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ON THE IMPORTANCE OF INHIBITION: CENTRAL AND PERIPHERAL MANIFESTATIONS OF NONLINEAR INHIBITORY PROCESSES IN NEURAL SYSTEMS

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□ Inhibitory processes provide for the sculpting of neural action at all levels of the neuraxis. Importantly, it appears that this inhibitory function may be decidedly nonlinear in nature such that a little inhibition goes a long way in guiding the behavior of neural systems. The neural control of the heart is used as a model system to illustrate the nature of this nonlinear inhibitory control. Similar inhibitory processes function in the prefrontal cortex, in the amygdala, and between the prefrontal cortex and the amygdala in the service of organism flexibility, adaptability, and health. It is suggested that a dynamical systems perspective of neural regulation involving nonlinear inhibitory processes may be a useful framework within which to investigate the complex behavior associated with health and disease.

INTRODUCTION

Inhibitory processes provide for the sculpting of neural action at all levels of the neuraxis. It appears that this inhibitory function may be decidedly nonlinear in nature such that a little inhibition goes a long way in guiding the behavior of neural systems. In the present paper I will try to provide an overview of the evidence for the importance of nonlinear inhibitory processes in neural systems. I will use the neural control of the heart as a model system to illustrate the nature of this nonlinear inhibitory control. I will then show that similar inhibitory processes function in the prefrontal cortex, in the amygdala, and between the prefrontal cortex and the amygdala in the service of organism flexibility, adaptability, and health. These structures were not chosen at random but were chosen because of their well recognized role in guiding the behavior of higher organisms. As such the illustration of the importance of nonlinear inhibitory processes in these neural systems may have great significance for the further understanding of health and disease. In addition it may provide a unifying framework within to view the complexity of biological systems and the diversity of extant data, as well as lead to novel testable hypotheses.

NEURAL CONTROL OF HEART RATE

Heart rate (HR) is under tonic inhibitory control via the vagus nerve. This fact has been known for nearly one hundred years but is as yet

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underappreciated in medicine and physiology. Heart rate is determined by intrinsic cardiac mechanisms and the joint activity of the sympathetic nerve and the parasympathetic nerve (vagus) at the sinoatrial node of the heart. An increase in sympathetic activity results in increased heart rate whereas increased vagal activity results in decreased heart rate. In healthy systems both branches of the autonomic nervous system are tonically active. However, their opposing effects are not algebraically additive with complex interactions being demonstrated in the sympathetic and parasympathetic determination of heart rate in animals.

Levy and Zieske (1969) published a classic paper on the neural control of the heart and the importance of inhibitory control mechanisms. Importantly, they also demonstrated the decidedly nonlinear nature of this control. In their classic experiment they used an open chest dog preparation to investigate the effects of direct systematic electrical stimulation of the stellate ganglia and the vagus nerve on cardiac chronotropy. Briefly, these researchers showed that direct maximal electrical stimulation of the stellate ganglia produced a heart rate acceleration of approximately 70 beats per minute. Similarly direct maximal electrical stimulation of the vagus nerve lead to a heart rate deceleration of approximately 70 beats per minute. The simultaneous maximal stimulation of the stellate ganglia and the vagus nerve lead to a heart rate deceleration of approximately 70 beats per minute--a net decrease of approximately 140 beats per minute. Thus the effect of a given level of vagal stimulation varied depending on the context within which it occurred such that the effect was larger the greater the level of background sympathetic stimulation. This vagal predominancy of heart rate control has been termed accentuated antagonism. In addition, they showed that the effect of vagal stimulation was nonlinear over the range of vagal stimulation they employed. This was evidenced by a significant quadratic term for the vagal stimulation in their regression equation. No such nonlinearity was found for the sympathetic stimulation.

Accentuated antagonism has been demonstrated in adult humans using pharmacological manipulations (Fukudo et al, 1992). Miyazoe, Harada, Yamasaki, and Tsuji (1998) have also demonstrated accentuated antagonism in children. This group showed that the increase in heart period in response to cold face immersion was significantly greater after a bout of exercise (73%) than before the exercise (54%). Our group has recently demonstrated accentuated antagonism in humans using non-invasive and non-pharmacological techniques (Uijtdehaage & Thayer, 2001). Briefly, we used respiratory sinus arrhythmia (RSA) as a non-invasive parasympathetic chronotropic index and left ventricular ejection time (LVET) as a non-invasive sympathetic chronotropic index to examine the effects of a broad range of behavioral manipulations on heart rate in healthy humans. Each subject experienced singly and in various com-

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binations, sixty tasks including graded hand grip, reaction time shock avoidance, graded forehead cold pressor, forearm cold pressor, and relaxation all while performing paced breathing at 15 breaths per minute. The experimental design was a stimulation or perturbation paradigm and the tasks were chosen such that sufficient heart rate changes across tasks would be observed, presumably due to different combinations of parasympathetic and sympathetic neural activity. The large number of data points per subject enabled us to conduct all analyses on the data of each subject separately as well as on group aggregated data.

