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Determining Psychoneuroimmunologic Markers of Yoga as an Intervention for Persons Diagnosed With PTSD: A Systematic Review

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Abstract

There is a growing body of research on yoga as a therapeutic intervention for psychological symptoms of post-traumatic stress disorder (PTSD) accompanied by speculations on underlying physiologic mechanisms. The purpose of this systematic review is to identify, qualitatively evaluate, and synthesize studies of yoga as an intervention for PTSD that measured physiologic outcomes in order to gain insights into potential mechanisms. The focus is on studies evaluating yoga as a therapeutic intervention for PTSD rather than for trauma exposure, PTSD prevention, or subclinical PTSD. Multiple databases were searched for publications from the past two decades using terms derived from the question, "In people with PTSD, what is the effect of yoga on objective outcomes?" Eligibility criteria included yoga-only modalities tested as an intervention for formally diagnosed PTSD with at least one physiologic outcome. Results of this review confirmed that, though much of the published literature proposes physiological mechanisms underlying yoga's effects on PTSD, very few studies ($n = 3$) have actually evaluated physiological evidence. Additionally, several studies had methodological limitations. In light of the limited data supporting yoga's beneficial effects on autonomic nervous system dysregulation, we present a theoretical model of the psychoneuroimmunologic processes associated with PTSD and the effects yoga may have on these processes to guide future research. Gaps in the literature remain for mechanisms related to activation of the hypothalamic–pituitary–adrenal axis and inflammation. Additional rigorous mechanistic studies are needed to guide development of effective yoga interventions for PTSD to augment existing evidence-based PTSD treatments.

Keywords

yoga, post-traumatic stress disorder, mechanism, measurement, psychoneuroimmunology, systematic review

Evidence-based, cognitively oriented treatments currently in use for addressing the symptoms of post-traumatic stress disorder (PTSD), such as prolonged exposure therapy, have significant limitations. They are not effective for as many as one third of individuals with PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), and the rates of dropout and nonresponsiveness to treatment in studies of standard PTSD treatments often exceed 50% due to fear of exposure-based treatment causing an increase in distress (Walser & Westrup, 2007). The development of innovative, evidence-based alternative and adjunctive PTSD treatment approaches, such as yoga, is thus a priority. Such development requires a solid understanding of the mechanisms of action underlying a potential intervention's effects on the symptoms of PTSD.

Yoga has long been used to promote a sense of well-being, to manage and reduce stress, and more recently as a form of exercise. The popularity of yoga has grown exponentially in recent years, and it is widely accessible in community settings such as health clubs and community centers. Yoga is also being used with increasing frequency as a clinical intervention for a variety of physical and mental health disorders including PTSD. However, its effectiveness for treatment of PTSD has not been established, and the science related to the use of yoga

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as a therapeutic intervention for PTSD remains limited in scope and methodology.

The authors of multiple recent systematic reviews and meta-analyses of research on yoga as a clinical intervention concluded that the evidence related to the use of yoga for treatment of PTSD and its associated symptoms is promising but limited by methodological problems; specifically, few of the studies were randomized-controlled trials (RCTs), most had small sample sizes and/or were inadequately powered, and there is inconsistency among studies regarding yoga procedures and measures used to assess yoga effects. Additionally, these studies have commonly had only psychological outcomes rather than both psychological and physiological outcomes; thus, measures have most often been subjective via either self-report or clinician report of symptoms or functioning. In some cases, the validity and clinical significance of some of the self-report measures have not been evaluated, whereas in other cases, researchers have used well-validated self-report and clinician-administered measures. Similarly, some studies have required formal PTSD diagnosis as an inclusion criterion, whereas others have used the broader criterion of exposure to trauma.

The authors of most of these studies speculate on the physiological mechanisms underlying the effects of yoga on psychological symptoms of PTSD. These posited mechanisms are consistent with the literature on the psychoneuroimmunology of PTSD. Studies of the use of yoga in non-PTSD populations that have mechanistic and objective outcome measures also support these physiological mechanisms, albeit by extrapolation, which weakens the strength of the evidence. Although the number of studies on the use of yoga in PTSD that include objective, physiological measures of yoga's effects is growing, there are still very few. Further, none of the existing literature reviews have focused specifically on evaluating such studies to gain insight into possible physiological mechanisms underlying these effects.

