ann. behav. med. (2009) 37:141–153
DOI 10.1007/s12160-009-9101-z

ORIGINAL ARTICLE

Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health

Julian F. Thayer, Ph.D. · Anita L. Hansen, Ph.D. · Evelyn Saus-Rose, Cand. Psychol. · Bjorn Helge Johnsen, Ph.D.

Published online: 8 May 2009

Abstract
Background 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.
Methods We detail the pathways involved in the neural regulation of the cardiovascular system and provide pharmacological and neuroimaging data in support of the neural structures linking the central nervous system to HRV in humans. We 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. These studies include comparisons of executive- and nonexecutive-function tasks in healthy participants, in both threatening and nonthreatening conditions. In addition, we show that manipulating resting HRV levels is associated with changes in performance on executive-function tasks. We also examine the relationship between HRV and cognitive performance in ecologically valid situations using a police shooting simulation and a naval navigation simulation. Finally, we review our studies in anxiety patients, as well as studies examining psychopathy.
Conclusion These findings in total suggest an important relationship among cognitive performance, HRV, and prefrontal neural function that has important implications for both physical and mental health. Future studies are needed to determine exactly which executive functions are associated with individual differences in HRV in a wider range of situations and populations.

Keywords Executive function · Prefrontal · Heart rate variability · Cognition · Health

J. F. Thayer
Department of Psychology, The Ohio State University,
1835 Neil Avenue,
Columbus, OH 43210, USA

J. F. Thayer
Mannheim Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, Heidelberg University,
Mannheim, Germany

J. F. Thayer (✉) · A. L. Hansen · E. Saus-Rose · B. H. Johnsen
University of Bergen,
Bergen, Norway
e-mail: Thayer.39@osu.edu

Introduction

Any comprehensive model of health must account for the complex mix of cognitive, affective, behavioral, and physiological factors that contribute to individual differences in health and disease. For example, individual differences in blood pressure, pulse pressure, and pulse wave velocity have been related to cognitive function across the lifespan [1, 2]. Individual differences in autonomic balance have long been linked to health and disease. For example, Stevo Julius and colleagues have articulated a model of autonomic imbalance and its relationship to cardiovascular disease [3]. Moreover, we have recently reviewed the literature on the relationship between vagal function and the risk for cardiovascular disease [4]. This review indicated that decreased vagal function was associated with a range of risk factors and that improvement of risk profiles was associated with increased vagal function. Over the past few years, our group has systematically investigated the role of individual differences in vagal function, as indexed by heart rate variability (HRV), in cognitive performance. In this work, we have linked vagally mediated HRV to a set of neural structures that have been implicated in cognitive, especially executive, function. Thus, vagally mediated HRV may serve to index the functional capacity of a set of brain structures that support the effective and efficient performance of cognitive executive-function tasks including working memory and inhibitory control. These studies of the relationship between vagal function and cognition parallel those that we have done on the relationship between vagal function and emotional regulation and between vagal function and physiological regulation [5, 6]. In the present paper, we briefly outline the model and review our studies that have shown that persons with greater vagally mediated HRV perform better on executive-function tasks in a wide range of situations. We hypothesize that this is due to the ability of HRV to index important aspects of prefrontal neural function.

More specifically, 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. Neural network studies in humans have reported increased activity in the prefrontal cortex during tasks involving executive function and working memory [7]. Compte, Brunel, Goldman-Rakic, and Wang [8] have proposed that the prefrontal cortex holds sensory information temporarily online through sustained activity. This continued activation of a neural network is essential for the linking of "input" with "output" to achieve flexible responding to changing environments. As such, optimal prefrontal functioning is necessary for the formation of associations and the representation of acquired relationships between disparate pieces of information, including information separated in time [9]. In addition, these cortical regions are implicated in inhibitory functions that are known to be critical for the performance of executive-function tasks. Relatedly performance on working memory tasks has been reported to be significantly related to general intelligence as indexed by standard IQ tests.

Direct and indirect pathways by which the frontal cortex modulates parasympathetic activity via subcortical inputs have been identified [10, 11]. A number of researchers have hypothesized inhibitory cortical–subcortical circuits [12–16]. However, Thayer and Lane [17] were the first to tie these circuits to HRV.

We will provide an overview of the neural structures linking the central nervous system (CNS) 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. We propose that these findings have important implications for psychopathology and health.

The Central Autonomic Network

There is growing evidence for the role of the autonomic nervous system (ANS) in a wide range of somatic and mental diseases. The ANS is generally conceived to have two major branches—the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions. Normally, the activity of these branches is in dynamic balance. When this changes into a static imbalance, for example, under environmental pressures, the organism becomes vulnerable to pathology. 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 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 [18]. 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 [19]. Low HRV is associated with increased risk of all-cause mortality, and low HRV has been proposed as a marker for disease [4].

Investigators have identified functional units within the CNS that support goal-directed behavior and adaptability. One such entity is the *central autonomic network* (CAN) [13, 14]. 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 (CeA); 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 (NA); the ventrolateral medulla; the ventromedial medulla; and the medullary tegmental field. These components are reciprocally interconnected such that information flows bidirectionally 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 sinoatrial node produces complex variability that characterizes the HR time series [18]. Thus, the output of the CAN is directly linked to HRV. Notably, vagal influences dominate cardiac chronotropic control [20]. 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 [15, 16, 21, 22]. Importantly for the present discussion, one such network, termed the rostral limbic system (RLS), has been associated with cognitive functions [22]. The RLS and its projections regulate behavior by monitoring the motivational quality of internal and external stimuli. The RLS network includes the anterior, insular, and orbitofrontal cortices; amygdala; periaquaductal gray; ventral striatum; and autonomic brainstem motor nuclei. Damasio [21] has recognized a similar neural "emotion circuit," for which there is considerable structural overlap with the CAN and the RLS [17].

We propose that the CAN, the RLS network, Damasio's "emotion circuit" [21], and related systems [15, 16] 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 [23–25]. 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.

Cortical Control of Cardiac Activity

HR is determined by intrinsic cardiac mechanisms and the joint activity of the sympathetic nerves and parasympathetic (vagus) nerves at the sinoatrial node. In healthy systems, both branches of the ANS are tonically active with sympathetic activity associated with HR acceleration and parasympathetic activity associated with HR deceleration [19, 20]. Importantly, HR in many species, including humans, is under tonic inhibitory control peripherally via the vagus [20, 26]. Both animal and human data suggest that cortical activity modulates cardiovascular function. An extensive body of research has been directed at identifying the pathways by which this neural control is achieved. As noted above, Benarroch [13, 14] has described the 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 NTS. Despite well documented species differences, in many mammals, including primates and humans, there appear to be both direct and indirect pathways linking the frontal cortex to autonomic motor circuits responsible for both the sympathoexcitatory and parasympathoinhibitory effects on the heart [11, 17, 27–37]. Figure 1 provides a composite model based upon the extant literature. (A similar model has been proposed for the cortical regulation of blood pressure [38].) In this model,

