Scandinavian Journal of Psychology, 2002, 43, 123–130

Stop that! Inhibition, sensitization, and their neurovisceral concomitants

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Thayer, J. F. & Friedman, B. H. (2002). Stop that! Inhibition, sensitization, and their neurovisceral concomitants. *Scandinavian Journal of Psychology, 43*, 123–130.

There is increasing evidence that the behavior of living systems can be conceptualized as a self-organizing dynamical system. Moreover, evidence suggests that inhibitory processes give these systems the flexibility that is necessary for efficient functioning in the face of changing environmental demands. The process of sensitization can be conceived as a breakdown of inhibitory neural processes that can lead to maladaptive, perseverative behavior. In this paper we describe a model of inhibition and sensitization from a dynamical systems perspective. We show that inhibition is important for adaptive behavior across a number of levels of system functioning. Using our work on attention, emotion, and anxiety disorders we show the importance of both central – for example gamma-aminobutyric acid (GABA)-ergic – and peripheral – for example heart rate variability (HRV) – inhibitory processes and how they may be linked by a network of neural structures that guide the organism from one state of relative stability to another.

Key words: Sensitization, inhibition, heart rate variability, anxiety, emotion.

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Inhibition can be viewed as a sculpturing process in which diffuse excitation is chiseled away, leaving a more specific synaptic form to guide neuronal performance. This suppressing action of inhibition is evident at higher levels of the brain, in which substances that block synaptic inhibition can lead to uncontrolled neural excitation, eventuating in convulsions (McGeer, Eccles & McGeer, 1978, pp. 133–134). Indeed, the importance of inhibitory processes to adaptive functioning has been long recognized. The ability to inhibit reflexive and pre-potent responses in the service of longer-range goals is associated with a mature and healthy organism. In mammals, this ability is often associated with intact frontal lobes.

Somewhere between inhibition and convulsions lies sensitization, which has been defined as a change in synaptic efficiency as a function of extreme or repeated stimulation of a synapse or neural network (Eriksen, Olff, Murison & Ursin, 1999). Compte, Brunel, Goldman-Rakic and Wang (2000) 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 (Miller, 2000). Sensitization with subsequent habituation may be an important process in many different types of learning and appears to function at many different levels of system functioning, from the cellular to the cognitive (Ursin, 1998). However, when this system becomes stuck and perseverative behavior develops, it can lead to an inflexible response disposition that prohibits adaptability at a number of levels of system functioning.

This paper describes a model of inhibition and sensitization and its neurovisceral concomitants based on dynamical systems theory, which can provide a unifying framework within which to view inhibition and sensitization. In addition, this framework offers a compelling description of the physiological "wet-ware" that instantiates these processes across multiple levels of analysis, from the cellular to the behavioral. Given that persons with anxiety disorders often present to their physicians with unexplained somatic complaints, we will use our work on attention, emotion, and anxiety disorders to illustrate this model, emphasizing the importance of inhibitory mechanisms for the efficient functioning of the organism. However, we think that these examples have a broader relevance to health, including subjective somatic complaints. As in anxiety disorders, compromised inhibitory processes also underlie inadequate internal feedback, which is believed to be a crucial aspect of subjective somatic complaints. The core of many subjective health problems is uncontrolled enhancement and consolidation of complaint-related bodily and environmental information. Our model emphasizing inhibitory processes can help to clarify the minute mechanisms underlying this sensitization and/or feed-forward process in creating chronic somatic problems. Furthermore, health-related anxiety plays an important role in these complaints, especially in somatization and hypochondriasis.

 Published by Blackwell Publishers, 108 Cowley Road, Oxford OX4 1JF, UK and 350 Main Street, Malden, MA 02148, USA. ISSN 0036-5564.

DYNAMICAL SYSTEMS MODELS OF HUMAN FUNCTIONING

From a dynamical systems perspective, an organism is a complex set of reverberating circuits or sub-systems working together in a coordinated fashion (a set of loosely coupled bio-oscillators). The individual elements of the organism can be thought of as a high-dimensional system with a large number of degrees of freedom. However, in the service of goal-directed behavior, these elements organize into coordinated assemblages that can be described by a smaller number of control parameters. This arrangement is similar to the factors of factor analysis, which reveal the latent structure underlying a large set of variables, thereby reducing or mapping high-dimensional item space into a lower-dimensional factor space. As this complex system moves through time on numerous scales, it needs various bi-directional feedback circuits to function efficiently. Moreover, various kinds of responses or preferred assemblages of system elements "emerge" from the interaction of subsystems with the environmental demands. These responses are not orchestrated from a central command center – it is a distributed system.

