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Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder

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ABSTRACT

A theory is proposed to explain the benefits of yoga practices in diverse, frequently comorbid medical conditions based on the concept that yoga practices reduce allostatic load in stress response systems such that optimal homeostasis is restored. It is hypothesized that stress induces (1) imbalance of the autonomic nervous system (ANS) with decreased parasympathetic nervous system (PNS) and increased sympathetic nervous system (SNS) activity, (2) underactivity of the gamma amino-butyric acid (GABA) system, the primary inhibitory neurotransmitter system, and (3) increased allostatic load. It is further hypothesized that yoga-based practices (4) correct underactivity of the PNS and GABA systems in part through stimulation of the vagus nerves, the main peripheral pathway of the PNS, and (5) reduce allostatic load. Depression, epilepsy, post traumatic stress disorder (PTSD), and chronic pain exemplify medical conditions that are exacerbated by stress, have low heart rate variability (HRV) and low GABAergic activity, respond to pharmacologic agents that increase activity of the GABA system, and show symptom improvement in response to yoga-based interventions. The observation that treatment resistant cases of epilepsy and depression respond to vagal nerve stimulation corroborates the need to correct PNS underactivity as part of a successful treatment plan in some cases. According to the proposed theory, the decreased PNS and GABAergic activity that underlies stress-related disorders can be corrected by yoga practices resulting in amelioration of disease symptoms. This has far-reaching implications for the integration of yoga-based practices in the treatment of a broad array of disorders exacerbated by stress.

Introduction

Proposed theory

A unifying theory is proposed to explain the effects of yoga in medical conditions with overlapping pathophysiologies based on the principle that yoga practices reduce allostatic load in stress response systems and restore optimal homeostasis. It is hypothesized that stress induces: (1) imbalance of the autonomic nervous system (ANS) with decreased parasympathetic nervous system (PNS) increased sympathetic nervous system (SNS) activity, (2) underactivity of the inhibitory neurotransmitter, gamma amino-butyric acid (GABA) and (3) increased allostatic load. It is further hypothesized that yoga practices (4) correct underactivity of the PNS and GABA system in part through stimulation of the vagal nerves and (5) reduce allostatic load resulting in symptom relief. Depression, epilepsy, post traumatic stress disorder (PTSD), and chronic pain exemplify conditions that are exacerbated by stress, have low PNS and low GABA system activity, respond to pharmacologic agents that increase activity of the GABA system, and improve in response to yoga-based interventions. It is proposed that as yoga-based interventions support the return towards optimal balance in the PNS and GABA system, function improves in regions of the brain that regulate response to threat, such as threat perception, interoception, fear processing, emotion regulation, and defensive reactions. As central regulatory systems become more balanced and flexible, allostatic load is reduced leading to health improvements.

Neurophysiological foundations and evidence

Allostatic load

The brain determines what is threatening and therefore stressful. Stress response involves two-way communication between the

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brain and the cardiovascular, immune, metabolic and other systems via the nervous system, endocrine system and hypothalamic–pituitary–adrenal (HPA) axis [1]. Homeostasis refers to the mechanisms that keep the parameters of an organism's internal milieu within the ranges necessary for survival [2]. In this discussion, optimal homeostasis is considered to be the state in which meeting the immediate needs of the organism incurs the least possible long-term costs. McEwen (2007) proposes that allostasis is the adaptive process of maintaining stability during conditions that are outside of the usual homeostatic range [1]. Allostatic load is the cost to the body for maintaining this stability during deviations from the usual homeostatic range, often reflected in pathophysiological conditions and disease progression [1]. Physiologic systems activated by stress can both protect the body in the short term and damage the body in the long term [1], especially when stress becomes chronic and an allostatic load is incurred. For example, increased SNS activity with elevated blood pressure and heart rate in response to real or perceived threat is beneficial in the short term for survival, but sustained high SNS activity incurs harmful long term effects such as hypertension, atherosclerotic disease and cardiac morbidity [3].

Stress activated systems and disorders

The proposed theory states that stress from psychological, physically external and physically internal sources results in allostatic load, which can be reduced by yoga-based practices that shift regulatory systems towards optimal homeostasis. This theory can encompass allostatic load on the following stress activated systems: ANS, neuroendocrine, HPA axis, cardiovascular, metabolic and immune [4]. Overactivity or underactivity of stress responsive systems is associated with increased symptoms in a wide range of disorders including: psychiatric disorders such as depression, anxiety, PTSD [5,6], alcohol and other substance dependence [7]; neurologic disorders such as epilepsy [8] and chronic pain [9]; cardiovascular disorders such as hypertension, vascular disease and myocardial infarction [10,11]; metabolic disorders such as metabolic syndrome, diabetes, and obesity [12]; and immune disorders such as infection, cancer and asthma [13]. These stress-exacerbated disorders include four of the major causes of mortality in the U.S., heart disease, cancer, stroke and diabetes [14], plus three major causes of morbidity, depression, anxiety disorders, and chronic pain [15]. The above disorders improve in response to yoga-based therapies underscoring the far-reaching implications of the proposed theory [16].