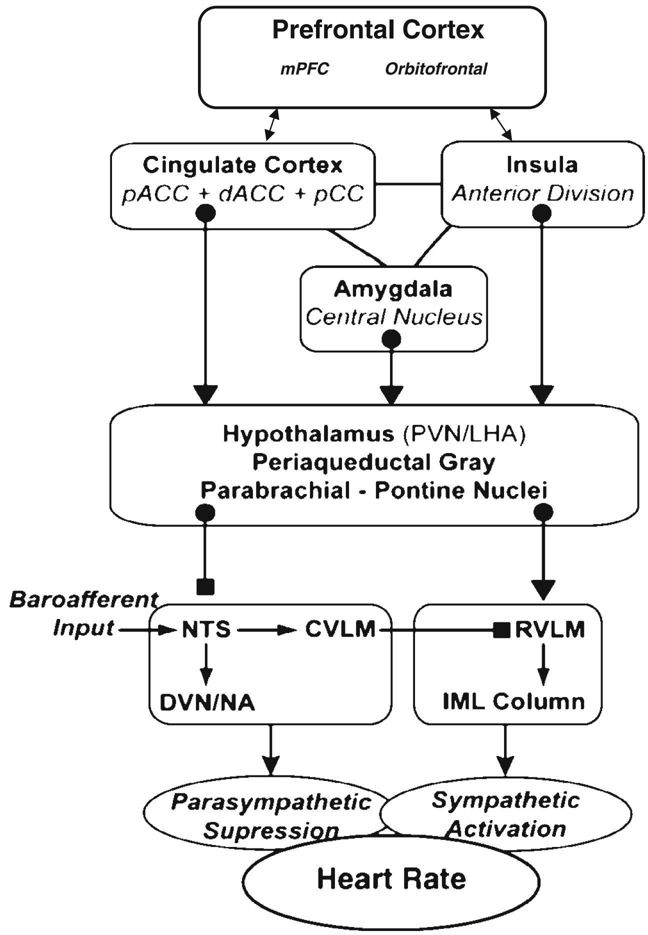

Fig. 1 A composite schematic diagram showing the pathways by which the prefrontal cortex might influence control of HR. The prefrontal, cingulate, and insula cortices form an interconnected network with bidirectional communication with the amygdala. The amygdala is under tonic inhibitory control via prefrontal vagal pathways to intercalated cells in the amygdala. The activation of the central nucleus of the amygdala (CeA) inhibits the nucleus of the solitary tract (*NTS*: *solid square*), which in turn inhibits inhibitory caudal ventrolateral medullary (*CVLM*) inputs to the rostral ventrolateral medullary (*RVLM*) sympathoexcitatory neurons (*solid square*), and simultaneously inhibits vagal motor neurons in the nucleus ambiguus (*NA*) and the dorsal vagal motor nucleus (*DVN*). In addition, the CeA can directly activate the sympathoexcitatory neurons in the RVLM. The net effect of pharmacological blockade of the prefrontal cortex would be a disinhibition of the CeA, leading to disinhibition of medullary cardioacceleratory circuits and an increase in HR. Figure adapted from Gianaros [38]

prefrontal cortical areas, including the orbitofrontal cortex and the medial prefrontal cortex, tonically inhibit the amygdala via pathways to intercalated GABAergic neurons in the amygdala [28, 35]. Moreover, activation (disinhibition) of the CeA (the major efferent source of modulation of cardiovascular, autonomic, and endocrine responses) may lead to increased HR and decreased HRV by three routes: (1) activation (disinhibition) of tonically active sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM) by decreased inhibition from tonically active neurons in the caudal ventrolateral medulla leading to a net increase in sympathetic activity; (2) inhibition of neurons in the NTS, which leads to inhibition of tonically active NA and dorsal vagal motor nucleus (DVN) neurons, leading to a net decrease of parasympathetic activity; and (3) direct activation of sympathoexcitatory RVLM neurons leading to a net increase in sympathetic activity ([33], Fig. 1, p. 453). However, this last route is a minor pathway associated with only a small percentage of the fibers connecting the CeA with the medullary ANS outputs. Thus, decreased activation of the prefrontal cortex would lead to disinhibition of the tonically inhibited CeA. This, in turn, would lead to a simultaneous disinhibition of sympathoexcitatory neurons in the RVLM via route number one, above, and an inhibition of parasympathoexcitatory neurons via route number two, above. Both would lead to an increase in HR and a concomitant decrease of vagally mediated HRV.

Importantly, modern retrograde viral staining studies in rodents have identified similar pathways to be specifically involved in the forebrain *parasympathetic* regulation of heart activity [11]. Specifically, following pseudorabies virus injections into the ventricular myocardium, labeled cardiac vagal motorneurons and higher-order command cells were found in the DVN, the NA, the NTS, the area postrema, the ventrolateral reticular formation, the locus ceruleus, the parabrachial nucleus, the periaquaductal gray, several regions of the hypothalamus, the bed nucleus of the stria terminalis, the CeA, the anterior cingulate cortex, the insula, and the frontal cortex, among others. Consistent with the above neural pathways, we showed that anterior cortical activity tonically inhibits cardioacceleratory circuits in humans based on an increase in HR and a decrease of HRV during pharmacological inactivation of either cerebral hemisphere [39].

Specifically, we have shown in a series of studies using both pharmacological and neuroimaging approaches that prefrontal cortical activity is associated with vagally mediated HRV [39–44]. For example, human evidence for the inhibitory role of the frontal cortex comes from a study of HR and HRV before and after right- and left-side intracarotid sodium amobarbital injection [39]. Qualitatively similar changes in HR were observed during each hemisphere's injection. During 10-min 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 cardioacceleratory 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 [41–44] and others [45] have provided evidence that activity of the prefrontal cortex is associated with vagal function. For example, Lane, McRae, Reiman, Chen, Ahern, and Thayer [42] have presented evidence that medial prefrontal activity is associated with HRV. To explore its central neural substrates, we correlated a spectrally derived index of vagally mediated HRV (HF-HRV) with measures of cerebral blood flow derived from positron emission tomography in 12 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. Across all conditions, HF-HRV correlated with blood flow in the right superior prefrontal cortex (BA 8, 9), the left rostral anterior cingulate cortex (BA 24, 32), the right dorsolateral prefrontal cortex (BA 46), and the right parietal cortex (BA 40). 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 prefrontal cortex via the vagus, as suggested by Ter Horst [10]. Taken together, these pharmacological blockade and neuroimaging studies provide support for the role of the prefrontal cortex in the modulation of subcortical cardioacceleratory 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 “offline” during emotional stress to let automatic, prepotent processes regulate behavior [46]. This selective prefrontal inactivation may be adaptive by facilitating predominantly nonvolitional 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.

Inhibition and the Right Prefrontal Cortex

One of the primary functions associated with the prefrontal cortex is that of inhibition. Inhibition involves the suppression of prepotent, irrelevant, or interfering stimuli or impulses associated with concomitant excitatory processes such that those processes that are not inhibited achieve a processing advantage [47]. William James [48], among others, noted the importance of the ability to selectively attend to a subset of stimuli from a complex, dynamic environment and juxtaposed this ability with the "confused, dazed, and scatter-brain state." In this way, inhibition serves to "sculpt" excitatory neural action to produce context-appropriate responses [17, 49, 50]. Failures of inhibition are well documented in clinical psychology and are implicated in psychopathological disorders such as anxiety, depression, schizophrenia, obsessive-compulsive disorder, attention-deficit disorder, and Parkinson's disease and other so-called "disinhibition syndromes." Inhibitory processes are a component of many tasks associated with so-called executive functions, including working memory, attentional set-shifting, and response inhibition. The prefrontal cortex has also been implicated in affective processes including emotional regulation, affective set-shifting, and extinction, all of which also rely heavily on inhibitory processes. It has been suggested that there is a common inhibitory network associated with a wide range of processes [51, 52]. As noted above, there are pathways that have linked the prefrontal cortex with the inhibition of medullary cardioacceleratory circuits. The neurovisceral integration model proposes that all of these processes of cognitive regulation, affective regulation, and physiological regulation may be related to each other in the service of goal-directed behavior [17]. In support of this idea, we have shown that cognitive, affective, and physiological regulation are all associated with vagally mediated cardiac function, as indexed by HR and HRV [5]. Importantly, these inhibitory functions have been linked with right-hemisphere prefrontal activity [39, 51, 53].