Linear regression analysis was used to fit the data of each subject as well as the group aggregated data to an equation of the form:

$$\text{HR} = b_0 + b_1 \text{LVET} + b_2 \text{RSA} + b_3 \text{LVET} \times \text{RSA}$$

This model fit the data quite well for each subject and for the group aggregated data. All of the regression coefficients including the interaction term were statistically significant. The changes in heart rate produced by various combinations of sympathetic activity and parasympathetic activity for one subject are shown in Figure 1.*

The response surface is derived from the regression equation. The upper left edge shows that increases in sympathetic tone (smaller LVET values) have a large positive chronotropic effect at low levels of vagal activation. The lower right edge shows that this same increase in sympathetic tone produces a small positive chronotropic response at high levels of vagal activation. The upper right edge shows the large negative chronotropic effect that increases in vagal activity have at the highest level of background sympathetic activity.

The results of this experiment confirm the importance of accentuated antagonism on cardiac chronotropic control in healthy intact humans. Furthermore, they point to the context dependent effect of neural action on peripheral end organs. Importantly, they illustrate that these effects are achieved by nonlinear inhibitory processes where a little inhibition can have large effects on system functioning.

In summary, accentuated antagonism has been demonstrated in many species of animals including humans, can be found using both heart rate and heart period as well as both pharmacological and behavioral manipulations, and is thought to be due to both pre-junctional and post-junctional neurotransmitter effects (Levy, 1997).

The inhibitory nature of cardiac control can also be exhibited at another level of analysis. In the next section, I describe a set of neural

*It should be noted that we also found a small but significant nonlinear term for the vagal influence in the data for most participants (cf, Levy & Zieske, 1969). However for ease of presentation it was not included in the equation used to derive the figure.

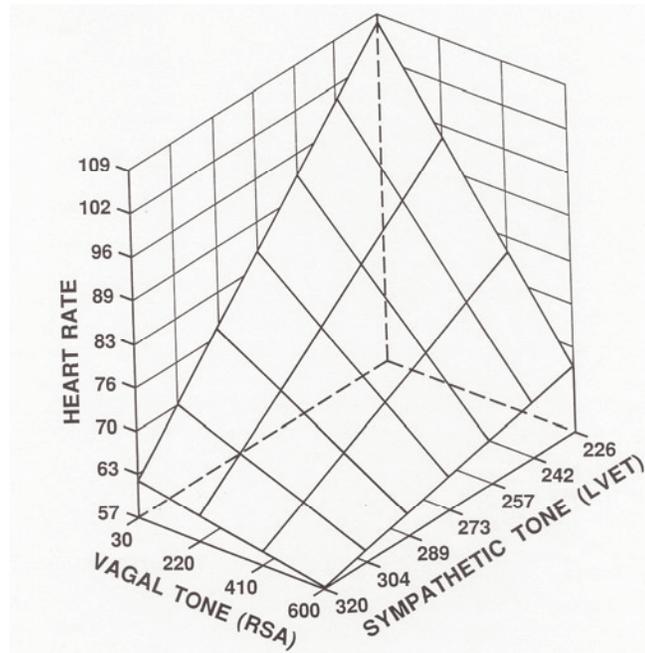
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FIGURE 1. Example of the interaction between sympathetic and parasympathetic control of heart rate in one individual subject showing the changes in heart rate produced by various combinations of sympathetic and parasympathetic tone. The response surface is derived from the fitted regression equation based on 63 observations from one subject: $HR = 48.276 - 0.982 (LVET) - 0.626 (RSA) + 5.947 (LVET \times RSA)$.

structures that serve to link the prefrontal cortex with heart rate variability (HRV). Diminished tonic HRV and the associated reduction of vagally mediated cardiovascular control has been associated with a variety of pathological states and dispositions including anxiety, depression, post-traumatic stress disorder, inflammation, diabetes, sudden cardiac death, coronary artery occlusion, and hypertension (see Friedman & Thayer, 1998; Malliani, Pagani, Lombardi, & Cerutti, 1991; Stein, Bosner, Kleiger, & Conger, 1994; Stein & Kleiger, 1999; and Thayer & Friedman, 2004 for reviews). As a measure of vagally mediated cardiovascular activity, HRV is an index of a negative feedback mechanism that is important for the self-regulation of behavior. Vagal activity has negative cardiac chronotropic and dromotropic effects that serve to produce efficient cardiovascular functioning through the restraint of cardiac rate and electrical conduction speed. This restraint or inhibition is necessary for cardiac stability, responsiveness, and flexibility (Levy, 1990; Verrier, 1987). A network of reciprocally interconnected neural structures, termed the central autonomic network, allows the prefrontal cortex to exert an inhibitory influence on subcortical structures associated with defensive behavior and thus allow the organism to flexibly regulate its behavior in response to changing environmental demands.