Exemplary disorders

The rationale for the proposed theory will be developed by focusing on the effects of stress-induced allostatic load on the autonomic and GABA systems and the reduction of allostatic load by yoga-based practices in the treatment of epilepsy, major depressive disorder (MDD), PTSD, and chronic pain. These four selected disorders have the following common characteristics: exacerbation by stress; low parasympathetic tone as measured by low heart rate variability (HRV); low GABAergic activity; improvement when treated with pharmacologic agents that increase activity of the GABA system; and improvement in response to yoga based therapies [8,17–35]. According to the proposed theory ANS imbalance with decreased PNS activity and increased SNS activity is important in the pathogenesis of epilepsy, MDD, PTSD, and chronic pain. This ANS imbalance is also associated with underactivity in the GABA system. Furthermore, stimulation of the vagus nerves by yoga-based practices corrects PNS underactivity leading to correction of GABA underactivity. Although reduction of overactivity of the SNS by yoga contributes to balancing the stress response systems, this discussion will focus on the PNS. The term 'GABAergic' indicates activity of the GABA system detectable by various methods of measurement. For the purpose of this paper the term 'yoga' is used to encompass ancient and modern mind–body techniques, including all forms of yoga and other traditions that incorporate postures, meditation, chanting or breathing techniques.

Anatomy of the autonomic nervous system

The ANS is comprised of the SNS and the PNS. The main peripheral pathways of the PNS are within the vagus nerves [36]. Each vagus is bidirectional containing two efferent fiber groups (transmitting signals from the central nervous system (CNS) to the body) and three afferent fiber groups (transmitting information from the body to the CNS). The first group of vagal efferents, unmyelinated General Visceral Efferent (GVE) fibers, originates in the dorsal motor nucleus (DMN) and predominately innervates thoracic and abdominal viscera. DMN fibers regulate subdiaphragmatic organs, but do not play a significant role in cardiac function [37]. The second group of vagal efferents, myelinated Special Visceral Efferent (SVE) fibers originating in the nucleus ambiguous (NA) innervate the pharynx, larynx, lungs, heart, and other viscera [37]. SVE fibers deliver inhibitory input to the sinoatrial node, slowing the heart rate [37].

The majority of afferent vagal fibers are General Visceral Afferents (GVA) that carry information from the pharynx, larynx, trachea, and viscera of the thorax and abdomen to the nucleus tractus solitarius (NTS) [38]. The second group of afferent fibers, General Somatic Afferents (GSA), carries sensations from the skin in the auditory meatus and taste receptors to synapse in the spinal trigeminal tract [36]. The third group of afferent fibers, Special Visceral Afferents (SVA), carries sensory taste information to the NTS [38]. As the main terminus for GVA fibers, the NTS is an important relay station providing the brain with information about the body's internal milieu [37,39]. The NTS has connections to autonomic, reticular and limbic structures via projections to the parabrachial nucleus (PBN), periacqueductal grey, central nucleus of the amygdala (CEA), hippocampus, hypothalamus, and thalamus [36]. The PBN sends projections to the thalamus, CEA, basolateral nucleus of the amygdala (BLA), hypothalamus, anterior insula, and prefrontal cortex [40]. Craig describes these neural connections as conveying information from the vagus nerves to the structures that mediate interoceptions (perceptions of the internal state of the body), threat perceptions and affective states [119]. Through this network, vagal activity influences emotional states and thought processes as well as their somatic expression (See Fig. 1).

Polyvagal theory and heart rate variability (HRV)

The polyvagal theory described by Porges identifies three phylogenetic developments in neural regulation of the ANS [37]. The oldest part, the unmyelinated visceral vagus, responds to threat by depressing metabolic activity. The next developmental stage, the SNS, is capable of increasing metabolic output and mobilization behaviors necessary for 'fight or flight'. The third and most advanced pathway, the myelinated vagus, promotes calm states consistent with the metabolic demands of growth, repair, and restoration. The myelinated vagus, found only in mammals, supports social engagement and engenders feelings of safety. Myelinated vagal efferent fibers from the NA serve as the vagal brake, which enables rapid control of heart rate (HR) by increasing vagal tone to reduce HR and blood pressure or decreasing vagal tone to accelerate heart rate [41]. Heart rate variability (HRV) refers to changes in the heart's beat-to-beat intervals. Vagal control allows more rapid adjustments in HR and thus greater HRV than does SNS control, which takes longer to turn on and longer to turn off