There is a growing body of literature that suggests that the right prefrontal cortex is preferentially related to inhibitory processes across a wide range of cognitive, motor, and affective tasks [51, 53–57]. A recent report that directly compared different modalities suggests that the right prefrontal cortex is involved in response inhibition across response modalities [52]. Given the predominant right-hemispheric innervation of the sinoatrial node of the heart, we have proposed that the well known right-hemisphere advantage for emotion may be secondary to the relative right-hemisphere innervation of the heart [39]. Similarly, we have proposed that the relationship between executive-function performance and HRV is related to the common neural basis for both functions [5, 17, 50]. Therefore, the right hemisphere may be a critical player in inhibitory processes involved in cognitive, affective, and physiological regulation [5, 17].

Our position, however, is to not overstate the evidence for right-hemispheric control of cardiac function. For example, the work of Bud Craig [58] has suggested that cortical regulation of vagal function is predominantly left-sided. It should be noted that patterns of cortical activation associated with even the simplest of tasks are incredibly dynamic and distributed [59]. Thus, simplistic models of hemispheric activations based on neuroanatomical and neuroimaging studies that do not take into account these spatial and temporal patterns are bound to be incomplete. Thus, we have suggested that a dynamical systems framework might be appropriate [50, 60]. In this context, we have proposed that a flexible network of neural structures that can be differentially recruited in response to challenges leads to "emergent" functional networks that are context-specific [17].

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 [17] 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 the prefrontal cortex to exert an inhibitory influence on subcortical 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 cognitive regulation.

Attentional Regulation and Executive Function

Attentional regulation and the ability to inhibit prepotent but inappropriate responses are 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 [46]. Deficits in these cognitive functions tend to accompany aging, and are also present in negative affective states and dispositions such as depression and anxiety. Stress can also impair cognitive function and may contribute to the cognitive deficits observed in various mental disorders and in extreme environments. 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 they are described below.

Recent research suggests that working memory may form the core of a set of cognitive operations that are essential for effective functioning in a complex environment [46, 61, 62]. Cognitive functions, such as selective attention, response selection, inhibition of prepotent responses, and executive control, are all thought to depend upon working memory [62]. Working memory involves the active short-term storage, online processing, and manipulation of information, and it is critically dependent upon inhibitory neural processes for efficient function [7, 46]. Importantly, the neural basis of working memory is thought to involve a distributed network of structures incorporating the prefrontal cortex as an important focus [7, 46, 62].

HRV and Executive Functions

As already mentioned, HRV has been related to the activity of the prefrontal cortex [42], and the prefrontal cortex has been inversely associated with activity in subcortical structures such as the amygdala [63]. Although HRV has shown a relationship to prefrontal activity, in this paper, we will show that HRV is also related to performance on abilities localized in the prefrontal cortex. As such, we propose that HRV is related to cognitive performance due to its ability to index activity in prefrontal neural structures.

In order to function adequately, humans have to plan and direct action and thought to perform goal-directed behavior [54]. This involves executive control of behavior. Executive functions are thought of as consisting of a central monitoring system called the central executive, as well as a phonological and visospatial short-term storage slave system [64]. The aspects of executive control involve selecting, maintaining, updating, and rerouting information [65]. This also involves the ability to suppress irrelevant or interfering information. Shimamura [65] pointed out that the executive functions have a maintaining aspect, which means the ability to keep a filter fixed across time, where attention and memory serve as an executive function. Thus, both sustained attention and working memory are core elements of executive functions.

One way to investigate sustained attention is by continuous performance tests (CPT). These tests are playing an increasing role in the assessment of attentional processes [66]. The tasks involve higher mental workload levels, such as memory search, choice reaction time, mental arithmetic, time estimation, simple tracking, and grammatical reasoning [67]. Parasuraman, Warm, and Dember [68] suggested that the increase in working memory load may be the key factor in perceptual sensitivity or decrement during vigilance tasks. Working memory is assumed to involve moment-to-moment updating and rehearsal of information to prolong storage [69]. Thus, working memory is seen as a very general resource that plays a role in a wide variety of cognitive tasks. The executive is used for both storage and processing. Consequently, when greater effort is required to process information, less capacity remains for the storage of that information [64]. There are individual differences in memory capacity, and it is suggested that high-working-memory-capacity individuals will also have more attentional resources. To understand the role of working memory in normal human information processing, it is of importance to go beyond the relationship between working memory and cognitive performance and investigate exactly why the relationship occurs [70]. The series of studies on the relationship between HRV and cognitive functions could shed some light on this.

In contrast to executive-function tasks, nonexecutive tasks are based on processes driven automatically or reflexively by stimulation. This occurs even when the person is instructed to be passive toward the event. In accordance with Cowan [71, 72], it could be argued that simple reaction time and choice reaction time tasks are nonexecutive tasks since they do not require short-term memory in addition to controlled and focused attention, or manipulation of new information. The main difference between the executive and the nonexecutive tasks is that the executive tasks require active attention, while nonexecutive task only require passive attention toward the event [73].

As mentioned, neural structures involved in cognitive, affective, and autonomic regulation are related to HRV and cognitive performance. Traditionally, correlations have been found between measures of cardiac vagal tone and cognitive performance data. Only two exceptions of this correlational approach were found outside our lab [74, 75]. One common approach to the studies of HRV and cognitive functioning has been to view HRV as a dependent variable. However, in a series of studies from our research group, we have investigated the relationship between HRV and executive- and nonexecutive-functions treating HRV as an independent variable. Thus, the predictive power of HRV on higher cortical functions could be further studied.

The use of HRV as an independent variable in studies of self-regulation and health has several important implications. First, individual differences in resting HRV have been associated with mortality and morbidity [4]. Specifically, low levels of resting HRV have been linked with increased mortality and morbidity. Second, resting levels of HRV are a relatively stable individual difference variable. For example, we have recently shown that resting HRV levels in Caucasian and African Americans are fairly stable over a one- and one-half-year period, whereas stress-evoked levels were less stable [76]. Third, using both molecular and behavioral genetic approaches, we and others have demonstrated significant genetic influences on HRV [77–80]. Importantly, the candidate genes that have thus far been identified also have been associated with prefrontal cortical function. For example, we found evidence for the angiotensin-converting enzyme insertion/deletion gene to be associated with HRV. This gene has also been associated with substance P in the brain and with cognitive function [81]. Fourth, and perhaps most importantly, we have suggested that HRV may be an endophenotype or intermediate phenotype linked to a range of both psychological and physiological processes that are important for health and disease [82]. For example, we have suggested that low HRV may be an endophenotype for at least certain anxiety disorders, such as panic disorder [83]. Whereas there is a significant genetic component to HRV, it should be noted that it is still possible to change one's level of HRV. Diet, exercise, biofeedback, and stress reduction techniques such as meditation are among several behavioral strategies that can be used to increase one's resting levels of HRV [82]. As such, individual differences in HRV represent a potentially malleable substrate for a wide range of processes associated with self-regulation, adaptation, and health. In the following, we make the case for resting HRV as an important factor in cognitive regulation and executive function.