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THE CENTRAL AUTONOMIC NETWORK

A number of researchers have identified functional units within the central nervous system (CNS) that appear to support goal-directed behavior and adaptability. One such functional unit 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 and adaptability (Benarroch, 1993). *Structurally*, the CAN includes the anterior cingulate, insular, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal 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 structures are reciprocally interconnected such that information flows in both directions—top-down and bottom-up, so to speak. The primary output of the CAN is mediated through the preganglionic sympathetic and parasympathetic neurons. Importantly, these neurons innervate the heart via the stellate ganglia and the vagus nerve. The interplay of these inputs to the sino-atrial node of the heart is the source of the complex variability that characterizes the healthy heart rate time series (Saul, 1990). Thus, the output of the CAN is directly linked to heart rate variability (HRV). In addition, vagal influences dominate cardiac chronotropic control, as illustrated earlier (Uijtdehaage & Thayer, 2001). In addition, sensory information from the peripheral end organs such as the heart are fed back to the CAN, one important example of which is cardiac pain (Foreman, 1999). As such, HRV is an index of central-peripheral neural feedback and CNS-autonomic nervous system (ANS) integration.

The CAN receives and integrates visceral, humoral, and environmental information and coordinates autonomic, endocrine, and behavioral responses to environmental challenges. Importantly, the CAN is under tonic inhibitory control. This is achieved by γ -aminobutyric acid (GABA) interneurons within the NTS. GABA is the main inhibitory neurotransmitter within the CNS. It is known that disruption of this inhibitory pathway may lead to such things as hypertension and sinus tachycardia, and represents a dis-inhibition of sympathoexcitatory circuits within the CAN (Benarroch, 1993, 1997; Masterman & Cummings, 1997; Spyer, 1989). The central neural mechanisms of inhibition will be detailed later.

Other functional units within the CNS subserving executive, social, affective, cognitive, and motivated behavior in humans and animals have also been identified (Damasio, 1998; Devinsky, Morrell, & Vogt, 1995; Masterman & Cummings, 1997; Posner & Peterson, 1990; Spyer, 1989). One such functional unit has been termed the anterior executive region (AER; Devinsky, et. al., 1995). Functionally, the AER and its projections

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“assesses the motivational content of internal and external stimuli and regulates context-dependent behaviors.” (Devinsky et al., 1995, p.279). The AER and its projections have been termed the “rostral limbic system” and structurally includes the anterior, insular, and orbitofrontal cortices, the amygdala, the periaqueductal gray, the ventral striatum, and autonomic brainstem motor nuclei. Damasio (1998) has identified another such functional unit as the neural substrate for emotions. The structural overlap of these circuits is quite substantial (see Thayer & Lane, 2000, 2002). Disruption of these circuits has been associated with a wide variety of perseverative behavior including a lack of habituation and inappropriate affect.

I have proposed elsewhere that the CAN, the AER and its projections, the “emotion circuit” (Damasio, 1998), and related systems (Masterman & Cummings, 1997; Mayberg et al., 1999; Spyer, 1989) are one and the same core functional network identified by different researchers from differing orientations. This network of CNS structures is associated with the processes of response organization and selection, and serves to modulate psychophysiological resources in cognition and emotion primarily via inhibition (Friedman & Thayer, 1998; Thayer & Friedman, 1997). Additional structures are flexibly recruited into this network in the service of specific behavioral adaptations. This multistructure neural network allows for maximal organism flexibility in adapting to rapidly changing environmental demands, facilitated by its relative sparse interconnectedness (Brunel, 2000). This point will be elaborated later. For now it is important to note that when this network is either completely uncoupled or rigidly coupled the organism is less able to dynamically assemble the appropriate neural support structures to meet a particular demand and is thus less adaptive.

AN INHIBITORY CORTICAL-SUBCORTICAL CIRCUIT

Skinner (1985) has 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, Sollers, Lane, Labinar, Herring, Weinand, Hutzler, & Thayer, 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

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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. It has similarly been reported that cortical inhibitory networks necessary for such things as working memory are right lateralized (Garavan, Ross, & Stein, 1999).

The effects of the ISA test are largely restricted to anterior neural structures, which include the orbital and medial prefrontal cortices (Ahern et al., 1994; Hong et al., 2000). As has been discussed above, these areas have been broadly associated with biopsychological functions such as affective, cognitive, and autonomic regulation (Thayer & Lane, 2000), and belong to the central autonomic network. In addition, these structures are linked with inhibitory control of behavior in general (Roberts & Wallis, 2000) and cardiac behavior in particular (Verberne & Owens, 1998), with direct and indirect pathways connecting these areas with parasympathetic (vagal) motor output regions (Ter Horst, 1999).

