What the Heart Says to the Brain (and *vice versa*) and Why We Should Listen

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Abstract

In the present paper we describe a model of neurovisceral integration in which a set of neural structures involved in cognitive, affective, and autonomic regulation are related to heart rate variability (HRV) and cognitive performance. We will provide pharmacological and neuroimaging data in support of the neural structures linking the central nervous system to HRV. Next, we will review a number of studies from our group showing that individual differences in HRV are related to performance on tasks associated with executive function and prefrontal cortical activity as well as with emotional regulation. In the first study, individual differences in resting HRV we related to performance on executive and non-executive function tasks. The results showed that greater HRV was associated with better performance on executive function tasks. In another experiment, HRV was manipulated by physical detraining. Again, those that maintained their HRV at the post-test showed better performance on executive function tasks. In an experiment investigating emotional regulation we showed that resting levels of HRV were related to emotion modulated startle responses such that those with higher HRV produced context appropriate responses compared to those with low HRV. We propose that these findings have important implications for the understanding of the two-way communication between the heart and the brain.

Keywords: heart rate variability, neurovisceral integration, executive function, working memory, emotional regulation

In the present paper we describe a model of neurovisceral integration in which a set of neural structures involved in cognitive, affective, and autonomic regulation are related to HRV and cognitive performance. We will provide an overview of the neural structures linking the central nervous system to HRV. Next, we will review a number of studies from our group showing that individual differences in HRV are related to performance on tasks associated with executive function and prefrontal

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cortical activity. We propose that these findings have important implications for the understanding of the two-way communication between the heart and the brain.

The Central Autonomic Network

Investigators have identified functional units within the central nervous system (CNS) that support goal-directed behavior and adaptability. One such entity is the central autonomic network (CAN; Benarroch, 1993, 1997). Functionally, this network is an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior, adaptability, and health. Structurally, the CAN includes the anterior cingulate, insular, orbitofrontal, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaquaductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field. These components are reciprocally interconnected such that information flows bi-directionally between lower and higher levels of the CNS. The primary output of the CAN is mediated through preganglionic sympathetic and parasympathetic neurons that innervate the heart via the stellate ganglia and vagus nerve, respectively. The interplay of these inputs to the cardiac sino-atrial node produces complex variability that characterizes the HR time series (Saul, 1990). Thus, the output of the CAN is directly linked to HRV. Notably, vagal influences dominate cardiac chronotropic control (Levy, 1990). In addition, sensory information from peripheral end organs such as the heart and the immune system are fed back to the CAN. As such, HRV is an indicator of central-peripheral neural feedback and CNS-ANS integration.

Other functional units within the CNS serving executive, social, affective, attentional, and motivated behavior in humans and animals have been identified (Damasio, 1998; Devinsky, Morrell & Vogt, 1995; Masterman & Cummings, 1997; Spyer, 1989). One such network has been termed the anterior executive region (AER; Devinsky et al., 1995). The AER and its projections regulate behavior by monitoring the motivational quality of internal and external stimuli. The AER network has been called the "rostral limbic system" and includes the anterior, insular, and orbitofrontal cortices, amygdala, periaquaductal gray, ventral striatum, and autonomic brainstem motor nuclei. Damasio (1998) has recognized a similar neural "emotion circuit", for which there is considerable structural overlap with the CAN and the AER (Thayer & Lane, 2000).

We propose that the CAN, the AER network, Damasio's "emotion circuit" 1998, and related systems (Masterman & Cummings, 1997; Spyer, 1989) represent a common central functional network recognized by different researchers from

diverse approaches. This CNS network is associated with the processes of response organization and selection, and serves to control psychophysiological resources in attention and emotion (Friedman & Thayer, 1998a,b; Thayer & Friedman, 1997). Additional structures are flexibly recruited to manage specific behavioral adaptations. This sparsely interconnected neural complex allows for maximal organism flexibility in accommodating rapidly changing environmental demands. When this network is either rigidly coupled or completely uncoupled, the ability to recruit and utilize appropriate neural support to meet a particular demand is hampered, and the organism is thus less adaptive.

