Evidence for PTSD as a Systemic Disorder

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Contents

Abstract

Post-traumatic stress disorder (PTSD) has a prevalence of 6.8 % among the American population and an even greater prevalence among combat veterans. The conventional view of PTSD has been as a psychological adjustment disorder characterized by depression and anxiety in response to stressful circumstances. Recently, however, it has become apparent that it is much more than a psychological adjustment disorder. This began with the appreciation of the fact that dementia is much more common in PTSD, suggesting neurological changes in the disorder. There is now evidence for psychiatric changes (e.g., mood disorders, substance use and abuse), cardiovascular changes, autoimmune changes (e.g.,

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rheumatoid arthritis), tumorigenic changes, etc. The goal of this chapter is to briefly review the evidence for systemic involvement in preparation for subsequent chapters that will focus on detailed discussions of each organ system.

List of Abbreviations

AB	Alcohol abuse
AD	Alcohol dependency
CRH	Corticotropin releasing hormone
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DSM	Diagnostic and statistical manual of mental disorders
FT3	Free triiodothyronine
FT4	Free thyroxine
HPA	Hypothalamic-pituitary-adrenal
HPT	Hypothalamic-pituitary-thyroid
HR	Heart rate
MDD	Major depressive disorder
PTSD	Post-traumatic stress disorder
T3	Protein-bound triiodothyronine
T4	Protein-bound thyroxine

Introduction

Post-traumatic stress disorder (PTSD) affects those exposed, either directly or indirectly, to life-threatening or severely traumatic events. The diagnosis of PTSD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), requires (1) presentation of symptoms associated with the four diagnostic symptom clusters (intrusion symptoms, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity), (2) all symptoms beginning or worsening after the trauma, (3) symptoms persisting for more than 1 month, (4) significant symptom-related or functional impairment, and (5) that these symptoms are not caused by medication, substance use, or a medical condition (American Psychiatric Association 2013).

PTSD is common in both civilian and military populations. In 2005, the prevalence of PTSD among the general population of the USA was estimated to be 6.8 % (Kessler et al. 2005). The disease is even more prevalent in military veterans, with estimated prevalence rates ranging from 19 % in 2006 for American Vietnam veterans (Dohrenwend et al. 2006) to 22 % in 2009 for US veterans of the Iraqi and/or Afghani theaters (Seal et al. 2009). In addition to the direct costs of treatment for PTSD, the associations of lost productivity, reduced quality of life, and increased incidence of domestic violence, homelessness, suicide, and family strain make PTSD a burdensome disease to both the individuals affected and society (McCrone and Cawkill 2003).

PTSD was first added to the DSM in the manual's third edition and has conventionally been classified as a psychiatric disorder. However, since its addition to the DSM in 1980, numerous studies have found correlations between PTSD diagnosis and/or severity and medical diseases in other organ systems, including arthritis, asthma, and myocardial infarction (Weisberg et al. 2002; Spitzer et al. 2009).

Systems Involved in PTSD

The goal of this paper is to discuss evidence for systemic involvement in PTSD. To do this, we reviewed published studies and our own work focused on PTSD symptomatology, comorbidities, and associated diseases. By collecting and presenting evidence substantiating the argument that PTSD is more than just a psychiatric disorder, we hope to support the new and constructive viewpoint of PTSD as a systemic disorder that needs to be addressed on multiple fronts in order to improve research and treatment of this critical condition.

Neurological Involvement

Neuroanatomical abnormalities implicated in PTSD include reduced ***hippocampal*** volume (Bremner et al. 1995; Pitman and Rauch 2001; Vythilingam et al. 2002; Kitayama et al. 2005; Smith 2005; Karl et al. 2006; Shin 2006; Wang et al. 2010; Morey et al. 2012) and parahippocampal gyrus volume (Meng et al. 2014), reduced ***amygdalar*** volume (Karl et al. 2006; Morey et al. 2012; Meng et al. 2014), increased amygdalar response (Pitman and Rauch 2001; Shin 2006), reduced ***prefrontal cortex*** activation (Bremner et al. 1995; Sherin and Nemeroff 2011), reduced anterior ***cingulate*** cortex volume (Bremner et al. 1995; Karl et al. 2006; Meng et al. 2014), reduced ***corpus callosum*** volume (Karl et al. 2006), reduced left ***insula*** volume (Meng et al. 2014), and increased gray matter volume of the left insula (Meng et al. 2014) and ***superior temporal*** gyrus (De Bellis et al. 2002). Many of these neurobiological abnormalities provide plausible explanations for clinical features associated with PTSD such as altered learning and extinction as well as hyperarousal. However, for many of these abnormalities, it remains unclear whether they are preexisting conditions that predispose patients to developing PTSD or are changes acquired through traumatic stress and subsequent stress responses (Childress et al. 2013).

