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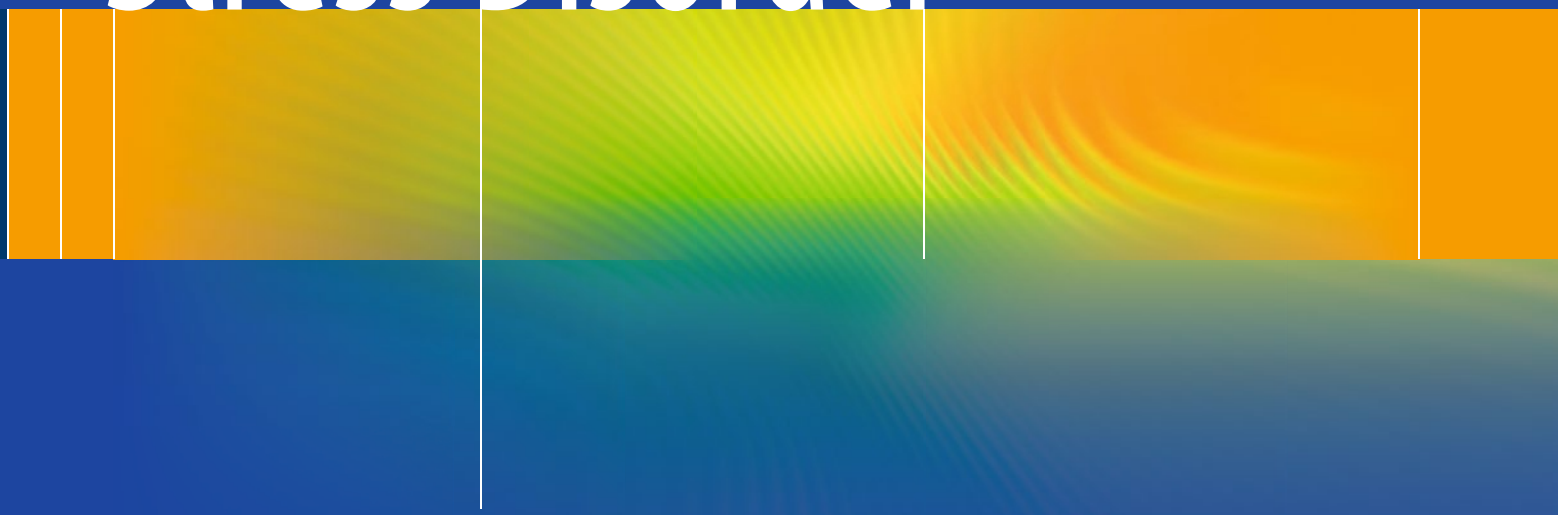
Sleep and Combat-Related Post Traumatic Stress Disorder



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Part I

Post-traumatic Stress Disorder and Other Axes of Distress Following Combat Exposure: The Role of Sleep

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The ubiquity of the risk of psychological injury following combat exposure is now accepted as an integral part of the costs of going to war [1]. Scientific observation and knowledge derived from epidemiological studies of combat-exposed populations in combination with studies of the underlying neurobiology, particularly of longitudinal cohorts prior to and following deployment, have been invaluable in countering many of the prejudices that plagued military psychiatry in the first seven decades of the twentieth century. The optimal way of maintaining the mental health of service personnel is a constantly evolving challenge because of the changing nature of conflict and operational tempo, particularly with multiple deployments to the conflicts in the Middle East [1]. Integrating this emerging body of knowledge into clinical practice represents a substantial challenge.

Post-traumatic stress disorder (PTSD) has been the primary focus of the documented psychological injuries from combat [2]. However, the range of traumatic stressors that occur in the combat environment represents significant risk factors for the other psychiatric disorders such as depression and obsessive compulsive [3] disorder as well as adverse physical health outcomes, including premature death [4]. PTSD also has increased comorbidity with many physical disorders, ranging from metabolic syndrome and related cardiovascular morbidity through to autoimmune disease such as rheumatoid arthritis [5, 6]. The comorbidity of PTSD and mTBI is a further example of how there can be both physical and psychological consequences from the same trauma event. In some regards, the focus on the differentiation of their symptoms and aetiology fails to integrate the aspects of their causation and neurobiology that are shared. An example of this is the commonality of the role of sleep plays in driving other symptoms of attentional difficulties and executive dysfunction [7]. In my opinion, the challenge for all clinicians is to ensure that a comprehensive psychological and physical assessment has been made when providing healthcare to veterans, rather than being confined to the perspective of siloed specialties.

