellar and [dorsolateral] striatal regions). As one moves up the hierarchy they suggest that the mix of control processes begins to incorporate longer and longer timescales, and therefore more and more goal-directed types of behavioral influence. At least at these higher levels, prior predictions governing skeletomotor action selection are constrained by interoceptive prediction-errors, keeping action adaptively directed toward outcomes predicted to meet present and future metabolic demands. Finally, they suggest that the posterior parietal cortex, ACC, and several neuromodulatory systems (e.g., the midbrain dopamine system) convey context-specific precision estimates about the expected reliability of each level of control, and thus play a central role in governing whether behavior in a given context mainly reflects habitual or goal-directed levels. Thus, when these regions assign high precision estimates to PFC regions, this would favor goal-directed control, whereas when high precision estimates are instead assigned to lower-level regions this would favor homeostatic and skeletomotor responses that are less sensitive to context information (and more sensitive to past reinforcement histories).

5. Extending the neurovisceral integration model

5.1. Overview of the extended model

Based on the information reviewed above, in this section we focus on how these insights might be incorporated into the NVI model. Specifically, adopting cardiac vagal control (i.e., vagal tone or HRV) as the low-level regulatory target of interest, there are several basic issues (spanning the multiple levels of control described above) that we aim to address:

1) How does a change in vagal tone coordinate with other functions within the cardiovascular system as a whole (such as blood pressure or cardiac output)?
2) How do vagal functions from different organ systems, such as cardiovascular, respiratory and gastrointestinal, coordinate with one another? And how are these changes coordinated with somatic motor control?
3) How can one's appraisal of the current environment be affected by past experience, leading to individual differences in vagal responses to the same stimuli?
4) How can the function of previously learned (or inherited) priors/predictions be modified and updated based on the current context, leading to context-specific vagal output?
5) How can bi-directional vagal influences between brain and body contribute to final decisions about how best to handle a metabolically demanding situation?

Each of these questions can be understood to involve one or more of the different levels of regulatory control described in section 3. In what follows we highlight how a particular hierarchical model of vagal control, drawing on both the PC model perspective and the structural levels of the CAN described above, can shed light on each of their answers.

Specifically, we propose that bidirectional interactions between each of the levels described above can be understood to consist of a series of nested neurovisceral integration loops (Fig. 1). We further propose that forward connections within each loop can be understood to convey prediction-error signals from "lower" (i.e., closer to the sensory periphery) to "higher" (i.e., farther from the sensory periphery) levels of control. Backward connections can in turn be understood to convey prediction signals from higher- to lower-level regions (based on current priors at the higher level). Based on this type of architecture, the CAN as a whole can be seen as continually engaged in a dynamic, iterative process of attempting to settle on a set of priors across all levels that effectively minimizes prediction-error with respect to each "wave" of new sensory input received from the body and the external world. As a brief example, consider a person who is not expecting to hear a loud "crashing" sound. When then this type of auditory input unexpectedly impinges on the tympanic membrane of the ear, it would be expected to lead to strong prediction-error signals propagating upward into subcortical and cortical regions (i.e., because current priors, and associated downward prediction signals, could not effectively account for this pattern of auditory input). These error signals would then drive a change in the priors that the brain uses to represent the most likely state of the world – in this case leading to an increase in the strength of priors for things like "threat/danger" and "increased metabolic demand" (i.e., because of innate/learned associations between crashing sounds and these other things). These updated priors would remain stable because they effectively minimize auditory prediction-error (i.e., they can successfully account for the "crashing" sound). Simultaneously, these updated priors would convey new downward (and in part vagally mediated) prediction signals about the state of the body (e.g., predictions about an increase in heart rate). The resulting prediction-errors (e.g., because heart rate is currently slow) would then be resolved through active inference (i.e., by changing the set points in the appropriate autonomic reflex arcs), ultimately leading to changes in the state of the body that make it match these new predictions (e.g., heart rate would speed up to the predicted rate). Below we will go into more detail about the different types

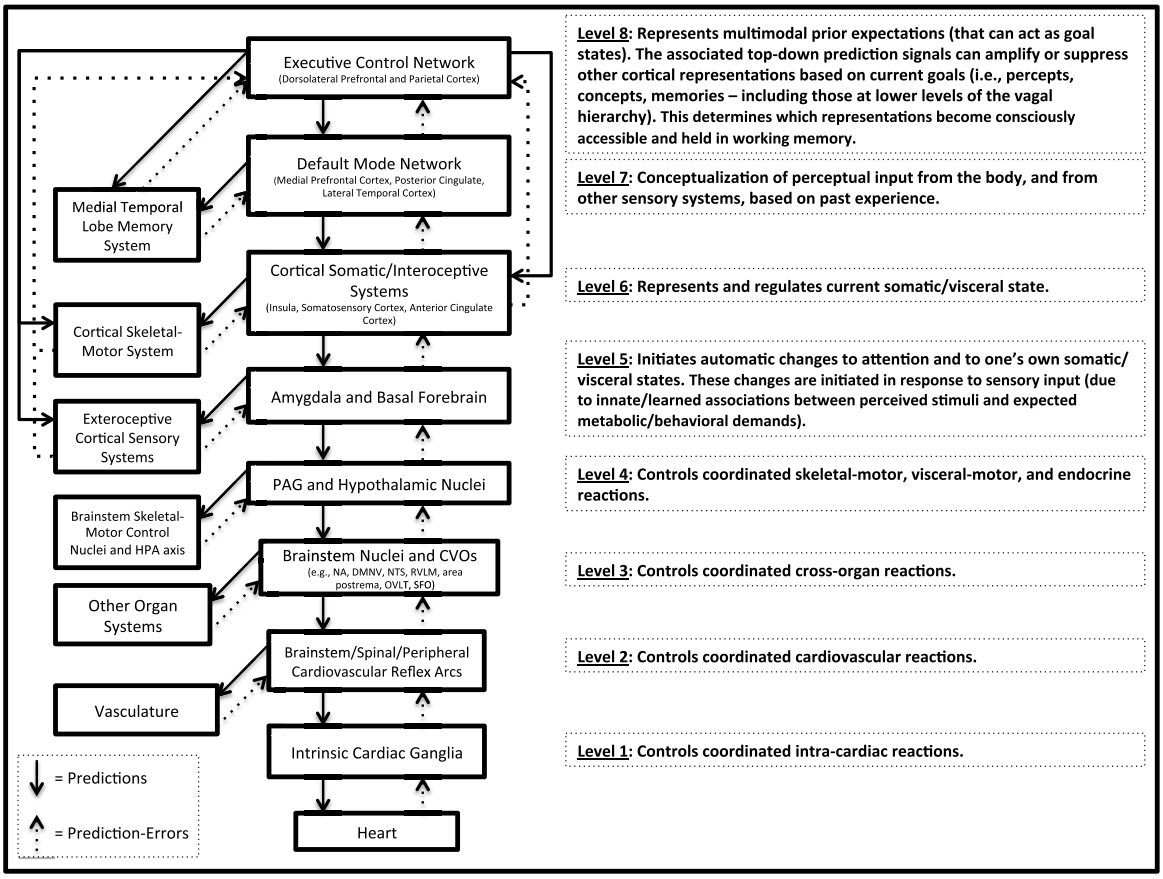

Fig. 1. As described in more detail within the text, this figure illustrates the 8 levels of the vagal control hierarchy within the present model, as well as the flow of information regarding predictions and prediction-errors between levels. The figure further illustrates the integration of additional information from different bodily/neural systems that occurs at each level.

of priors (and associated prediction-errors) represented at the different hierarchical levels. However, this initial example illustrates how a prediction-error signal generated from an unanticipated sensory input can lead the network as a whole, through an iterative error-minimization process, to update its "beliefs" (priors) about the state of the external world – and how this updating process can simultaneously drive a change in the downward vagal signals that predict/control the internal state of the body.

Because some sets of priors across levels will be much more internally consistent than others, only a limited set of global network states will be capable of minimizing error across all levels in this way. This will result in a set of error-minimizing attractor basins (corresponding to sets of highly consistent priors across levels) within the CAN's overall state-space (as described in Thayer and Lane (2000)'s original NVI model; see section 2 above). Importantly, however, the topography of the high-dimensional CAN state-space is not fixed. Instead, its topography (i.e., the locations of attractor basins) will fluctuate under the control of context-specific estimates of the precision associated with each of the signals being conveyed between levels (Figs. 2 and 3). Put another way, very different state-space locations (corresponding to different CAN outputs) will be capable of effectively minimizing prediction-error depending on which error signals are upwardly and downwardly weighted by attentional mechanisms (i.e., based on their predicted reliability in the present context). For example, in the context of a quiet office environment, auditory inputs might be expected to have high precision; as such, auditory prediction-error signals would be highly weighted and therefore have a strong influence on the priors represented within the CAN (e.g., as in the "crashing sound" example above). However, in the context of a noisy construction yard, auditory inputs might instead be expected to have low reliability/precision; in this case, auditory prediction-error signals may not be highly weighted, and so the detection of an unpredicted crashing sound could have much less influence on the CAN's priors for threat, heart rate, etc.

Precision-weighting thus dictates which error signals the CAN should "care about" minimizing in a given context, and this will manifest as a specific pattern of functional connectivity strengths between different CAN regions/levels (as well as between the CAN and other brain systems). Because connectivity between different regions/levels can be flexibly "turned up" and "turned down" by precision estimates in this manner, the influence of higher-level regions on vagal output will only be recruited in the contexts where their influence is estimated to be reliable. Thus, when precision estimates are accurate, this would be expected to lead to flexible regulation of both the viscera and skeletomotor output across different contexts. In contrast, contextually inappropriate cognitive/bodily responses might be understood to reflect inaccurate precision estimates, causing the CAN of such individuals to get "stuck" in a maladaptive attractor basin reflecting the brain's attempt to minimize unreliable error-signals. For example, consider an individual who has an intense/sustained unpleasant autonomic response to the sight of a friend displaying a frustrated facial expression – despite their knowledge that this facial expression is most plausibly the result of the individual's lack of sleep (and therefore is unrelated to their relationship). One way this could come about is if the higher CAN levels that incorporate context information and background knowledge are inappropriately estimated to have low precision. As such, even though the person "knows" they shouldn't feel so upset by the friend's expres-

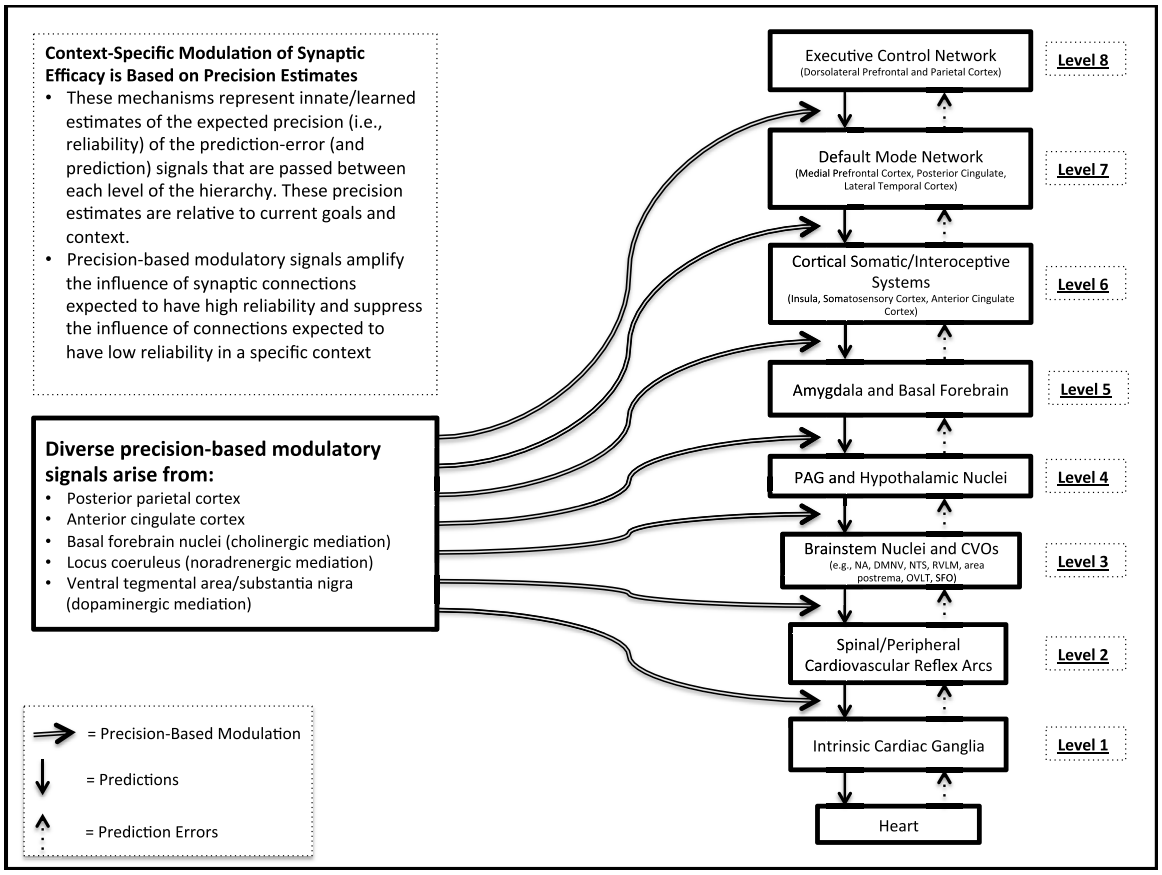

Fig. 2. Illustrates the role of precision estimation, and precision-based modulatory signaling, in amplifying/suppressing the influence of different prediction and prediction-error signals within a given context. The level(s) of control, and associated predictions, that are assigned high precision estimates in a given context will have a greater influence on CAN outputs within that context.

sion, the influence of this knowledge is insufficiently weighted to have a major influence on the ongoing autonomic reaction. Instead, lower CAN levels – that represent the (decontextualized) association between such expressions and particular autonomic responses – have inappropriately high estimated precision. Thus, the sustained autonomic response reflects the CAN's continual attempt to "focus on" minimizing the highly weighted error signals generated at these lower levels. While the original NVI model (Thayer and Lane, 2000) made a similar suggestion, the current model extends this by providing anatomical specificity and a computational framework for understanding the dynamic flow of information across the system.

