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Review

A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health

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ABSTRACT

The intimate connection between the brain and the heart was enunciated by Claude Bernard over 150 years ago. In our neurovisceral integration model we have tried to build on this pioneering work. In the present paper we further elaborate our model and update it with recent results. Specifically, we performed a meta-analysis of recent neuroimaging studies on the relationship between heart rate variability and regional cerebral blood flow. We identified a number of regions, including the amygdala and ventromedial prefrontal cortex, in which significant associations across studies were found. We further propose that the default response to uncertainty is the threat response and may be related to the well known negativity bias. Heart rate variability may provide an index of how strongly 'top–down' appraisals, mediated by cortical-subcortical pathways, shape brainstem activity and autonomic responses in the body. If the default response to uncertainty is the threat response, as we propose here, contextual information represented in 'appraisal' systems may be necessary to overcome this bias during daily life. Thus, HRV may serve as a proxy for 'vertical integration' of the brain mechanisms that guide flexible control over behavior with peripheral physiology, and as such provides an important window into understanding stress and health.

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"According to Darwin's *Origin of Species*, it is not the most intellectual of the species that survives; it is not the strongest that survives; but the species that survives is the one that is best able to adapt and adjust to the changing environment in which it finds itself." Megginson (p. 4, 1963)

The search for biomarkers of stress and health remains a challenging task for researchers and clinicians alike. Several obstacles exist in this search. One is a lack of consensus on the meaning and operationalization of the concept of stress. Another is the lack of a comprehensive framework in which to investigate the way in which organisms function and adapt in a constantly changing environment. To help organize research on the diverse types of stressors and adaptive responses to them we have proposed a model of Neurovisceral Integration (Thayer and Lane, 2000, 2009). In this model, adaptations to environmental challenges are shaped by influences from many sources: physiological, behavioral, affective, cognitive, social, and environmental. Despite this

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diversity, or perhaps because of it, a hallmark of successful adaptation is flexibility in the face of changing physiological and environmental demands. We have proposed that a core set of neural structures provides an organism with the ability to integrate signals from inside and outside the body and adaptively regulate cognition, perception, action, and physiology. This system functions both to continuously assess the environment for signs of threat and safety and to prepare the organism for appropriate action. In addition, it monitors the match between the external environment and the body's internal homeostatic processes in order to generate motivational drive states and adaptive physiological adjustments.

This system essentially operates as a "super-system" that integrates the activity in perceptual, motor, interoceptive, and memory systems into gestalt representations of situations and likely adaptive responses. Thus, it is undoubtedly extremely complex. However, it is still possible that physiological measures exist that can serve as indices of the degree to which this system provides flexible, adaptive regulation of its component systems. In a number of papers (Thayer and Brosschot, 2005; Thayer and Lane, 2000, 2009), we have proposed that heart rate variability (HRV) may provide just such an index. The motivation behind this comes from studies of complex dynamical systems—systems in which multiple processes each influence the others. When processes mutually constrain one another, the system as a whole tends to oscillate spontaneously within a range of states. The various processes are balanced in their control of the whole system, and thus the system can respond flexibly to a range of inputs. However, such systems can also become unbalanced, and a particular process can come to dominate the system's behavior, rendering it unresponsive to the normal range of inputs. In the context of physiological regulation, and regulation of the heart specifically, a balanced system is healthy, because the system can respond to physical and environmental demands (Thayer and Sternberg, 2006). A system that is "locked in" to a particular pattern is dysregulated. This is why the heart rate of a healthy heart oscillates spontaneously (i.e., shows high HRV), whereas a diseased heart shows almost no variability under certain conditions.

A critical idea is that HRV may be more than just an index of healthy heart function, and may in fact provide an index of the degree to which the brain's "integrative" system for adaptive regulation provides flexible control over the periphery. Thus, HRV may serve as an easily measured output of this neural network that may provide valuable information about the capacity of the organism to effectively function in a complex environment.

In spite of the tremendous amount of work on brain responses to threat and on HRV, the literatures on these topics are largely separate and few studies address the neuroanatomical basis of the "core integration" systems directly. The present paper was intended to address this issue, both by reviewing existing studies and providing a new, quantitative meta-analysis of the brain regions consistently correlated with HRV across studies and laboratories.

We will first provide a brief introduction to HRV. We then give an overview of the critical neural structures involved in perceptions of threat and safety. Here we emphasize the amygdala and the medial prefrontal cortex (mPFC). The mPFC is a particularly important part of the "core integration" system because it plays a critical role in the representation of both internal and external context in the brain and the use of both kinds of information to regulate behavior and peripheral physiology. Its role in cognition is centered around the construction of context, including autobiographical memory retrieval (McDermott et al., 2009) and expectations about future outcomes (Schoenbaum et al., 2009; Summerfield et al., 2006). It is also considered to be a key area for the representation of economic value (Hare et al., 2010; McClure et al., 2004; Plassmann et al., 2008), the sense of the self (Kelley et al., 2002; Northoff et al., 2006), and emotional appraisal (Urry et al., 2006; Wager et al., 2008c). Finally, it also plays a critical role in the regulation of both behavioral and physiological responses, including regulation of "fear responses" (Delgado et al., 2008; Milad et al., 2007; Schiller et al., 2008), heart-rate changes related to social threat (Wager et al., 2009c), and a variety of other peripheral responses to stressors (Lane and Wager, 2009) through connectivity with the brainstem (Keay and Bandler, 2001; Saper, 2002; Wager et al., 2008a, 2009b). Finally we report the results of a meta-analysis of studies that have recorded cerebral blood flow and HRV. Overall, the meta-analysis provides support for the idea that HRV may index the degree to which a mPFC-guided "core integration" system is integrated with the brainstem nuclei that directly regulate the heart.