These multiple intertwined physical and psychological health consequences of war argue for the role of shared mechanisms that underpinned the aetiology of these disorders which is further reinforced by the fact that PTSD is the sole diagnosis in a minority of cases [3]. The allostatic load model has been used to refocus the stress disease literature, emphasising that their multiple biological systems are vulnerable to a temporal cascade of dysregulation [9].

Progressive dysregulation leads to the emergence of a range of disease trajectories and disorders that arise from these common pathways. Allostasis recognises that physiological states change over time and that both physical and psychological stressors elicit various physiological reactions in an attempt to return to what is the steady state at that particular time [10]. Allostatic load refers to the wear and tear on the body that is incurred during the process of returning to a steady state [10]. My clinical experience has proven the value of the further dimension that the allostatic model provides in capturing a longitudinal perspective of the risk of disorder that interacts with the morbidity of age as well as stresses following return from deployment [11, 12].

A core component of self-regulation is the ability to sustain good quality sleep. As Adler et al. and Sipos [2] summarise, sleep disorder in the pre-deployment and the post-deployment period represents a significant risk for the development of PTSD. In general community populations, sleep has similarly been a significant marker of later risk of developing a psychiatric disorder [14]. This evidence highlights how subclinical distress and symptoms are markers of significant risk of later disorder and are critical for clinicians to document.

Recent literature has highlighted the importance of subsyndromal PTSD symptoms [15], including sleep disorder as a marker of the future probability of disorder. Various longitudinal studies have shown that general psychological distress is less ubiquitous than often claimed and therefore not normal phenomena in acutely traumatised populations, such as those who are combat exposed [16] or who have experienced accidents [17]. This would support the utility of taking a dimensional perspective of psychological symptoms following combat exposure with less emphasis on whether an individual has crossed the threshold to attract the full diagnostic criteria for PTSD. While there is a range of findings about the exact rates of PTSD in the aftermath of combat exposure [2], when a dimensional perspective is taken, these differences become of less relevance, as those who fall just below the cut-offs represent populations at significant risk.

In terms of early intervention, focusing on those with lower levels of distress may have benefits because of the fluidity of symptoms at this time. The demonstration of benefit of interventions for insomnia highlights how sleep disturbance has the potential to be an ideal target to decrease the risk of future disorder [18]. In my opinion, developing demonstrably effective clinical interventions for subsyndromal disorder is a priority area. Documenting the gender differences in the patterns of early psychological distress is important to ascertain whether differential strategies are required for optimal outcomes from early intervention [8].

A further extension of the dimensional approach to combat-related psychopathology is to adopt a staging approach to PTSD [19]. This approach [21] is built on the substantial body of research on the longitudinal course of PTSD and the sequential shifts in its neurobiology following traumatic stress exposure [20] and the progressive recruitment of symptoms with time [17]. Staging moves away from a reliance on cross-sectional descriptions and highlights the importance of studying a disorder longitudinally and, for example, the role of specific phenomenon such as sleep in the risk and progression of the disorder. The aim of the staging approach is to identify biomarkers that have an adequate degree of specificity for PTSD and to differentiate those that act as disease markers from indicators of risk and vulnerability across the different stages, markers of disease progression and epiphenomena [21]. My view is that the use of a staging approach in PTSD will allow the development of a more sophisticated approach to developing prevention strategies and treatment that will lead to the differentiation of the optimal strategies for recent-onset disorder from those for the chronic and relatively unremitting cases [13]. The one size fits all approach that has tended to be reflected in treatment guidelines has hampered the development of more effective treatments so needed by the field.

References

1. Santiago PN, Oravec GJ, Ursano RJ. War and war-related trauma: an overview. In: Vermetten E, Germain A, Neylan TC, editors. Sleep and Combat-Related Post Traumatic Stress Disorder. New York: Springer; 2017.
2. Adler AB, Sipos ML. Combat-related post traumatic stress disorder: prevalence and risk factors. In: Vermetten E, Germain A, Neylan TC, editors. Sleep and Combat-Related Post Traumatic Stress Disorder. New York: Springer; 2017.
3. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, Hobfoll SE, Koenen KC, Neylan TC, Hyman SE. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:15057.