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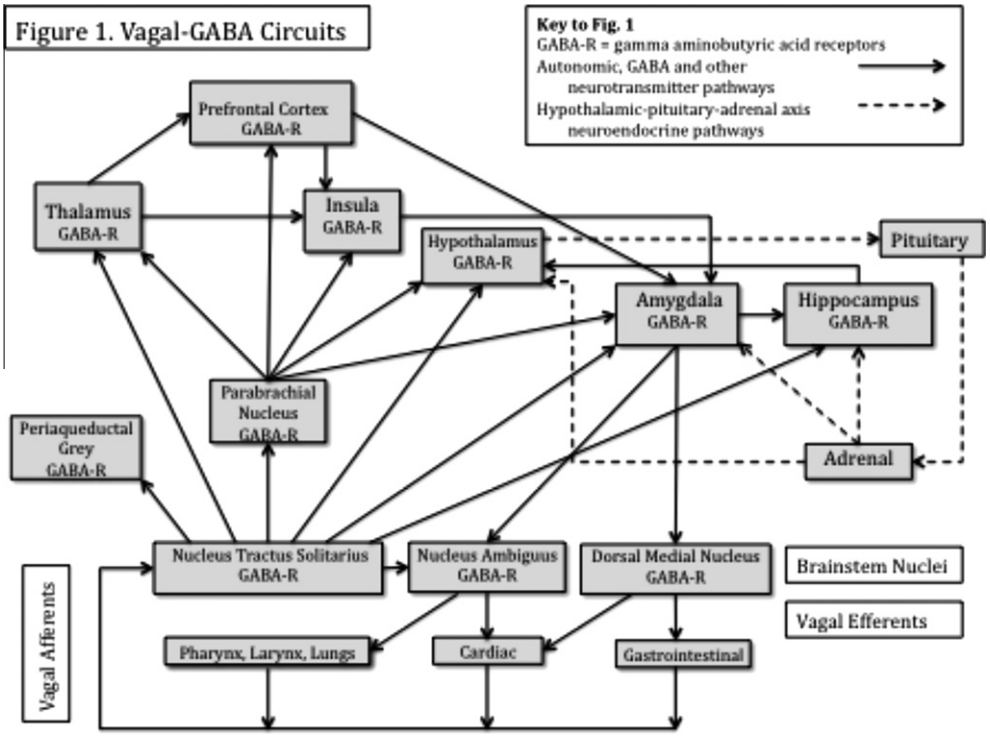

Fig. 1. Neuroanatomic Connections of Parasympathetic Nervous System with GABA System.

[42]. Accordingly, high HRV implies vagal dominance and is a sign that the stress response system has greater flexibility to respond to challenges [2]. Conversely, low HRV, indicating more restricted responsiveness, is associated with increased risk of all-causes of mortality related to cardiac disease [43]. An organism's response to internal and external challenges is limited by the need to maintain stability. When stability is maintained through allostasis, flexibility of the system declines and leads to pathological states and damage to the organism.

It is advantageous for an organism to use the most advanced level of the ANS, which affords the greatest flexibility of response. When the myelinated vagal brake fails, the phylogenetically older SNS is recruited to regulate metabolic output in response to stress [37]. This reduces the flexibility of response to threat and delays the return to a calm, resting, reparative, anti-inflammatory state when the threat has ceased [42]. Thus underactivity of the PNS, manifested by decreased HRV and reduced control by the vagal break, leads to greater dependence on sympathetic excitation of the cardiovascular and other systems, with negative health consequences such as hypertension, hyperarousal, and over reactivity [3].

Neurovisceral integration

The role of the vagus in social interactions in polyvagal theory is extended in the neurovisceral integration model of affect regulation described by Thayer, which proposes that dysfunctional psychological states are rooted in an impaired vagal inhibitory mechanism associated with low HRV [44,45]. Neurovisceral integration suggests that ANS imbalance, particularly with underactivity of the PNS, may be the final common pathway between negative emotions and poor health [10].

How yoga increases PNS activity

Although there are many kinds of yoga practices, the relationship between yoga and PNS activity is most easily demonstrated by yogic breathing. Emotional states affect respiratory rate, depth and pattern. Conversely, voluntary changes in the pattern of breath can account for 40% of the variance in feelings of anger, fear, joy and sadness [46]. Breathing is controlled by voluntary and involuntary mechanisms. Voluntarily controlled breathing patterns can affect the ANS and HRV [47,48].

The neurophysiologic model for the effects of yoga breathing

Brown and Gerbarg describe a neurophysiologic model for the effects of yoga breathing in which stretch receptors in the alveoli, baroreceptors, chemoreceptors, and sensors throughout the respiratory structures send information about the state and activity of the respiratory system through vagal afferents and brainstem relay stations to other CNS structures where they influence perception, cognition, emotion regulation, somatic expression, and behavior [49–52]. The fact that breathing is the only autonomic function that can easily be voluntarily controlled provides a portal through which specific selected breathing patterns can be used to send messages through PNS, SNS and interoceptive systems to affect how the brain perceives, interprets, and responds to stress or threat. Because breathing is vital to survival, information from the respiratory system must be noticed and attended to immediately. Therefore, their model suggests that signals from vagal afferents carrying information about changes in the rate, depth, or pattern of breathing receive the highest priority and have rapid, widespread effects on brain functions. Brown and Gerbarg have reviewed the evidence that yoga-breathing interventions increase HRV, improve sympatho-vagal balance, and promote stress resilience [49–51]. For example, Coherent Breathing and Resonant Breathing, using a fixed rate of three and a half to six breaths per minute (bpm), increase HRV and PNS activity [53–55]. Ujjayi (Ocean Breath) is one form of resistance breathing that uses laryngeal contracture and partial closure of the glottis to impede the flow of air. Resistance breathing techniques increase intrathoracic pressure, baroreceptor stimulation, respiratory sinus arrhythmia (RSA), and HRV [56]. Using breath-holds with Ujjayi further increase PNS activity [57]. The ancient 'Om' chant involves slow