1. Heart rate variability

Like many organs in the body, the heart is dually innervated. Although a wide range of physiologic factors determine cardiac functions such as heart rate (HR), the autonomic nervous system (ANS) is the most prominent. Importantly, when both cardiac vagal (the primary parasympathetic nerve) and sympathetic inputs are blocked pharmacologically (for example, with atropine plus propranolol, the so-called double blockade), intrinsic HR is higher than the normal resting HR (Jose and Collison, 1970). This fact supports the idea that the heart is under tonic inhibitory control by parasympathetic influences. Thus, resting cardiac autonomic balance favors energy conservation by way of parasympathetic dominance over sympathetic influences. In addition, the HR time series is characterized by beat-to-beat variability over a wide range, which also implicates vagal dominance as the sympathetic influence on the heart is too slow to produce beat to beat changes. There is an increasing interest in the study of heart rate variability among researchers from diverse fields. Low heart rate variability (HRV) is associated with increased risk of all-cause mortality, and low HRV has been proposed as a marker for disease (Thayer and Lane, 2007; Thayer et al., 2010b).

The basic data for the calculation of all the measures of HRV is the sequence of time intervals between heart beats. This interbeat interval time series is used to calculate the variability in the timing of the heart beat. As mentioned earlier the heart is dually innervated by the autonomic nervous system such that relative increases in sympathetic activity are associated with heart rate increases and relative increases in parasympathetic activity are associated with heart rate decreases. Thus relative sympathetic increases cause the time between heart beats (the interbeat interval) to become shorter and relative parasympathetic increases cause the interbeat interval to become longer. The parasympathetic influences are pervasive over the frequency range of the heart rate power spectrum whereas the sympathetic influences 'roll-off' at about 0.15 Hz (Saul, 1990). Therefore high frequency HRV represents primarily parasympathetic influences with lower frequencies (below about 0.15 Hz) having a mixture of sympathetic and parasympathetic autonomic influences. The differential effects of the ANS on the sinoatrial node, and thus the timing of the heart beats, are due to the differential effects of the neurotransmitters for the sympathetic (norepinephrine) and parasympathetic (acetylcholine) nervous systems. The sympathetic effects are slow, on the time scale of seconds, whereas the parasympathetic effects are fast, on the time scale of milliseconds. Therefore the parasympathetic influences are the only ones capable of producing rapid changes in the beat to beat timing of the heart.

A variety of measures have been used use to operationalize HRV. Long-term measures like the standard deviation of all interbeat intervals in 24 h, short-term measures like the standard

deviation of 5 min intervals and beat-to-beat measures like the root mean square of successive RR differences (RMSSD) have all been used. Respiratory sinus arrhythmia (RSA) is another measure and is defined as the change in heart period corresponding with the inspiratory and expiratory phases of the respiratory cycle. In addition, power spectral analysis of interbeat interval time series is frequently used to quantify HRV. The power spectrum of short-term time series contains two major components, a high (0.15–0.40 Hz) and low (0.01–0.15 Hz) frequency component reflecting cardiac vagal tone and a mixture of vagal and sympathetic influences, respectively. RSA, RMSSD and the high frequency component of the power spectrum (HF power) are closely related, and all reflect vagal cardiac influence.

HF power is primarily parasympathetically mediated. The HF band primarily reflects the respiration-mediated HRV at 0.15–0.4 Hz. The defined frequency band for this parameter usually encompasses the frequency range corresponding to the frequency of normal respiration. This index of vagally mediated cardiac control correlates highly with the time-domain based measure of RMSSD. The vagally mediated HRV is the topic of the present review. A detailed accounting of the other frequency bands is beyond the scope of the present paper (but see Thayer et al., 2010a for a recent review). Thus, consistent with Claude Bernard, we will focus on the vagal link between the brain and the heart.

An extensive body of research has been directed at identifying the pathways by which this neural control is achieved. For example, Benarroch (1993, 1997) has described the central autonomic network (CAN). The output of the CAN has connections to the sinoatrial node of the heart via the stellate ganglia and the vagus nerve. Importantly, the output of the CAN is under tonic inhibitory control via GABAergic neurons in the nucleus of the solitary tract (NTS). The NTS has direct connections to the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN) (see Thayer and Lane, 2009 for a complete description of these pathways). These connections are via interneurons between the NTS, NA, and DVN traversing the intermediate reticular zone and provide input to the cardiovagal motor neurons. In addition the NTS is a site where the afferent and efferent vagus meet.

Traffic in the vagus nerve flows in both directions. Vagal efferents are important for the control of a number of organs including the heart, lungs, kidneys, and liver (Thayer and Fischer, in press; Thayer et al., 2011). Vagal afferents are important for inflammation, pain, and the control of blood pressure via the baroreflex (Thayer and Sternberg, 2009).

A primary function of the cardiovascular system is to maintain optimal arterial blood pressure and to provide adequate blood flow to the brain 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 the arterial baroreflex. Baroreceptors mainly located in the central vascular tree and the heart sense changes in blood pressure via stretch receptors. These baroreceptors send afferent signals to the brain which reflexively adjust efferent outputs to regulate the changes in blood pressure. When blood pressure increases it elicits reflex decreases in heart rate, cardiac contractility, and vascular resistance via parasympathetic activation and sympathetic inhibition. Similarly, decreases in blood pressure elicit reflex increases in heart rate, cardiac contractility, and vascular resistance via parasympathetic inhibition and sympathetic activation (Amerena and Julius, 1995).