Reduced hippocampal volume is perhaps the most-studied and consistent neurological abnormality found in patients with PTSD (Childress et al. 2013). Volumetric reductions have been found in both hippocampal hemispheres in subjects with PTSD, either unilaterally [right hemisphere: (Bremner et al. 1995); left hemisphere: (Vythilingam et al. 2002; Morey et al. 2012)] or bilaterally (Pitman and Rauch 2001; Kitayama et al. 2005; Smith 2005; Karl et al. 2006; Wang et al. 2010). Karl et al. (2006) found that bilateral hippocampal volume in patients with PTSD was significantly smaller compared to trauma-exposed patients without PTSD and to

Table 1 Examples of neurological abnormalities associated with PTSD

Neuroanatomical region	Abnormality	Studies referenced
Hippocampus	Reduction in volume	*Right hemisphere*: Bremner et al. 1995
		Left hemisphere: Vythilingam et al. 2002; Morey et al. 2012
		Bilaterally: Pitman and Rauch 2001; Kitayama et al. 2005; Smith 2005; Karl et al. 2006; Wang et al. 2010
Parahippocampal gyrus	Reduction in volume	Meng et al. 2014
Amygdala	Reduction in volume	Karl et al. 2006; Morey et al. 2012; Meng et al. 2014
	Increase in response and activation	Pitman and Rauch 2001; Shin 2006
Prefrontal cortex	Reduction in response and activation	Bremner et al. 1995; Sherin and Nemeroff 2011
Anterior cingulate cortex	Reduction in volume	Bremner et al. 1995; Karl et al. 2006; Meng et al. 2014
Corpus callosum	Reduction in volume	Karl et al. 2006
Left insula	Reduction in overall volume	Meng et al. 2014
	Increase in gray matter volume	Meng et al. 2014
Superior temporal gyrus	Increase in gray matter volume	De Bellis et al. 2002

nonexposed patients; however, this difference was only apparent when analyzing the hippocampal volumes of adult samples but not pediatric samples. The lack of hippocampal size abnormalities observed in pediatric subjects suggests that PTSD-related reduction in hippocampal volume does not occur or become evident until adulthood. Interestingly, the duration of PTSD was not significantly related to changes in hippocampal volume. This example of altered hippocampal volume in adults with PTSD but not in children with PTSD demonstrates the difficulty in establishing the pathological relation between PTSD and anatomical abnormalities (Table 1).

Endocrine Involvement

The role of the endocrine system in regulating stress response has led to much research focused on the involvement of this system in PTSD. Both the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-thyroid (HPT) axis have been implicated in PTSD pathology (Table 2).

Table 2 Examples of endocrinological abnormalities associated with PTSD

Axis	Component(s)	Abnormalities	Studies referenced
Hypothalamic-pituitary-adrenal (HPA)	Cortisol	Decreased concentration in plasma and urine	Olff et al. 2006; Sherin and Nemeroff 2011; Wahbeh and Oken 2013
	Glucocorticoid receptor	Hyperfunction	Yehuda et al. 1991; Yehuda 2006
	Corticotropin releasing hormone	Increased concentration in cerebrospinal fluid	Baker et al. 1999, 2005
Hypothalamic-pituitary-thyroid (HPT)	Triiodothyronine; Thyroxine	Elevated triiodothyronine to thyroxine concentration ratio	Wang and Mason 1999; Sherin and Nemeroff 2011
	Thyroid-stimulating hormone (thyrotropin)	Decreased concentration	Boscarino 2004; Olff et al. 2006

PTSD has been associated with dysregulation of the HPA axis hormones at both basal levels and with low-dose dexamethasone suppression testing (Yehuda 2006). Several studies have found that patients with PTSD have decreased cortisol levels in plasma samples and urine samples (Olff et al. 2006; Sherin and Nemeroff 2011; Wahbeh and Oken 2013), increased ***glucocorticoid receptor*** function (Yehuda et al. 1991; Yehuda 2006), and increased corticotropin releasing hormone (***CRH***) concentrations in cerebrospinal fluid (CSF) from one-time lumbar puncture samples and serial samples taken throughout a 24-h period (Baker et al. 1999, 2005).