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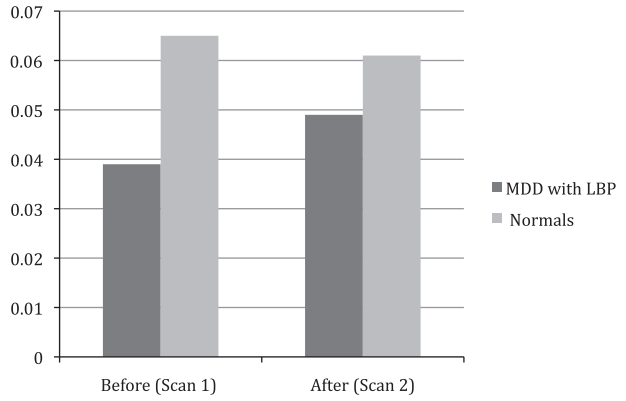

Fig. 2. Mean thalamic GABA levels in subjects with Major Depressive Disorder (MDD) and low back pain (LBP) ($n = 2$) compared to normal subjects ($n = 19$) before (Scan 1) and after (Scan 2) a 12-week yoga intervention.

breathing, airway resistance (contracting the vocal cords to generate sound), which increase vagal tone and physiologic relaxation [58]. Using fMRI, Kalyani, Gangadhar, and colleagues showed significant limbic system deactivation with 'OM' chanting [121]. Experienced Qigong trainees have higher HRV than age-matched sedentary controls [59]. Increases in HRV have been documented with an Iyengar yoga intervention compared to a walking control [60]. The pattern of slow resistance breathing with longer periods of exhalation than inhalation occurs during chanting, singing, and mind–body practices in many traditions. Bernardi suggested that a respiratory rate of 6 bpm augments 10-s (6/min) Mayer waves and increases the effect of respiratory sinus arrhythmia (RSA), a measurement correlated with HRV [61]. Bernardi also found that recitation of the rosary prayer in Latin at 6 bpm increased HRV and baroreflex sensitivity [61]. The appearance of similar respiratory rates in breathing, chanting, and meditative practices across cultures supports the theory that these techniques reduce imbalances in the ANS leading to improved mood, decreased anxiety and improved health [49–51].

Yoga practices associated with decreased cortisol

Cortisol levels and brain GABA levels are biologic markers of stress [62,63]. Elevated corticotrophin releasing factor and cortisol levels found in depression, PTSD and epilepsy indicate increased HPA axis activity [5,6,64]. These three disorders also show evidence for decreased activity in the GABA system [23–25]. Decreased cortisol levels have been reported after interventions using yoga postures and meditation [65–68]. In a study of Transcendental Meditation (TM), participants with 3–5 years of experience had significantly greater decreases in cortisol levels than novices with 3–4 months of TM experience [65]. Symptoms of epilepsy and depression can be ameliorated with either yoga interventions or pharmacologic agents that increase activity of the GABA system directly (e.g. anti-epileptic drugs) or indirectly (e.g. Selective Serotonin Reuptake Inhibitors—SSRIs) [27,31–35,69,70]. The proposed theory that stress-induced allostatic load is associated with increased symptoms in depression, PTSD, and epilepsy is buttressed by evidence of increased HPA axis activity and decreased GABAergic activity. Studies also suggest that yoga practices reduce stress-induced allostatic load in three stress reactive systems: the ANS, the HPA axis, and the GABAergic system (see Fig. 3).

Vagal nerve stimulation (VNS) addresses low PNS and GABA activity

VNS has been approved by the Federal Drug Administration for treatment resistant epilepsy and depression [36,71]. VNS provides an evidential link between peripheral stimulation of the vagus nerve and activation of brain regions that are modulated by GABA. Functional imaging studies show that VNS activates brain regions involved in cognition, emotion and affect. In epileptic and normal subjects respectively, VNS and transcutaneous vagal nerve stimulation (t-VNS) via GSA fibers in the auditory meatus were associated with functional changes in the thalamus, amygdala, insula, hippocampus, parahippocampal gyrus and prefrontal regions [40,72,73]. It is plausible that the beneficial effects of VNS in treatment resistant epilepsy and depression are mediated in part by normalization of an ANS imbalance that was not corrected by prior pharmacotherapy.

Vagal nerve stimulation (VNS) and neurotransmitters

VNS increases neurotransmitter levels in systems implicated in the treatment of epilepsy and depression: GABA, norepinephrine (NE), and serotonin [36]. Vagal afferents influence the noradrenergic locus ceruleus (LC), the serotonergic dorsal raphe nuclei, and GABA release via the NTS [36,74]. The antiepileptic effect of VNS is thought to be in part due to widespread release of GABA in the brainstem and cortex [74]. Gamma-vinyl-gamma-aminobutyric acid (GVG), an irreversible inhibitor of GABA transaminase, increases GABA levels by reducing the metabolism of GABA. The injection of GVG into the thalamus, hypothalamus and bulbar regions blocks pentylenetetrazol (PTZ) induced seizures [74]. PTZ induced seizures are also blocked by VNS [74]. Yoga-based therapies have been associated with increased PNS activity, increased GABA levels, and reduced symptoms in epilepsy and MDD [31,32,75]. These observations are consistent with the theory that VNS and yoga-based therapies could decrease seizures and depressive symptoms by increasing PNS activity that in turn increases GABA levels.