To address this gap in the literature, we present here a review of the state of the science regarding the potential physiological mechanisms underlying the effects of yoga on the symptoms of PTSD. This review comprises a definition of yoga and description of its components, a systematic review of the literature describing studies exploring the effects of yoga as a therapeutic intervention on objectively measured symptoms of PTSD, and a comparison of objective and subjective measures of PTSD symptoms. Based on our findings in this review, we developed a theoretical model of the effects that yoga may have on the psychoneuroimmunologic processes associated with PTSD, which we present below as well.

Defining Yoga

Yoga in its classical form is a multifaceted system that includes Indian philosophical principles and specific practices for promoting physical, emotional, and spiritual well-being (Feuerstein, 2001). According to classical yoga theory, as written in the ancient Yoga Sutras, the purpose of yoga is to control physiologic and cognitive reactivity and to enhance sensory awareness and mental tranquility (Iyengar, 1976; Satchidananda, 1990). Classical yoga includes several approaches or types. In the West, yoga commonly refers to only one of these types, hatha yoga. Hatha yoga includes physical postures (asanas), controlled breathing techniques (pranayama), ethics (whether implicit or explicitly taught), and meditative components (varying from simple observation of breath to advanced techniques). This type of yoga is primarily based on the use of the active, physical dimension of yoga and controlled breathing techniques as a foundation to access the philosophical and meditative dimensions. Asanas and pranayama are not necessary components in all types of yoga; however, they are the most commonly practiced components in modern applications of yoga. Used singularly or in various combinations as interventions in yoga research, these components represent a complex system by which yoga may positively affect physical and mental health. Example combinations may include physical postures and one or two breathing techniques; mostly breathing and some meditative techniques with ethics; or more evenly distributed use of breathing, meditation, and postures with a firm basis of ethics. For the purpose of this review, we define yoga as constituting a variable mixture of controlled breathing, ethics, a meditative component, and/or physical postures (Gard, Noggle Taylor, Park, Vago, & Wilson, 2014). We chose a broad definition due to our expectation of finding limited studies on the topic. The large variation in composition of yoga interventions across studies, however, makes comparison difficult and precludes more statistically grounded review such as meta-analysis.

Controlled Breathing Techniques (Pranayama) and Underlying Physiological Basis

Pranayamas involve deliberate breath regulation. These techniques range from simple observation of the breath and deep, even diaphragmatic breathing to more complicated unilateral nostril techniques and ratio breathing with or without breath retention. Authors have theorized that pranayamas affect mood and physiological function through changes in sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activation, which alter conditioned nervous system responses (Iyengar, 1976, 2001; Rosen, 2002). Also, the control of voluntary breathing practices is thought to improve mental focus and concentration, promoting mindfulness and enhancing relaxation while inducing a sense of calm (Satchidananda, 1990).

Meditative Component and Underlying Physiological Basis

The meditative component of yoga is difficult to describe because it involves overlapping phenomena, and yoga theorists, practitioners, and researchers all have different ways of explaining it. For example, Telles et al. (2015) operationalized yogic meditation as three phases of attention, based on traditional yogic texts: "focused attention" on thoughts related to a

particular topic, "meditative focusing," or effortful, focused attention on a single meditative object, and "pure meditation," or an unbroken, effortless stream of attention on a meditative object. Other descriptions also include guided or unguided awareness of bodily sensations for training attention (Gard et al., 2014; Mehling et al., 2012; Schmalzl, Powers, & Blom, 2015; Stankovic, 2011). In its totality, the meditative component incorporates physical relaxation, interoceptive and proprioceptive awareness, and various forms of present-moment attention, sometimes referred to as mindfulness. However, this component is not synonymous with mindfulness, a specific meditation technique, or relaxation alone.