In an unaltered HPA axis, CRH secreted from the hypothalamus binds to receptors on cells of the anterior pituitary, which in turn produce and secrete adrenocorticotropin from the anterior pituitary into the adrenal cortex. Glucocorticoids such as cortisol are then produced and secreted by the adrenal gland, thereby activating sympathetic nervous pathways and initiating negative feedback to the hypothalamus and anterior pituitary. The relation between PTSD and hypocortisolism suggests a disinhibition of the negative feedback to the hypothalamus and anterior pituitary, resulting in altered stress encoding and fear processing as well as sustained elevated levels of CRH (Kolber et al. 2008).

Prolonged exposure of the hippocampus to CRH is also associated with hippocampal neuronal degeneration (VanItallie 2002; Sherin and Nemeroff 2011). The hippocampus contains high concentrations of mineralocorticoid receptors and glucocorticoid receptors, which are thought to regulate basal-level HPA activity and mediate glucocorticoid negative feedback, respectively (McDonald et al. 2005; Smith and Vale 2006). Therefore, findings of an atrophic relation between elevated CRH exposure and hippocampal volume provide an explanation for this common neuroanatomical abnormality as well as evidence for the disinhibition of the negative feedback pathways of the HPA axis (Smith and Vale 2006).

Several studies have found a positive association between PTSD severity and a disproportionate increase of ***triiodothyronine*** (T3 and FT3) concentration relative to that of ***thyroxine*** (T4 and FT4), indicating elevation in the peripheral deiodination (Wang and Mason 1999; Sherin and Nemeroff 2011). PTSD has also been associated with a decrease in ***thyroid-stimulating hormone*** (thyrotropin) (Boscarino 2004; Olff et al. 2006).

Similar to the neurological involvement of PTSD, it is difficult to determine whether abnormalities in the endocrine system associated with PTSD are consequences of the body's response to traumatic stress or preexisting conditions that increase susceptibility to the development of PTSD. Therefore, further investigation regarding the pathological role of endocrine involvement in PTSD is necessary in order to better understand the complex stress responses and their systemic consequences in patients with PTSD.

Psychiatric Involvement

Major psychiatric comorbidities of PTSD include anxiety and depressive disorders, particularly ***major depressive disorder*** (MDD) (Marshall 2001; David 2004; Cohen et al. 2009; Rytwinski et al. 2013) and ***substance abuse***, such as alcohol abuse (AB) or alcohol dependency (AD) [***AB/AD***: (Cohen et al. 2009; Pietrzak et al. 2011; Debell et al. 2014)]; ***Opioid use*** (Meier et al. 2014); and, ***Cocaine use*** (Meier et al. 2014). PTSD has also been associated with increased ***suicidal*** ideation and behavior (Davidson et al. 1991; Marshall 2001; Sareen et al. 2007; Jakupcak et al. 2009; Nock et al. 2009; Gradus et al. 2010; Panagioti and Tarrier 2012), especially when comorbid with MDD (Jakupcak et al. 2009; Gradus et al. 2010; Panagioti and Tarrier 2012; Ramsawh et al. 2014), alcohol abuse or dependency (Rojas et al. 2014), or other substance abuse (Moylan et al. 2001; Table 3).

There are also associations between PTSD and increased prevalence of neuropsychiatric conditions, including ***dementia*** (Qureshi et al. 2010, 2011; Childress et al. 2013), both chronic and episodic ***migraines*** (Buse et al. 2013), ***attention deficit hyperactive disorder*** (Antshel et al. 2013), ***somatic pain symptoms*** (Andreski and Breslau 1998; Beckham et al. 1998; Sareen et al. 2007; Defrin et al. 2008; Moeller-Bertram and Strigo 2012), ***hypervigilance*** and ***insomnia*** (Pigeon 2013), heightened ***aggression*** (Taft et al. 2009), increased rates of ***smoking*** (Fu et al. 2007) and emotional ***eating*** (Talbot et al. 2013), and deficits in ***executive functioning*** (Qureshi et al. 2011; Polak et al. 2012; Flaks et al. 2014).