Unlike the prevailing homeostatic model, dynamical theory proposes that healthy biological systems function far from equilibrium. Therefore, these preferred assemblages and trajectories represent modes of relative stability in the constant flow of organism–environment interactions. From a dynamical systems perspective, cognitive, emotional, and behavioral states represent *attractors* (preferred assemblages) in the state-space (behavioral repertoire) of an organism. One consequence of this idea is that the high-dimensional system may be guided through state-space by a smaller number of dimensions of change or control parameters. We have recently presented evidence to this effect in the context of emotions (Faith & Thayer, 2001; Johnsen, Thayer & Hugdahl, 1995; Nyklicek, Thayer & van Doornen, 1997; Thayer & Friedman, 1997). Thus, discrete behaviors may be viewed as attractors in the state-space defined by a small set of control parameters. For emotion, research points to the dimensions of valence and arousal as being the most important control parameters (Faith & Thayer, 2001; Johnsen *et al.*, 1995; Nyklicek *et al.*, 1997; Ohman, Esteves, Flykt & Soares, 1993; Osgood, Suci & Tannenbaum, 1957; Russell, 1980). These dimensions represent the motivational systems of approach and avoidance (valence) and, together with an index of the amount of vigor with which these drives are pursued (arousal), have been suggested as the underpinnings of goal-directed behavior in a wide range of organisms (cf. Schneirla, 1959). Furthermore, discrete emotions such as happiness represent attractors or states of relative stability. Therefore, unlike homeostatic systems, dynamical systems are characterized by multiple stable states.

The unique combination of internal and external conditions (parameter values) that lead to the emergence of one behavioral state (attractor) over another is termed the *basin of attraction*. Within the context of the physiological constraints and the learning history of a given organism, this set of parameter values can vary greatly. The map of these conditions and related attractors defines the behavioral repertoire, emotional topography or state-space of each individual. This geometrical interpretation has a number of advantages. First, it aids in visualizing the behavior of a system. Second, it gives intuitive value to the mathematical underpinnings of system behavior, and, moreover, it allows for the spatial aspects of system coordinates to be easily grasped.

We have asserted that anxiety disorders may be viewed in terms of a stunted emotional state-space, in which one is unable to shift to an appropriate attractor or emotion for a given set of environmental demands (Friedman & Thayer, 1998a, 1998b; Thayer & Friedman, 1997). As such, the individual is "stuck" in an inflexible bio-behavioral pattern, manifested at multiple levels of organismic complexity, which is poorly matched to the environment. Put another way, the individual is unable to select the appropriate response or, more often the case, is unable to inhibit the inappropriate response. Thus, the response selection mechanism is somehow corrupted.

Recent work in cognitive neuroscience supports the view of humans as self-organizing dynamical systems (van Gelder, 1998). In a review of 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 (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. Importantly, in healthy systems the interaction of these synapses is dominated by inhibition.

CELLULAR MECHANISMS OF LEARNING

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, which 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. In the section below, it is shown that higher-level inhibition is also important for the expression of adaptive behavior. This similarity of processes across different levels of functioning is characteristic of dynamical systems.

PERSEVERATIVE THINKING: A FAILURE OF INHIBITION

Perseverative thinking, common to a number of negative affective states and dispositions, including anxiety disorders, post-traumatic stress disorder, and perhaps many medically unexplained syndromes, is repetitive, abstract, involuntary, and represents a failure of inhibitory neural processes. As such, this cognitive mode reflects a disinhibition of a potentially adaptive frontal lobe mechanism in higher organisms. The frontal lobes have reciprocal neural connections with subcortical structures that are associated with more evolutionarily primitive neural circuits that are in part responsible for basic approach and avoidance behavior. When these structures are disinhibited, a number of processes associated with response to threat are unleashed, including hypervigilance and fear, as well as autonomically induced changes such as increased heart rate and blood pressure. These processes could be conceptualized as sensitization-like as well as disinhibitory, and their behavioral "hallmarks" of hypervigilance and fear might pertain to any threat, including somatic harm and pain.