Like pranayama, the meditative component of yoga activates the PNS, modulating the stress response and SNS overactivity while inducing the relaxation response (Benson, 2000; Kabat-Zinn, 1982). Meditative practice improves attention and concentration, enhancing interoceptive sensory awareness, thereby reducing conditioned reactivity (Boccio, 2004). Activation of the PNS is thought to be one mechanism through which these changes in awareness and reactivity improve physical and psychological functioning (Feuerstein, 1989; Streeter, Gerbarg, Saper, Ciraulo, & Brown, 2012). More recent models of multicomponent yoga practices that include yogic meditation propose complex integration of bottom-up neurophysiological processes (e.g., afferent/reafferent input from interoceptive, proprioceptive, and cardiovascular processes) and top-down neurocognitive processes (e.g., frontoparietal network interacting bidirectionally with the PNS) as a mechanism of action (Gard et al., 2014; Schmalzl et al., 2015; Villemure, Čeko, Cotton, & Bushnell, 2014).

Physical Postures (Asanas) and Underlying Physiological Basis

Asanas are physical forms that involve repetitive stretching and force resistance movements that, like exercise, increase circulation to muscles and connective tissues (Riley, 2004). In fact, researchers commonly employ exercise as a comparison intervention in studies involving yoga asanas (Ross & Thomas, 2010). Yoga forms require coactivation of primary and antagonist muscle groups, which improves proprioceptive tone (Riley, 2004) and nervous system functioning (Iyengar, 2005), as evidenced by increased muscle size, strength, and endurance (Brochu et al., 2002) and improved joint range of motion and flexibility (Galantino et al., 2004). Investigators also have documented cardiopulmonary benefits such as improved lung function in healthy adults and those with chronic lung diseases (Raub, 2002). Asana practice also improves concentration, mental focus, mindful movement, and interoception, or awareness of body sensations (Emerson & Hopper, 2011; Satchidananda, 1990).

Ethics

Traditional yoga practices also include ethical guidance about inter- and intrapersonal attitudes and behaviors such as nonviolence, truthfulness, and self-reflection. Within modern yoga teaching, these ethics are often implicit, which makes them difficult to operationalize; thus, they are rarely evaluated.

Systematic Review

Method

Population, intervention, comparison, *and* outcome (PICO). The PICO question of interest for this review was, "In people with PTSD, what is the effect of yoga on objective outcomes?" More specifically:

- Population: Adults (18 years of age or older) diagnosed with PTSD. This population does not include individuals with exposure to trauma or traumatic stress symptoms without PTSD diagnosis.
- Intervention: Yoga defined broadly as a variable mixture of ethics, controlled breathing, meditative components, and/or physical postures.
- Comparison: Studies may or may not include any type of comparison group.
- Outcome: Objective, physiologic measures (which may be in addition to self- or clinician-reported psychological symptoms, which are usually the focus of PTSD outcome studies).

Data sources. We conducted systematic searches of PubMed®, Embase®, PsycINFO®, Cumulative Index to Nursing and Allied Health Literature®, Web of Science®, and Scopus® for articles published from January 1, 1994, to September 30, 2016. We selected this time frame based on the evolution of pertinent literature and the U.S. National Institutes of Health grant funding opportunities, both of which began increasing in the 1990s (Jeter, Slutsky, Singh, & Khalsa, 2015). We developed standard search terms based on the PICO question in consultation with a master librarian (Table 1), and limited searches to peer-reviewed journal articles of studies with participants 18 years or older that were available in English. We also reviewed systematic literature reviews to identify any studies we may have missed in our searches.

Study selection. Initially, we included articles in this review only if they were original reports of RCTs. However, given that only one study met this standard, we included non-RCTS in our discussion to present the current state of the science. Articles were excluded if they (1) were irrelevant to the search terms, (2) included interventions that incorporated both yoga and nonyoga modalities, for example, mindfulness-based cognitive therapy, (3) did not include an intervention, (4) did not include an intervention specifically for PTSD, (5) did not use quantifiable measures to establish a PTSD diagnosis based on the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000, 2013) like, for example, the Clinician-Administered PTSD Scale (Weathers, Ruscio, & Keane, 1999) or the Posttraumatic Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1994), or (6) did not include at least one objective physiologic outcome measure (see

Table 1. Search Terms Used to Identify Articles Evaluating Objective Measures of the Effects of Yoga as a Treatment for Post-Traumatic Stress Disorder (PTSD).