In summary, the heart and the brain are connected bidirectionally. Efferent outflow from the brain affects the heart and afferent outflow from the heart affects the brain. Importantly, the vagus is an integral part of this heart–brain system and vagally mediated HRV appears to be capable of providing valuable information about the functioning of this system.

2. Perceptions of threat and safety—the roles of the amygdala and the prefrontal cortex

What is stress? While researchers have debated the definition of stress for decades, perceptions of threat and safety appear to be a common, core element in “stressors” that are generated by mental events. Therefore, if HRV is to be considered as a potential marker of stress it needs to be tied to perceptions of threat and safety. These perceptions, and the associated actions that follow them, are important for the survival of the individual organism and ultimately of the species. As we argue below, HRV may be associated with neural structures that are involved in the appraisal (whether conscious or unconscious) of threat and safety. To the extent that HRV can be functionally and structurally linked to these processes, HRV may provide a useful index of stress.

To illustrate the fundamental importance of threat appraisal, imagine one of our ancestors walking in the woods. She sees something coiled on the path ahead—it could be a harmless vine or it could be a deadly snake. What is the appropriate, adaptive response? Our protagonist may assume that the path is safe and proceeds ahead, but if she is wrong, it may be the last choice she makes. On the other hand, if she assumes the amorphous shape is a threat, she will surely live to walk another day and perhaps procreate, passing on her genes to future generations. Thus, both the short-term and long-term adaptive response is to assume that the coiled object is a threat, and such appraisals can be made rapidly and without much deliberation.

LeDoux (1996) has described in detail the neural circuitry associated with such rapid emotional appraisals as well as more elaborate appraisals that unfold more slowly in time. He, and others, have suggested that the amygdala may serve as a rapid, “quick and dirty” detector of potential threats, and a mediator of adaptive “fear” responses. Others have shown that amygdala circuits figure prominently in the detection of biologically relevant stimuli more generally, be they aversive or appetitive (Belova et al., 2007; Holland and Gallagher, 2004; Johnson et al., 2009; Ruiz-Padial et al., 2011; Whalen et al., 2004; Whalen and Phelps, 2009). However, though there are amygdala neurons that encode both positive and negative emotional outcomes, a predominance of single neurons encode negative outcomes (Paton et al., 2006). Likewise, amygdala activation in human studies of emotion shows a bias toward negative information (Cunningham et al., 2008; Wager et al., 2008a).

Given the evolutionary advantage associated with the assumption of threat, the view that we and others have proposed is that the “default” response to uncertainty, novelty, and threat is the sympathoexcitatory preparation for action commonly known as the fight or flight response (Thayer and Lane, 2009; Herry et al., 2007). This default threat response may be related to the well-known ‘negativity bias,’ a phenomenon that describes the tendency to prioritize negative information over positive (Cacioppo et al., 1999). From an evolutionary perspective this represents a system that errs on the side of caution—when in doubt prepare for the worst—thus maximizing survival and adaptive responses (LeDoux, 1996).

However, in typical daily life in modern society, continual perception of threat is maladaptive, as it is associated with dysregulation in hippocampal circuits, endocrine and autonomic output, and cognitive and general health decline (Chrousos and Kino, 2005; McEwen, 2001; McEwen and Sapolsky, 1995; Sapolsky, 1996; Seeman et al., 2001). If an organism is to avoid living under a chronic state of threat, it is imperative to determine if and when threat appraisals are appropriate depending on the context. The prefrontal cortex and the mPFC in particular, appear to be important in this process.

In safe contexts, ‘fear’ or threat representations in the amygdala appear to be inhibited by the prefrontal cortex and the vmPFC in particular. A variety of manipulations of vmPFC, including

pharmacological or electrical stimulation of the vmPFC, inhibit subcortical threat circuits under some conditions and reduce 'stress' responses and 'fear' behavior (Amat et al., 2008; Milad and Quirk, 2002; Milad et al., 2004; Quirk and Beer, 2006). Studies in healthy humans suggest reciprocal inhibition between regions of the PFC and the amygdala (Delgado et al., 2008; Milad et al., 2007; Schiller et al., 2008). Clinically, patients with several types of anxiety disorders, including post-traumatic stress disorder (PTSD), social anxiety, and specific phobias, share a common feature of amygdala hyper-responsiveness to a variety of affective challenges (Etkin and Wager, 2007). In addition, PTSD specifically is associated with reduced activity in ventral mPFC systems implicated in the context-dependent inhibition of the amygdala (Etkin and Wager, 2007).

Interestingly, however, this relationship is likely to be more complicated than an automatic inhibition of the amygdala by the vmPFC, for several reasons. First, vmPFC stimulation does not automatically reduce fear or potentiate fear extinction; rather, in both animal and human studies cited above, it appears to play a role in the consolidation and retrieval of safety context memories. Second, it is associated with higher-level appraisal processes that operate under certain contexts, under the guidance of information retrieved from long-term memory. For example, in an elegant series of studies, Maier and colleagues demonstrate that vmPFC activity is necessary and sufficient for the protective effects of behavioral control on stress responses (for a review see Maier et al., 2006). They note that the common assumption has been that uncontrollability is the "active ingredient" that potentiates the stress response. Their studies offer an alternative view: *control* may be the active ingredient. Thus, the vmPFC may inhibit threat circuits that are by default 'on' in a manner that depends on integrating the external context (environmental threat) with the internal one (perceptions of control over the threat). This idea is consistent with other studies that show that the vmPFC plays a protective role when cognitive appraisals are specifically engaged to regulate emotion (Eippert et al., 2007; Urry et al., 2006; Wager et al., 2008c). Other research is consistent with the idea that the amygdala responds rapidly to biologically relevant positive or negative stimuli but may be subsequently inhibited if the stimuli are appraised to be safe or innocuous (Thayer and Siegle, 2002).