Perseverative thinking is central to many psychological disorders that have also been associated with poor physical health outcomes. In particular, anxiety, depression, and anger have all been linked with cardiovascular disease. There are at least two related ways in which this association may be causally explained. One pathway is via decreased vagally mediated heart rate variability (HRV). Diminished tonic HRV and the associated reduction of vagally mediated cardiovascular control have been associated with a variety of pathological states and dispositions (see Friedman & Thayer, 1998b; Stein & Kleiger, 1999, for reviews). HRV measures that index vagally mediated cardiovascular activity reflect important negative feedback mechanisms for the self-regulation of behavior. Vagal activity has negative chronotropic and dromotropic effects that promote efficient cardiac functioning through the restraint of rate and conduction velocity, which is necessary for cardiac stability, responsiveness, and flexibility (Levy, 1990).

In fact, chronic worry, a perseverative cognitive process endemic to anxiety, may be a risk factor for coronary heart disease (Kubzansky *et al.*, 1997). Furthermore, both acute and chronic worry are associated with decreased vagal activity (Thayer, Friedman & Borkovec, 1996). Thus, one mechanism that might link worry with increased disease risk is decreased vagal activity. Similar models of decreased vagal activity have recently been put forward to describe the relationship between other psychological factors (such as hostility) and cardiovascular disease risk (Brosschot & Thayer, 1998; Sroka, Peimann & Seevers, 1997).

Another possible pathway linking perseverative thinking to anxiety and health is via decreased medial prefrontal cortex activity. 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, and these mechanisms have been related to post-myocardial infarction depression and the related increased risk of re-infarction and death (Ter Horst, 1999; Ter Horst & Postema, 1997).

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 (Sollers, Ahern & Thayer, 2000). Qualitatively similar changes in HR were observed during each hemisphere's injection. During ten-minute inactivations of either hemisphere, HR increased, peaked at about minute three, and gradually declined toward baseline values. These data support the notion that cortical activity tonically inhibits brainstem sympathoexcitatory circuits. However, differential hemispheric effects appeared, with larger and faster HR increases during right hemisphere inactivations. Concomitant with these HR increases, vagally mediated HRV decreased, mirroring the HR changes with respect to differential hemispheric effects. Specifically, vagally mediated HRV decreases were greater in the right hemisphere inactivations. These results support the anatomical and physiological findings that right hemispheric autonomic inputs to the heart are associated with greater cardiac chronotropic control.

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). These areas have been broadly associated with biopsychological functions such as affective, attentional, and autonomic regulation (Thayer & Lane, 2000). In addition, these structures are linked with inhibitory control of behavior in general (Roberts & Wallis, 2000) and cardiac behavior in particular (Verberne & Owens, 1998). Importantly, direct and indirect pathways connect these areas with parasympathetic (vagal) motor output regions (Ter Horst, 1999). A number of researchers have hypothesized inhibitory cortical–subcortical circuits

(Benarroch, 1993, 1997; Masterman & Cummings, 1997; Mayberg *et al.*, 1999; Spyer, 1989); however, our group has been the first to tie these circuits to HRV (Thayer & Lane, 2000). The results of the ISA test experiment provide compelling evidence that cortical structures tonically inhibit sympathoexcitatory circuits and that this inhibition is via vagal mechanisms.

We propose that these two pathways linking perseverative thinking to health represent the breakdown of a common reciprocal inhibitory cortical–subcortical neural circuit. In the next section, a set of neural structures that link the prefrontal cortex with HRV is described in detail. This network of reciprocally interconnected neural structures 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. For example, when faced with threat, the tonic inhibitory control of subcortical structures can be rapidly decreased, leading to sympathoexcitatory fight or flight responses necessary for survival. However, when this network is disrupted, a rigid, defensive behavioral pattern emerges, with associated perseverative behavior manifesting in attentional, affective, and autonomic inflexibility.