Population	Intervention	Outcome
PTSD	Yoga	Skin conduction
posttraumatic stress disorder	Hatha	Galvanic skin response
post-traumatic stress disorder	Hatha yoga	Heart rate
	Yoga breathing	Glucose
	Yoga controlled breathing	Cytokines
	Pranayama	Acoustic startle response
	Yoga meditation	Acoustic startle
	Yoga meditative techniques	Cortisol
	Yoga nidra or yoganidra	Blood pressure
	Yoga relaxation	Heart rate variability or HRV
	Yoga stretch	
	Yoga poses	
	Yoga positions	
	Yoga postures	
	Yoga exercise	
	Yoga asana or asanas	
	Yama	
	Niyama	
	Yoga ethic or ethics	

Figure 1 for a PRISMA flow diagram of the search and selection process). All of the authors conducted the literature searches, screening, and selection of articles including two experts on PTSD (U.A.K., J.N.T.) and two on yoga (D.D.E., J.N.T.).

Results

Our initial searches yielded 46 records, and we identified 12 additional records by ancestry. Of these combined 58 records, 12 were duplicates, yielding 46 records to be screened (Figure 1). Most failed to meet all search criteria, although many were relevant. Half were review, theoretical, or commentary articles proposing physiological mechanisms yet lacking original research. Of the remaining 23 studies, 9 involved people diagnosed with PTSD and focused exclusively on psychological outcomes. Similar to the reviews, these studies postulated but did not investigate physiological mechanisms. Of the remaining studies, 11 were not relevant to traumatic stress, formal PTSD diagnosis, yoga, or adults. The three remaining studies met all search criteria (Noggle Taylor, Valenza, & Barbieri, 2014; Seppala et al., 2014; van der Kolk, 2006). Of the six studies that used a yoga intervention but did not include participants with formal PTSD diagnoses, two included physiological outcomes (Telles, Naveen, & Dash, 2007; Telles, Singh, Joshi, & Balkrishna, 2010); we describe them here for the sake of comparison.

Diagnosed PTSD. van der Kolk (2006) reported the first known study of yoga as an intervention for people diagnosed with PTSD using objective outcomes. The researchers compared 8 people with PTSD to 11 people without PTSD before and after eight sessions of hatha yoga (intervention details not disclosed). They could not analyze heart rate variability (HRV) reliably in the PTSD group due to movement artifacts, but the control group showed statistically significant improvement (increases) in HRV. These results suggested difficulty in analyzing HRV in people with PTSD.

In a feasibility study of an 8-week, twice weekly yoga intervention including postures, breathing, meditation, and ethics for people diagnosed with PTSD and insomnia, Noggle Taylor, Valenza, and Barbieri (2014) reported a novel method to evaluate complexity variability of HRV. Complexity variability is distinct from other methods. Most HRV measures collapse data across time into an estimate of central tendency (e.g., median), whereas HRV complexity variability measures variability (e.g., median standard deviation) of instantaneous complexity series. The investigators found a statistically significant decrease in variability of HRV complexity following yoga ($N = 12$), consistent with other clinical populations that show increased variability in HRV complexity, for example, people with depression. This method may overcome the analytical challenges in measuring cardiovascular dynamics that van der Kolk (2006) experienced.

Seppala et al. (2014) conducted an RCT with a wait-list control group to examine a 7-day multicomponent intervention that emphasized breathing among 21 male veterans with PTSD. Compared with controls, the yoga group had significant reductions in self-reported PTSD symptoms (total PCL-Military version score as well as reexperiencing and hyperarousal subscales) and anxiety that correlated with reductions in objective measures of hyperarousal, specifically, respiratory rate and the dark-enhanced startle (DES) response. These results are generally consistent with those of the previous two studies (Noggle Taylor et al., 2014; van der Kolk 2006), and, given that this study had the strongest design, they are most suggestive of yoga's beneficial influence (especially those of breathing practices) on physiological hyperarousal in people diagnosed with PTSD.

Trauma exposure without established PTSD diagnosis. Two additional community-based studies included objective outcomes to test the effects of yoga on individuals exposed to trauma following natural disasters (Telles et al., 2007, 2010), with one involving confirmation of traumatic stress symptoms but not a PTSD diagnosis (Telles et al., 2010). A month after floods, researchers randomized men living in temporary housing to a weeklong daily yoga regimen of 50% postures, 40% controlled breathing, and 10% meditation ($n = 11$) or to a wait list ($n = 11$). Primary analyses indicated no group differences over time in HRV (frequency and time domains) or respiratory rate or in subjective outcomes.