The tonic inhibition of the amygdala by the PFC is consistent with the so-called Hughlings Jackson principle of hierarchical integration through inhibition (Jackson, 1884). Thus, under conditions of uncertainty and threat, critical areas of the prefrontal cortex become hypoactive. Importantly the Hughlings Jackson principle implies that the removal of inhibition "permits" rather than "causes" an increase in physiological activity (disinhibition). As noted by Hughlings Jackson (Jackson, 1884), "In other words, the lower level of evolution is not 'goaded into activity,' but is 'let go'." This prefrontal hypoactive state is associated with disinhibition of sympathoexcitatory circuits that are essential for energy mobilization. However, when this state is prolonged, it produces the excess wear and tear on the system components that has been characterized by McEwen as allostatic load (McEwen, 1998).

Generally speaking, the research discussed above suggests that a predisposition to chronic threat perception, amygdala hyperactivation, and a large negativity bias should be associated with dysregulated brain-peripheral integration, and thus reduced levels of complex neurogenic rhythms and lower HRV. Consistent with this hypothesis, we have shown that greater resting HRV is associated with a smaller negativity bias and with greater willingness to approach positive novel objects (Shook et al., 2007a). In addition, we have recently reported that greater resting HRV is associated with more rapid extinction in an interoceptive fear conditioning paradigm (Smets et al., 2011). Thus, HRV may index the degree to which the brain's threat-detection systems produce chronic allostatic load.

The characterization above represents a new view of the stress response. For example, when a patient walks into the therapist's office and states that they are tense, and nervous, and can't relax the question is not what is causing these reactions but why are they not inhibited in a world that is relatively safe. As noted by Maier, Hoehn-Saric and ourselves, this appears to represent a failure to recognize safety signals as these patients do not necessarily show exaggerated responses to threat as much as they show threat responses to neutral or harmless stimuli (c.f., Ruiz-Padial et al., 2003; Thayer and Friedman, 2002). Consistent with this view, a growing body of research on anxiety disorders focuses on problems with the context-dependent regulation of anxiety rather than exaggerated threat responses (Bishop et al., 2004; Lissek et al., 2005).

It is also important to note that psychopathological states such as anxiety, depression, post-traumatic stress disorder, and schizophrenia are associated with prefrontal hypoactivity and a lack of inhibitory neural processes as reflected in poor habituation to novel neutral stimuli and therefore a failure to recognize safety signals, a pre-attentive bias for threat information including an increased negativity bias, deficits in working memory and executive function, and poor affective information processing and regulation (Shook et al., 2007b; Thayer and Friedman, 2002). In further support of these ideas, we have recently reported that patients with damage to the medial prefrontal cortex perceived a challenging social situation as more threatening compared to those with damage to another brain region or non-brain damaged controls (Buchanan et al., 2010). Therefore proper functioning of the prefrontal cortex, and vmPFC in particular, is vital to the detection of threat and safety, preservation of the integrity of the system, and therefore is vital to health. Reduced HRV has been shown to be associated with a range of risk factors for mortality and cardiovascular morbidity including psychosocial stress (Thayer and Lane, 2007; Thayer et al., 2010a,b). Importantly for our discussion, these inhibitory prefrontal processes can be indexed by measures of vagal function such as HRV.

Thus, if we could show that HRV is associated with the structures and functions of this neural network including the amygdala and the mPFC then HRV might be useful as an index of perceptions or appraisals of threat, safety, and therefore of stress. We start by reviewing some of the evidence linking HRV to important functions associated with the mPFC and the amygdala. We then present the results of the meta-analysis providing evidence structurally linking HRV to these neural structures.

3. HRV and emotional regulation

In addition to being linked to vmPFC and amygdala modulation, emotion regulation is linked to HRV (Appelhans and Luecken, 2006; Thayer and Brosschot, 2005). Individuals with greater emotion regulation ability have been shown to have greater levels of resting HRV (Appelhans and Luecken, 2006; Thayer and Lane, 2009). In addition, during successful performance on emotion regulation tasks HRV appears to be increased (Butler et al., 2006; Ingjaldsson et al., 2003; Smith et al., 2011).

The ability to regulate emotion is closely related to the ability to flexibly shape perceptual and affective brain processes in response to changing contexts. (By flexibly, we mean up- and down-regulating *both* negative and positive affect, as appropriate; a lack of negative emotion can also be pathological.) Emotions represent a distillation of an individual's perception of personally relevant environmental interactions, including not only challenges and threats but also the ability to respond to them (Frijda, 1986). Viewed as such, emotions reflect the status of one's ongoing adjustment to constantly changing environmental demands. In another sense, an adequate emotional response represents a selection of

an optimal integrated response (and the inhibition of less functional ones) from a broad behavioral repertoire, in such a way that behavior and energy use is matched to fit situational requirements.

Resting HRV, in our view, is a marker for flexible dynamic regulation of autonomic activity; thus, higher HRV signals the availability of context- and goal-based control of emotions. We have investigated the role of HRV in emotional regulation at two different levels of analysis. One level is at the trait or tonic level where individual differences in resting HRV have been associated with differences in emotional regulation. We have shown that individuals with higher levels of resting HRV, compared to those with lower resting levels, produce context appropriate emotional responses as indexed by emotion-modulated startle responses, fear-potentiated startle responses, and phasic heart rate responses in addition to behavioral and self-reported emotional responses (Melzig et al., 2009; Ruiz-Padial et al., 2003; Thayer and Brosschot, 2005). In addition, we have recently shown that individuals with low resting HRV show delayed recovery from psychological stressors of cardiovascular, endocrine, and immune responses compared to those with higher levels of resting HRV (Weber et al., 2010). Thus, individuals with higher resting levels of HRV appear more able to produce context appropriate responses including appropriate recovery after the stressor has ended.