THE CENTRAL AUTONOMIC NETWORK

Investigators have identified functional units within the central nervous system (CNS) that support goal-directed behavior and adaptability. One such entity is the *central autonomic network* (CAN; Benarroch, 1993, 1997). Functionally, this network is an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior and adaptability. 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 periaquaductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field. These components are reciprocally interconnected such that information flows 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 that innervate the heart via the stellate ganglia and the vagus nerve, respectively. The interplay of these inputs to the sino-atrial node of the heart generates complex variability that characterizes the HR time series (Saul, 1990). Thus, the output of the CAN is directly linked to HRV. Importantly, vagal influences dominate cardiac chronotropic control (Levy, 1990). In addition, sensory information from the peripheral end organs such as the heart is fed back to the CAN. As such, HRV is an index of central–peripheral neural feedback and CNS-autonomic nervous system integration.

Moreover, the CAN has many features of a dynamical system. First, the components of the CAN are reciprocally interconnected, allowing for continuous positive and negative feedback interactions and integration of autonomic responses. Second, the CAN comprises a number of parallel, distributed pathways, which permits multiple avenues to a given response. For example, a given HR change of 72 to 90 beats per minute can be achieved by various combinations of sympathetic and parasympathetic input, including increased sympathetic activity, decreased parasympathetic activity, or any combination of the two, as well as by other pathways such as circulating hormones. Moreover, within the CAN, direct and indirect pathways can modulate output to preganglionic sympathetic and parasympathetic neurons. Third, the activity of the CAN is state dependent and thus sensitive to initial conditions (see Glass & Mackey, 1988).

The CAN receives and integrates visceral, humoral, and environmental information, coordinates autonomic, endocrine, and behavioral responses to environmental challenges, and is under tonic inhibitory control. This inhibition is achieved by gamma-aminobutyric acid (GABA) interneurons within the NTS. GABA is the main inhibitory neurotransmitter within the CNS. Disruption of this inhibitory pathway may lead to hypertension and sinus tachycardia, and represents a disinhibition of sympathoexcitatory circuits within the CAN (Benarroch, 1993, 1997; Masterman & Cummings, 1997; Spyer, 1989). Moreover, anxiety has been associated with decreased GABA-ergic inhibition in the frontal cortex (Malizia *et al.*, 1998), consistent with cardiovascular concomitants of anxiety such as tachycardia (Friedman & Thayer, 1998b).

Other functional units within the CNS subserving executive, social, affective, attentional, and motivated behavior in humans and animals have also been identified (Damasio, 1998; Devinsky, Morrell & Vogt, 1995; Masterman & Cummings, 1997; Spyer, 1989). One such network has been termed the anterior executive region (AER; Devinsky *et al.*, 1995). Functionally, the AER and its projections regulate behavior by monitoring the motivational nature of internal and external stimuli. The AER and its projections have been termed the "rostral limbic system" and structurally include the anterior, insular, and orbitofrontal cortices, the amygdala, the periaquaductal gray matter, 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). Disruption of these circuits has been associated with a wide variety of perseverative behaviors, including a lack of habituation and inappropriate affect (cf. Crestani *et al.*, 1999).

We propose that the CAN, the AER and its projections, the "emotion circuit" (Damasio, 1998), and related systems (Masterman & Cummings, 1997; Spyer, 1989) are one and the same core functional network identified by different researchers

from diverse approaches. This CNS network is associated with the processes of response organization and selection, and serves to modulate psychophysiological resources in attention and emotion (Friedman & Thayer, 1998a, 1998b; Thayer & Friedman, 1997). Additional structures are flexibly recruited in the service of specific behavioral adaptations. This sparsely interconnected neural network allows for maximal organism flexibility in adapting to rapidly changing environmental demands. 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.

ANXIETY AND A LACK OF CENTRAL AND PERIPHERAL INHIBITION

Anxiety can be viewed as a sensitization or positive feedback loop that promotes perseverative activity at a number of functional levels. As noted above, the prefrontal cortex exerts tonic inhibitory control over sympathoexcitatory subcortical circuits. The CAN and related networks are also under tonic inhibitory control via GABA-ergic mechanisms. Recent animal and human work suggests that anxiety and its associated perseverative activity are related to decreased GABA receptor binding in the medial prefrontal and orbital frontal cortices. 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 heart rate 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, Friedman, Borkovec, Johnsen & Molina, 2000).

Positron emission tomography 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. Importantly, the largest decreases were found in the orbitofrontal and insular cortices. These areas have been implicated in anxiety and are also associated with HRV (Lane, Reiman, Ahern & Thayer, 2000). Grachev and Apkarian (2000) similarly found altered orbitofrontal chemistry in anxiety in healthy humans. Relative to low-anxiety subjects, high-anxiety subjects showed decreased levels of a number of chemicals in the orbitofrontal cortex, including GABA.