Previously, Telles, Naveen, and Dash (2007) had conducted a quasi-experimental study measuring similar outcomes in a prospective single-arm trial of yoga following an island tsunami. A month after the tsunami, 47 survivors (mainland [$n = 31$] or island [$n = 16$]) participated in a weeklong yoga regimen of strong ethical foundation, 50% postures, 25% breathing practices, and 25% meditative techniques. Pre-post

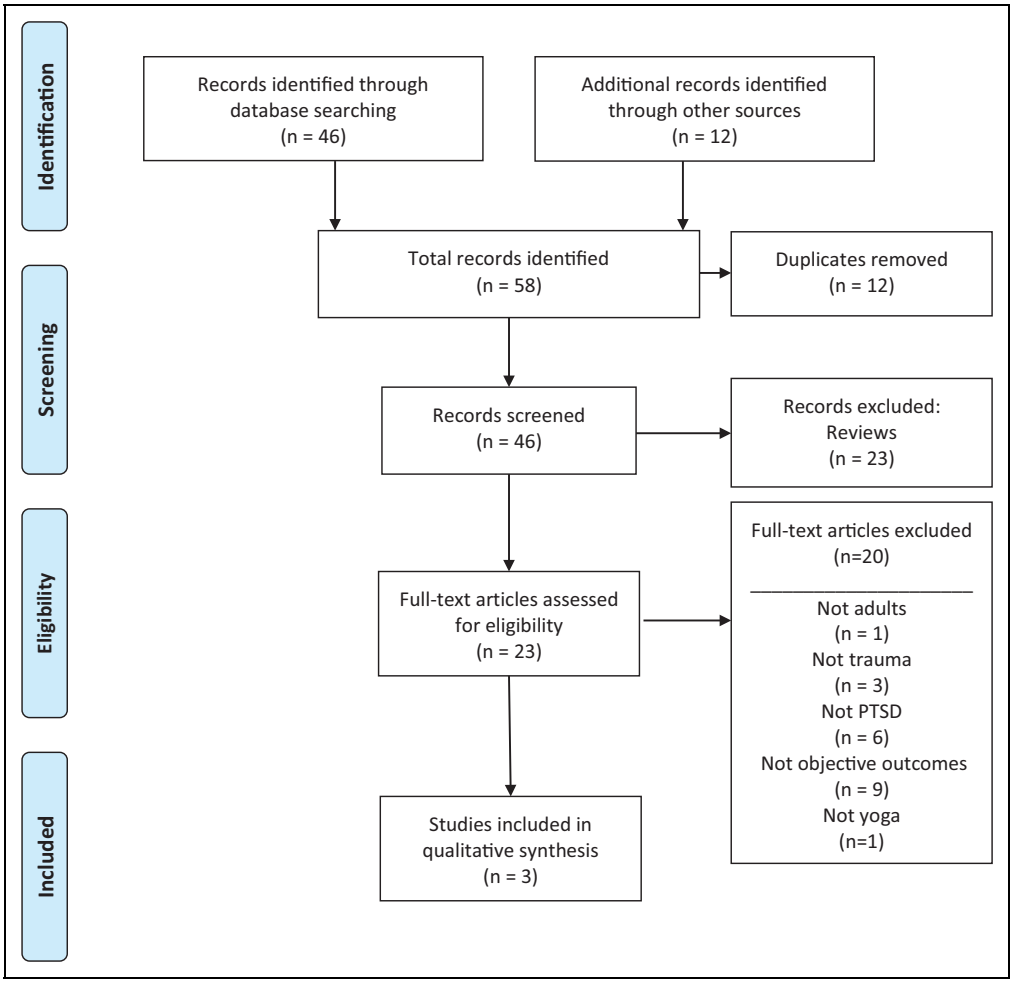

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Systematic identification of studies that evaluated the effects of yoga on physiological outcomes in adults with post-traumatic stress disorder.

results suggested that respiratory rate and heart rate (but not skin conductance) significantly improved following yoga. Given the lack of comparison groups in Telles, Singh, Joshi, and Balkrishna (2007), the null results of Telles et al. (2010) are more compelling.