HRV and Sustained Attention and Working Memory

In a series of studies on military personnel, we studied high- vs low-HRV personnel on attentional and memory tasks. In a study by Hansen, Johnsen, and Thayer [84], the personnel were allocated to high- or low-HRV groups based on the median split on root mean square successive difference recordings during a 5-min baseline. A total of 49 subjects participated in the study, and were presented both a CPT (CALCAP Norland Software, Los Angeles, CA, USA) and a two-back working memory test [85]. The CPT test consisted of four tasks tapping both nonexecutive and executive functions. The two nonexecutive functions where simple reaction time and response latencies to specific stimuli. The two executive tasks where detection of identical stimuli and a simple addition task. The two-back task was a standard memory task where subjects have to identify and react to digits presented two trials back in a continuous flow of digits. The results showed that the high-HRV group had superior performance compared to the low-HRV group. On the CPT, the high-HRV group showed faster reaction times to correctly identified stimuli compared to the low-HRV group (when pooling all subtests together). In addition, the high-HRV group showed fewer false-positive responses compared to the low-HRV group.

When separating the tasks into executive and nonexecutive tasks, the high-HRV group showed better performance on the executive-function tasks, on both the reaction time and accuracy parameters. This was further supported by the results from the working memory test (two-back). The high-HRV group had better accuracy, as reflected in detecting more true-positive responses compared to the low-HRV group. No differences were found on nonexecutive tasks. Thus, for the first time, support was found for the specificity of the effect of HRV to those cognitive tasks involving executive functioning.

If HRV is an essential index of adaptability of the organism, the subjects showing a high level of HRV should perform better under stressful conditions. Thus, the initial findings were followed up in a second study where the same cognitive tasks were investigated during stressful conditions [86]. One way to enhance stress in humans is by introducing aversive stimuli as a consequence of substandard performance. In the second study, half the subjects were introduced to a condition where they were told that performance below a set standard on the same tasks as in [84] would result in the administration of an electrical shock to the fingers. The subjects were instructed that the standard would vary, so in order to prevent shocks, a high and stable performance would be required. The shock level was individually determined before the administration of the cognitive tests, with the instruction to the subject in the threat condition that the shock should be unpleasant but not painful. During actual testing, no shocks were delivered. Sixty-five navy personnel participated in the study and were allocated to four groups (threat of shocks vs no threat and high vs low HRV). The HRV parameter was derived from spectral analyses of the interbeat intervals. The results from this study showed that subjects with high HRV had better performance than subjects with low HRV during nonthreat or normal conditions. This replicated the results from the first study [84]. Furthermore, during the threat of shock conditions, the low-HRV group showed faster mean reaction time on a nonexecutive or easy task compared to the high-HRV group. The experiment expanded knowledge concerning different patterns regarding activation or arousal and performance on different tasks. Frankenhaeuser, Nordhenden, Myrsten, and Post [87] and Broadbent [88] emphasize individual differences in the patterns of changes in physiology and performance on cognitive tasks. For instance, subjects with high arousal performed better compared to subjects with low arousal on simple tasks, while low-aroused subjects performed better than high-aroused subjects on more difficult tasks [87]. This is also in accordance with Broadbent [88], who suggested that subjects exposed to stress showed improved performance on simple tasks. Thus, the findings suggested an interaction between physiological characteristics of the individual, environmental stress, and task difficulty converged to account for individual differences in the ability to cope with cognitive demands in stressful environments.

The results of the working memory task showed that the high-HRV group had good and stable performance on accuracy data independent of environmental demands, while the low-HRV group showed improved performance on reaction time during threat of shock. The improvement of the low-HRV group during threat-of-shock conditions might be due to the fact that fear can facilitate the processing of sensory information caused by an increase in attention to the environment mediated by cortical arousal [89]. The good and stable performance for the high-HRV group on the cognitive tasks might be explained by the high vagal tone being associated with the ability to self-regulate, in addition to having a greater behavioral flexibility and adaptability in a threatening environment. The low-HRV group, on the other hand, is more dependent on environmental stimulation in order to perform.

In order to further investigate the relationship between HRV and human responses to cognitive workload, salivary cortisol sampled during the study of Hansen et al. [84] was analyzed [90]. Cortisol was sampled during the morning before the subjects had breakfast, 15 min before the cognitive tests started (baseline), immediately after each of the cognitive tests, and 15 min after the last test (recovery). In addition, evening cortisol was sampled where half the subjects gave saliva samples during the evening before the test and half the subjects gave during the evening after the test. As in the study of Hansen et al. [84], the subjects were divided into a low-HRV group and a high-HRV group based on the median score of the baseline HRV recordings. Baseline recordings of HRV correlated negatively with cortisol responses after the CPT, after a pop-out attention test, and after recovery. Importantly, between-group analyses showed no differences between the high- and the low-HRV groups during morning, baseline, and evening recordings, but cortisol levels during the cognitive tests, as well as during recovery, were higher in the low-HRV group compared to the high-HRV group. The study by Johnsen et al. [90] showed that HRV was related to the susceptibility to cognitive stress. This is evident not only in performance data, as shown previously, but also in stress responses measured in the endocrine system.

Since HRV was related to both performance and stress responses, an important question would be if it is possible to manipulate the HRV in order to produce changes in performance on cognitive tasks. Previously, studies on HRV have indicated that both pharmacological interventions [91, 92] and behaviorally based programs [93] are able to alter HRV. Fitness or training programs induce adaptation of the ANS, resulting in lowered resting HR, which is under predominantly parasympathetic control [20]. On the other hand, detraining is defined as the partial or total loss of training-induced anatomical or physical adaptation, as a consequence of a reduction or cessation of training. Hansen, Johnsen, Sollers, Stenvik, and Thayer [94], focusing on ecological validity, investigated the effect of a detraining paradigm on HRV using naval personnel. Thirty seven subjects were exposed to an 8-week training program (3 h per week of aerobic exercise). After the training program ended, half the subjects were deployed on a 4-week naval maneuver where no training was possible. The other half of the subjects continued their exercise program.

Analyses of the training diary showed that the instruction was followed by the groups, and a manipulation check showed that the trained group sustained their aerobic capacity as indexed by VO2max, while the detrained group decreased their VO2max from pretest (end of training program, but before the 4-week maneuver) to the posttest (end of the maneuver). Also, the detrained group showed lower resting HRV, measured in the high frequency (HF) power band, at the posttest. During the working memory test and recovery, an interaction effect was found with a decrease in HF power from pre- to posttest. This was evident only for the detrained group.