Another level of analysis is at the state or phasic level where HRV values increase during the successful regulation of emotion during emotion regulation tasks. Thus, it has been shown that phasic increases in HRV in response to situations that require emotional regulation facilitate effective emotional regulation. In an early study, we showed that HRV increased in recovering alcoholics in response to alcohol cues but only if they later reported an increased ability to resist a drink. Those recovering alcoholics that later reported an urge to drink did not exhibit increased HRV during the alcohol cues (Ingjaldsson et al., 2003). A recent replication and extension of this work reported increased HRV during the successful regulation of emotion by either reappraisal or suppression (Butler et al., 2006). We have recently shown that the increase in HRV associated with emotional regulation is accompanied by concomitant cerebral blood flow changes in areas identified as being important in emotional regulation and inhibitory processes (Lane et al., 2009). Taken together these findings suggest that HRV functions at both the trait and state levels as a resource that can be utilized in the service of emotional regulation. Future research is directed at assessing if this resource can be depleted and thus lead to subsequent failures of emotional regulation. Clearly then the relationship between HRV and emotional regulation will have important implications for those that study the link between emotional states and dispositions such as depression, anxiety, anger and hostility, alexithymia, and physical health.

As outlined above, the amygdala, which has outputs to autonomic, endocrine, and other physiological regulation systems, and becomes active during threat and uncertainty, is under tonic inhibitory control via GABAergic mediated projections from the prefrontal cortex (Davidson, 2000; Thayer, 2006). Importantly, sympathoexcitatory, cardioacceleratory subcortical threat circuits are under tonic inhibitory control by the prefrontal cortex (Amat et al., 2005; Thayer, 2006). That HRV might be related to this neural circuitry, associated with perceptions of threat and safety, would have important implications for HRV as an index of stress and resilience if supported by empirical data.

In summary, the neurovisceral integration model has identified a flexible neural network associated with self-regulation and adaptability that might provide a unifying framework within which to view the diversity of observed responses across domains. Thayer and Lane (2000) suggested that a common reciprocal inhibitory cortico-subcortical neural circuit serves as the structural link between psychological processes like emotion and cognition, and health-related physiological processes, and that this circuit can be indexed with HRV. Thus, because of these reciprocally interconnected neural structures that allow prefrontal cortex to exert an inhibitory influence on sub-cortical structures, the organism is able to respond to demands from the environment, and organize their behavior effectively. In the next section we briefly review the evidence for the relationship of HRV to this network of neural structures and further specify the prefrontal regions involved in the inhibitory control of the heart.

4. Meta-analysis of neuroimaging studies of HRV

One of the basic ideas of the Neurovisceral Integration Model is that HRV is important not so much for what it tells us about the state of the heart as much as it is important for what it tells us about the state of the brain. Thus the extent to which HRV reflects important aspects of neural functioning is an empirically testable hypothesis associated with the model with critical implications for HRV as a marker of stress and resilience. Whereas a number of individual studies including neuroimaging studies have suggested associations between HRV and specific brain regions, the problems associated with such individual studies, including small sample sizes and differing methodologies, are an obstacle that needs to be confronted to establish firm links between HRV and neural function. One approach to dealing with the problems associated with individual neuroimaging studies is the use of meta-analysis to aggregate the effects of these studies and to assess the consistency of the findings across studies. To this end, a major goal of the present paper is to provide a meta-analytic review of the extant neuroimaging studies linking HRV to regional cerebral blood flow activity and thus to try to put this basic notion of the Neurovisceral Integration Model on more firm footing.

5. Neural structures associated with HRV

As part of the exposition of the Neurovisceral Integration Model we have previously described at set of neural structures associated with HRV (Thayer and Lane, 2000, 2009). The various aspects of this network of neural structures have been gleaned from numerous sources including animal studies, human lesion studies, pharmacological blockade studies, and a few neuroimaging studies. Over the past several years however a number of human neuroimaging studies have appeared in which researchers have explicitly examined the brain structures associated with HRV. In the present paper we provide a meta-analysis of eight published studies in which HRV has been related to functional brain activity using either PET or fMRI (see Table 1). These studies represent the data from 191 participants (97 females and 94 males). Whereas other studies have reported results on this relationship, these studies were chosen because they primarily and explicitly examined the association between HRV and cerebral blood flow. Thus this meta-analysis is illustrative and not exhaustive. Furthermore important gender and age-related differences in the neural control of the heart exist but are beyond the scope of the present review (e.g., Nugent et al., 2011; Thayer et al., 2009).

The goal of this meta-analysis was to identify areas that were consistently associated with HRV across the ten contrasts in our dataset, and subsequently, to identify areas in which HRV was more closely associated with emotional versus cognitive/motor tasks. We addressed these goals using Multi-level Kernel Density Analysis (MKDA), which analyzes the distribution of peak coordinates from published studies across the brain. Unlike some methods based only on reported activation coordinates, MKDA treats contrast maps (not peaks) as the unit of analysis, and therefore is suitable for evaluating the consistency of activation across studies (Kober et al., 2008; Wager et al., 2007; Wager et al., 2009a).

Table 1
List of studies included in the meta-analysis with the name of the first author, year, the number of men and women participants, imaging modality, location of HRV measurement (inside or outside the scanner), and the task.