These null results, however, conflict with the results we delineated above for people diagnosed with PTSD (Noggle Taylor et al., 2014; Seppala et al., 2014; van der Kolk, 2006). Yet we must interpret them more from the perspective of secondary prevention, which may have a greater degree of variability in symptoms, in contrast to results of studies evaluating people formally diagnosed with PTSD, who may show less variability and greater symptom severity. Furthermore, the sample size was small (a characteristic of all the reviewed studies that included objective outcomes), which was unavoidable due to the challenging setting of temporary field housing (Kraft & Telles, 2010).

Discussion of Systematic Review

Results of this review indicate that, while much of the published literature proposes physiological mechanisms that may underlie yoga's effects on PTSD, very few studies have evaluated physiological evidence. Furthermore, all of the studies we reviewed were preliminary, with small sample sizes and inadequate power, making it difficult to generalize. The only RCT (Seppala et al., 2014) suggested that yoga may reduce physiologic hyperarousal. Yoga may or may not affect autonomic control of heart rate, given the conflicting results, although the diversity of HRV measurement methods makes the results difficult to interpret across studies (Noggle Taylor et al., 2014; Telles et al., 2010; van der Kolk, 2006).

Only one of the three studies involving diagnoses of PTSD included measures of both PTSD symptom severity and at least one physiological variable. Seppala et al. (2014) reported a significant correlation between reduced startle responses and reduced psychological symptoms of hyperarousal, which persisted through 1-year follow-up, reinforcing the idea that physiologic hyperarousal (measured by DES) is a mechanism worth exploring further. In general, the results regarding psychological outcomes in these three studies are consistent with those of the larger body of studies focusing on PTSD symptom severity that did not include evaluation of physiological outcomes. Collectively, these findings suggest that yoga may be a promising intervention for PTSD.

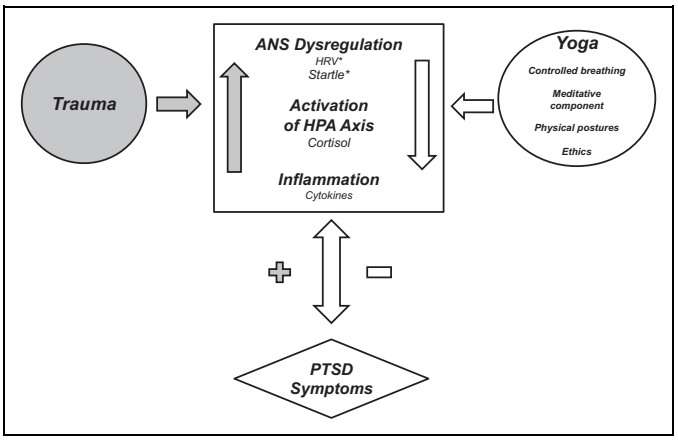

Figure 2. Theoretical model of the mechanisms underlying the effects of yoga on the symptoms of post-traumatic stress disorder (PTSD). The model broadly describes the psychoneuroimmunologic pathology associated with PTSD (noted as positive amplification) and yoga's potential ameliorating effects on these processes (noted as negative inhibition). Asterisks denote mechanistic biomarkers for which empirical data were identified in this review. ANS = autonomic nervous system; HPA = hypothalamic–pituitary–adrenal; HRV = heart rate variability.

It is worth noting that, in general, consistent with the process of knowledge development, published research regarding the physiologic basis and mechanisms of PTSD and yoga predate publications related to the effectiveness of yoga for PTSD by roughly a decade. The amount of research on the use of yoga for treating PTSD symptoms has increased significantly in the past 5–10 years, and we are aware of several studies currently underway that are testing yoga interventions in patients with PTSD. However, the fact remains that in our extensive and systematic review, we were able to identify only a limited number of peer-reviewed publications specific to this topic.

Theoretical Model for the Effects of Yoga on PTSD

Our theoretical model of the effects of yoga on the symptoms of PTSD is based on what is known about the psychoneuroimmunology of PTSD and what has been postulated about the psychoneuroimmunology of yoga (Figure 2). It is consistent with other proposed mechanistic models of the effects of yoga for behavioral health but specific to PTSD, and it uniquely treats endocrine and immune functions as equivalent to autonomic function in their contributions to these effects (Gard et al., 2014; Schmalzl et al., 2015; Streeter et al., 2012; Villemure et al., 2014). Furthermore, given the paucity of data discovered via this systematic review, it is a basic model. In contrast, these other proposed models have spoken broadly to behavioral health and multiple related disorders such as anxiety and depressive disorders and have expanded upon higher level neurocognitive processes in detail. Elaboration of the present theoretical model may well be informed by other models as additional physiologic and neurocognitive data on the effects of yoga on the symptoms of PTSD become available.