As one aspect of modulating connectivity in the manner described above, precision estimates in the CAN will also dictate whether particular prediction-errors are resolved via a change in perception (i.e., perceptual inference) or via a change in viscero-motor action (i.e., active inference); they thus play an important role in dictating the ultimate outputs of the CAN in a given situation (and which levels are primarily "in charge" in that situation). For example, they would determine whether cardiac-related prediction-errors in a given context are resolved via a change in perceived heart rate (i.e., to match the actual current rate) or by a change in actual heart rate (i.e., to match the current priors reflecting the perceived rate). The proposed architecture therefore allows attentional control mechanisms in PC models, which modulate synaptic strengths across the network based on predicted reliability, to play the role of the "control parameters" appealed to within the dynamical systems framework of the original NVI model (Thayer and Lane, 2000). This reproduces the same sets of adaptive and maladaptive attractor basins within the CAN state-space discussed in the original model, but also extends the original model by suggesting that such basins reflect states that minimize precision-weighted prediction errors. This extended model therefore opens the possibility for much more quantitative and anatomically grounded computational modeling of CAN dynamics in both healthy and diseased states.

5.2. Specific inter-level interactions

5.2.1. Levels 1–4: cardiovascular system and multi-organ system coordination

With respect to specific inter-level interactions, we suggest this framework may also allow for important additional functional insights. For example, at the lowest 2 levels, it suggests that cardiac reflex arcs may be driven to minimize error (when precise downward predictions modify their set points) with respect to the prediction signals conveyed to them by the lower brainstem nuclei comprising level 3 of the hierarchical model described above. The priors governing these level 3 predictions, however, will in turn be constrained by their ability to minimize error with respect to higher-level priors emanating from level 4 structures, and so forth. Each of these levels can be seen as integrating/coordinating additional information, and often with respect to priors for regularities at greater and greater spatiotemporal scales. For example, loops at levels 1–2 can be understood to involve minimizing error with respect to priors that only pertain to cardiac and vascular function (and thus coordinate regional cardiac changes with blood pressure). Fig. 1 depicts this by showing that, at level 2, prediction-errors begin to be incorporated from the vasculature (i.e., in addition to from intrinsic cardiac ganglia), and that this level also issues down-

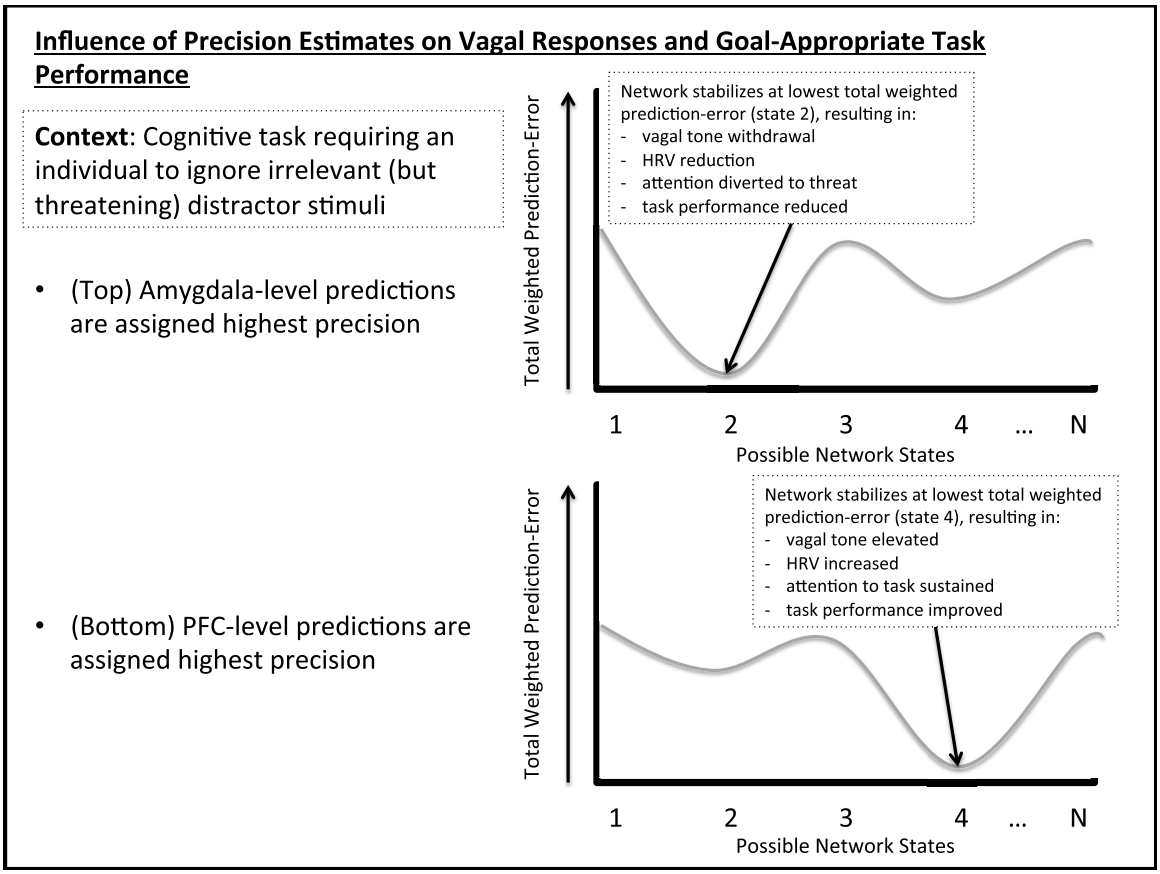

Fig. 3. Illustrates how high precision-estimates assigned to a higher (prefrontally-mediated) level of control (bottom) vs. a lower (amygdala-mediated) level of control (top) can influence the states/outputs of the CAN in a specific context (described further in Section 6 of the text). The possible network states listed ("1 2 3 4 . . . N") are arbitrary labels that refer to distinct possible states of activation across the CAN system as a whole (leading to different output signals that influence the state of the viscera). The figure depicts how, in the context of a goal-directed task that requires ignoring irrelevant emotional stimuli, higher HRV would be expected to positively co-vary with task performance (e.g., as in Krypotos et al., 2011). We propose that this is due to the fact that high HRV and better performance both reflect the assignment of high precision estimates to prefrontal levels of control that are sensitive to current goals and context.

ward predictions about both cardiac and vascular states (i.e., that can act as motor commands by altering set points in reflex arcs, as described above).

Level 3 structures further involve minimizing error with respect to priors for the relationship between cardiac activity and that of other visceral organs (e.g., coordinating with respiration and digestion). Fig. 1 depicts this by showing that, at level 3, prediction-errors also begin to be incorporated from other organ systems, and that this level also issues downward predictions that can modulate the states of these other organ systems (i.e., via active inference). Level 4 loops can next be seen to instantiate even larger scale error minimization processes, pertaining to priors regarding the relationship between visceromotor, somatomotor, and endocrine changes. Thus visceral and skeletal muscle changes (e.g., coordinated changes in facial expression and heart rate) might be triggered in order to keep predictions accurate at this level. As one example, if an individual made a particular facial expression voluntarily, this could generate a prediction-error driving the selection of a different prior at level 4–one that, for example, represents an innate/learned association between that facial expression and a particular autonomic/endocrine response. This new prior would then initiate that autonomic/endocrine response via downward influence on lower levels (e.g., as in Levenson et al., 1990). This is depicted in Fig. 1 by showing that, at level 4, prediction-error signals also begin to be received from, and prediction signals begin to be sent back to, brainstem-level skeletal-motor control nuclei (e.g., facial motor nucleus) and the HPA axis. In summary, loops at levels 1–4 can be understood as addressing the first two questions posed at the beginning of this section.

5.2.2. Levels 5–7: coordination of exteroceptive perception, memory, and body state

Starting at level 5, the CAN can be understood to begin to integrate exteroceptive information (e.g., as in the "crashing sound" example above), as well as associated expectations gained from past experience (i.e., where these learned expectations reflect stable changes to the priors of an internal model that predict state transitions – due to the effects of repeated prediction-error signals over long timescales; see Pezzulo et al., 2015). For example, based on the work described above, the amygdala could be understood to represent priors for the expected significance/value of perceived stimuli (i.e., stimulus appraisal; Cunningham et al., 2008). These priors would then convey predictions to level 4 structures regarding needed autonomic/behavioral changes (based on represented stimulus relevance). While this can involve appraisal of unconditioned stimuli (such as a painful shock), the amygdala is also known to play an important role in both learning, and initiating reactions to, conditioned stimuli as well (e.g., responses to a tone that has reliably predicted a shock in one's past experience; LeDoux, 1996). The amygdala would also convey its "conclusion" widely across the brain, serving various functions (reviewed in Pessoa, 2013; Ch. 2). For example, its predictive signals would be expected to affect (both directly and through the LC and BF) changes in precision estimates, leading to changes in the automatic focus of one's attention. Thus, at

this level cardiac control begins to be coordinated with changes in cognitive factors like learning, exteroceptive perception, and attention (i.e., in addition to changes in other visceral organs and skeletal muscle). This is depicted in Fig. 1 by showing that level 5 begins to include the exchange of prediction and prediction-error signals with exteroceptive cortical sensory systems; it is also illustrated in Fig. 2, which shows that the BF can direct attention by modulating synaptic efficacy across the brain (i.e., in a manner that amplifies/suppresses processing of sensory prediction-error signals with high/low estimated precision).

Level 6 and 7 of the CAN represent diverse sets of cortical regions. These regions plausibly represent learned priors over a range of different hypothesis spaces, broadly associated with perceptual and conceptual processing, respectively. For example, cortical columns within the insula, dorsal ACC, and somatosensory cortex may play a role in bodily perception/regulation (i.e., level 6) by representing priors for (and calculating prediction-errors with respect to) high-dimensional states of the whole body (e.g., particular combinations of states across different bodily systems; see Smith and Lane, 2015). Fig. 1 illustrates this by showing that, at level 6, prediction and prediction-error signals begin to be exchanged with the cortical skeletal-motor system (i.e., which primarily functions to minimize proprioceptive prediction-errors in PC models). The proposed function of these level 6 regions is consistent with the known role of the AI and ACC in the "salience network" – a system thought to assess the homeostatic needs of the whole body and direct cognitive resources accordingly (Barrett and Satpute, 2013). It is also consistent with recently proposed PC models of visceromotor control (Barrett and Simmons, 2015; also see Gu et al., 2013; Seth, 2013), which have suggested that both the AI and the ACC represent priors for interoceptive states (including cardiac states), and that these priors can sometimes act as visceromotor commands (i.e., when interoceptive prediction-errors are resolved via autonomic reflex arcs).[2]

At the same time, cortical columns within level 7 regions associated with the default mode network (e.g., OFC, VMPFC, and rostral/subgenual ACC) may represent priors for the context-specific conceptual significance of one's overall situation. This level of control may initiate autonomic reactions in response to the abstract meaning of particular stimuli – such as a letter informing a person of an upcoming tax audit – in which the perceptual properties of those stimuli are themselves unassociated with metabolic demand. This idea of a more abstract, concept-based level of control is consistent with recent reviews suggesting that these areas, in conjunction with other regions also associated with declarative memory (e.g., the MTL and PCC), may function to conceptualize the overall "affective meaning" of one's situation, based in part on currently unobservable factors known only from past experience (Barrett and Satpute, 2013; Roy et al., 2012; Wilson et al., 2014). This notion of "affective meaning" could be thought of as an internal description/construal of one's position in the world, including both exteroceptive and interoceptive/emotional dimensions. Finally, as reviewed by Pezzulo et al. (2015), loops between many of these regions and the striatum may implement a continuum between more habitual and more goal-directed forms of skeletomotor control that are constrained by interoceptive prediction-errors (e.g., error signals associated with low glucose levels might drive the selection of priors for context-specific eating behaviors). Fig. 1 summarizes these points by illustrating that level 7 incorporates information from long-term memory systems to conceptualize the meaning of bodily percepts represented at level 6. Although not shown, level 7 also conceptualizes the meaning of percepts represented in exteroceptive cortical sensory systems, and such conceptualizations of perceived external events could also lead to the predicted need for additional metabolic resources (and thus to adjustments in vagal output).