4. Lee KA, Vaillant GE, Torrey WC, et al. A 50-year prospective study of the psychological sequelae of World War II combat. Am J Psychiatr. 1995;152(4):516–22.
5. Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: A meta-analytic review. J Anxiety Disord. 2013;27(1):33–46.
6. O'Donovan A, Cohen BE, Seal KH, et al. Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. Biol Psychiatr. 2015;77(4):365–74.
7. Picchioni D, Balkin TJ. Sleep as a mediator of mTBI and PTSD. In: Vermetten E, Germain A, Neylan TC, editors. Sleep and Combat-Related Post Traumatic Stress Disorder. New York: Springer; 2017.
8. Burkman K, Maguen S. Symptomatology of war zone-related posttraumatic stress disorder: men vs. women. In: Vermetten E, Germain A, Neylan TC, editors. Sleep and Combat-Related Post Traumatic Stress Disorder. New York: Springer; 2017.
9. Goldstein DS, McEwen BS. Allostasis, homeostats, and the nature of stress. Stress. 2002;5(1):55–8.
10. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann New York Acad Sci. 1998;840:33–44.
11. McFarlane AC. The long-term costs of traumatic stress: Intertwined physical and psychological consequences. World Psychiatr. 2010;9(1):3–10.
12. Lohr JB, Palmer BW, Eidt CA, et al. Is post-traumatic stress disorder associated with premature senescence? A review of the literature. Am J Geriatr Psychiatry. 2015;23(7):709–25.
13. McFarlane AC, Lawrence Wood E, Van Hooff M, et al. The need to take a staging approach to the biological mechanisms of PTSD and its treatment. Curr Psychiatr Rep. 2015;19(2):1–9.
14. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. Biol Psychiatr. 1996;39(6):411–8.
15. Pietrzak RH, Goldstein MB, Malley JC, Johnson DC, Southwick SM. Subsyndromal posttraumatic stress disorder is associated with health and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom. Depress Anxiety. 2009;26(8):739–44.
16. Hughes JH, Cameron F, Eldridge R, Devon M, Wessely S, Greenberg N. Going to war does not have to hurt: preliminary findings from the British deployment to Iraq. Br J Psychiatr. 2005;186(6):536–7.
17. Bryant RA, Nickerson A, Creamer M, O'Donnell M, Forbes D, Galatzer-Levy I, McFarlane AC, Silove D. Trajectory of post-traumatic stress following traumatic injury: 6-year follow-up. Br J Psychiatr. 2015;206(5):417–23.
18. Ritterband LM, Thorndike FP, Ingersoll KS, Lord HR, Gonder-Frederick L, Frederick C, Quigg MS, Cohn WF, Morin CM. Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year follow-up: a randomized clinical trial. JAMA Psychiatr. 2017;74(1):68–75.
19. McFarlane AC, Lawrence-Wood E, Van Hooff M, et al. The need to take a staging approach to the biological mechanisms of PTSD and its treatment. Curr Psychiatr Rep (in Press).
20. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012;13(11):769–87.
21. McGorry P, Keshavan M, Goldstone S, Amminger P, Allott K, Berk M, Lavoie S, Pantelis C, Yung A, Wood S, Hickie I. Biomarkers and clinical staging in psychiatry. World Psychiatr. 2014;13(3):211–23.

War, Sleep and PTSD War, and War-Related Trauma: An Overview

1

Patcho N. Santiago, Geoffrey J. Oravec, and Robert J. Ursano

Brief History of War and Traumatic Events

Throughout history, times of massive destruction create an atmosphere of chaos that compels individuals to face the terror of unanticipated injury, loss, and death. During natural or man-made disasters, war, and acts of terror, psychological injury may occur on its own or in conjunction with physical injury. This psychological trauma may occur following exposure to the injury and death of others, the disruption of the physical environment, or as a consequence of the terror and helplessness that these events combine to evoke [1].

The causes of emotional symptoms in response to war and disaster have been historically attributed to a variety of sources ranging from the Gods, the concussive force of projectiles and explosions, to various natural or supernatural sources of contagion. Descriptions of the emotional consequences of terror date as far back as the ancient Greeks and are captured in Homer's The Iliad. Napoleon's surgeons commented on the ill effects of war on soldiers' health. Combat-related disorders similar to the modern diagnosis of post-traumatic stress disorder (PTSD) are described in Civil War medical treatises. Throughout much of the nineteenth and twentieth centuries, various concepts emerged to characterize conditions for which no demonstrable neuroanatomical pathology could be identified. As early as World War I and II, physicians were developing treatment for conditions such as *the thousand yard stare*, *soldier's heart*, *shell shock*, *neurosis*, *conversion paralysis*, and *combat fatigue* [1–3]. From these early observations emerged today's understanding that unwanted environmental changes brought about by war or disaster result in emotional trauma [1]. Table 1.1 reveals the changing nature of war over time, examining declining rates of physical casualties and fatalities in war, but enduring high rates of the mental wounds of war.