The effects of detraining on cognitive functions showed that the detrained group (low HRV) showed faster reaction times to the nonexecutive-function tests, while the trained group (high HRV) showed faster reaction time to the executive-function tests measured on the posttest. The accuracy data showed that the trained group showed an increase from the pre- to the posttest in true positive responses on the tasks tapping executive functions. This learning effect was not evident in the detrained group. The study by Hansen et al. [94] showed that HRV could be altered by behavioral programs and that the manipulation of HRV also affects cognitive functions. The effect on high-HRV subjects is specific to executive-function tasks. By manipulating HRV and observing corresponding changes in cognitive functions, the hypothesized causal relationship between neural processes indexed by HRV and executive functions was strengthened. These results suggest that engaging in exercise may be associated with improvements in executive functioning. In fact, several researchers have noted that exercise improves executive function and have identified the associated brain regions, including many of those linked to HRV [95].

As mentioned, the central executive involves planning and decision making. A core element of this involves overriding prepotent tendencies, which involve the processes of inhibition, disinhibition, and excitation. Inhibition is thought of as suppression of prepotent responses, while disinhibition is the process in which subjects disengage from inhibition in order to execute a response. Excitation involves an execution of a proper response to a target stimulus. These phenomena were studied in a Go–NoGo task, and the results were reported in a study by Johnsen, Hansen, Eid, Sollers, Hugdahl, and Thayer (unpublished manuscript). Forty-six subjects characterized as either high or low on HRV were administered a modified Go–NoGo task. The subjects had to respond and inhibit their responses to culturally relevant (green–red circles) and neutral (blue–pink circles) stimuli. The Go–NoGo task consisted of four subtasks with trials consisting of circles presented in four colors. During the first subtask, subjects were to respond to a green circle and restrain from responding to a red circle. This condition was called the GreenGo condition and represented the culturally learned aspect of a green symbol signaling activation of a response (or go), and the red symbol representing inhibition (or stop). In the second subtask, the subjects were to respond to a red circle and not respond to a green circle. This subtask was called the RedGo condition and represented the condition where the subjects have to override the cultural effect of the symbols. The third subtask (BlueGo) consisted of trials where the subjects were to respond to a blue circle and inhibit responding to a pink circle. This and the subtask where subjects were to respond to pink circles and not respond to blue circles (PinkGo) were neutral conditions unbiased by cultural learning effects. The comparisons showed faster reaction times in the high-HRV compared to the low-HRV group on all the subtasks except for the GreenGo condition. This included the RedGo, BlueGo, and the PinkGo subtasks. The analyses of the accuracy data revealed higher numbers of correct commissioned responses for the high-HRV group compared to the low-HRV group for the RedGo subtask and fewer false omitted responses on the same task. Furthermore, marginally fewer total errors were found in the high-HRV group compared to the low-HRV group during the RedGo subtest. The results were interpreted as the high-HRV group showing increased ability to adapt to environmental stimuli. This was especially the case when the subjects had to override prepotent response tendencies and the high-HRV group showed both higher excitatory ability and disinhibition, compared to the low-HRV group.

HRV and Situational Awareness

Adaptive human functioning involves using and combining executive functions in a flexible manner in order to cope with a rapidly changing dynamic environment. In this way, the central executive would control and coordinate different attentional and memory functions into higher-order cognitive functions. One critical factor for the central executive to make adequate decisions and actions in critical situations is to generate and maintain situational awareness (SA) [96, 97]. SA refers to cognitive processes involved in perceiving and comprehending the meaning of a given environment. This in turn will lead to the ability to make timely and good decisions, and a core element in order to make these decisions is the ability to make projections of likely events in the near future [98]. Thus, SA could be viewed as a conscious, dynamic reflection of the situation, which reflects the past, the present, and the future. A three-stage model has been proposed, which emphasizes perception of, and defining the situation, with some aspect of prediction of the near future [99]. SA is closely linked to human decision-making and performance and can be critical to adaptive behavior in stressful and critical situations [98, 100]. As an example, Svensson and Wilson [101] showed that mission complexity affects workload, which again affects SA and performance. This link is often reported in aviation accidents resulting from inadequate situational assessment and awareness [102, 103].

In order to follow up on the studies by Hansen et al. [84, 94] (Johnsen et al., unpublished manuscript), the relationship between HRV and SA was further investigated. This was done in a study of training effects in a shooting simulator at the Norwegian Police Academy [104]. The study investigated 20 cadets involved in scenario-based training compared to 20 matched controls involved in regular shooting practice. While the scenario-based training group practiced on simulated scenarios (shoot–no-shoot), the control group practiced on the same aspects, but not in a scenario context (i.e., moving targets, reversing target, shoot–no-shoot instructions). Both groups trained in the same simulator, for the same amount of time, and with the same weapons, and the only manipulation was type of training. The target session involved a scenario that included a baseline period, a preparation phase (receiving information and orders, preparing equipment, etc.), an execution phase, and a recovery phase. The study reported higher SA scores in the scenario-trained group compared to the control and a positive correlation between SA scores and actual performance measured as number of shots fired and number of hits on target. When pooling the groups together, relationships between HRV and SA scores were found. Positive correlations were found between SA scores and baseline measures of HRV and recordings during the preparation phase and during the execution phase. Significant correlations were also found between ratings of subjective evaluation of learning from the experience and HRV measured at baseline, during the preparation phase, as well as during the execution phase. The study also reported a suppression of HRV from baseline to the preparation phase and a further suppression of HRV from the preparation phase to the execution phase, as well as a return of HRV to baseline levels in the recovery phase. A differential effect between the two groups was found where the scenario-trained group did not show suppression of HRV from the preparation phase to the execution phase. This was in contrast to the control group, which showed this suppression. Mental effort and anxiety have been closely related to HRV [105, 106], and this could explain why the effect was most dominant in the control group. A similar pattern was found for the relation between HRV and learning. Since learning would also rely on executive functioning, the previous reported link between HRV and executive functioning could explain these results. The study by Saus et al. [104] revealed a positive association between HRV and executive functions in a virtual reality setting, which increases even further the ecological validity of the tasks. The simulator gives us an opportunity to test the relationship between HRV and cognition in a setting with an increased degree of realism, while exerting a high degree of experimental control. Thus, HRV was positively related to SA, and SA was positively related to performance.

The study by Saus et al. [104] was followed up by another study whose main aim was to investigate predictors of SA in navigation simulators [107]. Thirty six naval cadets underwent a procedure of baseline, sailing in the simulator, and recovery. In addition to revealing personality factors of neuroticism, extraversion, and conscientiousness as predictors of SA, HRV was also found to be related to SA. HRV recorded during recovery showed a positive correlation with SA measures. When separating the subjects into high- vs low-SA groups, based on a median split, the analyses further revealed that the high-SA group showed a reduction in the HF power band of HRV from baseline recordings to sailing and an increase in the recovery phase. These results showed that the high-SA subjects were able to modulate their internal environment in order to match external demands. In contrast, the low-SA group had no differentiation of their HRV from rest to execution of the task and back to recovery.

HRV and Psychopathology

So far, we have argued that HRV is related to successful adaptation of well-functioning subjects since the use of military and police personnel involves subjects screened for comorbidity. In a series of studies from our laboratory, HRV has also been investigated in relation to psychopathology. A key aspect of these studies has been the high ecological validity. For instance, Johnsen et al. [108] investigated odontophobics using a modified Stroop paradigm while the subjects were situated in a dental treatment unit. The study was conducted on 20 odontophobic patients, and the results showed that resting HRV was able to predict responses on the modified Stroop task. Dental anxiety subjects with high HRV showed faster reaction time when color-naming threat stimuli, as well as incongruent color words, compared to odontophobics with low HRV. This was explained by a lack of ability to modulate attentional processes for the low-HRV group. Since the subjects have to keep in mind the instruction of the color-naming task, and override the automatic tendency of naming the content of the word, this task has been regarded as an executive-function task.