Interactions between each of these level 6 and 7 structures could thus be seen as predicting needed autonomic, endocrine, cognitive, and behavioral adjustments, based on one's overall appraisal of the current situation, and then triggering those adjustments via their influence over lower-level structures in the hierarchy. This is consistent with the suggestion of Pezzulo et al. (2015), for example, that insula-mediated prediction errors may function to update multimodal priors in the (medial) PFC, leading to homeostatically adaptive skeletomotor behavior. Similarly, this could also include interactions between level 6/7 and level 5 structures, as in the VMPFC-amygdala interactions known to underlie conditioned fear extinction and the context-specific modulation of automatic emotional attention (Etkin et al., 2006; Mitchell and Greening, 2011; Mitchell, 2011; Sotres-Bayon et al., 2009). However, it could further involve downward connections that "jump" multiple levels, as in the direct connections between the cingulate gyrus and the PBN and NTS (Vogt and Derbyshire, 2009). Overall, however, levels 5–7 therefore appear to provide potential mechanistic answers to the third and fourth questions posed above, and relatedly allow for even greater coordination of the CAN based on the predicted demands of a given cognitive or emotional task.

5.2.3. Level 8: coordination of goals, decision-making, and body state

Our fifth and final question above pertained to how deliberative, voluntary decisions are ultimately made regarding the way to deal with a challenging situation, and how this is related to bidirectional vagal interactions between brain and body. This we suggest depends in part on level 8 dorsal frontal-parietal structures that are thought to represent high-level goals and drive goal-directed thought and behavior in a variety of ways. We propose that, by representing priors for long timescale goal states, these structures issue downward predictions (including those pertaining to associated precision estimates) that function to dynamically filter what is attended to, selected for global broadcasting, and held in working memory. For example, if one were quite hungry, but had the goal of finishing a particular task, this could temporarily amplify task-related exteroceptive percepts and suppress representations of hunger-related situational appraisals (i.e. in level 7). In contrast, the goal of finding food might instead amplify representations of hunger-related situational appraisals in level 7, and potentially alter hunger-related autonomic responses as a result. Fig. 1 depicts this by illustrating the presence of downward signals from level 8 to several other regions/systems (e.g., exteroceptive sensory systems, somatic/interoceptive sensory systems, and long-term memory systems); Fig. 2 also illustrates the influence of parietal and ACC regions of the executive control network on precision-based modulation of synaptic efficacy. Thus, if goal-specific precision estimates suggest that signals from the body are most reliable for deciding on a course of action in a given moment, these will be amplified by precision-weighting mechanisms and made globally accessible to the regions forming the brain's core-circuit (or global workspace). Only then can this goal-relevant bodily information effectively drive iterative rounds of simulating different actions, and predicting/comparing their likely outcomes, and ultimately lead to a consensus regarding the best course of action (for detailed reviews of these processes, see Dayan and Daw, 2008; Dehaene and Sigman, 2012; Pezzulo, 2012; Zylberberg et al., 2011, 2010). This corresponds to the highest form of goal-directed control referred to in Pezzulo et al.'s (2015) model, requiring that high-precision esti-

[2] In contrast, these models suggest that PI computes the prediction-error signal that results from comparing priors with afferent bodily input; this error signal can then feed forward to the AI and adjust priors accordingly.

mates are assigned to multimodal priors in the PFC pertaining to long timescale regularities.

At the same time, afferent prediction-error signals from the vagus should play an important role in constraining the multimodal priors (and associated precision estimates) in frontal-parietal regions. Thus, if these afferent vagal signals convey strong deviations from expected/adaptive physiological states in a given context, this should have a strong influence on one's current goals and also on what exteroceptive features are considered reliable/salient (and should therefore be attended to). Thus, for example, if vagal afferents conveyed information about extremely low blood glucose levels (i.e., if one were incredibly hungry), it should be more difficult to maintain the goal of attending to an otherwise boring cognitive task than if glucose levels were at expected levels (i.e., if one were satiated). This highlights how appropriate processing of prediction-error signals arising through vagal afferents, and specifically how much precision they are afforded in a given context, should have a direct influence on one's ability to maintain the right goals and the right attentional focus at the right times to accomplish one's goals. As described in the following section, this has important potential implications for understanding the relationship between vagal tone and cognitive performance.

5.3. Applications

We believe that the hierarchical extension of the NVI model described above offers several, potentially important advantages for organizing and advancing current thinking regarding the relationship between the body, emotion, cognition, and both mental and physical health. One reason is that it provides a clear, unified model for integrating across a) multiple organ systems and b) multiple levels of behavioral and physiological organization. In doing so, it can explain a very diverse set of findings with HRV in a unified way.

For example, because the types of goal-directed control required to successfully perform demanding cognitive/attentional tasks and voluntary emotion regulation tasks are both known to engage medial and lateral PFC regions, it follows that this type of control will require that high precision estimates are assigned to their associated hierarchical levels (i.e., levels 6–8). When this fails to occur, conditioned/habitual responses associated with lower hierarchical levels (e.g., amygdala/lateral striatum) will instead dominate action selection, leading to behavior that is less sensitive to one's current goals/context and more sensitive to previously learned associations between perceptual cues. Importantly, in the cases of high cognitive conflict where these conditioned/habitual responses will lead to performance errors, one would also expect this to reduce HRV. This is because PFC-level goals/priors convey multimodal predictions regarding both exteroceptive and interoceptive states, and performance errors associated with inappropriately down-weighting prefrontal influence will therefore be associated with less accurate predictions (and therefore greater prediction-error) in both domains. The associated reductions in efficient visceromotor control would further engage priors for greater metabolic demand, and result in both the withdrawal of vagal tone and a (slower) increase in sympathetic tone. Thus, in any case where one fails to perform an adaptive goal-directed task (as a result of failing to assign high precision to PFC levels of the hierarchy that are sensitive to context cues), and that task is either directly or indirectly motivated by the predicted need to maintain homeostasis over long timescales, then this performance reduction will be expected to coincide with lower HRV.

In addition, consider the fact that performance errors in demanding cognitive/emotion regulation tasks are very often understood as being the result of an inappropriate deployment of attention (where "attention" includes both modulatory amplification- and inhibition-related functions). In our model, such lapses in adaptive attentional control (e.g. Williams et al., 2016) would result from assigning inappropriately high precision to irrelevant exteroceptive or interoceptive (e.g., vagal afferent) input signals, leading to poor responses to (and to poor learning from) relevant task stimuli. This highlights further how individual differences in the accuracy of learned precision estimates in a given context can lead to differences in cognitive performance. Simultaneously, these same differences in accuracy should be expected to lead to differences in autonomic regulation, including differences in HRV. Essentially, high HRV should reflect the same context-appropriate precision estimates that act to inhibit (i.e., down-weight) the influence of irrelevant distractors, where such distractors would otherwise be inappropriately appraised as salient and trigger priors for increased metabolic demand (which would in turn lead to a withdrawal in vagal tone and reduce HRV). This basic notion that inappropriate appraisals of (and subsequent attention to) goal-irrelevant stimuli should lead to both task errors and reduced HRV may therefore further help explain why high HRV can predict better performance in cognitive control tasks. In other words, *higher HRV may index a greater tendency, either in general (i.e., resting HRV) or during a task (i.e., task-related HRV), to assign high precision to prefrontal levels of control that are sensitive to goals and context* – and these high prefrontal precision estimates will in turn prevent distracting, goal-/task-inappropriate responses to irrelevant stimuli, and therefore improve performance (e.g., as in the relationship between HRV and performance in the presence of emotional distractors reported by Krypotos et al., 2011; also see Park and Thayer, 2014; Park et al., 2014).

An example of the phenomenon described above is depicted in Fig. 3. This figure illustrates how, during a cognitive task that requires one to ignore threatening distractor stimuli (e.g., a briefly flashed image of a knife), goal-appropriate precision estimates (potentially reflected by high resting HRV) will promote both better task performance and higher task-related HRV (e.g., see Park et al., 2014). In the top half of the figure, amygdala-level predictions are inappropriately (i.e., relative to current goals/context) assigned the highest estimated precision; the network then settles into the attractor state associated with minimal precision-weighted prediction-error (i.e. "state 2" in the figure), resulting in diverted attention toward the distracting stimulus and reduced HRV. In the bottom half of the figure, PFC-level predictions are instead assigned the highest estimated precision; the network then settles into a different attractor state (i.e., the one associated with minimal prediction-error given goal-/context-appropriate precision-weighting; "state 4" in the figure), resulting in sustained attention to the task and relatively higher HRV. Thus, higher HRV would be expected to co-vary with better task performance (e.g., as in Hansen et al., 2004; Hansen et al., 2003, 2009; Johnsen et al., 2003; Saus et al., 2006; Thayer et al., 2005). Because goal-directed emotion regulation strategies recruit common PFC-mediated control resources (Buhle et al., 2014), the structure of this example could also explain the relation between higher HRV and better performance on voluntary emotion regulation tasks (Appelhans and Luecken, 2006; Butler et al., 2006; Ingjaldsson et al., 2003; Lane, 2008; Melzig et al., 2009; Ruiz-Padial et al., 2003; Thayer and Brosschot, 2005). This therefore clarifies the underlying mechanisms that may support the known association between HRV, cognitive performance, and emotion regulation ability.

6. Discussion

Until the advent of functional neuroimaging, the field of psychophysiology focused on the association between mental states and physiological measurements taken from the body surface. Once

the ability to image the brain became available, it became possible to relate brain structure and function to both mental states and peripheral physiology. This exciting development raised important questions about how the brain could be integrated into this field. In this new territory, concepts and principles were needed to formulate hypotheses that could guide the interpretation of previous findings and the planning of new research. The NVI model was introduced in this context, focusing on the linkages between the central and autonomic nervous systems, with special emphasis on the parasympathetic branch of the latter.

We proposed in 2000 (Thayer and Lane, 2000) that central and peripheral aspects of the autonomic nervous system were hierarchically organized. We pointed out that cognitive, affective, and behavioral systems used the same (i.e., the one and only) autonomic nervous system and that the challenge was to understand how brain structure and function dovetailed with, and contributed to, the regulation of autonomic nervous system function. Using affect and parasympathetic function as our starting point, focusing on both anxiety and affective disorders, and using HRV as an index of parasympathetic function, we put forward evidence that psychopathology was associated with decreases in vagal regulation – which we interpreted as withdrawal of inhibitory top-down control. A corollary of this conclusion was that affective functioning in healthy individuals was characterized by greater differentiation and complexity of emotional experience, which was supported by greater differentiation and complexity of peripheral physiology (as indexed by greater HRV). Subsequent research has provided support for this hypothesis by demonstrating the important role of the MPFC in both emotional awareness (e.g., Frewen et al., 2008; McRae et al., 2008; Silani et al., 2008; Smith et al., 2014a,b) and the regulation of vagal tone (reviewed in Thayer et al., 2012), as well as a positive correlation between emotional awareness and vagal tone (Verkuil et al., 2016). Moreover, a growing body of evidence using advanced imaging methods and modern psychophysiologic techniques in a variety of cognitive, affective and behavioral contexts, provides substantial evidence supporting the NVI model (reviewed in Thayer and Lane, 2009; Thayer et al., 2012).

Given this progress, and the availability of ever-more precise methods, we concluded that it was important to add even greater specificity to our model of hierarchical neural regulation of vagal function. In the current paper we capitalize on the growing body of relevant literature, and advances in computational neuroscience, to add much greater anatomical, physiological, and computational specificity to the NVI model. As with the original model, this is being done to assist in the interpretation of extant findings, as well as to guide future research. We now turn to important issues in NVI research to which this new perspective may be applied. In doing so it is hoped that this will stimulate research that will either support the model or leads to its refinement or revision.

Examples have been given above that help to explain in general how activity in prefrontal cortex could lead to greater HRV. This general conceptual model provides the opportunity to study in detail some of the original issues addressed in the NVI model. For example, there are many different ways of quantifying and categorizing depressive and anxiety disorders, as well as assessing depressive symptoms and anxiety symptoms in the subclinical range. A key challenge for the field addressed by Research Domain Criteria (RDoC) is how to parse brain and behavioral function in a way that is clinically meaningful. We would argue that the model that we have specified may add to this, in that it will be possible using the whole range of structural and functional imaging methods – including resting state paradigms, task-based paradigms, and the latest methods in connectivity analysis – to define what the critical mechanisms may be that account for reduced HRV in the context of psychopathology (and the mechanisms needed to restore HRV to healthy levels). A growing body of evidence indicates that autonomic abnormalities are observed in other severe forms of psychopathology, such as schizophrenia (Bär et al., 2010) as well as severe neurological disorders such as Parkinson's disease (Micieli et al., 2003). Perhaps insights gained in the contexts of depression and anxiety may be applied to the latter, and provide new mechanistic insights and new opportunities for intervention.

In the area of depression and HRV, growing evidence indicates that depressed women have higher HRV than non-depressed women or depressed men (Thayer et al., 1998; Verkuil et al., 2015). Using the current model as a guide, to what extent can we use future advances in understanding sex differences in the neural basis of depression, and the neural basis of vagal regulation, to understand why such a difference exists? Perhaps relatedly, recent evidence indicates that Caucasian individuals have lower HRV than people of color, and that darker skin color is positively correlated with HRV (Hill et al., 2015; Kemp et al., 2016). A recent genome-wide association study indicates that these differences are not genetically based (Jeff et al., 2013), raising the possibility that environmental, psychosocial, and other learning-related factors are likely at work. These findings suggest that the general prediction-error-based learning processes we have described, as well as psychological and social factors influencing function at levels 6–8 of the hierarchy in particular, could both be important to consider. The current model therefore provides some guidance in examining the mechanisms of such ethnic differences.