A recent neuroimaging study to investigate the neural origins of HRV during emotional arousal has provided additional evidence for disinhibition related to decreased activity in the prefrontal cortex. Lane, Reiman, Ahern, & 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. Correlations between HF-HRV and rCBF attributable to emotion (emotion minus neutral scans) as well as correlations between HF-HRV and rCBF during the emotion scans and the neutral scans separately were examined. During the emotion conditions HF-HRV correlated with rCBF in the medial prefrontal cortex and in the region of the left orbitofrontal and anterior insular cortices. During the neutral conditions HF-HRV correlated with blood flow in the right inferior frontal cortex and the inferior pontine tegmentum (brainstem). 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

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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).

It has been suggested that during emotional stress the prefrontal cortex is taken “off-line” allowing automatic and pre-potent processes to regulate behavior (Arnsten & Goldman-Rakic, 1998). These authors further suggest that this selective inactivation of the prefrontal cortex may have survival value by allowing automatic and pre-potent behaviors associated with subcortical neural structures such as the amygdala to rapidly organize responses without interference from the more deliberative and consciously guided processes associated with the prefrontal cortex. Clearly, however, in modern society where inhibition, delayed responding, and mental flexibility are necessary for successful organism adaptability and self-regulation, prolonged inactivation of the prefrontal cortex by stress will lead to hypervigilance, a defensive behavioral disposition, and perseverative behavior.

INHIBITORY PROCESSES IN THE PREFRONTAL CORTEX

The presence of a large prefrontal cortex is one of the defining characteristics of higher mammals and is particularly developed in humans. This set of neural structures allows for extensive processing and elaboration of sensory information in the service of goal-directed behavior. The ability to inhibit pre-potent and reflexive responses provides the organism with the ability to delay immediate responding to achieve long term goals associated with both individual and species survival. As such the healthy functioning of the prefrontal cortex is critical for flexibility, adaptability, and survival.

The ability to maintain information ‘online’ and to manipulate that information provides a mechanism by which an organism can extend their temporal horizon to include recall of past associations and the prediction of future outcomes. This expansion of the organism’s temporal world has been associated with the ability to link disparate pieces of information over time and to be the basis of learning and memory. As such the prefrontal cortex serves to guide the behavior of an organism through the selection of appropriate responses from a more or less broad behavioral repertoire of response options. Importantly, the prefrontal cortex serves to inhibit distractions, perseverative behavior, and inappropriate responding thus allowing the organism flexibility to respond efficiently to ever changing environmental challenges. In sum, the prefrontal cortex provides the top-down context in which subsequent sensory information is processed thus modulating the bottom-up sensory inputs (Friston, 2002).

Recent work in cognitive neuroscience supports the view of humans as self-organizing nonlinear dynamical systems (NDS) (van Gelder, 1998).

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In a review on the neural basis of decision making, Schall (2001) noted that these processes are often implemented by a surprisingly small number of neurons in discrete parts of the brain. These sparsely interconnected neural networks, which are characteristic of dynamical systems, have been shown to be associated with flexible systems with large associative memory capacity and thus multiple stable states or attractors (Brunel, 2000). Such networks, composed of excitatory and inhibitory neurons, are in fact critically dependent upon inhibitory neurons for their ability to exhibit phase transitions—that is, to shift from one behavioral state to another. Compte et al. (2000), in a model linking working memory to prefrontal activity, found that modulation by recurrent synapses is essential for robust memory storage and resistance to distractors. In healthy systems the interaction of these synapses is dominated by inhibition.

Long-term potentiation (LTP) is the leading model of synaptic changes associated with learning and memory (Malenka & Nicoll, 1999). LTP represents a sensitization of neurons such that after firing, the probability of their subsequent firing is enhanced due to a lower threshold for reactivation. These activity-dependent changes in synaptic efficiency can cause increases in synaptic strength that can last for days. LTP is common in excitatory neurons, but is more difficult to induce in inhibitory neurons in part because of differences in calcium channel kinetics. Furthermore, inhibitory neurons are faster than excitatory neurons due to differences in synaptic kinetics (Miles, 2000). It has been hypothesized that these fast inhibitory neurons gate information flow in excitatory pathways via negative feedback and are necessary for the generation of brain rhythms. Though it is true that inhibitory neurons can express receptors for specific inhibitory neurotransmitters such as GABA and serotonin that link cortical and subcortical nuclei, such neurons are diverse and neurochemically complex. Notably, different behavioral states may be associated with the reconfiguration of cortical networks via the modulation of specific groups of inhibitory neurons. Thus, inhibition at the cellular level appears important for the flexible expression of behavioral states.