Study first author/year	Imaging modality	HR-HRV measurement	Task
Critchley, 2003 (2♀ 4♂)	*f*MRI	IN	*n*-back + Handgrip
Gianaros, 2004 (39♀ 54♂)	PET	IN	Working memory
Matthews, 2004 (Matthews et al., 2004) (7♀ 11♂)	*f*MRI	Outside	Counting stroop
Neuman, 2006 (Neumann et al., 2006) (14♀ 8♂)	*f*MRI	Outside	Ekman faces Go/No Go
O'Connor, 2007 (O'Connor et al., 2007) (8♀)	*f*MRI	Outside	Grief (words)
Napadow, 2008 (Napadow et al., 2008) (3♀ 4♂)	*f*MRI	IN	Handgrip
Lane, 2009 (12♀)	PET	IN	Emotional and neutral filmclips emotion specific
Ahs, 2009 (Åhs et al., 2009) (15♀ 13♂)	PET	IN	Speech stressor

The MKDA method analyzes the distribution of peak coordinates from published studies across the brain. Essentially, the reported x (left–right), y (posterior–anterior), and z (inferior–superior) coordinates in a standard stereotaxic space (i.e., Montreal Neurological Institute space) are treated as a sparse representation of activated locations. In the literature, peak coordinates are reported in reference to a particular statistical contrast map (SCM); for example, a study might compare high memory load vs. low memory load. Studies may report results from multiple contrast maps (e.g., load effects for verbal stimuli and load effects for object stimuli), so we refer to the maps as SCMs rather than as study maps.

To integrate peaks across space, we reconstructed a map of whether each SCM activated within 20 mm of a local neighborhood surrounding each voxel in the brain (typical values range between 10 and 20 mm: Nee et al., 2007; Wager et al., 2004). Thus, the sum of these maps provides an overall meta-analytic map of how many contrasts activated within 20 mm of each voxel in the brain. In practice, we weighted this map by the sample size in each study (see Wager et al., 2009a for details of the procedure).

The final step is to establish a statistical threshold for determining what constitutes a significant number of activating SCMs in a local area. The threshold is determined using a Monte Carlo procedure, and a natural null hypothesis is that the 'activated' regions in the SCM indicator maps are not spatially consistent; that is, they are distributed randomly throughout the brain. Thus, the reported meta-analytic results in the tables and figures are the consistently activated regions across studies – regions in which *more studies* activated in a local neighborhood than would be expected by chance ($p < 0.05$ family-wise error rate corrected across the whole brain).

Fig. 1b provides a map of the coordinates from the contrasts derived from the eight studies at various levels of the neuroaxis. As can be clearly seen these activations are not randomly distributed across the brain but appear to cluster into spatially consistent locations. Fig. 1a presents a map of the whole brain showing the significant activations across all contrasts, for the emotion > cognitive/motor tasks, and for the cognitive/motor > emotion tasks. Table 2 provides the associated coordinates for these activations as well as for the contrast of the activations associated with emotion tasks versus those associated with cognitive/motor tasks.

Table 2
Stereotactic coordinates for the most consistent peak activation foci with putative brain region, laterality (right or left), XYZ coordinates in MNI space, number of voxels in each cluster (Vol) and the weighted percentage of Contrast Indicator Maps (CIMs) that activated each cluster (%Act).

Name	Lat	*X*	*Y*	*Z*	Vol	%Act
Average across all tasks						
Left SLEA/Ventral Striatum	L	−24	0	−12	3968	54
Sub-genual anterior cingulate	R	2	22	−2	64	52
Pre-genual anterior cingulate	R	2	46	6	1200	60
Emotion > cognitive/motor						
Rostral medial prefrontal cortex	R	10	54	18	4632	65
Cognitive/motor > emotion						
Left posterior putamen	L	−26	−8	2	16	50

In the overall analyses three regions show significant activations (see Fig. 1a). One region in the medial PFC (MPFC) is the right pregenual cingulate (BA 24/32). Another MPFC region is the right subgenual cingulate (BA 25). The third region is the left sublenticular extended amygdala/ventral striatum (SLEA). This region extends into the basolateral amygdalar complex, and also covers the superior amygdala (central nucleus) and extends into the ventral striatum.

To further examine regions specifically associated with emotion tasks we compared the contrasts associated with the emotion tasks versus those associated with the cognitive/motor tasks (see Fig. 1a). One significant activation was associated with the emotion tasks. This activation is in the right rostral MPFC (BA 10/32) and extends into BA 9. On the other hand there was one activation in the left posterior putamen associated with the cognitive/motor tasks.

6. Functional divisions of the medial PFC

To gain an understanding of the functional significance of the HRV-brain region associations identified in our meta-analysis it would be useful to know more about the functional subdivisions of mPFC and their differential role in cognitive and emotional processes. Though the subdivisions of the mPFC have been categorized in varying ways and a consensus on the functional boundaries and their definitive names has not yet been achieved, a number of useful schemes have been proposed. Bush et al. (2000) and later Amodio and Frith (Amodio and Frith, 2006; Frith et al., 1991) have provided similar, useful descriptions of the functional divisions of the mPFC. Amodio and Frith (2006), propose three functional subdivisions, as shown in Fig. 2. A first, posterior and dorsal region of the rostral PFC is linked with more "cognitive" sensorimotor selection and action monitoring tasks, and encompasses the dorsal anterior cingulate and pre-SMA. A second region—the anterior rostral (arMFC), centered on the dorsomedial prefrontal cortex (DMPFC)/medial Brodmann's Area 9—is associated with "emotion" tasks and is reliably engaged during person perception and social cognition. This also extends into the pregenual anterior cingulate (pgACC). Finally, a third, most ventral subdivision—which covers part of the pgACC, the subgenual anterior cingulate (sgACC), and the medial orbitofrontal cortex (mOFC) and anterior ventral prefrontal cortex—is associated with "autonomic and visceral aspects of emotional responses" (p. 270) and "rewards and punishments" (p. 271). Based on this description, the areas identified in our analysis fall into the anterior rostral (arMFC) and orbital mPFC (oMFC) regions identified by Amodio and Frith (2006). Specifically, the pregenual ACC region identified across HRV studies in the meta-analysis and the rostral medial PFC region identified in the emotion specific tasks would fall in the "emotional" arMFC region, whereas the subgenual ACC region identified in the across task analysis would fall