In recent years important links have also been observed between autonomic and immune function (Andersson and Tracey, 2012). One important example is the anti-inflammatory effect of vagal activity (Thayer et al., 2011). Recent evidence indicates that inflammation alters activity in neural circuits important for affect and affect regulation (Ohira et al., 2008). The current model highlights the need to identify at what levels such effects influence the brain and vagal regulation. Delineating such mechanisms will help in uncovering, and potentially reversing, the pathophysiological effects of autonomic and immune dysregulation in a variety of costly and debilitating disease contexts (e.g., coronary artery disease, diabetes, rheumatoid arthritis, and others).

In the context of coronary artery disease (CAD), sudden cardiac death is the first manifestation of disease in roughly 50% of cases (Wellens et al., 2003). We routinely screen for CAD risk factors, but an important factor that may contribute greatly to CAD mortality is the emotional response to painful ischemia. Early research demonstrated that, relative to silent ischemia, painful ischemia is associated with recruitment of additional cortical brain areas (Rosen et al., 1996). Experimental research in dogs (Vanoli et al., 1991) and clinical follow up studies in patients (La Rovere et al., 1998) also demonstrate that greater vagal tone is associated with lower mortality rates in the context of CAD. A key set of questions, which to our knowledge have not been previously addressed, involve how to understand individual differences in the emotional response to ischemia, how such responses interact with autonomic regulation, and in turn how such interactions influence vulnerability to fatal arrhythmias. The current model provides guidance in knowing where to look in the brain for such interactions, and potentially has implications for screening tools that could be used to identify individuals at risk before fatal clinical events occur.

This further raises questions about interventions to enhance vagal tone, particularly in real-time, context-appropriate ways. A new science of peripheral neurology, with a focus on electrical stimulation, is emerging and has the potential to be as complex as CNS stimulation methods (Birmingham et al., 2014). In addition to direct vagus nerve stimulation in the surgically accessible area of the neck (near the carotid artery), other methods for stimulating vagal activity include transdermal electrical stimulation of this same area (electrocore.come), electrical stimulation of a branch of the vagus nerve in the auricular nerve (Murray et al., 2016), non-

invasive methods such as slow yoga breathing (Pal and Velkumary, 2004), and activation of reflex bradycardia by stimulating the dive reflex by applying cold to the forehead or ocular pressure (Friedman et al., 1996). Our model will be useful in studying the differential brain effects of such stimulation methods, both acutely and after a course of chronic treatment. Such knowledge may then be correlated with growing understanding of how different mental/brain disorders are instantiated in the brain and provide new methods for primary and secondary prevention.

Other potential implications of our model may pertain to interactions between stress, learning, and development. To see this, it is helpful to first consider that a large body of previous work suggests that function within both lateral and medial prefrontal regions, as well as within MTL regions implicated in declarative memory, displays an "inverted-U" relation with indicators of stress/arousal (Arnsten and Robbins, 2002; Arnsten, 1998; Nadel and Jacobs, 1998; Robbins and Arnsten, 2009; Thayer et al., 2012). This suggests that when arousal is very low or very high, these regions go relatively more "offline," potentially reducing the ability to consciously reason/deliberate, keep long-term goals in mind, stay empathically connected with another person, and so forth. In our model, this effect of very high (or very low) stress could be understood to reflect a state-dependent reduction in the influence of levels 7–8 (i.e., a reduction in the estimated precision assigned to these levels during very high/low stress). This would in turn reduce the ability for autonomic function to be effectively coordinated with an overall combined assessment of the current internal and external context, and it would also reduce the ability for autonomic function to be effectively influenced by multi-step conscious reasoning processes.

In adulthood, this type of high arousal state would therefore be associated with higher precision estimates assigned to conditioned/habitual levels of control and lower precision estimates assigned to higher goal-directed (PFC) levels of control (e.g., perhaps because it has been learned over phylogenetic/ontogenetic time that these higher levels do not operate quickly enough to reliably deal with dangerous/threatening situations that demand immediate action). This pattern of precision estimates would therefore temporarily reduce context-specific flexibility in cognitive, autonomic, and behavioral responding in a state-dependent manner. However, if this type of high arousal state were fairly chronic in childhood (as in abuse/neglect), it could also prevent these higher levels of the CAN from learning priors that would be appropriately "tuned" for dealing with healthy adult social contexts. For example, it could lead to impoverished internal conceptual descriptions of one's state (at level 7), because one failed to learn to apply emotion concepts appropriately to self and others (as in alexithymia or "affective agnosia"; see Colvert et al., 2008; Lane et al., 2015). It could also lead to a failure to learn the sorts of deliberative reasoning habits (e.g., intentionally imagining another person's perspective) that would facilitate selection of an appropriate social problem-solving strategy. Such learning failures could lead to poor emotion regulation, reduced HRV, and even increases in chronic inflammation (e.g., Slavich and Irwin, 2014), all as a result of inappropriate CAN dynamics at these higher levels. Such effects might also interact with findings from other developmental work on individual differences in "life history strategy," which suggest that harsh/uncertain developmental conditions promote increased risk-taking and an increased preference for small immediate rewards over larger delayed rewards (i.e., because in such conditions long-term rewards are not reliably obtained; see Ellis et al., 2012).

The above considerations also lead to interesting further questions. One such question is: What is the potential role of frontal lobe maturation during the developmental learning processes described above? One possibility is that slow frontal lobe maturation actually facilitates CAN-based response learning in childhood, because it allows lower levels to "tune" priors appropriately before higher levels begin to have a strong top-down biasing influence. Future research should therefore examine the extent to which coordination of HRV with higher cognitive/emotional functions increases with increasing frontal lobe maturity in development (e.g., as in Thayer et al., 2009b).

Another related question might be: How much inter-individual variability exists in "stress tolerance" (i.e., variability in how much stress is required to significantly impact levels 7 and 8 between individuals), and how might these differences best be understood? This second question is related to current "Window of Tolerance" models that attempt to explain the long-term effects of severe emotional trauma (Corrigan et al., 2011). These models suggest that there is a limited range of arousal states (between extreme sympathetic hyperarousal and parasympathetic hypoarousal) where the associated thoughts and feelings are tolerable and can be effectively integrated with past experience, but there is little work to date examining whether tolerances differ across individuals. This question is complex, however, because, based on differences in learned expectations, two people might in fact experience different stress responses in the same objectively "high stress" situation. This highlights the need for future research to differentiate people who react more adaptively in cases of a high internal stress response, and those who respond adaptively in challenging circumstances because they in fact have a lower internal stress response. Based on our model it is easier to understand the latter possibility, which could be explained as the result of having learned more adaptively tuned priors at high levels, and therefore not getting "inappropriately" stressed due to misinterpreting the situation or making inaccurate interoceptive/exteroceptive predictions about its likely future consequences. The former possibility is less easily understood because it might be seen to require that regions in levels 7 and 8 are structurally less sensitive to stress-related neurochemical and endocrine changes; this would be less readily accounted for in our model. In contrast, it might instead be understood to indicate that lower levels of the CAN have learned more adaptive habitual responses through past experience, such that even when the flexibility of higher levels has been removed one automatically responds in more broadly adaptive ways. These considerations highlight the need to investigate how past experience, learning, and attention may interact at different levels of the CAN, leading to adaptive responses emanating primarily from either lower or higher levels in a given context.

The above considerations may also have implications for psychotherapy. For instance, if maladaptive autonomic/emotional responses can arise from a mismatch between the priors learned in an impoverished childhood and those that would lead to more accurate interpretations and adaptive responses in adulthood, an important role of psychotherapy might be that of facilitating the "re-tuning" of a client's priors to reflect more adaptive top-down estimates. This could include, for example, adjusting priors for what others are likely thinking/feeling in particular contexts, priors for internal vs. external attributions of blame and responsibility, and priors for one's own life skills and abilities. In re-tuning maladaptive priors in this way, one should expect increases in adaptive vagal responses as a result of more adaptive/accurate automatic appraisals of one's current situation (for several preliminary examples of the impact of psychotherapy on vagal tone, see Hinton et al., 2009; Lü et al., 2013). Although speculative, it may be possible that the resulting overall increases in vagal tone could also lead to better physiological/immune regulation and improved physical health more generally (e.g., successful psychotherapy may lead to lower mortality rates; see Doidge, 2001).

Finally, our proposed model also provides specifiable predictions about brain imaging findings. It suggests that the information-/coordination-based levels of function we have

described should correlate with activation in the brain regions that we have suggested likely implement them. To empirically examine these facets of the model, novel neuroimaging experiments could be designed to maximize prediction-error and/or precision estimates at a given level of function, and test for increases in activity in the regions our model would predict. Relatedly, one could test the hypothesis that changes in HRV would accompany these induced prediction-errors/precision estimate changes, as these would often be expected to induce error-minimizing changes in CAN output. Given recent advances in the ability to functionally image brainstem structures (Beissner et al., 2014), it may now also be possible to test model predictions at this level to a much greater extent, and also allow for better tests of the interactions between cortical and brainstem structures that we hypothesize. For example, our model suggests that lower brainstem nuclei will increase in activation with increasing prediction-errors, and that minimal prediction-error at this level will be reflective of well-balanced homeostatic regulatory control (and therefore higher HRV). This suggests that such nuclei should appear relatively inhibited during neuroimaging in individuals with higher HRV, as both would reflect that the CAN as a whole is efficient at accurately predicting/adjusting visceral activity in the context of current task demands.

It is important to highlight, however, that the model we have proposed is also limited in certain ways, and that further extensions/refinements may be necessary to take full advantage of the potential applications we have described. For example, aside from testing some of the model predictions described above, one area in which it could be strengthened is with regard to additional organ systems. We have here focused on the heart, but an important question remains about how lower levels of the vagal hierarchy will work for other vagally controlled systems (e.g., gastrointestinal function). It also remains unclear exactly how differentiated the vagal hierarchy's control is over different organ systems. A second area for further model development pertains to elucidating the precise roles of the cerebellum and striatum in vagal control. For example, while our discussion of the striatum has been largely constrained to its known role in habitual cognition and skeletomotor behavior (Cisek, 2007; Grahn et al., 2008; McNab and Klingberg, 2008; Seger and Spiering, 2011), when considering its known interactions with many regions of the vagal hierarchy we have described (e.g., Fudge et al., 2005; Kelley, 1999), perhaps it is possible that particular striatal regions (e.g., the ventral striatal regions linked to the "limbic network" discussed in Barrett and Satpute, 2013) could also contribute to the selection/reinforcement of autonomic/vagal responses. The cerebellum is instead thought to play an important role in the prediction-based optimization of both cognitive and skeletomotor responses (Buckner, 2013), and specific cerebellar regions have also been shown to be functionally and/or structurally connected to cortical networks subserving both interoception (Shirer et al., 2012) and cognitive control (Buckner, 2013). These considerations suggest the possibility that such cerebellar regions may optimize cortical processes in these domains as well, which could plausibly have an indirect influence on vagal control. Such details will need to be further examined and added to the model in future work. This paper simply represents an important step in that direction.

In conclusion, the goal of this paper has been to add a greater level of anatomical, physiological, and computational detail to the NVI model. In doing so, we have sought to illustrate how this detail should improve the ability to address important research questions with greater precision. Many of these questions pertain to the relation between physical and mental health, as well as the relation between visceral regulation and performance on a range of cognitive, emotional, and behavioral tasks. We have described an anatomical hierarchy with specific physiological processes that implement bidirectional adaptive control across nested loops of brain circuits. This may clarify how neurovisceral integration can occur in a graded and flexible fashion, and how it may issue multimodal predictions that simultaneously guide perception and action across the domains of interoception, exteroception, and attentional control. Future research should apply the guiding principles of this model to address many specific questions at the forefront of current neurovisceral integration research. This includes questions, for example, about what hierarchical levels are functioning maladaptively in different psychiatric/emotional disorders. It also includes questions about how, when considering the hierarchical control system described above, one could best design interventions to successfully increase vagal tone. Finally, while we have focused on cardiac regulation as an example case, the vagus nerve regulates many other organ systems as well that could each have their own "level 1 and 2" systems. We have not considered these here in any detail, and future work should further examine these different organ-specific low-level control loops, and also how they may interact with the higher-level control loops we have described. We believe the model we have outlined above should be useful in guiding future hypothesis testing and study design with respect to each of these questions, as well as future neuroimaging work aimed at further testing the NVI model more generally.

References

Acevedo, B., Aron, A., Fisher, H., Brown, L., 2012. Neural correlates of long-term intense romantic love. Soc. Cogn. Affect. Neurosci. 7, 145–159, http://dx.doi.org/10.1093/scan/nsq092.

Ahs, F., Sollers, J., Furmark, T., Fredrikson, M., Thayer, J., 2009. High-frequency heart rate variability and cortico-striatal activity in men and women with social phobia. Neuroimage 47, 815–820, http://dx.doi.org/10.1016/j.neuroimage.2009.05.091.

Ainley, V., Apps, M., Fotopoulou, A., Tsakiris, M., 2016. Bodily precision: a predictive coding account of individual differences in interoceptive accuracy. Philos. Trans. R. Soc. London B Biol. Sci., 371.

Allen, G., Cechetto, D., 1992. Functional and anatomical organization of cardiovascular pressor and depressor sites in the lateral hypothalamic area: I. Descending projections. J. Comp. Neurol. 315, 313–332, http://dx.doi.org/10.1002/cne.903150307.

Allen, G., Cechetto, D., 1993. Functional and anatomical organization of cardiovascular pressor and depressor sites in the lateral hypothalamic area. II. Ascending projections. J. Comp. Neurol. 330, 421–438, http://dx.doi.org/10.1002/cne.903300310.

Amaral, D., Price, J., 1984. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J. Comp. Neurol. 230, 465–496, http://dx.doi.org/10.1002/cne.902300402.