Constantinidis, Williams, and Goldman-Rakic (2002) have recently detailed the role of inhibition in the temporal flow of information in the prefrontal cortex. Using simultaneous single cell recordings in monkeys they demonstrated inhibitory interactions between neurons active at different time points during the course of a complex working memory task. They note that the influence of inhibition was particularly evident at transition points in the action sequence thus supporting the idea that inhibitory neurons are critical for behavioral state changes. These findings suggest that a little inhibition at the right time can have a large influence on the behavior of the organism highlighting the nonlinear nature of the inhibitory control.

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These researchers also noted the importance of GABA for the efficient functioning of inhibitory processes. They note that previous research has shown that GABA is crucial for the shaping of the receptive fields of individual neurons. Specifically, iontophoretic application of GABA antagonists in the prefrontal cortex has been shown to increase neural discharge rates and is frequently observed to broaden the receptive fields leading to less differentiated neural action.

Similarly, animal and human work often converge to suggest that anxiety and its associated perseverative activity are related to decreased GABA receptor binding in the prefrontal cortex. For example, in a murine model of anxiety, decreased GABA_A-receptor clustering was associated with harm avoidance behavior and an explicit memory bias for threat cues (Crestani et al., 1999). Mice with reduced GABA_A-receptor clustering showed enhanced reactivity to threat stimuli (an effect that was reversed by diazepam), a facilitation of trace conditioning in a fear conditioning paradigm, and a deficit in ambiguous cue discrimination. These findings are remarkably similar to the HR acceleration to and explicit memory bias for threat words, and failure to habituate to neutral words, found in generalized anxiety disorder patients in a conditioning paradigm (Friedman, Thayer, & Borkovec, 2000; Thayer et al., 2000).

Positron emission tomography (PET) has been used to examine benzodiazepine GABA_A-receptor kinetics in humans with and without panic disorder (Malizia et al., 1998). Compared to non-anxious controls, panic disorder patients showed a global decrease in benzodiazepine site binding, with the largest decreases in the orbitofrontal and insular cortices. Decreased blood flow in the right medial frontal cortex also has been reported in self-induced anxiety (Kimbrell et al., 1999). These cortical areas have been implicated in anxiety and are also associated with HRV (Lane, Reiman, Ahern, & Thayer, 2001). Similar altered orbitofrontal chemistry has been found in anxious humans (Grachev & Apkarian, 2000). Relative to low anxious subjects, high anxious subjects showed reduced levels of a number of orbitofrontal neurochemicals, including GABA. In addition it has recently been reported that low post trauma GABA levels in plasma predict future development of acute posttraumatic stress disorder (Vaiva et al., 2004).

Recent neuroimaging studies have also examined patterns of cerebral blood flow associated with anger and aggressive behavior. Using single photon emission computed tomography (SPECT), decreased prefrontal activity was found in forty psychiatric patients that exhibited aggressive behavior within the six-month period prior to scanning compared to psychiatric patients without a history of aggression (Amen, Stubblefield, Carmichael, & Thisted, 1996). In non-aggressive individuals, it is clear that anger inhibition is the most common response to provocation, mainly due to social norms (Brosschot & Thayer, 1998). Consistent with this

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notion, PET data showed lateral orbitofrontal cortex (LOFC) activation during imagery-driven anger in men (Dougherty, Shin, Alpert, Pitman, Orr, Lasko, Macklin, Fischman, & Rauch, 1999). These researchers noted that the LOFC and the associated ‘prefrontal’ circuit are considered pivotal to response inhibition and the mediation of social behavior. Therefore, the reported LOFC activation was hypothesized to represent inhibition of an aggressive response during the anger provocation. Similar right prefrontal activation during self-induced anger, as compared to self-induced anxiety, has been reported (Kimbrell et al., 1999). However, in this study both self-induced anxiety and self-induced anger were associated with decreased frontal activity relative to a neutral condition, suggesting that inhibition may pertain to emotional behavior in general. That is, when all emotional arousal is inhibited as in the neutral condition prefrontal activation would be greatest while the relatively more active emotion of anger would still require more prefrontal inhibition than the ostensibly less active emotion of anxiety. A similar effect was found in a recent experiment on thought suppression. The increase in prefrontal activation was greater in the ‘suppress all thoughts’ condition compared to the ‘suppress a single thought’ condition (Wyland, Kelley, Macrae, Gordon, & Heatherton, 2003).