The large number of psychiatric comorbidities in PTSD is critical to address because they cause significant functional impairment to those affected by PTSD. Furthermore, patients with PTSD-associated affective disorders will often self-medicate with alcohol and other illicit substances, which can further contribute to the severity and complexity of their affective disorders and can produce additional neurological damage and dysfunction (Fig. 1). Therefore, proper screenings and treatments for comorbid psychiatric and behavioral disorders in patients with PTSD are crucial in order to maintain patients' well-being and avoid further neuropsychiatric damage.

Table 3 Examples of psychiatric comorbidities associated with PTSD

DSM-5 diagnostic category (American Psychiatric Association 2013)	Comorbid disorder or symptom	Studies referenced
Depressive disorders	Major Depressive Disorder	Marshall 2001; David 2004; Cohen et al. 2009; Rytwinski et al. 2013
	Suicidal ideation / behavior	Davidson et al. 1991; Marshall 2001; Sareen et al. 2007; Jakupcak et al. 2009; Nock et al. 2009; Gradus et al. 2010; Panagioti and Tarrier 2012
Substance use and addictive disorders	Alcohol abuse / dependency	Cohen et al. 2009; Pietrzak et al. 2011; Debell et al. 2014
	Opioid Use	Meier et al. 2014
	Cocaine use	Meier et al. 2014
	Nicotine dependence	Fu et al. 2007
Neurocognitive disorders	Dementia	Qureshi et al. 2010, 2011; Childress et al. 2013
	Executive dysfunction	Qureshi et al. 2011; Polak et al. 2012; Flaks et al. 2014
Neurodevelopmental disorders	Attention-deficit/ hyperactivity disorder	Antshel et al. 2013
Somatic symptom and related disorders	Somatic pain symptoms, (general)	Andreski and Breslau 1998; Beckham et al. 1998; Sareen et al. 2007; Defrin et al. 2008; Moeller-Bertram and Strigo 2012
	Migraines	Buse et al. 2013
Trauma- and stressor-related disorders	Hypervigilance	Pigeon 2013
Sleep-wake disorders	Insomnia	Pigeon 2013
Disruptive, impulse-control, and conduct disorders	Heightened aggression	Taft et al. 2009
Feeding and eating disorders	Emotional eating	Talbot et al. 2013

Cardiovascular Involvement

Cardiovascular associations with PTSD include ***hypertension*** (Buckley and Kaloupek 2001; Norman et al. 2006; O'Toole and Catts 2008; Cohen et al. 2009; Qureshi et al. 2009; McFarlane 2010; Pietrzak et al. 2012; Paulus and Egge 2013), ***angina pectoris*** (Spitzer et al. 2009; Pietrzak et al. 2012), ***tachycardia*** (Gerardi et al. 1994; Buckley and Kaloupek 2001; Blechert et al. 2007; Pole 2007; Pietrzak et al. 2012; Paulus and Egge 2013), ***elevated heart rate*** (HR) and ***blood pressure*** in response to trauma-related cues (Shalev et al. 1992; Gerardi et al. 1994; Buckley and Kaloupek 2001; Barkay et al. 2012; Paulus and Egge 2013), ***peripheral arterial***