Amaral, D., Price, J., Pitkanen, A., Carmichael, S., 1992. Anatomical organization of the primate amygdaloid complex. In: Aggleton, J. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Wiley-Liss, New York, pp. 1–66.

Anderson, M., Kinnison, J., Pessoa, L., 2013. Describing functional diversity of brain regions and brain networks. Neuroimage 73, 50–58, http://dx.doi.org/10.1016/j.neuroimage.2013.01.071.

Andersson, U., Tracey, K., 2012. Neural reflexes in inflammation and immunity. J. Exp. Med. 209.

Appelhans, B., Luecken, L., 2006. Heart rate variability as an index of regulated emotional responding. Rev. Gen. Psychol. 10, 229–240, http://dx.doi.org/10.1037/1089-2680.10.3.229.

Armour, J., Ardell, J., 2004. Basic and Clinical Neurocardiology. Oxford University Press, New York.

Armour, J., 2004. Cardiac neuronal hierarchy in health and disease. Am. J. Physiol. Regul. Integr. Comp. Physiol. 287, R262–71, http://dx.doi.org/10.1152/ajpregu.00183.2004.

Arnsten, A., Robbins, T., 2002. Neurochemical modulation of prefrontal cortical function in humans and animals. In: Principles of Frontal Lobe Function., pp. 51–84.

Arnsten, A., 1998. Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn. Sci. 2, 436–447.

Arthur, J.M., Bonham, A.C., Gutterman, D.D., Gebhart, G.F., Marcus, M.L., Brody, M.J., 1991. Coronary vasoconstriction during stimulation in hypothalamic defense region. Am. J. Physiol. Regul. Integr. Comp. Physiol. 260, R335–345.

Augustine, J., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Rev. 22, 229–244, http://dx.doi.org/10.1016/S0165-0173(96)00011-2.

Averbeck, B., Seo, M., 2008. The statistical neuroanatomy of frontal networks in the macaque. PLoS Comput. Biol. 4, e1000050, http://dx.doi.org/10.1371/journal.pcbi.1000050.

Bär, K.-J., Berger, S., Metzner, M., Boettger, M., Schulz, S., Ramachandraiah, C., Terhaar, J., Voss, A., Yeragani, V., Sauer, H., 2010. Autonomic dysfunction in unaffected first-degree relatives of patients suffering from schizophrenia. Schizophr. Bull. 36, 1050–1058, http://dx.doi.org/10.1093/schbul/sbp024.

Bandler, R., Shipley, M.T., 1994. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci. 17, 379–389, http://dx.doi.org/10.1016/0166-2236(94)90047-7.

Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala-frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. 2, 303–312, http://dx.doi.org/10.1093/scan/nsm029.

Barbas, H., Saha, S., Rempel-Clower, N., Ghashghaei, T., 2003. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neurosci. 4, 25, http://dx.doi.org/10.1186/1471-2202-4-25.

Barbas, H., 1995. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. Neurosci. Biobehav. Rev. 19, 499–510, http://dx.doi.org/10.1016/0149-7634(94)00053-4.

Bard, P., 1928. A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. Am. J. Physiol. 84, 490–515.

Bard, P., 1929. The central representation of the sympathetic system. Arch. Neurol. Psychiatry 22, 230, http://dx.doi.org/10.1001/archneurpsyc.1929.02220020046002.

Bard, P., 1934. On emotional expression after decortication with some remarks on certain theoretical views: part I. Psychol. Rev. 41, 309–323.

Barrett, L., Satpute, A., 2013. Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. Curr. Opin. Neurobiol. 23, 361–372, http://dx.doi.org/10.1016/j.conb.2012.12.012.

Barrett, L., Simmons, W., 2015. Interoceptive predictions in the brain. Nat. Rev. Neurosci. 16, 419–429, http://dx.doi.org/10.1038/nrn3950.

Bastos, A., Usrey, W., Adams, R., Mangun, G., Fries, P., Friston, K., 2012. Canonical microcircuits for predictive coding. Neuron 76, 695–711, http://dx.doi.org/10.1016/j.neuron.2012.10.038.

Behbehani, M., 1995. Functional characteristics of the midbrain periaqueductal gray. Prog. Neurobiol. 46, 575–605, http://dx.doi.org/10.1016/0301-0082(95)00009-K.

Beissner, F., Schumann, A., Brunn, F., Eisenträger, D., Bär, K.-J., 2014. Advances in functional magnetic resonance imaging of the human brainstem. Neuroimage 86, 91–98.

Benarroch, E., 1993. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin. Proc.

Benarroch, E., 2008. The arterial baroreflex: functional organization and involvement in neurologic disease. Neurology 71, 1733–1738, http://dx.doi.org/10.1212/01.wnl.0000335246.93495.92.

Benarroch, E., 2011. Circumventricular organs: receptive and homeostatic functions and clinical implications. Neurology 77, 1198–1204, http://dx.doi.org/10.1212/WNL.0b013e31822f04a0.

Birmingham, K., Gradinaru, V., Anikeeva, P., Grill, W., Pikov, V., McLaughlin, B., Pasricha, P., Weber, D., Ludwig, K., Famm, K., 2014. Bioelectronic medicines: a research roadmap. Nat. Rev. Drug Discov. 13, 399–400, http://dx.doi.org/10.1038/nrd4351.

Blackford, J.U., Buckholtz, J.W., Avery, S.N., Zald, D.H., 2010. A unique role for the human amygdala in novelty detection. Neuroimage 50, 1188–1193, http://dx.doi.org/10.1016/j.neuroimage.2009.12.083.

Brandão, M.L., Zanoveli, J.M., Ruiz-Martinez, R.C., Oliveira, L.C., Landeira-Fernandez, J., 2008. Different patterns of freezing behavior organized in the periaqueductal gray of rats: association with different types of anxiety. Behav. Brain Res. 188, 1–13, http://dx.doi.org/10.1016/j.bbr.2007.10.018.

Brosch, T., Sander, D., 2013. The appraising brain: towards a neuro-cognitive model of appraisal processes in emotion. Emot. Rev. 5, 163–168, http://dx.doi.org/10.1177/1754073912468298.

Brosschot, J., Van Dijk, E., Thayer, J., 2007. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. Int. J. Psychophysiol. 63, 39–47, http://dx.doi.org/10.1016/j.ijpsycho.2006.07.016.

Brown, H., Friston, K., Bestmann, S., 2011. Active inference, attention, and motor preparation. Front. Psychol. 2, 218, http://dx.doi.org/10.3389/fpsyg.2011.00218.

Buckner, R., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network. Ann. N. Y. Acad. Sci. 1124, 1–38, http://dx.doi.org/10.1196/annals.1440.011.

Buckner, R., 2013. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 80, 807–815, http://dx.doi.org/10.1016/j.neuron.2013.10.044.

Buhle, J., Silvers, J., Wager, T., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., Ochsner, K., 2014. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb. Cortex 24, 2981–2990, http://dx.doi.org/10.1093/cercor/bht154.

Butler, E., Wilhelm, F., Gross, J., 2006. Respiratory sinus arrhythmia, emotion, and emotion regulation during social interaction. Psychophysiology 43, 612–622, http://dx.doi.org/10.1111/j.1469-8986.2006.00467.x.

Cannon, W., Britton, S., 1925. Studies on the conditions of activity in endocrine glands:XV: Pseudaffective medulliadrenal secretion. Am. J. Physiol. Content 72, 283–294.

Cannon, W.B., 1929. Bodily Changes in Pain, Hunger, Fear, and Rage, 2nd ed. Appleton, New York.

Carmichael, S., Price, J., 1996. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. J. Comp. Neurol. 371, 179–207, http://dx.doi.org/10.1002/(SICI)1096-9861(19960722)371:2<179:AID-CNE1>3.0.CO;2-#.

Cechetto, D., Chen, S., 1990. Subcortical sites mediating sympathetic responses from insular cortex in rats. Am. J. Physiol. 258, R245–55.

Chapleau, M., 2012. Baroreceptor reflexes. In: Robertson, D., Biaggioni, I., Burnstock, G., Low, P., Paton, J. (Eds.), Primer on the Autonomic Nervous System. , 3rd edition. Elsevier, London.

Chuang, K., Liu, W., Liou, N., Liu, J., 2004. Horseradish peroxidase localization of sympathetic postganglionic and parasympathetic preganglionic neurons innervating the monkey heart. Chin. J. Physiol. 47, 95–99.

Cisek, P., 2007. Cortical mechanisms of action selection: the affordance competition hypothesis. Philos. Trans. R. Soc. Lond. B Biol. Sci. 362, 1585–1599, http://dx.doi.org/10.1098/rstb.2007.2054.

Clark, A., 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav. Brain Sci. 36, 181–204, http://dx.doi.org/10.1017/S0140525x12000477.

Colvert, E., Rutter, M., Kreppner, J., Beckett, C., Castle, J., Groothues, C., Hawkins, A., Stevens, S., Sonuga-Barke, E., 2008. Do theory of mind and executive function deficits underlie the adverse outcomes associated with profound early deprivation? Findings from the english and romanian adoptees study. J. Abnorm. Child Psychol. 36, 1057–1068, http://dx.doi.org/10.1007/s10802-008-9232-x.

Comte, M., Schön, D., Coull, J., Reynaud, E., Khalfa, S., Belzeaux, R., Ibrahim, E., Guedj, E., Blin, O., Weinberger, D., Fakra, E., 2014. Dissociating bottom-up and top-down mechanisms in the cortico-limbic system during emotion processing. Cereb. Cortex bhu185, http://dx.doi.org/10.1093/cercor/bhu185.

Corrigan, F., Fisher, J., Nutt, D., 2011. Autonomic dysregulation and the Window of Tolerance model of the effects of complex emotional trauma. J. Psychopharmacol. 25, 17–25, http://dx.doi.org/10.1177/0269881109354930.

Craig, A.D., 2002. How do you feel?: Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 3, 655–666.

Craig, A.D., 2009. How do you feel–now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10, 59–70.

Critchley, H., Rotshtein, P., Nagai, Y., O'Doherty, J., Mathias, C., Dolan, R., 2005. Activity in the human brain predicting differential heart rate responses to emotional facial expressions. Neuroimage 24, 751–762, http://dx.doi.org/10.1016/j.neuroimage.2004.10.013.

Cunningham, W., Van Bavel, J., Johnsen, I., 2008. Affective flexibility: evaluative processing goals shape amygdala activity. Psychol. Sci. 19, 152–160, http://dx.doi.org/10.1111/j.1467-9280.2008.02061.x.

D'Argembeau, A., Ruby, P., 2007. Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective taking. J. Cogn. Neurosci. 19, 935–944.

Damasio, A., 1994. Descartes' error: emotion, reason, and the human brain. Putnam, New York.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Mol. Psychiatry 6, 13–34, http://dx.doi.org/10.1038/sj.mp.4000812.

Davis, R., 1958. The domain of homeostasis. Psychol. Rev. 65, 8–13.

Daw, N., Niv, Y., Dayan, P., 2005. Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. Nat. Neurosci. 8, 1704–1711, http://dx.doi.org/10.1038/nn1560.

Dayan, P., Daw, N., 2008. Decision theory, reinforcement learning, and the brain. Cogn. Affect. Behav. Neurosci. 8, 429–453, http://dx.doi.org/10.3758/CABN.8.4.429.

Dayan, P., 2012. How to set the switches on this thing. Curr. Opin. Neurobiol. 22, 1068–1074, http://dx.doi.org/10.1016/j.conb.2012.05.011.

Dehaene, S., Sigman, M., 2012. From a single decision to a multi-step algorithm. Curr. Opin. Neurobiol. 22, 937–945, http://dx.doi.org/10.1016/j.conb.2012.05.006.

Dehaene, S., 2014. Consciousness and the Brain. Viking Press.

Doidge, N., 2001. Introduction to Jeffery: why psychoanalysts have low mortality rates. J. Am. Psychoanal. Assoc. 49, 97–102.

Dum, R., Levinthal, D., Strick, P., 2016. Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. Proc. Natl. Acad. Sci. U. S. A. 113, 9922–9927, http://dx.doi.org/10.1073/pnas.1605044113.

Duncan, J., Emslie, H., Williams, P., Johnson, R., Freer, C., 1996. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cogn. Psychol. 30, 257–303, http://dx.doi.org/10.1006/cogp.1996.0008.

Duschek, S., Reyes del Paso, G., 2007. Quantification of cardiac baroreflex function at rest and during autonomic stimulation. J. Physiol. Sci. 57, 259–268, http://dx.doi.org/10.2170/physiolsci.RP008807.

Dykes, R., 1997. Mechanisms controlling neuronal plasticity in somatosensory cortex. Can. J. Physiol. Pharmacol. 75, 535–545.

Ellis, B., Del Giudice, M., Dishion, T., Figueredo, A., Gray, P., Griskevicius, V., Hawley, P., Jacobs, W., James, J., Volk, A., Wilson, D., 2012. The evolutionary basis of risky adolescent behavior: implications for science, policy, and practice. Dev. Psychol. 48, 598–623, http://dx.doi.org/10.1037/a0026220.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51, 871–882.

Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15, 85–93, http://dx.doi.org/10.1016/j.tics.2010.11.004, S1364-6613(10)00252-4[pii].

Feldman, H., Friston, K., 2010. Attention, uncertainty, and free-energy. Front. Hum. Neurosci. 4, 215, http://dx.doi.org/10.3389/fnhum.2010.00215.