Consistent with the above findings, the idea that the prefrontal cortex functions to modulate intense emotion responses has recently been given support in a review of neuroimaging studies of human emotion (Phan, Wager, Taylor, and Liberzon, 2004). They note that blood flow in the prefrontal cortex is inversely associated with blood flow in the amygdala. Thus they state that the prefrontal cortex might ‘serve as the “top-down” modulator of intense emotional responses, especially those generated by the amygdala.’ This is completely consistent with the thesis presented here. However an important caveat concerning neuroimaging studies needs to be mentioned (see below).

These negative emotional states such as anger and anxiety are often associated with stress. It has recently been demonstrated that chronic stress produces reduced prefrontal neural plasticity (Kuipers, Trentani, Den Boer, & Ter Horst, 2003). These researchers examined the effects of both acute and chronic stress induced by foot shock in rats. They report changes in prefrontal cortical signal transcription cascades that underlie neuronal plasticity. They suggest that decreased brain-derived neurotrophic factor (BDNF) may be involved. BDNF is critical for the coupling of activity-dependent changes in synaptic strength to lasting effects on synaptic function which is essential for maintaining cortical plasticity.

Recent computational models based on neuroimaging also suggest a critical role for inhibitory processes. Friston (2002) has provided a detailed analysis of distributed neural circuitry from the perspective of neuroimaging. He suggests that the evidence supports generative models

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and predictive coding over information theoretic models. There are many significant implications of this for the present discussion. Importantly, the generative models emphasize the role of inhibitory connections in the top-down context setting that allows for the appropriate processing of bottom-up inputs. Specifically, the predictive coding models require feedback from higher brain regions such as the prefrontal cortex to modulate inputs from lower input levels such as the amygdala. Efficient prefrontal (higher level) modulation needs neuronal plasticity and thus low stress states to function. Thus more stress tolerant systems will be more context sensitive and therefore more adaptive. From a NDS perspective this means they will be able to generate more stable states (attractors) with which to meet environmental challenges and have greater behavioral complexity. Our group has recently summarized a series of studies on affective, cognitive, and autonomic regulation showing that persons with higher levels of HRV (and thus greater prefrontal inhibitory control) are more stress tolerant and more adaptive in the face of diverse environmental challenges than persons with low HRV (Thayer & Friedman, 2004).

One way in which this context sensitivity might be instantiated is via respiratory sinus arrhythmia and is illustrated in Figure 2. The term respiratory sinus arrhythmia (RSA) has been used to describe the fact that during inhalation heart rate increases and during exhalation heart rate decreases. This is due to both mechanical and neural gating of the vagus nerve such that during inhalation vagal traffic is reduced causing heart

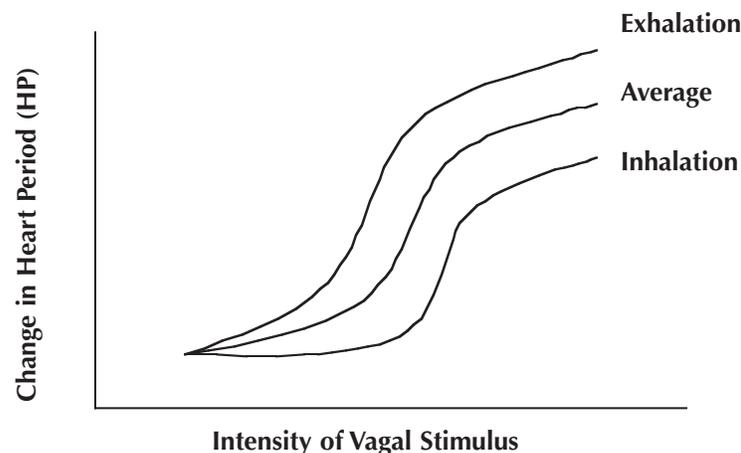


FIGURE 2. Hypothetical representation of the transfer function of vagal nerve activity to heart period change during inhalation and exhalation in response to a vagal input. Heart period is the inverse of heart rate so that larger numbers reflect slower heart rate. The response to a given vagal input will produce a greater heart period change (decrease in heart rate) at a lower intensity of stimulation during exhalation than during inhalation.

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rate to increase whereas during exhalation vagal traffic is enhanced causing heart rate to decrease. The sigmoidal functions displayed in Figure 2 represent the transfer functions of vagal nerve activity to heart period (the inverse of heart rate) change during exhalation (the top trace) and inhalation (the bottom trace) with the average represented by the middle trace. The differential effects of a given stimulus presented during different phases of the cardiac cycle, including those corresponding to inhalation and exhalation, are well known and have been termed cardiac cycle time effects (Jennings, van der Molen, & Somsen, 1998). The changing threshold represents a range of context modulation (the effective dynamic range) with greater dynamic range associated with more stable states and thus greater system complexity. A dynamic threshold allows for spontaneous context-sensitive learning (unsupervised learning).