Stress, medial temporal lobe, GABA and hypothalamic–pituitary–adrenal axis (HPA)

Neural circuits that mediate effects of the ANS and HPA axis converge in the hippocampus, a component of the limbic system. Vagal nerve projections to the NTS are relayed to the amygdala directly as well as indirectly via the PBN [36]. Through connections in the LC, PBN input reaches the hippocampus [76]. Embedded in the medial temporal lobe, the amygdala and hippocampus are vital for memory function, emotion processing, mediation of psychological stress, and modulation of HPA response to stress [1,38,77]. The hippocampus is essential for declarative memory while the amygdala is essential for threat perception and emotional memory [78]. Together they contribute to the retention and influence of significant memories [79]. The hippocampus plays a major role in the perception of threat, the experience of stress, and memory functions via its interactions with the PNS, HPA axis and GABA systems. Individuals with PTSD have been shown to have impaired declarative memory and reduced hippocampal volume [79]. Within the hippocampus the presence of high concentrations of both mineralocorticoid and glucocorticoid receptors is indicative of its role in stress experience and threat perception [1]. The HPA axis response to stress begins when the paraventricular nucleus (PVN) of the hypothalamus secretes corticotrophin-releasing hormone (CRH) carried via the portal system to the anterior pituitary lobe where it binds to CRH receptors and stimulates secretion of adrenocorticotrophic hormone (ACTH), which induces the adrenal glands to release mineralocorticoids and glucocorticoids [7]. CRH receptors are also found in the hypothalamus, amygdala, hippocampus, basal nucleus of the striatum (BNST), central gray area, locus ceruleus (LC), parabrachial nucleus (PBN), dorsal vagal nucleus, prefrontal cortex and anterior cingulate gyrus [5,80]. Chronic stress results in

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Stress	Yoga-Based Practices
↑ Sympathetic Nervous System (SNS)	↑ Parasympathetic Nervous System
↑ Hypothalamic-pituitary-adrenal Axis	↓ Hypothalamic-pituitary-adrenal Axis
↓ GABA Activity	↑ GABA Activity

Fig. 3. Stress related imbalance corrected by yoga-based practices.

prolonged increases in glucocorticoid levels [1]. High levels of circulating glucocorticoids provide negative feedback that reduces PVN synthesis of CRH, but activates CRH release in the central nucleus of the amygdala (CEA) [7]. The action of CRH in the amygdala constitutes an additional mechanism for mediating autonomic and behavioral responses to stress including the promotion of anxiety, fear-based behaviors, and defensive reactions [5,7]. Stress is associated with neuronal pruning and volume reduction in the hippocampus, which results in prolongation of HPA axis response to stress [1,79]. In contrast, stress leads to increased dendritic branching in the amygdala [81]. In summary, lesions of the hippocampus increase HPA axis response, whereas lesions in the medial amygdala decrease HPA axis response. Accordingly, there is a reduction in hippocampal function, reflected in decreased declarative memory, and an amplification in amygdala activity evidenced by increased fear response to behavioral stress [78].

Stress is associated with decreased hippocampal GABA levels [82]. Used as a model for depression, inescapable shock is associated with decreased hippocampal GABA levels [83]. The same behavior seen after inescapable shock can be produced by injections of the $GABA_A$ antagonist, bicuculline [83]. As cortisol levels rise, the frequency of GABA receptor mediated synaptic events declines [1]. In contrast $GABA_A$ agonists, such as benzodiazepines, that increase GABAergic activity, are used to reduce anxiety. The benzodiazepine, alprazolam, inhibits the activity of the HPA by blunting increases in CRH, ACTH and cortisol [84,85]. A cholecystokinin-tetrapeptide (CCK-4) challenge induces panic attacks in patients with panic disorder and in healthy volunteers [86]. CCK-4 panic attacks are associated with increased ACTH and cortisol levels. Subjects pre-treated with the GABA agonists, alprazolam and vigabatrin, before a CCK-4 challenge showed decreased symptoms of panic and blunted response of ACTH and cortisol [86,87]. These studies are consistent with the proposed theory, that increased activity in the GABA system associated with yoga-based practices would decrease anxiety and stress reactivity.

HPA axis abnormalities, as indicated by higher CRH levels in cerebrospinal fluid (CSF), have been found in PTSD subjects [79]. Compared to normal controls, individuals with PTSD can have lower PNS tone, higher cardiac SNS activity, and decreased activity in the GABA system [19–21]. In humans low plasma GABA levels after a traumatic event predict the development of PTSD [88]. Transmagnetic stimulation studies of individuals with PTSD revealed bilateral decreases in the $GABA_A$ system activity [89]. Functional imaging studies of PTSD subjects have documented decreased benzodiazepine-$GABA_A$ receptor binding in the prefrontal cortex (PFC), hippocampus, amygdala, and thalamus, the same regions that are affected by VNS, suggesting an association between the GABA and ANS systems [25,40,72,73,90].