We have shown in a series of studies using both pharmacological and neuroimaging approaches that prefrontal cortical activity is associated with vagally mediated HRV (Ahern, Sollers, Lane, Labiner, Herring, Weinand, Hutzler & Thayer, 2001; Lane, Reiman, Ahern & Thayer, 2001). A reciprocal, inhibitory pathway linking cortical and subcortical structures has been described by a number of researchers (Mayberg et al, 1999; Thayer & Lane, 2000). It has been suggested that an intact frontal cortex may tonically inhibit subcortical (amygdala) activity that in turn is associated with autonomically mediated defensive behavior. Direct and indirect pathways by which the frontal cortex modulates parasympathetic activity via subcortical inputs have been identified (Ter Horst & Postema, 1997; Ter Horst, 1999). Human evidence for the inhibitory role of the frontal cortex comes from a recent study of HR and HRV before and after right and left side intracarotid sodium amobarbital (ISA) injection (Ahern, et al 2001). Qualitatively similar changes in HR were observed during each hemisphere's injection. During ten-minute inactivations of either hemisphere, HR increased, peaked at about minute three, and gradually declined toward baseline values. These data support the notion that cortical activity tonically inhibits brainstem sympathoexcitatory circuits. However, differential hemispheric effects appeared, with larger and faster HR increases during right hemisphere inactivations. Concomitant with these HR increases, vagally mediated HRV decreased, mirroring the HR changes with respect to differential hemispheric effects. Specifically, vagally mediated HRV decreases were greater in the right hemisphere inactivations. These results support the anatomical and physiological findings that right hemispheric autonomic inputs to the heart are associated with greater cardiac chronotropic control.

Using neuroimaging we and others (Gianaros et al., 2004) have provided evidence that activity of the prefrontal cortex is associated with vagal function. A recent neuroimaging study to investigate the neural origins of HRV during emotional arousal has provided additional evidence for disinhibition of sympathoexcitatory circuits related to decreased activity in the prefrontal cortex. Lane, Reiman, Ahern and Thayer (2001) have presented evidence that medial prefrontal activity is associated with HRV. Vagally mediated HRV is considered to reflect antagonism of sympathoexcitatory influences. To explore its central neural substrates we correlated a spectrally derived index of vagally mediated HRV (HF-

HRV) with measures of cerebral blood flow (rCBF) derived from positron emission tomography (PET) in twelve healthy women. Happiness, sadness, disgust, and three neutral conditions were each induced by film clips and recall of personal experiences. Interbeat intervals from the electrocardiogram during six emotion and six neutral scans were derived and analyzed. During the emotion minus neutral conditions, HF-HRV correlated with blood flow in the medial prefrontal cortex and the left posterior orbitofrontal and anterior insular cortices. Emotional arousal was associated with a decrease in HRV and concomitant *decreases* in brain activation in these regions. These findings are consistent with a general inhibitory role for the medial prefrontal cortex via the vagus as suggested by Ter Horst (1999). Taken together these pharmacological blockade and neuroimaging studies provide support for the role of the prefrontal cortex in the modulation of subcortical sympathoexcitatory circuits via an inhibitory pathway that is associated with vagal function and can be indexed by HRV.

It has been proposed that the prefrontal cortex is taken "off-line" during emotional stress to let automatic, prepotent processes regulate behavior (Arnsten & Goldman-Rakic, 1998). This selective prefrontal inactivation may be adaptive by facilitating predominantly non-volitional behaviors associated with subcortical neural structures such as the amygdala to organize responses without delay from the more deliberative and consciously guided prefrontal cortex. In modern society, however, inhibition, delayed response, and cognitive flexibility are vital for successful adjustment and self-regulation, and prolonged prefrontal inactivity can lead to hypervigilance, defensiveness, and perseveration.

The Importance of Inhibition

Sympathoexcitatory subcortical threat circuits are under tonic inhibitory control by the prefrontal cortex (Amat, Barata, Paul, Bland, Watkins & Maier, 2005; Thayer, 2006). For example, 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 (Thayer, 2006; Davidson, 2000). Thus the default response to uncertainty, novelty, and threat is the sympathoexcitatory preparation for action commonly known as the fight or flight response. 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 normal, modern life this response has to be tonically inhibited and this inhibition is achieved via top-down modulation from the prefrontal cortex. Thus, under conditions of uncertainty and threat the prefrontal cortex becomes hypoactive. This 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). 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, a pre-attentive bias for threat information, deficits in working memory and executive function, and poor affective information processing and regulation (Thayer & Friedman, 2004). Proper functioning of inhibitory processes is vital to the preservation of the integrity of the system and therefore is vital to health. Importantly for our discussion, these inhibitory processes can be indexed by measures of vagal function such as HRV as we will illustrate below.

Attentional Regulation and Executive Function

Attentional regulation and the ability to inhibit pre-potent but inappropriate responses is also important for health and optimal performance in a complex environment. Many tasks important for survival in today's world involve cognitive functions such as working memory, sustained attention, behavioral inhibition, and general mental flexibility. These tasks are all associated with prefrontal cortex activity (Arnsten & Goldman-Rakic, 1998). It is also possible that autonomic dysregulation contributes to deficits in attention and cognitive performance. A series of experiments in our lab have been conducted to examine this issue, and are described below.