Modulation of heart rate by respiration provides a dynamic threshold for autonomic influences (inputs) with greater modulation (higher HRV) being associated with superior context-sensitive learning and system complexity. The difference in heart rate between inhalation and exhalation over numerous respiratory cycles has been used to characterize the tonic vagal modulation of heart rate which is sometimes referred to as vagal tone. Lower tonic vagal modulation of heart rate is associated with lower RSA and lower vagally-mediated HRV. It is also associated with less dynamic range, less context sensitivity, fewer stable states, and less system complexity. This pattern of response is evident in organisms with low HRV and we have shown this to be true for many conditions associated with low HRV including male gender, various affective and anxiety disorders, stress, and pathophysiology such as hypertension (Friedman & Thayer, 1998; Rossy & Thayer, 1998; Thayer & Friedman, 2002; Thayer & Friedman, 2004). These effects are due to nonlinearities in the cardiac control system, a prime example of which is accentuated antagonism which is greater in organisms with greater HRV or vagal modulation (Fukudo et al., 1992). Consistent with these findings is the fact that enhanced vagal modulation induced by exercise is associated with a number of salubrious effects including increased levels of BDNF (Cotman & Berchtold, 2002) and that vagus nerve stimulation in humans, which has been used to treat both epilepsy and depression, has been associated with enhanced recognition memory (Clark et al, 1999).

In summary, it is evident that inhibitory processes function at numerous levels of cortical function to produce complex behavior and the ability to meet environmental challenges. Our group has also shown that this prefrontal cortical activity can be indexed by HRV with greater prefrontal activity and HRV associated with greater inhibition of subcortical threat circuits. One locus of subcortical threat circuits is the amygdala. I will next provide an overview of the evidence for inhibitory processes in amygdala function.

INHIBITORY PROCESSES IN THE AMYGDALA

The amygdala is often held to be the key limbic structure in emotional behavior. For example, electrical stimulation of the amygdala has been associated with a range of defensive behaviors including increased cortisol, heart rate, and blood pressure (see Davis & Whalen, 2001, for review). Brain imaging data show that both depression severity and dispositional negative affect are correlated with amygdala activity (Davidson, 2002; Drevets, 1999). Although there is evidence that the amygdala responds to both appetitive and aversive stimuli, recent conceptualizations suggest that vigilance regulation and the detection of biologically relevant stimuli is the basic function of the amygdala (Davis & Whalen, 2001). Prolonged amygdaloid activation can lead to excess threat awareness and may form the foundation of psychiatric disorders such as anxiety and depression. This overalert state also has been linked to decreased cardiac output and increased peripheral vascular resistance (Winters, McCabe, Green, & Schneiderman, 2000). Interestingly, this cardiovascular pattern is relatively more prevalent in African Americans and may be a factor in the increased levels of hypertension and related morbidity and mortality in this group (Anderson, McNeilly, & Myers, 1991; Brosschot & Thayer, 1998, 1999). Furthermore, variation in alpha-adrenergically mediated vascular tone may be associated with insulin resistance and thus provide a link to the increased diabetes risk found in African Americans (Brook & Julius, 2000).

Quirk and Gehlert (2003) have recently reviewed the animal evidence suggesting the importance of inhibition of the amygdala for healthy functioning. Evidence suggests a role for both prefrontal inhibition of amygdala function as well as intra-amygdaloid inhibition. These researchers noted that both aversive and appetitive conditioned responses are indelibly encoded via the amygdala. These conditioned associations are essential for survival. However the appropriate expression of these conditioned responses appears to require a high degree of inhibition of the amygdala. One source of this inhibition is from the context setting prefrontal cortex. Extensive reciprocal inhibitory connections exist between the prefrontal cortex and the amygdala. These authors note that the spontaneous firing rates of neurons in the lateral and central nuclei of the amygdala are among the lowest in the brain suggesting profound inhibition. Thus they conclude that overexpression of conditioned associations due to decreased inhibitory control of the amygdala may be responsible for pathological states such as anxiety and addiction. Consistent with our suggestion of the importance of HRV as an index of prefrontal inhibitory control we have reported decreased HRV in both anxiety disorders and addiction (Friedman & Thayer, 1998; Ingjaldsson, Laberg, & Thayer, 2003).

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An important role for GABA in amygdala inhibition has also been suggested (Quirk & Gehlert, 2003; Pare, Royer, Smith, & Lang, 2003). Daily priming of basolateral amygdala (BLA) neurons with subthreshold levels of the GABA antagonist bicuculline for five days lead to behavior similar to anxiety on the fifth dose including reduced social interaction, and increased heart rate and blood pressure. Excitatory BLA inputs to the central nucleus of the amygdala (CE) also appear to be under tonic inhibitory control via groups of GABAergic neurons that have been termed intercalated cell masses. Taken together, the animal evidence suggests that inhibitory mechanisms in the amygdala and between the amygdala and the prefrontal cortex are critical for the flexible, context dependent expression of emotional responses. As detailed below, our group has recently provided evidence for such context dependent modulation of the amygdala in humans.