Autonomically mediated HRV is critical as an index of neurovisceral integration and organism self-regulatory ability. The interplay of sympathetic and parasympathetic outputs of the CAN at the sino-atrial node produces the complex beat-to-beat variability that is characteristic of a healthy, adaptive organism. Vagal influences dominate HR control, and thus HR is under the tonic inhibitory control of the vagus (Levy, 1990). There are several lines of research that point to the importance of HRV in anxiety and anxiety disorders. First, a relative reduction in vagally mediated HRV is consistent with the cardiac symptoms of panic anxiety as well as with the psychological symptoms of poor attentional control, ineffective emotional regulation, and behavioral inflexibility (Friedman & Thayer, 1998a, 1998b). Similar reductions in HRV have been found in depression (Thayer, Smith, Rossy, Sollers & Friedman, 1998), generalized anxiety disorder (Thayer, Friedman & Borkovec, 1996), and post-traumatic stress disorder (Cohen, Matar, Kaplan & Kotler, 1999). This reduction of vagally mediated cardiovascular control serves to disinhibit sympathoexcitatory influences. Due to differences in the temporal kinetics of the autonomic neuroeffectors, sympathetic influences on cardiac control are relatively slow (order of magnitude seconds) compared with vagal influences (order of magnitude milliseconds; see Saul, 1990). Thus, when the fast vagal modulation of cardiac function is decreased, the organism is less able to track rapid environmental changes and respond appropriately.

In a recent experiment, Johnsen *et al.* (in press) examined inhibitory responses in an emotional Stroop paradigm. Dental phobics were first exposed to recorded scenes of dental procedures and then administered the emotional Stroop test. In addition to the traditional color-congruent and color-incongruent words, they also were asked to respond to neutral words and dental-related words, such as "drill" and "cavity", which were threatening to these patients. All subjects exhibited longer reaction times to the color-incongruent words and the dental-related threat words, and, thus, displayed a difficulty in inhibiting pre-potent responses. However, greater HRV was associated with faster reaction times to these words, consistent with the link among vagally mediated HRV, inhibitory ability, and frontal lobe function. These results support the idea that vagally mediated HRV is associated with efficient attentional regulation and greater ability to inhibit pre-potent but inappropriate responses. Consistent with this view, Brosschot (this issue) discusses Stroop interference as an operationalization of what he calls cognitive-emotional sensitization in the context of medically unexplained symptoms.

In summary, there is ample evidence that anxiety as well as other related negative psychological and physiological conditions are associated with decreases in both central and peripheral inhibitory activity. For example, panic disorder may be due to excessive, inappropriate activation of evolutionarily important defensive systems resulting from the failure of inhibition secondary to benzodiazepine GABA dysfunction (Malizia *et al.*, 1998). Moreover, we have repeatedly reported decreased vagally mediated HRV in persons with panic attacks and anxiety disorders (Friedman *et al.*, 1993;

Friedman & Thayer, 1998a; Thayer *et al.*, 1996), a finding that has been widely replicated across laboratories (see Cohen *et al.*, 1999, for review). Our model linking frontal cortex inhibition of subcortical sympathoexcitatory defensive circuits provides a framework to integrate central and peripheral findings with the behavioral, affective, and cognitive aspects of anxiety disorders. Additionally, in the dynamical systems model view, the disinhibition of sympathoexcitatory defensive circuits represents a sensitization or positive feedback that perpetuates anxiety and leads to a broad basin of attraction for this defensive style.

SENSITIZATION FOLLOWED BY INHIBITION IN ADAPTIVE FUNCTIONING

Ursin (1998) notes that the classical finding of a large orienting response followed by habituation is also an example of sensitization. Similarly, the phenomenon of long-term potentiation, so important for memory, can be viewed as a kind of sensitization. This tuning of the organism to novel stimuli followed by habituation to innocuous stimuli is characteristic of a healthy and adaptive organism. A failure to habituate to innocuous stimuli leads to a hypervigilant, defensive style that is the hallmark of anxiety disorders. This maladaptive mode exemplifies perseverative behavior that can be seen as a positive feedback loop. Importantly, the interruption of this ongoing state is associated with inhibitory processes and negative feedback mechanisms. In the context of our model of neurovisceral integration, parasympathetic nervous system control of cardiovascular function (as well as activity of the prefrontal cortex) is associated with these inhibitory processes.