Decreases in benzodiazepine binding in regions of the brain known to support emotions and affect are consistent with abnormalities seen in imaging studies of individuals with PTSD. Positron Emission Tomography (PET) studies of PTSD subjects show decreased activation of the medial PFC and increased activation of the amygdala in response to the reading of trauma related scripts and threatening faces [91]. A similar pattern is seen in individuals with a genetic predisposition to depression, who show increased left amygdala activation in response to threatening faces [92].

Exemplary disorders

Yoga treatment for epilepsy

Stress is associated with increased seizure frequency [93]. Most adults with poorly controlled seizures have complex partial seizures with a temporal lobe focus [17]. As part of the limbic system, medial temporal lobe structures including the amygdala, hippocampus and entorhinal cortex are considered to be an anatomical link between emotional stress and its neurophysiological consequences [10,94]. Eggers theorized that resonator neurons, which process information from sensory stimuli and other neurons, are at increased risk for epileptogenic discharge during psychological stress due to inputs from the circuit of emotion which includes the hippocampus, amygdala, entorhinal cortex and dorsal raphe nucleus [17]. Evidence that stress can increase seizure frequency is consistent with the hypotheses that stress-induced allostatic load leads to pathological conditions such as increased seizure activity. According to the neurovisceral integration theory, stress is associated with impaired vagal tone, decreased HRV, and poor health. Furthermore, studies show that individuals with epilepsy have low HRV, greater risk of sudden death, and increased morbidity [8]. Therefore, the reduction of seizure frequency by yoga practices may be attributable to increased vagal tone and GABA activity, reduced stress reactivity, and diminished allostatic load.

A search of the literature between 1994 and 2009 through Pub Med using the words 'yoga' and 'epilepsy' identified five controlled studies in adults who had continued to have seizures despite treatment with antiepileptic drugs [27,32–35]. All five studies reported significant decreases in seizure frequency in groups treated with yoga. In addition, one study documented concurrent decreases in biological markers of stress: galvanic skin response, blood lactate, and urinary vinyl mandelic acid [35,95]. In normal subjects, the practice of Iyengar yoga is associated with increased PNS activity, improved mood, decreased anxiety and increased thalamic GABA levels, all of which could contribute to decreased seizure frequency [60,75]. Thus reduction in stress, increased PNS activity and increased brain GABA levels associated with yoga-based interventions would all contribute to improved seizure control.

Yoga treatment for depression

Controlled studies have found yoga-based interventions to be effective in treating depression ranging from mild depressive symptoms to major depressive disorder (MDD) [31]. The yoga-based interventions have included Sudarshan Kriya Yoga (emphasizing breath practices), Iyengar Yoga, and Resonance Breathing [54,96,97]. Iyengar yoga has been shown to decreased depressive symptoms in subjects with depression [97]. Iyengar yoga is associated with increased HRV, supporting the hypothesis that yoga breathing and postures work in part by increasing PNS tone [60]. The success of yoga-based therapies in alleviating depressive symptoms is consistent with the proposed neurophysiological mechanisms: yoga breathing induces increased parasympathetic tone which increases GABAergic activity associated with improved mood and anxiety reduction.

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Yoga treatment for stress, anxiety disorders, and PTSD

Controlled studies have demonstrated that yoga practices decreased symptoms in PSTD, Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Panic Disorder, and anxiety after natural disasters [29,30,98–100]. For example, a controlled study of 183 survivors of the 2004 Southeast Asia tsunami found that within one week, an eight-hour yoga breathing intervention resulted in a 60% decline in scores on the Post-traumatic Stress Disorders Checklist (PCL-17) and a 90% drop in scores on the Beck Depression Inventory (BDI). These improvements were sustained at 6-week and 6-month follow-up. In comparison, no significant change occurred in PCL-17 or BDI scores between baseline and 6-weeks in the wait-list control group [30]. These findings indicate that comorbid symptoms of depression and PTSD were decreased by a yoga breath-based intervention. Yoga practices also reduce stress and anxiety in subjects without a psychiatric diagnosis, suggesting that the beneficial effects of yoga are generalizable to larger populations [101,102]. Evidence that yoga-responsive anxiety disorders, including PTSD, Generalized Anxiety Disorder, and Panic Disorder, have low HRV and low GABA activity is in accord with the theory that imbalances in the ANS and GABA systems constitute an allostatic load that can be reduced by yoga-based therapies [19–21,89,103–106].

Correcting ANS and GABA abnormalities decreases PTSD symptoms**.** The interactions of the prefrontal cortex (PFC), hippocampus and amygdala in conjunction with inputs from the ANS and GABA system provide a network through which yoga-based practices may decrease symptoms. In response to stressful tests, for example, subjects with PTSD show a pattern of decreased PFC activation and increased amygdala activation consistent with failure of the PFC to inhibit the amygdala [2]. In response to emotionally laden cues, PFC activity decreases in PTSD subjects, a group known to have reduced PNS activity, as opposed to the increased PFC activation seen in subjects with higher PNS activity [107]. Compared to subjects with low HRV, subjects with high HRV had faster reaction time and fewer errors on a continuous performance task that requires the support of the PFC [108]. In addition, subjects with high HRV had lower cortisol levels after a cognitive test compared to subjects with low HRV, implying that high HRV is associated with a decrease in perceived stress [109]. To summarize, subjects with PTSD have low HRV, decreased activation of the prefrontal cortex, and increased activation of the amygdala.