To date, due to the significant gaps in the literature that we identified during this review, there is little specific evidence from studies evaluating the mechanisms underlying yoga's effects on physiological indicators of PTSD to support much of this model. The psychoneuroimmunology of PTSD is well established and links psychological symptoms to three major physiological mechanisms: (1) autonomic dysregulation, especially hyperarousal; (2) activation of the hypothalamic–pituitary–adrenal (HPA) axis; and (3) activation of the inflammatory immune response. Researchers have used several physiological biomarkers (HRV, DES, cortisol, and pro-inflammatory cytokines) to quantify these responses to trauma.

Understanding of the physiological mechanisms of yoga is in its infancy but growing and includes research using physiological biomarkers similar to those used to quantify PTSD. In a systematic review of the use of yoga as treatment for neuropsychiatric disorders, Balasubramaniam, Telles, and Doraiswamy (2012) suggested a model in which yoga down-regulates the HPA axis, reduces cortisol levels, and influences several neurotransmitters, increasing neurotrophic factors and thereby reducing inflammation. These combined physiological effects likely counteract the stress response, reducing anxiety and associated symptoms and improving mood.

Autonomic Dysregulation

PTSD is associated with autonomic nervous system (ANS) dysregulation, notably increased SNS activity (increased heart rate, cardiac output, and blood pressure) along with decreased PNS activity opposing these responses (Hall, 2010). ANS dysregulation is associated with decreased HRV (central tendencies). HRV reflects the ability of the central nervous system (CNS) to respond immediately to fluctuations in blood pressure. Researchers have found correlations between decreased HRV and morbidity and mortality from diverse diseases including anxiety and depression (Barr, 2010).

Authors have postulated that the beneficial effects of yoga result from control of physiologic reactivity, decreased sympathetic activity, and activation of the PNS, counteracting PTSD-associated physiologic dysregulation and hyperarousal. Yoga increases vagal tone and HRV, evidence of improved PNS function (Khattab, Khattab, Ortak, Richardt, & Bonnemeier, 2007). Slow, rhythmic yoga breathing techniques synchronize SNS and PNS vagal activity outflow, resulting in increased HRV and arterial baroreceptor sensitivity characterized by a sense of calm (Satyapriya, Nagendra, Nagarathna, & Padmalatha, 2009). Yoga may reduce hyperarousal by decreasing respiratory rates (Spicuzza, Gabutti, Porta, Montano, & Bernardi, 2000) and increasing cardiac vagal modulation and HRV (Khattab et al., 2007; Raghuraj & Telles, 2008). Results of the present review suggest that HRV may be difficult to measure accurately in people diagnosed with PTSD, and it may be difficult to generalize across studies because of the variation in HRV measurement techniques. Standardization in the

measurement of HRV might increase the likelihood of its use as an important biomarker of yoga's effect on the psychoneuroimmunological effects of PTSD.

Another aspect of autonomic dysregulation in individuals with PTSD is overgeneralization of fear and inability to inhibit fear responses in the presence of safety. Impaired fear inhibition may be a specific psychophysiologic marker of PTSD autonomic hyperarousal (Jovanovic, Kazama, Bachevalier, & Davis, 2012). The acoustic startle response has been established as an objective measure of fear and anxiety behaviors. In humans, the startle response is increased in darkness as compared to well-lit environments, a phenomenon termed dark-enhanced startle (DES). DES may be a useful tool for assessing autonomic hyperarousal and PTSD symptom severity. Results of the present review support this potential, specifically Seppala and colleagues' (2014) finding that a breathing-based meditation intervention (pranayama) led to a significant reduction in DES.

Activation of the HPA Axis

Increased or chronic activation of the SNS can also impact cortisol levels and the immune response (Pace, Hu, & Miller, 2007). However, studies examining basal cortisol changes related to PTSD have yielded inconsistent findings (Kim et al., 2013; Mason et al., 2002). These discrepancies may reflect differences in cortisol sampling techniques, menstrual influences, or normal fluctuations in cortisol levels throughout the day. Also, cortisol levels may become unpredictable as a result of glucocorticoid resistance or dysregulation in negative feedback pathways between cortisol and pro- and anti-inflammatory cytokine levels due to prolonged activation of the stress response (Pace et al., 2007).