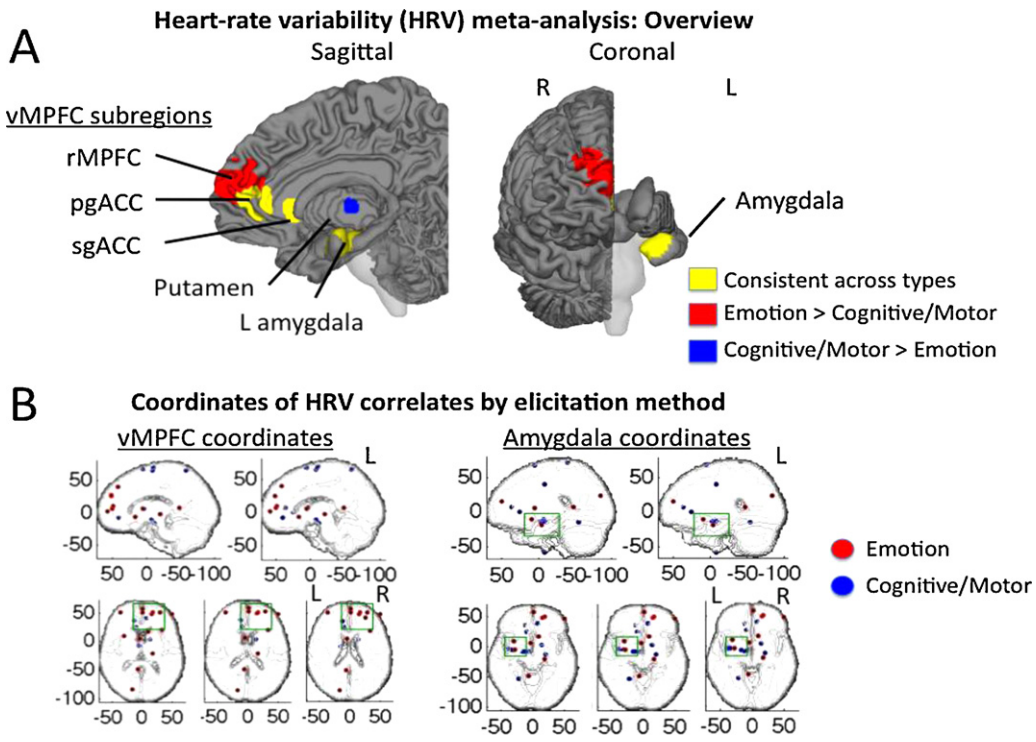

Fig. 1. (a) map of the whole brain showing significant activations, (b) map of the coordinates of the contrasts at various levels of the neuroaxis.

in the oMFC region. Thus the areas of PFC associated with HRV are located in regions previously associated with "emotions" and the physiological aspects of emotional responses.

As discussed above, vmPFC has also been associated with emotion regulation and context-dependent reduction of fear behavior, providing a link between our meta-analytic findings and successful regulation of negative emotion. For example, Wager et al. (2008b) found that both vmPFC and dmPFC activity during cognitive reappraisal of aversive images was associated with greater reduction of negative emotion, as mediated by increases in the ventral striatum/nucleus accumbens. Given that other studies (for example Butler et al., 2006) found HRV associated with successful reappraisal, these findings converge to suggest that HRV may be linked to successful emotion regulation via these shared brain regions. In another study of individual differences, van Reekum et al. (2007) identified an area associated with psychological well-being (−3, 29, −2) that overlaps with the sgACC region associated with HRV in the meta-analysis. Van Reekum et al. (van Reekum et al., 2007) suggested that this region was associated with positive well-being, down regulation of the amygdala, and goal-directed positive affect.

Similarly, Wager et al. (2009c) identified a region of vmPFC that was deactivated during social-evaluative threat (SET), complementing the increases found with positive reappraisal. The magnitude of deactivation predicted increased heart rate responses to the stressor both within and between participants. The effect was replicated in a second study (Wager et al., 2009b), which also found that vmPFC deactivation predicted threat-induced increases in the periaqueductal gray, a mediator of physiological and behavioral responses to threat (Bandler et al., 2000; Davis, 1992). Relatedly, Buchanan et al. (2010) have reported that persons with damage to vmPFC perceived a SET task as more threatening compared to those with damage to another region or no brain damage. Interestingly, both of these studies showed more dorsal parts of the MPFC that showed increases in response to SET (consistent with many previous findings; e.g. (Critchley et al., 2003), suggesting that there may be valence specificity in the vmPFC: more dorsal regions may mediate threat responses, whereas more ventral regions in the mOFC