The PFC exerts tonic inhibitory control over the amygdala via GABA projections [2]. Under conditions of uncertainty and threat, the PFC can become hypoactive [2] leading to a failure to inhibit overactivity of the amygdala with emergence of PTSD symptoms such as hyperarousal and re-experiencing. This could represent a neural correlate of the failure of extinction of fear reactions over time as seen in PTSD [79]. PFC activation associated with increased PNS activity could improve inhibitory control over the amygdala via PFC GABA projections, decreasing amygdala overactivity and reducing PTSD symptoms.

The insular cortex also sends inhibitory GABAergic projections to the Central Extended Amygdala (CEA) [110]. From the CEA, GABAergic neurons project to the PBN and dorsal vagal complex [110]. The insular cortex is located deep in the Sylvian fissure between the temporal and frontal lobes. Sensory information from the environment and interoceptive information about the internal homeostatic condition of the body are conveyed by the PNS via the NTS to the insular cortex where, according to Craig's neuroanatomical theory, a map of the internal state of the body is maintained [111]. While activation of the amygdala is necessary for energy mobilization, over activation of the amygdala as seen in PTSD reflects allostatic load associated with the hypervigilant condition (excess arousal) [91]. According to our proposed theory, restoration of strong tonic GABAergic inhibition of the amygdala would result in decreased output from the CEA to the hypothalamus and brainstem nuclei, reducing symptoms of hyperarousal, over reactivity, and re-experiencing in PTSD [112]. Psychological states such as anxiety, depression, and PTSD, associated with PFC hypoactivity and lack of inhibitory control, are characterized by poor habituation to novel neutral stimuli, pre-attentive bias for threat information, deficits in working memory and executive function, and poor affective information processing and regulation [10]. The presence of GABA neurons in the thalamus, insular cortex, amygdala, and hippocampus as well as GABA projections from both the insular cortex and the PFC to the amygdala completes the pathways that would constitute an anatomical substrate for the effects of ANS balance and imbalance on emotion regulation and cognitive function (see Fig. 1).

Empirical data-yoga treatment for chronic pain and depression

Chronic pain is associated with ANS abnormalities [113]. In humans, the antinociceptive effect of VNS may rely on central inhibition rather than alterations of peripheral nociceptive mechanisms [114]. The NTS sends projections to the periacqueductal grey (PAG), a pontine structure containing GABA neurons which is important in behavioral responses to threat, stress and pain [115]. Stimulation of the PAG increases HRV and decreases pain [116]. GABA receptors in the thalamus are implicated in pain control [117]. Following a 60-min yoga posture session, a 34% increase in thalamic GABA levels has been shown in experienced yoga practitioners and a 15% increase in novices with 12 weeks of yoga posture training [75,118]. Back pain and depression are frequently comorbid and have both been successfully treated with yoga-based interventions in randomized controlled studies [31,119,120]. Two studies are discussed in detail as a foundation for empirical data not presented elsewhere on the effects of a 12-week yoga intervention in two depression subjects with chronic low back pain.

Yoga and walking (YW) study

Normal subjects with no prior yoga experience were randomized to either a 12-week Iyengar yoga intervention ($n = 19$) or a 12-week metabolically matched walking intervention ($n = 15$). Both groups were scanned by magnetic resonance spectroscopy (MRS) before (Scan 1) and after (Scan 2) the 12-week interventions. After completing Scan 2, the yoga subjects performed a 60-min yoga session followed immediately by Scan 3. After completing Scan 2, the walking group subjects performed a 60-min walking session followed immediately by Scan 3. In both groups of normal subjects there were no significant increases in tonic GABA levels (Scan 2–Scan 1) over the 12-week study. However, there was an acute increase in thalamic GABA levels immediately after the 60-min yoga session (Scan 3–Scan 2). These increases in thalamic GABA levels in the yoga group were positively correlated with improved mood and decreased anxiety. There were no significant changes in GABA levels in the walking group. The yoga group also showed a significant improvement in mood and decreased anxiety during the 12-week intervention compared to the walking group. Such observations support the hypothesis that part of the effect of yoga is vagal afferent activation by slower breath rates often used during yoga posture techniques, but not during walking.

Chronic low back pain (CLBP) study

In a randomized controlled trial, a 12-week Hatha yoga intervention designed for treatment of chronic low back pain was compared to usual care [121]. Subjects in the yoga intervention showed significantly greater reduction in pain scores compared to subjects

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receiving standard care. Two subjects with comorbid chronic low back pain and MDD were recruited from the CLBP Study so that GABA levels before and after the 12-week Hatha yoga intervention could be obtained using the same acquisition sequence used in the YW Study.