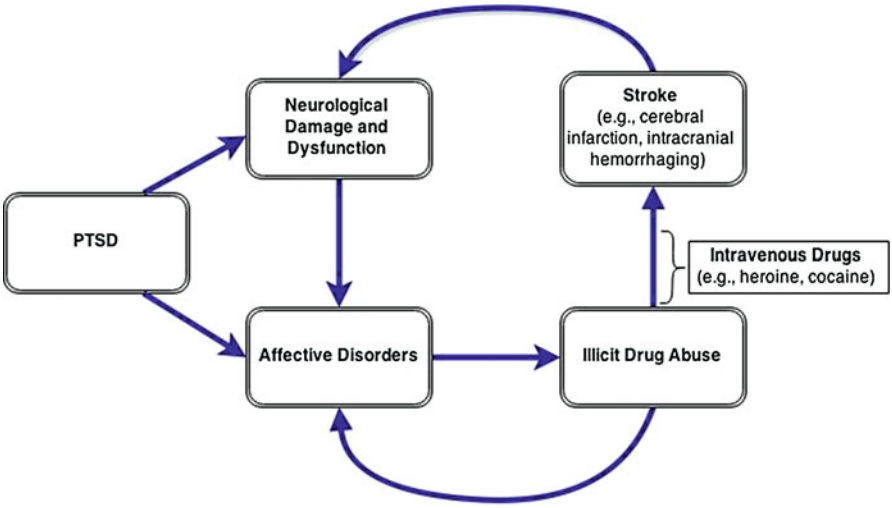

Fig. 1 Potential positive-feedback mechanisms compounding neuropsychiatric impairment in patients with PTSD. PTSD-inducing stimuli may directly impair neurological function and may produce mood disorders. Patients may self-medicate their mood disorders with illicit drugs and alcohol, which causes a positive-feedback loop thereby producing further neurological damage. This, in turn, may further enhance the neurological impairment and mood disorders associated with PTSD. This model supports the need for comprehensive screenings for both physical (e.g., cardiovascular risk factors) and behavioral changes (e.g., alcohol and drug use) in patients with PTSD

disease (Spitzer et al. 2009), atherosclerotic ***coronary artery disease*** (Ahmadi et al. 2011), ***heart failure*** (Spitzer et al. 2009; Pietrzak et al. 2012), ***myocardial infarction*** (Qureshi et al. 2009; Spitzer et al. 2009), and general ***cardiovascular disease*** (McFarlane and Rafalowicz 1994; Boscarino 1997; Schnurr and Paris 2000; David 2004; Sareen et al. 2007; Qureshi et al. 2009; Pietrzak et al. 2012).

One possible explanation for the cardiovascular abnormalities and damage associated with PTSD is increased sympathetic arousal (Bedi and Arora 2007) indicated by greater skin conductance (Shalev et al. 1992; Blechert et al. 2007; Pole 2007), elevated HR (Buckley and Kaloupek 2001; Pole 2007; Paulus and Egge 2013), low respiratory sinus arrhythmia (Blechert et al. 2007), and dysregulation of HPA axis hormones (VanItallie 2002; Bedi and Arora 2007). Because of the many interactions between the HPA axis and the sympathetic nervous system, the cardiovascular involvement of PTSD is likely to originate from a combination of both autonomic nervous system and HPA axis dysregulation (Bedi and Arora 2007; Dedert et al. 2010; Table 4).

Because of the greater cardiovascular involvement in PTSD than in controls, we tested the hypothesis that patients with PTSD would have a shorter life expectancy than control veterans. We compared controls to veterans with Purple Hearts (awarded for significant physical injury in battle) and to veterans with PTSD.

Table 4 Examples of cardiovascular abnormalities associated with PTSD

Abnormality	Studies referenced
Hypertension	Buckley and Kaloupek 2001; Norman et al. 2006; O'Toole and Catts 2008; Cohen et al. 2009; Qureshi et al. 2009; McFarlane 2010; Pietrzak et al. 2012; Paulus and Egge 2013
Angina pectoris	Spitzer et al. 2009; Pietrzak et al. 2012
Tachycardia	Gerardi et al. 1994; Buckley and Kaloupek 2001; Blechert et al. 2007; Pole 2007; Pietrzak et al. 2012; Paulus and Egge 2013
Elevated *heart rate* and *blood pressure* in response to trauma-related cues	Shalev et al. 1992; Gerardi et al. 1994; Buckley and Kaloupek 2001; Barkay et al. 2012; Paulus and Egge 2013
Peripheral arterial disease	Spitzer et al. 2009
Atherosclerotic coronary artery disease	Ahmadi et al. 2011
Heart failure	Spitzer et al. 2009; Pietrzak et al. 2012
Myocardial infarction	Qureshi et al. 2009; Spitzer et al. 2009
General cardiovascular disease	McFarlane and Rafalowicz 1994; Boscarino 1997; Schnurr and Paris 2000; David 2004; Sareen et al. 2007; Qureshi et al. 2009; Pietrzak et al. 2012

The mortality rates in veterans over 65 years of age were greater for patients with PTSD than for controls (Kimbrell et al. 2011). Interestingly, veterans both with and without PTSD who had received a Purple Heart had a longer life expectancy.