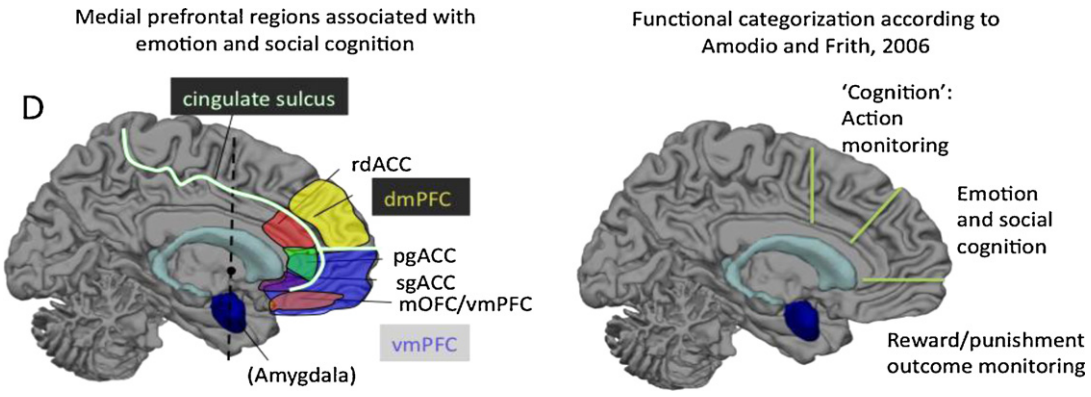

Fig. 2. Subdivisions of the medial prefrontal cortex.

may track positive value and antagonize threat responses. These results converge to suggest that HRV may be linked to reduced perceptions of threat via these shared brain regions, particularly the ventral aspect of the vmPFC.

The reciprocal dorsal/ventral pattern of findings is also consistent with findings from human and animal studies of fear conditioning (reviewed above and in Wager et al., 2009c), and it is perhaps no accident that HRV, emotion regulation, and fear extinction share a common substrate in the vmPFC. Both Quirk and Beer (2006) and Hartley and Phelps (2010) have directly linked fear extinction with emotion regulation. In one important study, Delgado et al. (2008) showed that skin-conductance responses to classically conditioned cues—a primary indicator of 'fear responses' in humans—could be modified by cognitive reappraisal, and that this modulation is paralleled by increases in ventral vmPFC/mOFC (Frith et al., 1991). In another study, Schiller et al. (2008) identified regions associated with perceptions of safety (1, 38, −4: BA 32/10) and —pgACC; (3, 32, −7)—sgACC that overlap with the pgACC and sgACC regions, respectively, that we found associated with HRV. As noted above we have recently reported that individual differences in resting HRV were associated with extinction in an interoceptive fear conditioning study (Smets et al., 2011). Taken together these numerous findings suggest that perceptions of threat and safety may be linked to HRV via shared brain regions.

Somewhat surprisingly, studies of brain structure suggest that greater gray matter density and/or cortical thickness in vmPFC are associated with markers of adaptive behavior and fear regulation. For example, Gianaros et al. (2007) reported that increased vmPFC gray matter density was associated with higher self-perceived social status. Milad et al. (2005) found that cortical thickness in the ventral aspect of vmPFC was associated with enhanced fear extinction. And in a direct link with HRV, Woodward et al. (2008) found volume in the right ACC to be positively associated with HRV during quiet periods of the Trier Social Stress Test.

More generally, the pgACC/rmPFC correlation with HRV in our meta-analysis suggests that this region is part, and the most reliably activated part in studies to date, of a descending "visceromotor" system that controls the autonomic nervous system and possibly other responses (neuroendocrine) based on emotional context. A very large animal literature links the vmPFC—and the ventral, infralimbic aspect in particular—with visceromotor control (Gabbott et al., 2007; Owens and Verberne, 1996), but this link has not often been explicitly considered in studies of emotion regulation and fear conditioning. The link with HRV suggests both that autonomic regulation may be an important outcome shaped by cognitive appraisal and learning and that HRV may be a marker for the degree to which a healthy brain provides context-dependent regulation.

Findings of consistent vmPFC activity in other areas elaborate on the notion of "context" and provide some important clues about what kinds of cognitive processes are likely to be critical in the modulation of affect. vmPFC is extremely active at rest (and is part of the so-called "default mode" network), is co-activated with the hippocampus (Kahn et al., 2008) and specifically involved in autobiographical memory (McDermott et al., 2009) but apparently not other cognitive control tasks (van Snellenberg and Wager, 2009). In contrast, control of sensorimotor ('external') attention produces extremely reliable increases in another subdivision of MPFC, the dorsal cingulate motor area (posterior ACC; BA 6/9/32) (Dosenbach et al., 2006; van Snellenberg and Wager, 2009). Thus, the retrieval of context from long term memory and its use in the construction of affective value to the self may be a core function of the vmPFC. This 'context' appears to be qualitatively distinct from the type of immediate sensorimotor and task context associated with the dorsolateral prefrontal cortex (Miller and Cohen, 2001). Thus, in summary, HRV may index the degree of functional integration in the axis connecting the vmPFC, brainstem, and peripheral physiology—and, in psychological terms, the degree to which affective context provides flexible control over the peripheral autonomic nervous system.

7. Summary and conclusion

In the present paper we have presented a meta-analysis of studies relating cerebral blood flow to HRV. We have shown that several areas including the amygdala and the medial PFC that are involved in perceptions of threat and safety are also associated with HRV. The meta-analysis provides support for the idea that HRV may index the degree to which a mPFC-guided "core integration" system is integrated with the brainstem nuclei that directly regulate the heart. Thus these results support Claude Bernard's idea that the vagus serves as a structural and functional link between the brain and the heart. We have proposed that this neural system essentially operates as a "super-system" that integrates the activity in perceptual, motor, interoceptive, and memory systems into gestalt representations of situations and likely adaptive responses. These findings suggest that HRV may index important organism functions associated with adaptability and health. It is our hope that this review highlights the importance of HRV as a potential marker of stress and health and provides evidence for the neural correlates that serve to underpin this relationship.

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