Iyengar yoga is a branch of Hatha yoga. Review of the two manualized 12-week interventions, Iyengar yoga from the YW study and Hatha yoga from the LBP study showed that the two 12-week interventions were comparable, thus allowing comparison of MRS data from subjects from the LBP study with the normal subjects from the YW study [75,121]. The depression module of the Patient Health Questionnaire 9 (PHQ-9) was used to measure depressive symptoms [122]. PHQ-9 scores $\geqslant 10$ have 88% specificity and 88% sensitivity for the diagnosis of MDD [123]. Subjects had PHQ-9 scores of 22 (severe depression) and 20 (moderately severe depression) at the beginning of the yoga intervention and scores of 7 (mild depression) and 4 (not depressed enough to be considered MDD) respectively at the end of the study. The depressed subjects with chronic low back pain had mean thalamic GABA levels of 0.039 ± 0.004 GABA/Creatine ratios (GABA levels) before the 12-week yoga intervention (Scan 1) and mean GABA levels of 0.049 ± 0.010 after the intervention (Scan 2) for a change of 0.014 ± 0.006. The normal subjects had mean GABA levels of 0.065 ± 0.021 for Scan 1, and 0.061 ± 0.021 for Scan 2, for a change of -0.004 ± 0.017 (see Fig. 2). There were no significant changes in tonic GABA levels over the 12-week intervention in the normal subjects ($t = -1.01$, $df = 18$, $p = 0.33$), presumably because they had been screened to not to have any disorders associated with low GABA levels such as depression, anxiety or chronic pain. In contrast the chronic low back pain group showed a greater increase in GABA levels over the course of the study. Although the small number of low back subjects ($n = 2$) precludes statistical analysis, their lower GABA levels at baseline increased after the yoga intervention towards the level seen in the normal group. Both subjects had been unresponsive to pharmacologic treatments with agents known to increase the activity of the GABA system. Subject #1 was taking duloxetine, atomoxetine, clonazepam and eszopiclone; Subject #2 was taking fluoxetine. Medications were taken at the same time prior to each scan to reduce any acute effect of the medications on GABA levels. The results from these two subjects are consistent with the proposed theory that predicts (1) the lower GABA levels found in subjects with depression or low back pain, (2) an increase in GABA levels towards those of normal subjects after a 12-week yoga intervention, (3) improved mood in association with increased GABA levels, (4) subjects remained symptomatic with low GABA levels until they received the yoga intervention that presumably corrected their PNS imbalance, after which GABA levels increased and depressive symptoms decreased, (5) the comorbidity frequently seen in depression and chronic pain can be explained by imbalances in the PNS and GABA systems seen in both disorders.

Discussion

The autonomic nervous system plays a central role in the response to stress. The imbalances that develop under conditions of stress can be traced to decreased PNS activity and increased SNS activity. Stress exacerbates symptoms in disorders associated with low GABA activity, such as epilepsy, depression, PTSD, and chronic pain. These stress exacerbated disorders are marked by PNS underactivity as indicated by low HRV, increased HPA Axis activity as indicated by increased cortisol, and reduced GABAergic activity in the CNS (see Fig. 3).

Stress and its consequence, allostatic load, exacerbate symptoms of epilepsy, depression, PTSD, chronic pain and other disorders that are impacted by stress reactive systems. The therapeutic effects of yoga can be understood in part through its direct effects on the autonomic nervous system and indirect effects on the GABA system. Evidence suggests that interventions such as VNS and yoga, which increase PNS and GABA activity, may be effective in treatment resistant subjects who failed to respond to pharmacologic agents that increase activity in the GABA system [71]. Accordingly in some cases, correction of ANS imbalance may be a necessary factor that allows for the improvement of GABA function, and possibly in other systems as well.

The components of the proposed theory will need further testing and refinement using controlled studies, larger sample sizes, brain imaging, and other emerging technologies. The model presented may be of heuristic value as a framework for the integration of new research information about the pathophysiology and innovative treatment of conditions with significant morbidity and mortality.

Summary and future implications

An explanatory framework is presented that attributes the benefits of yoga to the reduction of allostatic load in frequently comorbid conditions. Neurophysiological, neuroanatomical, and clinical evidence converge in support of the proposed theory of shared pathogenesis and responsiveness to treatments, such as yoga, that stimulate an under active parasympathetic nervous system and increase the inhibitory action of a hypoactive GABA system in brain pathways and structures that are critical for threat perception, emotion regulation, and stress reactivity. Furthermore, yoga practices can be used as non-invasive probes to explore dynamically the body's stress response and regulatory systems. The insights gained from such studies could be utilized to develop a lexicon of specific mind–body practices for prevention and treatment of a wide range of neuropsychiatric and stress-related medical conditions.

Conflict of interest

C.C. Streeter reports no conflicts of interest. P.L. Gerbarg reports no conflicts of interest. D.A Ciraulo reports no conflicts of interest. R.B. Saper reports no conflicts. R.P. Brown reports a possible conflict with a pending patent, Confirmation No. 9891, using 7-keto DHEA for the treatment of Post Traumatic Stress Disorder.

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