Immunological Changes in PTSD

Considering the many changes found in the neuroendocrine system in PTSD and the significant impact of the neuroendocrine system on immune function (Bornstein and Rutkowski 2002; Boscarino 2004; Baker and O'connor 2012), significant PTSD-related immune abnormalities are plausible. In fact, autoimmune conditions associated with PTSD include ***rheumatoid arthritis*** (Weisberg et al. 2002; Boscarino 2004; Norman et al. 2006; O'Toole and Catts 2008; Qureshi et al. 2009; Pietrzak et al. 2012), ***anemia*** (Weisberg et al. 2002), autoimmune-related dermatological diseases [***eczema***: (Weisberg et al. 2002; Boscarino 2004; O'Toole and Catts 2008; Qureshi et al. 2009); ***psoriasis***: (Boscarino 2004); ***chronic idiopathic urticaria***: (Chung et al. 2010)], ***diabetes*** [***type 1*****:** (Weisberg et al. 2002; Boscarino 2004); ***type 2*****:** (Boyko et al. 2010; Lukaschek et al. 2013; Vaccarino et al. 2014); and ***unspecified*****:** (Weisberg et al. 2002; David 2004; Qureshi et al. 2009)] (Table 5).

Studies have also found correlations between PTSD and decreased natural killer cell cytotoxicity (Gotovac et al. 2010), elevated T-lymphocyte counts, increased immunoglobulin-M levels (Boscarino 2004), and greater C-reactive protein levels (Spitzer et al. 2010).

Table 5 Examples of immunological abnormalities associated with PTSD

Abnormality	Studies referenced
Rheumatoid arthritis	Weisberg et al. 2002; Boscarino 2004; Norman et al. 2006; O'Toole and Catts 2008; Qureshi et al. 2009; Pietrzak et al. 2012
Anemia	Weisberg et al. 2002
Eczema	Weisberg et al. 2002; Boscarino 2004; O'Toole and Catts 2008; Qureshi et al. 2009
Psoriasis	Boscarino 2004
Chronic idiopathic urticaria	Chung et al. 2010
Diabetes	*Type 1*: Weisberg et al. 2002; Boscarino 2004
	Type 2: Boyko et al. 2010; Lukaschek et al. 2013; Vaccarino et al. 2014
	Unspecified type: Weisberg et al. 2002; David 2004; Qureshi et al. 2009
Decreased natural killer cell cytotoxicity	Gotovac et al. 2010
Elevated T-lymphocyte counts	Boscarino 2004
Elevated immunoglobulin-M levels	Boscarino 2004
Elevated C-reactive protein levels	Spitzer et al. 2010

Table 6 Examples of musculoskeletal abnormalities associated with PTSD

Abnormality	Studies referenced
Fibromyalgia	Amir et al. 1997
Osteoarthritis	David 2004
Temporomandibular disorder	Afari et al. 2008

Musculoskeletal Involvement in PTSD

Poorer overall musculoskeletal condition is associated with PTSD (McFarlane and Rafalowicz 1994; Schnurr and Paris 2000; O'Toole and Catts 2008). Particular musculoskeletal disorders that have been associated with PTSD include ***fibromyalgia*** (Amir et al. 1997), ***osteoarthritis*** (David 2004), and ***temporomandibular disorder*** (Afari et al. 2008). The exact relationship between musculoskeletal diseases and PTSD is unclear, but these findings could be related to the association of PTSD with generalized somatic pain (Andreski and Breslau 1998; Defrin et al. 2008; Table 6).

Digestive and Genitourinary Involvement

PTSD has been associated with a higher prevalence of gastrointestinal disorders (Boscarino 1997; Schnurr and Paris 2000; Graham-Bermann and Seng 2005;

Table 7 Examples of digestive and genitourinary comorbidities associated with PTSD

System	Comorbidity	Studies referenced
Digestive	Irritable bowel syndrome	Irwin et al. 1996
	Gastroesophageal reflux	Li et al. 2011
	Hepatic disease	Spitzer et al. 2009; von Känel et al. 2010
	Renal disease	Weisberg et al. 2002; Boscarino 2004
	Gastritis	Pietrzak et al. 2012
	Ulcer development	Davidson et al. 1991; Weisberg et al. 2002; Qureshi et al. 2009; Pietrzak et al. 2012
Genitourinary	Endometriosis	Seng et al. 2006; Qureshi et al. 2009
	Cervical dysplasia	Seng et al. 2006; Qureshi et al. 2009