This phenomenon was examined in a conditioning experiment that compared patients with generalized anxiety disorder to a matched control group who were exposed to cued threat and non-threat words in an S1–S2 paradigm (Thayer *et al.*, 2000). Briefly, the S1–S2 paradigm involves the presentation of a series of paired stimuli in which an initial cue stimulus (S1) is followed after a fixed inter-stimulus interval (ISI) by a second stimulus (S2). A robust tri-phasic HR response has been described during the ISI (Bohlin & Kjellberg, 1979). An initial HR deceleration following S1 is followed by a HR acceleration over the next several cardiac beats. Finally, just prior to S2, a second HR deceleration occurs. The initial deceleration has been interpreted as an orienting response to novelty (Sokolov, 1963). The phasic cardiac changes found in the S1–S2 paradigm have been shown to be vagally mediated (Porges, 1992).

We (Thayer *et al.*, 2000) reasoned that individuals with generalized anxiety disorder (GAD) vigilantly monitor their environment for threat and do not disengage from unimportant events. This attentional style would lead the persons with GAD to fail to habituate to novel innocuous stimuli, whereas non-anxious controls would show habituation. The magnitude of cardiac responses is positively related to vagally mediated HRV (Porges, 1992). Therefore, relative to persons with GAD, it was predicted that non-anxious controls would show initially larger orienting responses that would rapidly habituate.

Results supported these predictions. Relative to non-anxious controls, persons with GAD showed smaller cardiac orienting responses and impaired habituation to neutral words. The diminished orienting is consistent with findings of low HRV in GAD, and the weakened habituation suggests hypervigilance to a perceived perpetually threatening environment. The inability to inhibit attention to harmless stimuli leads to a positive feedback loop that spirals out of control. Thus, worry becomes the preferred response to an ever-widening range of situations, maintaining anxiety in the face of large amounts of disconfirming data. However, the perception of a threatening environment may lead to a restriction of behavior such that the individual is exposed to less novel, disconfirming information. Again, a positive feedback mechanism perpetuates the existing, dysfunctional state.

These mechanisms could operate at a precognitive or preconscious level. One of us has recently found similar phenomena at work in alcoholics exposed to briefly presented (Ingjaldsson, Thayer & Laberg, in press) and non-consciously presented alcohol stimuli (Ingjaldsson, Thayer & Laberg, under review b). These findings are consistent with classic work on perceptual defense (see Mackinnon & Dukes, 1962, for review) and the psychophysiology of attention (e.g., Graham & Clifton, 1966; Sokolov, 1963), as well as more contemporary notions of pre-attentive discrimination and selective processing of threat in anxiety (Mathews, 1990). Furthermore, this rapid mobilization of resources for action is consistent with the dynamical systems characterization of emotion as an emergent response or attractor driven by motivational factors (see Globus & Arpaia, 1994).

SUMMARY AND CONCLUSIONS

In this paper we have tried to provide the outlines of a dynamical systems model of inhibition and sensitization. Both inhibition and sensitization are important for normal system functioning. In this model inhibitory processes "sculpt" the behavior of an organism to meet changing environmental demands. When these inhibitory processes are dysfunctional perseverative activity appears at numerous levels of system functioning, from the cellular to the cognitive. This perseverative activity represents a form of sensitization. This type of sensitization or perseverative activity may be the basis of numerous disorders and somatic complaints, including cardiovascular disease, cardiac pain, and panic attacks but also somatization-like or medically unexplained complaints. In the case of anxiety disorders this perseverative activity represents a disinhibition of normally adaptive defensive systems. We have also provided evidence that suggests that vagally mediated HRV may index these inhibitory processes and may represent the output of a set of neural structures

that are important for efficient and flexible functioning. When viewed from the perspective of dynamical systems complex behaviors can be understood in geometrical terms (i.e., as attractors in a state-space), thereby greatly reducing the mathematics necessary to describe and predict the behavior of the system. It is hoped that this formulation will enhance our ability to generate and test hypotheses and to ultimately better understand human behavior.

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