Frewen, P., Lane, R., Neufeld, R., Densmore, M., Stevens, T., Lanius, R., 2008. Neural correlates of levels of emotional awareness during trauma script-imagery in posttraumatic stress disorder. Psychosom. Med. 70, 27–31.

Friedman, B., Thayer, J., 1998. Autonomic balance revisited: panic anxiety and heart rate variability. J. Psychosom. Res. 44, 133–151 (S002239999700202X[pii]).
Friedman, B., Thayer, J., Tyrrell, R., 1996. Spectral characteristics of heart period variability during cold face stress and shock avoidance in normal subjects. Clin. Auton. Res. 6, 147–152, http://dx.doi.org/10.1007/BF02281901.
Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9, 474–480, http://dx.doi.org/10.1016/j.tics.2005.08.011.
Friston, K., Daunizeau, J., Kilner, J., Kiebel, S., 2010. Action and behavior: a free-energy formulation. Biol. Cybern. 102, 227–260, http://dx.doi.org/10.1007/s00422-010-0364-z.
Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. Lond. B Biol. Sci. 360, 815–836, http://dx.doi.org/10.1098/rstb.2005.1622.
Friston, K., 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11, 127–138, http://dx.doi.org/10.1038/nrn2787.
Fudge, J., Breitbart, M., Danish, M., Pannoni, V., 2005. Insular and gustatory inputs to the caudal ventral striatum in primates. J. Comp. Neurol. 490, 101–118, http://dx.doi.org/10.1002/cne.20660.
Gündel, H., O'Connor, M.-F., Littrell, L., Fort, C., Lane, R., 2003. Functional neuroanatomy of grief: an FMRI study. Am. J. Psychiatry 160, 1946–1953, http://dx.doi.org/10.1176/appi.ajp.160.11.1946.
Georgopoulos, A., Kettner, R., Schwartz, A., 1988. Primate motor cortex and free arm movements to visual targets in three- dimensional space. II. Coding of the direction of movement by a neuronal population. J. Neurosci. 8, 2928–2937.
Ghashghaei, H., Hilgetag, C., Barbas, H., 2007. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage 34, 905–923, http://dx.doi.org/10.1016/j.neuroimage.2006.09.046.
Gläscher, J., Daw, N., Dayan, P., O'Doherty, J.P., 2010. States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning. Neuron 66, 585–595, http://dx.doi.org/10.1016/j.neuron.2010.04.016.
Goard, M., Dan, Y., 2009. Basal forebrain activation enhances cortical coding of natural scenes. Nat. Neurosci. 12, 1444–1449, http://dx.doi.org/10.1038/nn.2402.
Gorman, J., Sloan, R., 2000. Heart rate variability in depressive and anxiety disorders. Am. Heart J. 140, S77–S83, http://dx.doi.org/10.1067/mhj.2000.109981.
Grahn, J., Parkinson, J., Owen, A., 2008. The cognitive functions of the caudate nucleus. Prog. Neurobiol. 86, 141–155, http://dx.doi.org/10.1016/j.pneurobio.2008.09.004.
Gray, M., Taggart, P., Sutton, P., Groves, D., Holdright, D., Bradbury, D., Brull, D., Critchley, H., 2007. A cortical potential reflecting cardiac function. Proc. Natl. Acad. Sci. U. S. A. 104, 6818–6823, http://dx.doi.org/10.1073/pnas.0609509104.
Gross, J., 1998. The emerging field of emotion regulation: an integrative review. Rev. Gen. Psychol. 2, 271–299.
Gu, X., Hof, P., Friston, K., Fan, J., 2013. Anterior insular cortex and emotional awareness. J. Comp. Neurol. 521, 3371–3388, http://dx.doi.org/10.1002/cne.23368.
Gupta, R., Koscik, T., Bechara, A., Tranel, D., 2011. The amygdala and decision-making. Neuropsychologia 49, 760–766, http://dx.doi.org/10.1016/j.neuropsychologia.2010.09.029.
Gusnard, D., Akbudak, E., Shulman, G., Raichle, M., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc. Natl. Acad. Sci. 98, 4259–4264.
Guyenet, P., 2006. The sympathetic control of blood pressure. Nat. Rev. Neurosci. 7, 335–346, http://dx.doi.org/10.1038/nrn1902.
Gyurak, A., Gross, J.J., Etkin, A., 2011. Explicit and implicit emotion regulation: a dual-process framework. Cogn Emot 25, 400–412, http://dx.doi.org/10.1080/02699931.2010.544160 (933887834[pii]).
Hansen, A., Johnsen, B., Thayer, J., 2003. Vagal influence on working memory and attention. Int. J. Psychophysiol. 48, 263–274, http://dx.doi.org/10.1016/S0167-8760(03)00073-4.
Hansen, A., Johnsen, B., Sollers, J., Stenvik, K., Thayer, J., 2004. Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. Eur. J. Appl. Physiol. 93, 263–272, http://dx.doi.org/10.1007/s00421-004-1208-0.
Hansen, A., Johnsen, B., Thayer, J., 2009. Relationship between heart rate variability and cognitive function during threat of shock. Anxiety. Stress. Coping 22, 77–89.
Hassanpour, M., Yan, L., Wang, D., Lapidus, R., Arevian, A., Simmons, W., Feusner, J., Khalsa, S., 2016. How the heart speaks to the brain: neural activity during cardiorespiratory interoceptive stimulation. Philos. Trans. R. Soc. London B Biol. Sci. 371.
Hesse, C., Charkoudian, N., Liu, Z., Joyner, M., Eisenach, J., 2007. Baroreflex sensitivity inversely correlates with ambulatory blood pressure in healthy normotensive humans. Hypertension 50, 41–46, http://dx.doi.org/10.1161/HYPERTENSIONAHA.107.090308.
Hill, L., Hu, D., Koenig, J., Sollers, J., Kapuku, G., Wang, X., Snieder, H., Thayer, J., 2015. Ethnic differences in resting heart rate variability: a systematic review and meta-analysis. Psychosom. Med. 77, 16–25, http://dx.doi.org/10.1097/PSY.0000000000000133.
Hinton, D., Hofmann, S., Pollack, M., Otto, M., 2009. Mechanisms of efficacy of CBT for Cambodian refugees with PTSD: improvement in emotion regulation and orthostatic blood pressure response. CNS Neurosci. Ther. 15, 255–263, http://dx.doi.org/10.1111/j.1755-5949.2009.00100.x.
Hohwy, J., 2014. The Predictive Mind. Oxford University Press.
Holland, P., 2007. Disconnection of the amygdala central nucleus and the substantia innominata/nucleus basalis magnocellularis disrupts performance in a sustained attention task. Behav. Neurosci. 121, 80–89, http://dx.doi.org/10.1037/0735-7044.121.1.80.
Huys, Q., Dayan, P., 2009. A Bayesian formulation of behavioral control. Cognition 113, 314–328, http://dx.doi.org/10.1016/j.cognition.2009.01.008.
Ingjaldsson, J., Laberg, J., Thayer, J., 2003. Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. Biol. Psychiatry 54, 1427–1436, http://dx.doi.org/10.1016/S0006-3223(02)01926-1.
Jänig, W., 2008. Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis. Cambridge University Press.
Jeff, J., Ritchie, M., Denny, J., Kho, A., Ramirez, A., Crosslin, D., Armstrong, L., Basford, M., Wolf, W., Pacheco, J., Chisholm, R., Roden, D., Hayes, M., Crawford, D., 2013. Generalization of variants identified by genome-wide association studies for electrocardiographic traits in African Americans. Ann. Hum. Genet. 77, n/a–n/a, http://dx.doi.org/10.1111/ahg.12023.
Johnsen, B., Thayer, J., Laberg, J., Wormnes, B., Raadal, M., Skaret, E., Kvale, G., Berg, E., 2003. Attentional and physiological characteristics of patients with dental anxiety. J. Anxiety Disord. 17, 75–87, http://dx.doi.org/10.1016/S0887-6185(02)00178-0.
Kelley, A., 1999. Functional specificity of ventral striatal compartments in appetitive behaviors. Ann. N. Y. Acad. Sci. 877, 71–90, http://dx.doi.org/10.1111/j.1749-6632.1999.tb09262.x.
Kemp, A., Quintana, D., 2013. The relationship between mental and physical health: insights from the study of heart rate variability. Int. J. Psychophysiol. 89, 288–296, http://dx.doi.org/10.1016/j.ijpsycho.2013.06.018.
Kemp, A., Quintana, D., Gray, M., Felmingham, K., Brown, K., Gatt, J., 2010. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol. Psychiatry 67, 1067–1074.
Kemp, A., Quintana, D., Felmingham, K., Matthews, S., Jelinek, H., 2012. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One 7, e30777, http://dx.doi.org/10.1371/journal.pone.0030777.
Kemp, A., Koenig, J., Thayer, J., Bittencourt, M., Pereira, A., Santos, I., Dantas, E., Mill, J., Chor, D., Ribeiro, A., Benseñor, I., Lotufo, P., 2016. Race and resting-state heart rate variability in Brazilian civil servants and the mediating effects of discrimination. Psychosom. Med. 78, 950–958, http://dx.doi.org/10.1097/PSY.0000000000000359.
Kern, M., Aertsen, A., Schulze-Bonhage, A., Ball, T., 2013. Heart cycle-related effects on event-related potentials, spectral power changes, and connectivity patterns in the human ECoG. Neuroimage 81, 178–190, http://dx.doi.org/10.1016/j.neuroimage.2013.05.042.
Kersting, A., Ohrmann, P., Pedersen, A., Kroker, K., Samberg, D., Bauer, J., Kugel, H., Koelkebeck, K., Steinhard, J., Heindel, W., Arolt, V., Suslow, T., 2009. Neural activation underlying acute grief in women after the loss of an unborn child. Am. J. Psychiatry 166, 1402–1410, http://dx.doi.org/10.1176/appi.ajp.2009.08121875.
Khalsa, S., Rudrauf, D., Feinstein, J., Tranel, D., 2009. The pathways of interoceptive awareness. Nat. Neurosci. 12, 1494–1496, http://dx.doi.org/10.1038/nn.2411.
Kilgard, M., Merzenich, M., 1998. Cortical map reorganization enabled by nucleus basalis activity. Science 279, 1714–1718, http://dx.doi.org/10.1126/science.279.5357.1714.
Kim, M.J., Loucks, R.A., Palmer, A.L., Brown, A.C., Solomon, K.M., Marchante, A.N., Whalen, P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav. Brain Res. 223, 403–410, http://dx.doi.org/10.1016/j.bbr.2011.04.025.
Knill, D.C., Pouget, A., 2004. The Bayesian brain: the role of uncertainty in neural coding and computation. Trends Neurosci. 27, 712–719.
Krypotos, A.-M., Jahfari, S., van Ast, V., Kindt, M., Forstmann, B., 2011. Individual differences in heart rate variability predict the degree of slowing during response inhibition and initiation in the presence of emotional stimuli. Front. Psychol. 2, 278, http://dx.doi.org/10.3389/fpsyg.2011.00278.
Lü, W., Wang, Z., Liu, Y., 2013. A pilot study on changes of cardiac vagal tone in individuals with low trait positive affect: the effect of positive psychotherapy. Int. J. Psychophysiol. 88, 213–217, http://dx.doi.org/10.1016/j.ijpsycho.2013.04.012.
La Rovere, M., Bigger, J., Marcus, F., Mortara, A., Schwartz, P., 1998. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 351, 478–484, http://dx.doi.org/10.1016/S0140-6736(97)11144-8.
LaBar, K., Gitelman, D.R., Parrish, T.B., Kim, Y.-H., Nobre, A.C., Mesulam, M., 2001. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav. Neurosci. 115, 493–500.
Lane, R., Fink, G., Chua, P., Dolan, R., 1997. Neural activation during selective attention to subjective emotional responses. Neuroreport 8, 3969–3972.
Lane, R., Weihs, K., Herring, A., Hishaw, A., Smith, R., 2015. Affective agnosia: expansion of the alexithymia construct and a new opportunity to integrate and extend Freud's legacy. Neurosci. Biobehav. Rev. 55, http://dx.doi.org/10.1016/j.neubiorev.2015.06.007 (in press).
Lane, R., 2008. Neural substrates of implicit and explicit emotional processes: a unifying framework for psychosomatic medicine. Psychosom. Med. 70, 214–231.
LeDoux, J., 1996. The Emotional Brain: the Mysterious Underpinnings of Emotional Life. Simon & Schuster, New York.