In a recent paper [109], we investigated HRV and its relationship to psychopathy using Hare's four-facet model. In this model, psychopathic deviance could be separated into four facets in which psychopathic subjects vary. One facet is represented by interpersonal style. The core characteristic of this facet is the manipulation of other subjects, superficial charm, grandiose sense of self-worth, and pathological lying. The second facet is called affective style, which includes the lack of empathy and remorse or guilt, often observed in this disorder. The third facet encompasses the impulsive lifestyle, such as sensation-seeking, parasitic lifestyle, lack of realistic goals, and irresponsibility. The last facet represents antisocial behavior, such as violence. As already outlined, HRV is closely linked to executive functions, which involve abilities, reasoning, problem-solving, and planning goal-oriented behaviors. In addition, inhibition such as impulse control is also viewed as an executive function [109]. Although both an anatomical [111] and a functional link [112] between executive functions and psychopathic disorder have been suggested, others have not been able to report such a relation [113]. The subjects in the study by Hansen et al. [109] were inmates in a prison, and all testing was performed inside the prison, ensuring a high degree of ecological validity. The procedure involved recordings of HRV during baseline, cognitive testing of nonexecutive and executive functions, and recovery. The regression analysis found that the interpersonal facet showed a positive relationship with HRV during baseline. The interpersonal facet accounted for 29% of the total variance. The other facets had no significant associations. It also turned out that the interpersonal facet, compared to the other facets, had the strongest influence on HRV measured during the test conditions. Here, the facet accounted for 15% of the variance. There were no significant relationships between any of the facets and recovery. Subjects with high scores on the interpersonal facet exhibited better performance on cognitive tasks that taxed executive function compared to those with low scores. Thus, the study suggests that it might be useful to investigate the different dimensions of psychopathy in relation to underlying physiological and cognitive characteristics, instead of the traditional view where the disorder is considered to consist of one unique set of characteristics.

Conclusions

In this paper, we have tried to present evidence in support of the notion that resting levels of vagally mediated HRV are associated with individual differences in cognitive performance, particularly executive function. First, we reviewed the neural basis for such an association in which we showed that prefrontal neural function was related to HRV based on pharmacological and neuroimaging studies.

As such, we proposed that HRV may serve as a peripheral index of the integrity of CNS networks that support goal-directed behavior. The similarity of the structures and networks identified between those associated with the physiological regulation of cardiac control and those associated with cognitive regulation, particularly inhibitory processes, suggests to us a common neural basis for these functions. We then provided a review of the studies from our group that have systematically examined the functional relationship between HRV and executive function. Across diverse tasks and populations, we have found evidence for an association between higher levels of resting HRV and superior performance on tasks that tap executive functions. Importantly, these results contrast with those on nonexecutive function tasks to provide a degree of specificity that is consistent with the neural structures that we and others have shown to be associated with HRV and with executive function. The importance of these findings for the understanding of the complex mix of cognitive, affective, behavioral, and physiological factors associated with health and disease should not be lost. By providing a common neural basis for these diverse functions, the neurovisceral integration model may serve as a unifying framework within which to examine associations among these various self-regulatory processes that together represent the components of adaptability and good health.

References

1. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: The Baltimore longitudinal study of aging. *Hypertension*. 2005; 45(3): 374–379.
2. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension*. 2008; 55: 99–104.
3. Amerena J, Julius S. The role of the autonomic nervous system in hypertension. *Hypertens Res*. 1995; 18(2): 99–110.
4. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol*. 2007; 74: 224–242.
5. Thayer JF, Brosschot JF. Psychosomatics and psychopathology: Looking up and down from the brain. *Psychoneuroendocrinology*. 2005; 30: 1050–1058.
6. Thayer JF, Sternberg EM. Beyond heart rate variability: Vagal regulation of allostatic systems. *Ann N Y Acad Sci*. 2006; 1088: 361–372.
7. Goldman-Rakic PS. The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. In: Roberts AC, Robbins TW, Weiskrantz L, eds. *The Prefrontal Cortex: Executive and Cognitive Function*. Oxford: Oxford University Press; 1998:87–102.
8. Compte A, Brunel N, Goldman-Rakic PS, Wang XJ. Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. *Cereb Cortex*. 2000; 10: 910–923.
9. Miller EK. The prefrontal cortex and cognitive control. *Nat Rev*. 2000; 1: 59–65.
10. Ter Horst GJ. Central autonomic control of the heart, angina, and pathogenic mechanisms of post-myocardial infarction depression. *Eur J Morphol*. 1999; 37: 257–266.
11. Ter Horst GJ, Postema F. Forebrain parasympathetic control of heart activity: retrograde transneuronal viral labeling in rats. *Am J Physiol*. 1997; 273: H2926–H2930.
12. Mayberg HS, et al. Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999; 156: 675–682.
13. Benarroch EE. The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clin Proc*. 1993; 68: 988–1001.
14. Benarroch EE. The central autonomic network. In: Low PA, ed. *Clinical Autonomic Disorders*. 2nd ed. Philadelphia: Lippincott-Raven; 1997:17–23.
15. Masterman DL, Cummings JL. Frontal-subcortical circuits: The anatomical basis of executive, social and motivated behaviors. *J Psychopharmacol*. 1997; 11: 107–114.
16. Spyer KM. Neural mechanisms involved in cardiovascular control during affective behavior. *Trends Neurosci*. 1989; 12: 506–513.
17. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord*. 2000; 61: 201–216.
18. Saul JP. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News Physiol Sci*. 1990; 5: 32–37.
19. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res*. 1970; 4: 160–167.
20. Levy MN. Autonomic interactions in cardiac control. *Ann N Y Acad Sci*. 1990; 601: 209–221.
21. Damasio AR. Emotion in the perspective of an integrated nervous system. *Brain Res Rev*. 1998; 26: 83–86.
22. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. *Brain*. 1995; 118: 279–306.
23. Friedman BH, Thayer JF. Anxiety and autonomic flexibility: A cardiovascular approach. *Biol Psychol*. 1998a; 49: 303–323.
24. Friedman BH, Thayer JF. Autonomic balance revisited: Panic anxiety and heart rate variability. *J Psychosom Res*. 1998b; 44: 133–151.
25. Thayer JF, Friedman BH. The heart of anxiety: A dynamical systems approach. In: Vingerhoets A, ed. *The (Non) Expression of Emotions in Health and Disease*. Amsterdam: Springer; 1997.
26. Uijtdehagge SBH, Thayer JF. Accentuated antagonism in the control of human heart rate. *Clin Auton Res*. 2000; 10: 107–110.
27. Balaban CD, Thayer JF. Neurological bases for balance-anxiety links. *J Anxiety Disord*. 2001; 15: 53–79.
28. Barbas H, Saha S, Rempel-Clower N, Ghashghaei T. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci*. 2003; 4: 25–36.
29. Barbas H, Zikopoulos B. The prefrontal cortex and flexible behavior. *Neurosci*. 2007; 13: 532–545.
30. Grace AA, Rosenkranz JA. Regulation of conditioned responses of basolateral amygdala neurons. *Physiol Behav* . 2002; 77: 489–493.
31. Rempel-Clower NL. Role of orbitofrontal cortex connections in emotion. *Ann N Y Acad Sci*. 2007; 1121: 72–86.
32. Resstel LBM, Correa FMA. Involvement of the medial prefrontal cortex in central cardiovascular modulation in the rat. *Autonomic Neuroscience: Basic and Clinical*. 2006; 126–127: 130–138.
33. Saha S. Role of the central nucleus of the amygdala in the control of blood pressure: Descending pathways to medullary cardiovascular nuclei. *Clin Exp Pharmacol Physiol*. 2005; 32: 450–456.