Numerous studies in both animals and humans suggest that the presence of an intact amygdala is associated with larger magnitude startle and with emotion potentiated startle during an unpleasant foreground (Aggleton & Young, 2000; Angrilli, Mauri, Palomba, Flor, Birbaumer, Sartori, & di Paola, 1996). A related structure, the bed nucleus of the stria terminalis, has been implicated in the general startle sensitivity associated with anxiety in rats and negative affect in humans (Bradley & Lang, 2000). Recent neuroimaging data has also shown increased blood flow in the amygdala during affective startle modulation in humans (Pissiota et al, 2003). Relatedly, Davidson (2000) has reported that medial prefrontal cortex activity is inversely associated with activity of the amygdala and is involved in the modulation of the startle response.

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. Eyeblink strength to startle probes was recorded both during affective foregrounds and inter-trial intervals, and the relationships between resting HRV and startle magnitudes was examined. Resting HRV was found to be inversely related to both inter-trial interval and emotion-modulated startle magnitude. 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

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stimuli as if they were aversive and threatening, and also had a tendency to react to positive stimuli similarly. In addition, individuals with high HRV were able to best match their response to situational demands and thus respond most appropriately to the demands of the situation. The findings are consistent with our model that posits that prefrontal cortical activity modulates subcortical motivation circuits in the service of goal-directed behavior. Moreover, persons with low HRV showed evidence of hypervigilance and the activation of a defensive behavioral system in response to non-threatening stimuli. These results bear a striking similarity to the animal data reviewed earlier in this section.

The reported relationship between startle modulation and HRV provides further support for the notion that prefrontal activity is inversely related to structural functions associated with defensiveness, and thereby moderates interactions with the environment (Thayer & Lane, 2000). These results also further suggest that HRV can be used to index activity in this network of neural structures associated with self-regulation and flexible adaptivity.

A CAVEAT ABOUT BRAIN IMAGING OF INHIBITORY NEURAL PROCESSES

Put simply, the imaging of inhibitory neural processes is not straightforward. This is true for several reasons. One, whereas the neurometabolic coupling responsible for the excitatory neurotransmitter glutamate has been detailed and shown to be consistent with the commonly held notion that increased signal in neuroimaging studies is associated with increased neural activity this seems not to be true for the inhibitory neurotransmitter GABA (Chatton, Pellerin, & Magistretti, 2003); two, inhibitory neurons are 5-6 times less numerous than excitatory neurons; and three, combined with their more advantageous location near the soma of pyramidal cells inhibitory neurons appear to be less metabolically demanding than excitatory neurons (Waldvogel, van Gelderen, Muellbacher, Ziemann, Immisch, & Hallett, 2000). Thus, increased activity in inhibitory neurons is not associated with a concomitant increase in observed signal. The result is that inhibitory neural processes are more efficient than excitatory neural processes and as noted by Waldvogel and colleagues 'in order to be functionally relevant only a little inhibition is necessary'. This is consistent with the idea of accentuated antagonism in cardiac control detailed above. Thus there appears to be evidence for a type of 'neural accentuated antagonism' between inhibitory and excitatory neurons. One important consequence of this phenomenon is that the results of neuroimaging studies may not accurately portray the workings of inhibitory neural processes.

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SUMMARY AND CONCLUSIONS

In the present paper I have tried to provide a broad overview of the importance of both central and peripheral inhibitory processes for the efficient functioning of the organism. Using the neural control of the heart as an example I have shown that nonlinear inhibitory processes are essential for effective cardiac regulation. Importantly I have suggested that this cardiac regulation is part of a larger self-regulation system that is associated with a reciprocal inhibitory cortical-subcortical network involving the prefrontal cortex and the amygdala that is critical for the flexible adaptation to changing environmental demands. Detailed evidence was presented explicating the mechanisms of inhibition within the prefrontal cortex and within the amygdala as well as between the two neural structures. Finally, it was suggested that a type of ‘neural accentuated antagonism’ may exist such that in the brain as in the heart a little inhibition may go a long way. Again this is due to the lack of linearity between neural action and the effect on the behavior of the system. One extremely important consequence of this is that patterns of activation observed in neuroimaging studies may underestimate (or at best misrepresent) the activity of inhibitory neural processes.

In conclusion I suggest that a dynamical systems perspective of neural regulation involving nonlinear inhibitory processes may be a useful framework within which to investigate the complex behavior associated with health and disease. Future empirical, computational, and theoretical work will be needed to flesh out this model and to assess its utility for understanding the process by which organisms interact in a consistent manner with a constantly changing environment.

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