LeDoux, J., 2012. Rethinking the emotional brain. Neuron 73, 653–676, http://dx.doi.org/10.1016/j.neuron.2012.02.004.
Levenson, R., Ekman, P., Friesen, W., 1990. Voluntary facial action generates emotion-specific autonomic nervous system activity. Psychophysiology 27, 363–384, http://dx.doi.org/10.1111/j.1469-8986.1990.tb02330.x.
Li, W., Mai, X., Liu, C., 2014. The default mode network and social understanding of others: what do brain connectivity studies tell us. Front. Hum. Neurosci. 8, 74, http://dx.doi.org/10.3389/fnhum.2014.00074.
Liao, D., Carnethon, M., Evans, G., Cascio, W., Heiss, G., 2002. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes 51, 3524–3531.
Longhurst, J., 2011. Regulation of autonomic function by visceral and somatic afferents. In: Lewellyn-Smith, I., Verberne, A. (Eds.), Central Regulation of Autonomic Functions. Oxford University Press, pp. 161–179.
Maddux, J.-M., Kerfoot, E., Chatterjee, S., Holland, P., 2007. Dissociation of attention in learning and action: effects of lesions of the amygdala central nucleus, medial prefrontal cortex, and posterior parietal cortex. Behav. Neurosci. 121, 63–79, http://dx.doi.org/10.1037/0735-7044.121.1.63.
McNab, F., Klingberg, T., 2008. Prefrontal cortex and basal ganglia control access to working memory. Nat. Neurosci. 11, 103–107, http://dx.doi.org/10.1038/nn2024.
McRae, K., Reiman, E., Fort, C., Chen, K., Lane, R., 2008. Association between trait emotional awareness and dorsal anterior cingulate activity during emotion is arousal-dependent. Neuroimage 41, 648–655, http://dx.doi.org/10.1016/j.neuroimage.2008.02.030.
Medford, N., Critchley, H., 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct. Funct. 214, 535–549, http://dx.doi.org/10.1007/s00429-010-0265-x.
Melzig, C., Weike, A., Hamm, A., Thayer, J., 2009. Individual differences in fear-potentiated startle as a function of resting heart rate variability: implications for panic disorder. Int. J. Psychophysiol. 71, 109–117, http://dx.doi.org/10.1016/j.ijpsycho.2008.07.013.
Mesulam, M., Hersh, L., Mash, D., Geula, C., 1992. Differential cholinergic innervation within functional subdivisions of the human cerebral cortex: a choline acetyltransferase study. J. Comp. Neurol. 318, 316–328, http://dx.doi.org/10.1002/cne.903180308.
Mesulam, M., 1998. From sensation to cognition. Brain 121, 1013–1052.
Mesulam, M., 2000. Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In: Mesulam, M. (Ed.), Principles of Behavioral and Cognitive Neurology. Oxford University Press, New York.
Micieli, G., Tosi, P., Marcheselli, S., Cavallini, A., 2003. Autonomic dysfunction in Parkinson's disease. Neurol. Sci. 24, s32–s34, http://dx.doi.org/10.1007/s100720300035.
Mimee, A., Smith, P.M., Ferguson, A.V., 2013. Circumventricular organs: targets for integration of circulating fluid and energy balance signals? Physiol. Behav. 121, 96–102, http://dx.doi.org/10.1016/j.physbeh.2013.02.012.
Mitchell, D., Greening, S., 2011. Conscious perception of emotional stimuli: brain mechanisms. Neuroscience 18, 386–398, http://dx.doi.org/10.1177/1073858411416515.
Mitchell, D., 2011. The nexus between decision making and emotion regulation: a review of convergent neurocognitive substrates. Behav. Brain Res. 217, 215–231, http://dx.doi.org/10.1016/j.bbr.2010.10.030.
Modha, D., Singh, R., 2010. Network architecture of the long-distance pathways in the macaque brain. Proc. Natl. Acad. Sci. U. S. A. 107, 13485–13490, http://dx.doi.org/10.1073/pnas.1008054107.
Morawetz, C., Bode, S., Baudewig, J., 2015. Changes in effective connectivity between dorsal and ventral prefrontal regions moderate emotion regulation. Cereb. Cortex, 1–15.
Morrison, S.F., Nakamura, K., 2011. Central neural pathways for thermoregulation. Front. Biosci. 16, 74–104.
Morrison, S.F., 2001. Differential control of sympathetic outflow. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R683–698.
Murray, A., Atkinson, L., Mahadi, M., Deuchars, S., Deuchars, J., 2016. The strange case of the ear and the heart: the auricular vagus nerve and its influence on cardiac control. Auton. Neurosci. 199, 48–53, http://dx.doi.org/10.1016/j.autneu.2016.06.004.
Nadel, L., Jacobs, W., 1998. Traumatic memory is special. Curr. Dir. Psychol. Sci. 7, 154–157.
Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E., Barbieri, R., 2008. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. Neuroimage 42, 169–177, http://dx.doi.org/10.1016/j.neuroimage.2008.04.238.
Neafsey, E., 1990. Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. Prog. Brain Res. 85, 147–165 (discussion 165-6).
Ochsner, K., Gross, J., 2005. The cognitive control of emotion. Trends Cogn. Sci. 9, 242–249.
Ochsner, K., Gross, J., 2007. The neural architecture of emotion regulation. In: Gross, J. (Ed.), Handbook of Emotion Regulation. Guilford Press, New York, pp. 87–109.
Ochsner, K., Bunge, S.A., Gross, J., Gabrieli, J., 2002. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J. Cogn. Neurosci. 14, 1215–1229, http://dx.doi.org/10.1162/089892902760807212.
Ohira, H., Isowa, T., Nomura, M., Ichikawa, N., Kimura, K., Miyakoshi, M., Iidaka, T., Fukuyama, S., Nakajima, T., Yamada, J., 2008. Imaging brain and immune association accompanying cognitive appraisal of an acute stressor. Neuroimage 39, 500–514, http://dx.doi.org/10.1016/j.neuroimage.2007.08.017.
Ongur, D., Price, J., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219, http://dx.doi.org/10.1093/cercor/10.3.206.
Pal, G., Velkumary, S., 2004. Effect of short-term practice of breathing exercises on autonomic functions in normal human volunteers. Indian J. Med. Res. 120, 115–121.
Parati, G., Di Rienzo, M., Mancia, G., 2000. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. J. Hypertens. 18, 7–19.
Park, G., Thayer, J., 2014. From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. Front. Psychol. 5, 278, http://dx.doi.org/10.3389/fpsyg.2014.00278.
Park, G., Vasey, M., Van Bavel, J., Thayer, J., 2014. When tonic cardiac vagal tone predicts changes in phasic vagal tone: the role of fear and perceptual load. Psychophysiology 51, 419–426, http://dx.doi.org/10.1111/psyp.12186.
Peck, C., Salzman, C., 2014. The amygdala and basal forebrain as a pathway for motivationally guided attention. J. Neurosci. 34, 13757–13767, http://dx.doi.org/10.1523/JNEUROSCI.2106-14.2014.
Pessoa, L., Adolphs, R., 2010. Emotion processing and the amygdala: from a low road to many roads of evaluating biological significance. Nat. Rev. Neurosci. 11, 773–783, http://dx.doi.org/10.1038/nrn2920.
Pessoa, L., 2008. On the relationship between emotion and cognition. Nat. Rev. Neurosci. 9, 148–158, http://dx.doi.org/10.1038/nrn2317.
Pessoa, L., 2013. The Cognitive-Emotional Brain: From Interactions to Integration. MIT Press.
Petrovich, G., Canteras, N., Swanson, L., 2001. Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. Brain Res. Rev. 38, 247–289, http://dx.doi.org/10.1016/S0165-0173(01)00080-7.
Pezzulo, G., Rigoli, F., Friston, K., 2015. Active Inference, homeostatic regulation and adaptive behavioural control. Prog. Neurobiol. 134, 17–35, http://dx.doi.org/10.1016/j.pneurobio.2015.09.001.
Pezzulo, G., 2012. An Active Inference view of cognitive control. Front. Psychol. 3, 478.
Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol. Psychiatry 57, 210–219, http://dx.doi.org/10.1016/j.biopsych.2004.10.030.
Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13 (829), 833–857.
Pires, S., Julien, C., Chapuis, B., Sassard, J., Barrès, C., 2002. Spontaneous renal blood flow autoregulation curves in conscious sinoaortic baroreceptor-denervated rats. Am. J. Physiol. Renal Physiol. 282, F51–8, http://dx.doi.org/10.1152/ajprenal.00186.2001.
Pollatos, O., Kirsch, W., Schandry, R., 2005. On the relationship between interoceptive awareness, emotional experience, and brain processes. Cogn. Brain Res. 25, 948–962, http://dx.doi.org/10.1016/j.cogbrainres.2005.09.019.
Pollatos, O., Herbert, B., Mai, S., Kammer, T., 2016. Changes in interoceptive processes following brain stimulation. Philos. Trans. R. Soc. London B Biol. Sci. 371.
Pouget, A., Dayan, P., Zemel, R., 2000. Information processing with population codes. Nat. Rev. Neurosci. 1, 125–132, http://dx.doi.org/10.1038/35039062.
Ranganath, C., Rainer, G., 2003. Neural mechanisms for detecting and remembering novel events. Nat. Rev. Neurosci. 4, 193–202, http://dx.doi.org/10.1038/nrn1052.
Rempel-Clower, N., Barbas, H., 1998. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. J. Comp. Neurol. 398, 393–419.
Reyes del Paso, G., Langewitz, W., Robles, H., Pérez, N., 1996. A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. Int. J. Psychophysiol. 22, 163–171, http://dx.doi.org/10.1016/0167-8760(96)00020-7.
Risold, P., Thompson, R., Swanson, L., 1997. The structural organization of connections between hypothalamus and cerebral cortex. Brain Res. Rev. 24, 197–254, http://dx.doi.org/10.1016/S0165-0173(97)00007-6.
Robbins, T., Arnsten, A., 2009. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu. Rev. Neurosci. 32, 267–287, http://dx.doi.org/10.1146/annurev.neuro.051508.135535.
Rosen, S., Paulesu, E., Nihoyannopoulos, P., Tousoulis, D., Frackowiak, R., Frith, C., Jones, T., Camici, P., 1996. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. Ann. Intern. Med. 124, 939, http://dx.doi.org/10.7326/0003-4819-124-11-199606010-00001.
Roy, M., Shohamy, D., Wager, T.D., 2012. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn. Sci. 16, 147–156, http://dx.doi.org/10.1016/j.tics.2012.01.005, S1364-6613(12)00027-7[pii].
Ruiz-Padial, E., Sollers, J., Vila, J., Thayer, J., 2003. The rhythm of the heart in the blink of an eye: emotion-modulated startle magnitude covaries with heart rate variability. Psychophysiology 40, 306–313, http://dx.doi.org/10.1111/1469-8986.00032.