34. Saha S, Batten TFC, Henderson ZA. GABAergic projection from the central nucleus of the amygdala to the nucleus of the solitary tract: A combined anterograde tracing and electron microscopic immunohistochemical study. *Neuroscience*. 2000; 99: 613–626.
35. Shekhar A, Sajdyk TJ, Gehlert DR, Rainnie DG. The amygdala, panic disorder, and cardiovascular responses. *Ann N Y Acad Sci*. 2003; 985: 308–325.
36. Spyer KM. Central nervous mechanisms contributing to cardiovascular control. *J Physiol*. 1994; 474: 1–19.
37. Wong SW, Masse N, Kimmerly DS, Menon RS, Shoemaker JK. Ventral medial prefrontal cortex and cardiovagal control in conscious humans. *Neuroimage*. 2007; 35: 698–708.
38. Gianaros PJ. Brain–body pathways to cardiovascular disease risk. Herbert Weiner Early Career Award Lecture, 66th Annual Meeting of the American Psychosomatic Society, Baltimore, MD, March 2008.
39. Ahern GL, Sollers JJ, Lane RD, et al. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital (ISA) test. *Epilepsia*. 2001; 42: 912–921.
40. Lane RD, Reiman EM, Ahern GL, Thayer A. Activity in medial prefrontal Cortex correlates with vagal component of heart rate variability during emotion. *Brain Cogn*. 2001; 47: 97–100.
41. Lane RD, Weidenbacher H, Fort CL, Thayer JF, Allen JJB. Subgenual anterior cingulate (BA25) activity covaries with changes in cardiac vagal tone during affective set shifting in healthy adults. *Psychosom Med*. 2008; 70: A-42.
42. Lane RD, McRae K, Reiman EM, Chen K, Ahern GL, Thayer JF. Neural correlates of heart rate variability during emotion. *Neuroimage*. 2009; 44: 213–222.
43. Nugent AC, Bain EE, Thayer JF. Drevets WC Anatomical correlates of autonomic control during a motor task. *Psychosom Med*. 2007; 69: A-74.
44. Nugent AC, Bain EE, Sollers JJ, Thayer JF, Drevets WC. Alterations in neural correlates of autonomic control in females with major depressive disorder. *Psychosom Med*. 2008; 70: A-99.
45. Gianaros PJ, Van Der Veen FM, Jennings JR. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology*. 2004; 41: 521–530.
46. Arnsten AFT, Goldman-Rakic PS. Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. *Arch Gen Psychiatry*. 1998; 55: 362–368.
47. Engle RW, Conway ARA, Tuholski SW, Shisler RJ. A resource account of inhibition. *Psychol Sci*. 1995; 6: 122–125.
48. James W. In: Gazzaniga MS, ed. *Conversations in the Cognitive Neurosciences*. Cambridge, MA: MIT Press; 1997.
49. McGeer PL, Eccles JC, McGeer EG. *Molecular neurobiology of the mammalian brain*. New York: Plenum Press; 1978.
50. Thayer JF, Lane RD. The importance of inhibition in dynamical systems models of emotion and neurobiology. *Brain Behav Sci*. 2005; 28: 218–219.
51. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci*. 2004; 8: 170–177.
52. Chikazoe J, Konishi S, Asari T, Jimura K, Miyashita Y. Activation of right inferior frontal gyrus during response inhibition across response modalities. *J Cogn Neurosci*. 2007; 19: 69–80.
53. Kalisch R, Wiech K, Critchley HD, et al. Anxiety reduction through detachment: Subjective, physiological, and neural effects. *J Cogn Neurosci*. 2005; 17: 874–883.
54. Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proc Natl Acad Sci*. 1999; 96: 8301–8306.
55. Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*. 1999; 122: 981–991.
56. Chambers CD, Bellgrove MA, Stokes MG, et al. Executive “brake failure” following deactivation of human frontal lobe. *J Cogn Neurosci*. 2006; 18: 444–455.
57. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM. Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol Sci*. 2007; 18: 421–428.
58. Craig AD. Forebrain emotional asymmetry: A neuroanatomical basis? *Trends Cogn Sci*. 2005; 19: 566–571.
59. Gevins A, Smith ME, McEvoy LK, Leong H, Le J. Electroencephalographic imaging of higher brain function. *Philos Trans R Soc Lond B*. 1999; 354: 1125–1134.
60. Thayer JF. On the importance of inhibition: Central and peripheral manifestations of nonlinear inhibitory processes in neural systems. *Dose Response*. 2006; 4: 2–21. (formerly Nonlinearity in Biology, Toxicology, and Medicine).
61. Baddeley AD, Della Sala S. Working memory and executive control. *Philos Trans R Soc Lond*. 1996; B351: 1397–1404.
62. Garavan H, Ross TJ, Li S-J, Stein EA. A parametric manipulation of central executive functioning. *Cereb Cortex*. 2000; 10: 585–592.
63. Davidson RJ. The functional neuroanatomy of affective style. In: Lane RD, Nadel L, eds. *Cognitive neuroscience of emotion*. New York: Oxford University Press; 2000:106–128.
64. Baddeley AD, Hitch G. Working memory. In: Bower GA, ed. *The psychology of learning and motivation, Vol. 8*. New York: Academic Press; 1974:47–89.
65. Shimamura AP. The role of the prefrontal cortex in dynamic filtering. *Psychophysiology*. 2000; 28: 207–218.
66. Baker DB, Taylor CJ, Levy C. Continuous performance test: a comparison of modalities. *J Clin Psychol*. 1995; 51: 548–551.
67. Warm JS. Vigilance and target detection. In: Huey BM, Wickens CD, eds. *Workload transition: Implications for individual and team performance*. Washington, DC: National Academy Press References; 1993.
68. Parasuraman R, Warm JS, Dember W. Vigilance: Taxonomy and development. In: Mark LS, Warm JS, Huston RL, eds. *Ergonomics and human factors: Recent research*. New York: Springer-Verlag; 1987:11–32.
69. Logie RH, Zucco GM, Baddeley AD. Interference with visual short-term memory. *Acta Psychol*. 1990; 75: 55–74.
70. Conway ARA, Engle RW. Individual differences in working memory capacity: More evidence for a general capacity theory. *Memory*. 1996; 4: 577–590.
71. Cowan N. Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information processing system. *Psychol Bull*. 1988; 104: 163–191.
72. Cowan N. Menchanisms of verbal short-term memory. *Curr Dir Psychol Sci*. 1994; 3: 185–189.
73. Posner MI, Raichle MI. *Images of Mind*. New York: Scientific American Library; 1999.
74. Richards JE. Infant visual sustained attention and respiratory sinus arrhythmia. *Child Dev*. 1987; 58: 488–496.
75. Suess PE, Porges SW, Plude DJ. Cardiac vagal tone and sustained attention. In school-aged children. *Psychophysiology*. 1994; 31: 17–22.
76. Li Z, Snieder H, Su S, Ding X, Thayer JF, Trieber FA, Wang X. A longitudinal study in youth of heart rate variability at rest and in response to stress. *Int J Psychophysiol*. 2009 (in press)
77. Neumann SA, Lawrence EC, Jennings JR, Ferrell RE, Manuck SB. Heart rate variability is associated with polymorphic