Cortisol is one of the most common biomarkers researchers use to assess yoga's impact on the stress response via the HPA axis. Investigators have studied yoga's effects on cortisol levels in a variety of populations, including healthy adults, patients with cancer, pregnant women, postmenopausal women, and yoga practitioners, but results have been inconsistent, similar to those of studies measuring cortisol in patients with PTSD. Collectively, these results suggest that cortisol may not be a sensitive biomarker of yoga's impact on the psychoneuroimmunological effects of PTSD.

Inflammatory Immune Response

The CNS response to trauma results in increased cellular inflammation and immunosuppression. As in PTSD, the SNS and PNS have opposite effects on inflammation and the immune response. SNS stimulation of white blood cells increases pro-inflammatory cytokine release, while PNS stimulation of macrophages and other white blood cells inhibits pro-inflammatory cytokine release (Corwin & Williams, 2007). Researchers have found elevated levels of inflammatory markers in survivors of trauma and individuals with PTSD (Pace & Heim, 2011). Alterations in cytokine activity are also associated with symptoms that commonly co-occur with PTSD, including depressive symptoms, fatigue, chronic tissue inflammation, and enhanced sensitivity to pain (Ren & Dubner, 2010).

Preliminary research has demonstrated that yoga affects the immune system. Yoga reduces levels of markers of inflammation, such as C-reactive protein and pro-inflammatory cytokines, and increases immunoglobulin A and natural killer cells (Gopal, Mondal, Gandhi, Arora, & Bhattacharjee, 2011; Kiecolt-Glaser et al., 2010). These effects on the immune system may be the mechanism through which yoga reduces pain, connective tissue damage, and the adverse nervous system remodeling resulting from sustained inflammation (Langevin & Sherman, 2007). Although none of the studies we reviewed on the use of yoga as an intervention in people with PTSD evaluated cytokines, evidence from these other studies suggests that yoga may counteract the pro-inflammatory state of PTSD.

Conclusion and Implications

Based on the interacting mechanisms of action underlying yoga that are supported in the broader literature, we have proposed a theoretical model to explain how yoga reverses the physiological changes associated with PTSD via the synergistic effects of controlled breathing, a meditative component, ethics, and physical postures (Figure 2).The science to support this theoretical model, however, is in its infancy. We found only three studies that met the eligibility criteria for our systematic review. Placing these studies in context within the theory of psychoneuroimmunology illustrated that the limited mechanistic data available on the effects of yoga on PTSD symptoms support the proposal that it has beneficial impacts on ANS dysregulation. DES is an especially promising biomarker, while further methodological development is required to determine the utility of HRV as a biomarker of ANS reactivity in individuals with PTSD. We identified no evidence regarding mechanisms of action for the effects of yoga on PTSD related to HPA-axis dysfunction or inflammatory immune responses, leaving these two aspects of the model theoretical. Since findings of cytokine changes in mechanistic studies of both PTSD and yoga are more consistent than those associated with cortisol, cytokines may be a better biochemical measure of yoga's effects on the psychoneuroimmunological impacts of PTSD. The variation in styles and components of yoga that researchers have been using in their studies on its effects on PTSD further complicates discovery of mechanisms. Further research on the use of yoga as an intervention in PTSD using more standardized descriptions of the intervention as well as additional biomarker outcome measures based upon the theoretical model we have presented is needed to refine the model and improve the science of the use of yoga as an adjunctive or alternative treatment of PTSD.

Yoga is low cost and low tech and supports self-management of a wide array of symptoms, characteristics that support widespread uptake and implementation of therapeutic interventions. Advances in the science to establish the

mechanisms of action and effectiveness of the use of yoga as an initial, adjunctive, or alternative treatment for PTSD have the potential to expand PTSD treatment modalities and access.

Authors' Contribution

Ursula Ann Kelly contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Dian Dowling Evans contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Helen Baker contributed to design, acquisition, and analysis; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Jessica Noggle Taylor contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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