Sah, P., Faber, E., Lopez De Armentia, M., Power, J., 2003. The amygdaloid complex: anatomy and physiology. Physiol. Rev. 83, 803–834, http://dx.doi.org/10.1152/physrev.00002.2003.
Sakaki, M., Yoo, H., Nga, L., Lee, T.-H., Thayer, J., Mather, M., 2016. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. Neuroimage, http://dx.doi.org/10.1016/j.neuroimage.2016.05.076.
Saper, C., Loewy, A., 1980. Efferent connections of the parabrachial nucleus in the rat. Brain Res. 197, 291–317, http://dx.doi.org/10.1016/0006-8993(80)91117-8.
Saper, C., 2002. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu. Rev. Neurosci. 25, 433–469, http://dx.doi.org/10.1146/annurev.neuro.25.032502.111311.
Sarter, M., Bruno, J., 1999. Abnormal regulation of corticopetal cholinergic neurons and impaired information processing in neuropsychiatric disorders. Trends Neurosci. 22, 67–74, http://dx.doi.org/10.1016/S0166-2236(98)01289-2.
Satpute, A.B., Wager, T., Cohen-Adad, J., Bianciardi, M., Choi, J.-K., Buhle, J.T., Wald, L.L., Barrett, L., 2013. Identification of discrete functional subregions of the human periaqueductal gray. Proc. Natl. Acad. Sci. U. S. A. 110, 17101–17106, http://dx.doi.org/10.1073/pnas.1306095110.
Saul, J., 1990. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. Physiology 5, 32–37.
Saus, E.-R., Johnsen, B., Eid, J., Riisem, P., Andersen, R., Thayer, J., 2006. The effect of brief situational awareness training in a police shooting simulator: an experimental study. Mil. Psychol. 18, 3–21.
Schadt, J.C., Hasser, E.M., 2001. Defense reaction alters the response to blood loss in the conscious rabbit. Am. J. Physiol. Regul. Integr. Comp. Physiol. 280, R985–993.
Schwartz, C.E., Wright, C.I., Shin, L.M., Kagan, J., Whalen, P.J., McMullin, K.G., Rauch, S.L., 2003. Differential amygdalar response to novel versus newly familiar neutral faces: a functional MRI probe developed for studying inhibited temperament. Biol. Psychiatry 53, 854–862, http://dx.doi.org/10.1016/S0006-3223(02)01906-6.
Seger, C., Spiering, B., 2011. A critical review of habit learning and the Basal Ganglia. Front. Syst. Neurosci. 5, 66, http://dx.doi.org/10.3389/fnsys.2011.00066.
Seth, A., Friston, K., 2016. Active interoceptive inference and the emotional brain. Philos. Trans. R. Soc. London B Biol. Sci. 371.
Seth, A.K., 2013. Interoceptive inference, emotion, and the embodied self. Trends Cogn. Sci. 17, 565–573, http://dx.doi.org/10.1016/j.tics.2013.09.007.
Shirer, W., Ryali, S., Rykhlevskaia, E., Menon, V., Greicius, M., 2012. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb. Cortex 22, 158–165, http://dx.doi.org/10.1093/cercor/bhr099.
Shivkumar, K., Ajijola, O., Anand, I., Armour, J., Chen, P.-S., Esler, M., De Ferrari, G., Fishbein, M., Goldberger, J., Harper, R., Joyner, M., Khalsa, S., Kumar, R., Lane, R., Mahajan, A., Po, S., Schwartz, P., Somers, V., Valderrabano, M., Vaseghi, M., Zipes, D., 2016. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. J. Physiol. 594, 3911–3954, http://dx.doi.org/10.1113/JP271870.
Silani, G., Bird, G., Brindley, R., Singer, T., Frith, C., Frith, U., 2008. Levels of emotional awareness and autism: an fMRI study levels of emotional awareness and autism: an fMRI study. Psychology 3, 97–112, http://dx.doi.org/10.1080/17470910701577020.
Silvetti, M., Alexander, W., Verguts, T., Brown, J., 2014. From conflict management to reward-based decision making: actors and critics in primate medial frontal cortex. Neurosci. Biobehav. Rev. 46 (Pt 1), 44–57, http://dx.doi.org/10.1016/j.neubiorev.2013.11.003.
Slavich, G., Irwin, M., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140, 774–815, http://dx.doi.org/10.1037/a0035302.
Smith, R., Lane, R., 2015. The neural basis of one's own conscious and unconscious emotional states. Neurosci. Biobehav. Rev. 57, 1–29, http://dx.doi.org/10.1016/j.neubiorev.2015.08.003.
Smith, R., Allen, J., Thayer, J., Fort, C., Lane, R., 2014a. Increased association over time between regional frontal lobe BOLD change magnitude and cardiac vagal control with sertraline treatment for major depression. Psychiatry Res. Neuroimaging 224, 225–233, http://dx.doi.org/10.1016/j.pscychresns.2014.08.015.
Smith, R., Fass, H., Lane, R., 2014b. Role of medial prefrontal cortex in representing one's own subjective emotional responses: a preliminary study. Conscious. Cogn. 29, 117–130, http://dx.doi.org/10.1016/j.concog.2014.08.002.
Solomon, A., De Fanti, B., Martínez, J., 2006. The nucleus tractus solitari (NTS) participates in peripheral ghrelin glucostatic hunger signalling mediated by insulin. Neuropeptides 40, 169–175, http://dx.doi.org/10.1016/j.npep.2006.03.003.
Sotres-Bayon, F., Diaz-Mataix, L., Bush, D.E., LeDoux, J., 2009. Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: NR2B contribution. Cereb. Cortex 19, 474–482, http://dx.doi.org/10.1093/cercor/bhn099 (bhn099[pii]).
Sporns, O., Honey, C., Kötter, R., 2007. Identification and classification of hubs in brain networks. PLoS One 2, e1049, http://dx.doi.org/10.1371/journal.pone.0001049.
Sripada, C., Angstadt, M., Kessler, D., Phan, K., Liberzon, I., Evans, G., Welsh, R., Kim, P., Swain, J., 2014. Volitional regulation of emotions produces distributed alterations in connectivity between visual, attention control, and default networks. Neuroimage 89, 110–121, http://dx.doi.org/10.1016/j.neuroimage.2013.11.006.
Stephan, K., Manjaly, Z., Mathys, C., Weber, L., Paliwal, S., Gard, T., Tittgemeyer, M., Fleming, S., Haker, H., Seth, A., Petzschner, F., 2016. Allostatic self-efficacy: a metacognitive theory of dyshomeostasis-induced fatigue and depression. Front. Hum. Neurosci. 10, 550, http://dx.doi.org/10.3389/fnhum.2016.00550.
Sternson, S.M., 2013. Hypothalamic survival circuits: blueprints for purposive behaviors. Neuron 77, 810–824, http://dx.doi.org/10.1016/j.neuron.2013.02.018.
Strominger, N.L., Demarest, R.J., Laemle, L.B., 2012. Reflexes and muscle tone. In: Noback's Human Nervous System. Humana Press, Totowa, NJ, pp. 143–154.
Swanson, L., 2000. Cerebral hemisphere regulation of motivated behavior. Brain Res. 886, 113–164, http://dx.doi.org/10.1016/S0006-8993(00)02905-X.
Swanson, L., 2003. The amygdala and its place in the cerebral hemisphere. Ann. N. Y. Acad. Sci. 985, 174–184, http://dx.doi.org/10.1111/j.1749-6632.2003.tb07081.x.
Talman, W., Dragon, D., Ohta, H., 1994. Baroreflexes influence autoregulation of cerebral blood flow during hypertension. Am. J. Physiol. 267, H1183–9.
Ter Horst, G., Postema, F., 1997. Forebrain parasympathetic control of heart activity: retrograde transneuronal viral labeling in rats. Am. J. Physiol. – Hear. Circ. Physiol. 273, 42–46.
Thayer, J., Brosschot, J., 2005. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 30, 1050–1058, http://dx.doi.org/10.1016/j.psyneuen.2005.04.014.
Thayer, J., Fischer, J., 2009. Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. J. Intern. Med. 265, 439–447, http://dx.doi.org/10.1111/j.1365-2796.2008.02023.x.
Thayer, J., Friedman, B., 1997. The heart of anxiety: a dynamical systems approach. In: Vingerhoets, A. (Ed.), The (Non) Expression of Emotions in Health and Disease. Springer, Amsterdam.
Thayer, J., Lane, R., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 61, 201–216.
Thayer, J., Lane, R., 2007. The role of vagal function in the risk for cardiovascular disease and mortality. Biol. Psychol. 74, 224–242, http://dx.doi.org/10.1016/j.biopsycho.2005.11.013.
Thayer, J., Lane, R., 2009. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci. Biobehav. Rev. 33, 81–88.
Thayer, J., Sternberg, E., 2006. Beyond heart rate variability: vagal regulation of allostatic systems. Ann. N. Y. Acad. Sci. 1088, 361–372, http://dx.doi.org/10.1196/annals.1366.014.
Thayer, J., Smith, M., Rossy, L., Sollers, J., Friedman, B., 1998. Heart period variability and depressive symptoms: gender differences. Biol. Psychiatry, http://dx.doi.org/10.1016/s0006-3223(98)00008-0.
Thayer, J., Hansen, A., Sollers III, J., Johnsen, B., 2005. Heart rate variability as an index of prefrontal neural function in military settings. In: Caldwell, J.A., Wesensten, N.J. (Eds.), Proceedings of SPIE – The International Society for Optical Engineering, 71–77, http://dx.doi.org/10.1117/12.604420.
Thayer, J., Hansen, A., Saus-Rose, E., Johnsen, B., 2009a. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. 37, 141–153, http://dx.doi.org/10.1007/s12160-009-9101-z.
Thayer, J., Sollers, J., Labiner, D., Weinand, M., Herring, A., Lane, R., Ahern, G., 2009b. Age-related differences in prefrontal control of heart rate in humans: a pharmacological blockade study. Int. J. Psychophysiol. 72, 81–88, http://dx.doi.org/10.1016/j.ijpsycho.2008.04.007.
Thayer, J., Loerbroks, A., Sternberg, E., 2011. Inflammation and cardiorespiratory control: the role of the vagus nerve. Respir. Physiol. Neurobiol. 178, 387–394, http://dx.doi.org/10.1016/j.resp.2011.05.016.
Thayer, J., Ahs, F., Fredrikson, M., Sollers, J.J., Wager, T.D., 2012. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 36, 747–756.
Tzeng, Y.-C., Lucas, S., Atkinson, G., Willie, C., Ainslie, P., 2010. Fundamental relationships between arterial baroreflex sensitivity and dynamic cerebral autoregulation in humans. J. Appl. Physiol. 108, 1162–1168, http://dx.doi.org/10.1152/japplphysiol.01390.2009.
van den Heuvel, M., Sporns, O., 2011. Rich-club organization of the human connectome. J. Neurosci. 31, 15775–15786, http://dx.doi.org/10.1523/JNEUROSCI.3539-11.2011.
van den Heuvel, M., Sporns, O., 2013. An anatomical substrate for integration among functional networks in human cortex. J. Neurosci. 33, 14489–14500, http://dx.doi.org/10.1523/JNEUROSCI.2128-13.2013.
van den Heuvel, M., Stam, C., Boersma, M., Hulshoff Pol, H., 2008. Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain. Neuroimage 43, 528–539, http://dx.doi.org/10.1016/j.neuroimage.2008.08.010.
Vanoli, E., De Ferrari, G., Stramba-Badiale, M., Hull, S., Foreman, R., Schwartz, P., 1991. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ. Res. 68.
Verkuil, B., Brosschot, J., Marques, A., Kampschroer, K., Sternberg, E., Thayer, J., 2015. Gender differences in the impact of daily sadness on 24-h heart rate variability. Psychophysiology 52, 1682–1688, http://dx.doi.org/10.1111/psyp.12541.
Verkuil, B., Brosschot, J., Tollenaar, M., Lane, R., Thayer, J., 2016. Prolonged non-metabolic heart rate variability reduction as a physiological marker of

psychological stress in daily life. Ann. Behav. Med. 1 -11, http://dx.doi.org/10.1007/s12160-016-9795-7.
Vinje, W., Gallant, J., 2000. Sparse coding and decorrelation in primary visual cortex during natural vision. Science 287, 1273–1276, http://dx.doi.org/10.1126/science.287.5456.1273.
Vogt, B., Derbyshire, S., 2009. Visceral circuits and cingulate-mediated autonomic functions. Cingulate neurobiology and disease. In: Vogt, B. (Ed.), Cingulate Neurobiology and Disease. Oxford University Press, Oxford, pp. 220–235.
Vogt, B., Vogt, L., 2009. Mu-opiod receptors, placebo map, descending systems, and cingulate-mediated control of vocalization and pain. In: Vogt, B. (Ed.), Cingulate Neurobiology and Disease. Oxford University Press, Oxford, pp. 339–366.
Vogt, B., Aston-Jones, G., Vogt, L., 2009. Shared norepinephrinergic and cingulate circuits, nociceptive and allostatic interactions, and models of functional pain and stress disorders. In: Vogt, B. (Ed.), Cingulate Neurobiology and Disease. Oxford University Press, Oxford, pp. 467–498.
Vogt, B., 2009. Cingulate Neurobiology and Disease. Oxford University Press, Oxford.
Vuilleumier, P., Huang, Y.-M., 2009. Emotional attention: uncovering the mechanisms of affective biases in perception. Curr. Dir. Psychol. Sci. 18, 148–152, http://dx.doi.org/10.1111/j.1467-8721.2009.01626.x.
Wake, E., Brack, K., 2016. Characterization of the intrinsic cardiac nervous system. Auton. Neurosci., http://dx.doi.org/10.1016/j.autneu.2016.08.006.
Weinberger, N., 2003. The nucleus basalis and memory codes: auditory cortical plasticity and the induction of specific, associative behavioral memory. Neurobiol. Learn. Mem. 80, 268–284, http://dx.doi.org/10.1016/S1074-7427(03)00072-8.
Wellens, H., Gorgels, A., de Munter, H., 2003. Sudden death in the community. J. Cardiovasc. Electrophysiol. 14, S104–S107, http://dx.doi.org/10.1046/j.1540-8167.14.ss9.1.x.
Whalen, P., Kagan, J., Cook, R., Davis, F., Kim, H., Polis, S., McLaren, D., Somerville, L., McLean, A., Maxwell, J., Johnstone, T., 2004. Human amygdala responsivity to masked fearful eye whites. Science 306, 2061, http://dx.doi.org/10.1126/science.1103617.
Williams, D., Thayer, J., Koenig, J., 2016. Resting cardiac vagal tone predicts intra-Individual reaction time variability during an attention task in a sample of young and healthy adults. Psychophysiology (in press).
Wilson, R., Takahashi, Y., Schoenbaum, G., Niv, Y., 2014. Orbitofrontal cortex as a cognitive map of task space. Neuron 81, 267–279, http://dx.doi.org/10.1016/j.neuron.2013.11.005.
Winkelmann, T., Thayer, J., Pohlack, S., Nees, F., Grimm, O., Flor, H., 2016. Structural brain correlates of heart rate variability in a healthy young adult population. Brain Struct. Funct. 1–8, http://dx.doi.org/10.1007/s00429-016-1185-1.
Yasui, Y., Breder, C., Saper, C., Cechetto, D., 1991. Autonomic responses and efferent pathways from the insular cortex in the rat. J. Comp. Neurol. 303, 355–374, http://dx.doi.org/10.1002/cne.903030303.
Young, M., Scanneil, J., Burns, G., Blakemore, C., 1994. Analysis of connectivity: neural systems in the cerebral cortex. Rev. Neurosci. 5, 227–250, http://dx.doi.org/10.1515/REVNEURO.1994.5.3.227.
Zaborszky, L., Pang, K., Somogyi, J., Nadasdy, Z., Kallo, I., 1999. The basal forebrain corticopetal system revisited. Ann. N. Y. Acad. Sci. 877, 339–367, http://dx.doi.org/10.1111/j.1749-6632.1999.tb09276.x.
Zaborszky, L., 2002. The modular organization of brain systems. Basal forebrain: the last frontier. Prog. Brain Res. 136, 359–372, http://dx.doi.org/10.1016/S0079-6123(02)36030-8.
Zippo, A., Gelsomino, G., Van Duin, P., Nencini, S., Caramenti, G., Valente, M., Biella, G., 2013. Small-world networks in neuronal populations: a computational perspective. Neural Netw. 44, 143–156, http://dx.doi.org/10.1016/j.neunet.2013.04.003.
Zylberberg, A., Fernández Slezak, D., Roelfsema, P., Dehaene, S., Sigman, M., 2010. The brain's router: a cortical network model of serial processing in the primate brain. PLoS Comput. Biol. 6, e1000765, http://dx.doi.org/10.1371/journal.pcbi.1000765.
Zylberberg, A., Dehaene, S., Roelfsema, P., Sigman, M., 2011. The human Turing machine: a neural framework for mental programs. Trends Cogn. Sci. 15, 293–300, http://dx.doi.org/10.1016/j.tics.2011.05.007.