variation in the choline transporter gene. *Psychosom Med*. 2005; 67: 168–171.
78. Snieder H, van Doornen LJP, Boomsma D, Thayer JF. Sex differences and heritability of two indices of heart rate dynamics: A twin study. *Twin Res Human Genet*. 2007; 10: 364–372.
79. Wang X, Thayer JF, Treiber F, Snieder H. Ethnic differences and heritability of heart rate variability in African- and European American youth. *Am J Cardiol*. 2005; 96: 1166–1172.
80. Thayer JF, Merritt MM, Sollers JJ 3rd, et al. Effect of angiotensin-converting enzyme insertion/deletion polymorphism DD genotype on high-frequency heart rate variability in African Americans. *Am J Cardiol*. 2003; 92: 1487–1490.
81. Gard PR. The role of angiotensin II in cognition and behaviour. *Eur J Pharmacol*. 2002; 43: 1–14.
82. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: Further elaboration of a model of Neurovisceral Integration. *Neurosci Biobehav Rev*. 2009; 33: 81–88.
83. Melzig CA, Weike AI, Hamm AO, Thayer JF. Individual differences in fear-potentiated startle as a function of resting heart rate variability: Implications for panic disorder. *Int J Psychophysiol*. 2009; 71: 109–117.
84. Hansen AL, Johnsen BH, Thayer JF. Vagal influence in the regulation of attention and working memory. *Int J Psychophysiol*. 2003; 48: 263–274.
85. Hugdahl K, Thomsen T, Landrø NI, et al. Separating mental arithmetic from working memory: A fMRI-study. *NeuroImage*. 2000; 11: 384.
86. Hansen AL, Johnsen BH, Thayer JF. Relationship between heart rate variability and cognitive function during threat of shock. *Anxiety Stress Coping*. 2009; 22: 77–89.
87. Frankenhaeuser M, Nordhenden B, Myrsten A-L, Post B. Psychophysiological reactions to understimulation and overstimulation. *Acta Psychol*. 1971; 35: 298–308.
88. Broadbent DE. *Decision and stress*. London: Academic Press; 1971.
89. Foote SL, Bloom FE, Aston-Jones G. Nucleus locus ceruleus: New evidence of anatomical and physiological specificity. *Physiol Rev*. 1983; 63: 845–914.
90. Johnsen BH, Hansen AL, Sollers JJ 3rd, Murison R, Thayer JF. Heart rate variability is inversely related to cortisol reactivity during cognitive stress. *Psychosom Med*. 2002; 64: 289.
91. Sandrone G, Mortara A, Torzillo D, La Rovere ML, Malliani A, Lombardi F. Effects of Beta-blockers (atenolol or metropolol) on heart rate variability after acute myodardional infarction. *Am J Cardiol*. 1994; 74: 340–345.
92. Stein PK, Kleiger RE. Insights from the study of heart rate variability. *Annu Rev Med*. 1999; 50: 249–261.
93. Stein PK, Rottman JN, Kleiger RE, Ehsanin AA. Exercise training increases heart rate variability in normal older adults. *J Am Coll Cardiol*. 1996; 27: 146A.
94. Hansen AL, Johnsen BH, Sollers JJ, Stenvik K, Thayer JF. Heart rate variability and it's relation to prefrontal cognitive function: The effects of training and detraining. *Eur J Appl Physiol*. 2004; 93: 263–272.
95. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: Exercise effects on brain and cognition. *Nat Rev Neurosci*. 2008; 9: 58–65.
96. Endsley, M.R. (1999). Situation awareness and human error: Designing to support human performance. *In Proceedings of the high consequence system surety conference*, Albuquerque, NM.
97. Klein G. Analysis of situation awareness from critical incident reports. In: Endsley MR, Garland DJ, eds. *Situation awareness and measurement*. Mahwah, NJ: Lawrence Erlbaum Associates; 2000.
98. Matthews MD, Strater LD, Endsley MR. Situation awareness requirements for infantry platoon leaders. *Mil Psychol*. 2004; 16(3): 149–161.
99. Endsley MR. *Design and evaluation for situation awareness enhancement. In proceedings of the human factors society 32ned annual meeting*. Santa Monica, CA: Human Factors Society; 1988:97–101.
100. Endsley, M.R. & Garland, D. J. (2000). Pilot situation awareness training in general aviation. *In proceedings of the triennial congress of the international ergonomics association and the 44td annual meeting of the human factors and ergonomics society*.
101. Svensson EA, Wilson GF. Psychological and psychophysiological models of pilot performance for systems development and mission evaluation. *Int J Aviat Psychol*. 2002; 12(1): 95–110.
102. Garland DJ, Wise JA, Hopkin VD. *Handbook of Aviation Human Factors*. Mahwah, NJ: Lawrence Erlbaum Associates; 1999.
103. Shebilske WL, Goettl BP, Garland DJ. Situation awareness, automaticity, and training. In: Endsley MR, Garland DJ, eds. *Situation Awareness and Measurement*. Mahwah, NJ: Lawrence Erlbaum Associates; 2000.
104. Saus ER, Johnsen BH, Eid J, Riisem PK, Andersen R, Thayer J. The effect of brief situational awareness training in a police shooting simulator: An experimental study. *Mil Psychol*. 2006; 18: 3–21.
105. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry*. 1996; 39: 255–266.
106. Verkuil B, Brosschot JF, Borkovec TD, Thayer JF. Acute autonomic effects of experimental worry and cognitive problem solving: Why worry about worry? *Int J Clin Health Psychol* 2009 (in press).
107. Saus ER, Johnsen BH, Eid J, Thayer J. Personality factors predicting situational awareness in a navigation simulator. 2006
108. Johnsen BH, Thayer JF, Laberg JC, et al. Physiological and attentional characteristics of patients with dental anxiety. *J Anxiety Disord*. 2003; 40: 1–13.
109. Hansen AL, Johnsen BH, Thornton D, Waage L, Thayer JF. Facets on psychopathy checklist—Revised predicts heart rate variability and cognitive function. *J Pers Disord*. 2007; 21: 565–579.
110. Fowles DC. Electrodermal hyporeactivity and antisocial behavior: does anxiety mediate the relationship? *J Affect Disord*. 2000; 61: 177–189.
111. Morgan AB, Lilienfeld SO. A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. *Clin Psychol Rev*. 2000; 20: 113–136.
112. Gorenstein EE. Frontal lobe functions on psychopaths. *J Abnorm Psychol*. 1982; 91: 368–379.
113. Hare RD. Performance of psychopaths on cognitive tasks related to frontal lobe function. *J Abnorm Psychol*. 1984; 93: 133–140.