Norman et al. 2006; Sareen et al. 2007), a relation that is common with anxiety disorders (Mayer et al. 2001). Digestive conditions with a greater prevalence in patients with PTSD include ***irritable bowel syndrome*** (Irwin et al. 1996), ***gastro-esophageal reflux*** disease and subsequent dyspepsia (Li et al. 2011), ***hepatic*** disease (Spitzer et al. 2009; von Känel et al. 2010), ***renal*** diseases such as glomerulonephritis (Weisberg et al. 2002; Boscarino 2004), ***gastritis*** (Pietrzak et al. 2012), and ***ulcer*** development (Davidson et al. 1991; Weisberg et al. 2002; Qureshi et al. 2009; Pietrzak et al. 2012). PTSD has also been associated with several genitourinary diseases, including ***endometriosis*** (Seng et al. 2006; Qureshi et al. 2009) and ***cervical dysplasia*** (Seng et al. 2006; Qureshi et al. 2009; Table 7).

Respiratory Involvement

Respiratory issues have also been associated with PTSD (McFarlane and Rafalowicz 1994; Boscarino 1997; Blechert et al. 2007; Sareen et al. 2007), including ***shortness of breath*** (Baker et al. 1997), increased frequency of sighing (Blechert et al. 2007), and general pulmonary diseases (Weisberg et al. 2002; Spitzer et al. 2009) such as ***asthma*** (Davidson et al. 1991; Weisberg et al. 2002; Graham-Bermann and Seng 2005; O'Toole and Catts 2008; Qureshi et al. 2009; Spitzer et al. 2009) and ***bronchitis*** (Spitzer et al. 2009; Table 8).

Tumorigenic Involvement

A few studies have shown a significant association between PTSD and the prevalence of cancer (Norman et al. 2006; Sareen et al. 2007); however, the pathophysiological relation of the two conditions remains uncertain. It has been suggested that enhanced tumorigenesis in PTSD is caused by dysregulation of the sympathetic nervous system and HPA axis, as well as compromised cellular immunity

Table 8 Examples of respiratory abnormalities associated with PTSD

Abnormality	Studies referenced
Shortness of breath	Baker et al. 1997
Increased frequency of sighing	Blechert et al. 2007
Asthma	Davidson et al. 1991; Weisberg et al. 2002; Graham-Bermann and Seng 2005; O'Toole and Catts 2008; Qureshi et al. 2009; Spitzer et al. 2009
Bronchitis	Spitzer et al. 2009

Table 9 Examples of tumorigenic abnormalities associated with PTSD

Abnormality	Studies referenced
Increased prevalence of cancer (unspecified type)	Norman et al. 2006; Sareen et al. 2007
Increased frequency of DNA breakage	Morath et al. 2014

(McDonald et al. 2005). The recent finding of an association between PTSD and DNA breakage supports the possible relationship between PTSD and tumorigenic pathways (Morath et al. 2014; Table 9).

Practice and Procedures

PTSD is very common and is associated with great morbidity and suffering. It is critical to understand more about the disease in order to design new, innovative therapies. It has become increasingly evident that PTSD is more than simply a psychological adjustment disorder, and this article offers the thesis that PTSD is, in fact, a systemic disorder. This article did not cover all of the systems affected by PTSD but gives a broad overview, upon which other articles will expand. Nonetheless, enough systems were discussed here to support the assertion that PTSD involves much more than just the brain. This, in turn, indicates that one may study other organ systems to gain great insights into the pathophysiological underpinnings of PTSD: investigations will no longer be limited to the brain or direct effects of neuroanatomical changes. Moreover, the systemic hypothesis also helps explain the many symptoms outside the brain from which PTSD patients suffer.

As a result of systemic involvement, we suggest that patients with PTSD undergo comprehensive screenings for associated disorders, particularly for cardiovascular diseases and dementias, in order to prevent or mitigate their effects. While this paper recommends broadening the scope of conventional screenings for patients with PTSD because of the systemic nature of PTSD, it remains critical to screen and treat for psychiatric diseases in light of the highly negative compounding effect of comorbid major depressive disorder as well as increases in high-risk behaviors, impulsivity, and suicide in patients with PTSD, whose substance abuse to self-medicate may further impair neurological function.