A series of studies from our group have examined executive function and working memory in healthy individuals. In the first experiment, subjects performed a number of tasks involving continuous performance including a simple reaction time task, a choice reaction time task, and three tasks that involved delayed responding and working memory (Hansen, Johnsen & Thayer, 2003; Johnsen, Sollers, Hansen, Murison & Thayer, 2002). These latter three tasks involved aspects of delayed responding and working memory, and have been shown to be associated with prefrontal activity (Goldman-Rakic, 1998). HRV and cortisol responses were recorded, and subjects were grouped into low and high HRV groups.

Performance on tasks involving simple and choice reaction times did not differ between these groups. However, on tasks associated with prefrontal activity, subjects in the low HRV group performed more poorly in terms of reaction time, number of errors and number of correct responses than those in the high HRV group. In addition, the groups did not differ in baseline, morning, or evening cortisol, but the low HRV group showed larger cortisol responses to cognitive tasks that lasted into the post-task recovery period. Stress is associated with an increased cortisol release, and cortisol plays a major role in immune function through its

association with proinflammatory cytokines (Kiecolt-Glaser et al., 2002). Cortisol is also known to impair function on cognitive tasks associated with prefrontal cortex (Lupien, Gillin & Hauger, 1999). Thus, the low HRV group was less stress tolerant as indexed by cortisol responses and more impaired cognitively than the high HRV group.

Another study in the series involved the manipulation of HRV. In this study, HRV was manipulated by having half of the subjects in a physically active group undergo mild de-training for four weeks (Hansen, Johnsen, Sollers, Stenvik & Thayer, 2004). Aerobic capacity and HRV were significantly reduced in the detrained group compared to those that maintained their fitness and HRV levels. All subjects again performed the above cognitive tasks: once before the four-week de-training period, and once after. The de-trained, lower HRV group failed to show the expected learning effect associated with repeated performance of the cognitive tasks, and thus, did not reap the typical benefit of previous task exposure.

Affective Regulation

Affect regulation is a valuable skill that has clear implications for health. 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, 1988). Viewed as such, emotions reflect the integrity of one's ongoing adjustment to constantly changing environmental demands. When the affective system works properly, it promotes flexible adaptation to shifting environmental demands. In another sense, an adequate emotional response represents a selection of an optimal response and the inhibition of less functional ones from a broad behavioral repertoire, in such a way that energy use is matched to fit situational requirements.

Several psychophysiological measures have proven to be useful indices of affect regulation. One is the reflexive startle blink, the magnitude of which can be affected by emotional state. The emotion-modulated startle is a robust phenomenon that has been demonstrated in a wide range of experimental situations, and has been broadly linked to affective and motivational phenomena (Lang, 1995). Similarly, HRV has been associated with a diverse range of processes, including affective and attentional regulation (Porges, 1992; Porges, Doussard-Roosevelt & Maita, 1994). The relationship between these two important measures of affective regulation was recently investigated (Ruiz-Padial, Sollers, Vila & Thayer, 2003). Ninety female participants viewed pleasant, neutral, and unpleasant pictures while exposed to acoustic startle stimuli. Eye blink strength to startle probes was recorded both during affective foregrounds and intertrial intervals, and the relationship between resting HRV and startle magnitudes was examined. Resting HRV was found to be inversely related to both intertrial interval and emotion-modulated startle

magnitude. These findings further support the notion that the prefrontal cortex tonically inhibits amygdala output. In addition, subjects with the highest HRV showed the most differentiated emotion-modulated startle effects, whereas those with the lowest HRV showed significant augmentation of startle to neutral foregrounds and marginally potentiated startle to pleasant foregrounds. Thus, individuals with low HRV reacted to neutral, harmless stimuli as if they were aversive and threatening, and also had a tendency to react similarly to positive stimuli. This failure to recognize safety signals can lead to prolonged action readiness and sympathetic nervous system overactivity.

Recent research in collaboration with the University of La Laguna further supports the role of individual differences in HRV in emotion regulation. This work involved an extension of our prior work to include a more social emotional situation. In an experiment in which appraisals of blame were manipulated it was found that those persons with higher resting HRV were less likely to assign blame when they were intentionally wronged compared to those with lower resting HRV. In addition, structural equation modeling suggested that is was not due to an effect on the emotion of anger directly but via a pathway that involved cognitive appraisal. These findings support the notion that the prefrontal cortex serves a context setting function and thus influences assessments of threat in social settings.

CONCLUSIONS

Taken together, these results support the usage of HRV to index efficient allocation of attentional and cognitive resources needed for efficient functioning in a challenging environment in which delayed responding and behavioral inhibition are key. In addition, these data show that low HRV marks increased risk to stress exposure. Significantly, these results provide a connection among stress-related cognitive deficits, high negative affect, and negative health consequences via the common mechanism of autonomic imbalance and low parasympathetic activity.

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