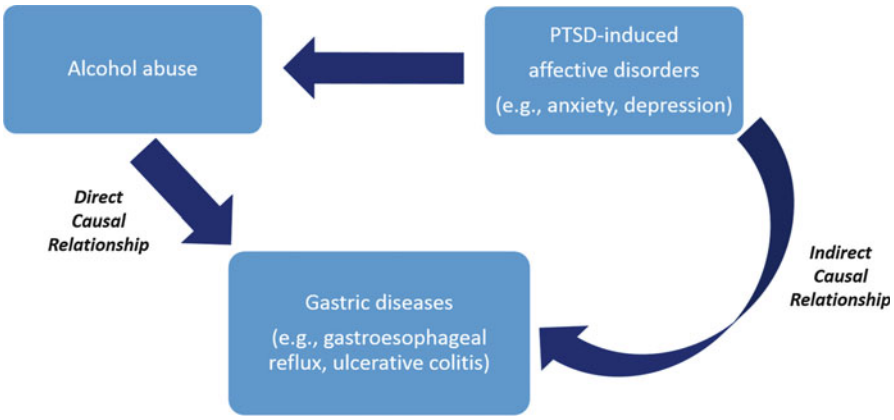

Fig. 2 Potential PTSD-related pathological pathways leading to development of gastric diseases. Just as with the neuropsychiatric disorders noted in Fig. 1, PTSD may have both direct and indirect effects on other systemic organs. For example, PTSD-induced affective disorders may be associated with gastric diseases. But PTSD may also be associated with alcohol abuse, which further promotes the development of gastric disease. For many such systemic disorders, PTSD may act via several pathways, and it can be difficult to determine whether it has direct, indirect, or both effects when producing organ dysfunction

Key Facts About Systemic Involvement in PTSD

- PTSD has conventionally been considered to be primarily a psychiatric illness; consequently, much of the PTSD-related research and treatments heretofore have focused on the psychiatric manifestations of PTSD.
- Recent studies have associated PTSD with diseases in multiple other organ systems, thus supporting the thesis that PTSD is a systemic disorder.
- Behavioral changes, particularly an increase in substance abuse and tobacco use, have been identified in many patients with PTSD. These behaviors can enhance neurological impairment associated with PTSD, for example, via producing stroke. These can add to the other disorders associated with PTSD, such as mood disorders, and can indirectly impact the systemic manifestations of PTSD (Fig. 1).
- The role of PTSD in more complex pathologies (e.g., tumorigenic, gastric, and respiratory diseases) is also enhanced by PTSD-associated behavioral changes that are implicated in the pathology of these diseases, such as increased tobacco use and alcohol consumption (Fig. 2).
- A major area of research needed in PTSD is determining whether findings in PTSD, such as abnormally small hippocampal volumes, are caused by PTSD or are preexisting conditions that are risk factors for the development of PTSD.

Summary Points

- Studies have begun to explicate the specific neuroanatomical changes associated with PTSD that underlie certain neuropsychiatric symptoms and findings.
- This article summarizes recent findings that support the thesis that PTSD produces systemic changes that extend far beyond the brain.
- PTSD is associated with behavioral changes, including tobacco consumption, illicit drug use, and alcohol abuse, that can have additional deleterious effects on brain and body function.
- This review supports the thesis that a broader perspective on the systemic symptomatology and pathophysiology of PTSD is appropriate in future studies and treatments.
- The increased incidence of serious systemic disorders in PTSD suggests that clinicians should be vigilant in screening for many systemic disorders and unhealthy behaviors in PTSD patients, including risk factors for heart attacks and stroke, digestive diseases, dementia, and drug abuse.
- Despite the advancement in our understanding of PTSD, further research is needed to elucidate the cause-and-effect relationship between PTSD and distinct physical abnormalities, such as whether small hippocampal volumes are a risk factor for PTSD or are caused by PTSD.
- More research is needed to better understand whether treating PTSD-induced psychiatric symptoms leads to a change in behaviors that reduces downstream physiological effects, such as PTSD-induced anxiety, alcohol abuse, and gastric disease (Fig. 2).

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