Regardless of the source, potential stressors in military and disaster environments include exposure to the dead and grotesque, immediate and pending threat to life, loss of loved ones, loss of personal property, and physical injury with associated disability and pain. Chronic loss, depletion of natural resources, and exposure to reminders of recent tragedies shape and define the environment in which emotional and behavioral response to military operations and disaster may evolve [1].

Stressors of Modern Warfare (The Changing Nature and Character of War)

The Composition of the Force

Current members of the military have been selected and trained differently from their predecessors, and the overall environment, expectations, and responsibilities of the modern military force have also changed dramatically over the past few decades. In prior wars, military service was seen as a necessary and difficult but temporary interruption to civilian life. Soldiers joined or were conscripted, were quickly trained, sent into combat, and then returned to civilian life once hostilities ceased. During these conflicts, the primary risk for stress-related disorders was direct exposure to intense combat. Following Vietnam, however, the era of the Cold War resulted in a more stable military structure. The US military transitioned to an all-volunteer force composed of both active-duty and reserve components [7]. This modern fighting force tends to include more women, more married service members, and generally well-educated individuals who are more socially and politically conservative than their

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Table 1.1 Epidemiology of the psychological impacts of war (United States)

	WWI	WWII	Korea	Vietnam	Persian Gulf	OIF	OEF
Total US service members (worldwide)	4,743,826[a]	16,353,659[a]	5,764,143[a]	8,744,000[a]	2,322,000[a]		
Mobilized to region			1,789,000[a]	3,403,000[a]	694,550[a]	>1,500,000[b]	>1,500,000[b, c]
Killed	53,402[a]	292,557[a]	33,739[a]	47,434[a]	148[a]	4,411[d]	2,346[d]
Wounded	204,002[a]	670,846[a]	103,284[a]	153,303[a]	467[a]	31,953[d]	20,092[d]
PTSD	159,000[e]	648,500[f]	>370,000[g]	1,390,703[h]	~47,000[i]	~103,792[j]	~103,792[j]
Depression	159,000[e]	648,500[f]	>370,000[g]				
Substance abuse		43,339[k]		~400,000[l]			
Accidents	63,195[m]	115,185[m]	NA[m]	10,799[m]	145[m]	566[n]	245[o]
Completed suicides				>150,000[p]	102[q]	235[n]	97[o]

Exact figures are still in dispute, because of different definitions used in each category, the questionable accuracy of the recording system used, and the loss or destruction of a number of official documents. The data in the table above reflect numbers from several sources and are consistent with most experts' current estimates [4]

[a]Total US Forces. Does not include civilian casualties [4]

[b]Total number US troops served [6]

[c]http://www.nap.edu/openbook.php?record_id=12812&page=17#p2001aba69960017001

[d]Current US Department of Defense statistics [5]

[e]Total US soldiers out of action for psychiatric problems – A Short History of PTSD: From Thermopylae to Hue Soldiers Have Always Had A Disturbing Reaction To War, STEVE BENTLEY, The VVA Veteran, 1991 – http://www.vva.org/archive/TheVeteran/2005_03/feature_HistoryPTSD.htm

[f]Total number US Army Soldiers admitted worldwide for psychoneurosis, 1942–45 – p. 216 – *Hospitalization and Disposition, Norman Brill in Neuropsychiatry in WWII, Medical Department US Army V. 1*

[g]Total psychiatric casualties were recorded as 37 per 1,000 among US servicemen – British Journal of Psychiatry – psychiatric battle casualties: an intra- and interwar comparison, EDGAR JONES and SIMON WESSELY, 2001, 178, 242–247

[h]Total number of Vietnam veterans with at least one specialty mental health service visit for post-traumatic stress disorder for fiscal years 1997–2010 – *Recent Trends in the Treatment of Posttraumatic Stress Disorder and Other Mental Disorders in the VHA by Eric D. A. Hermes, M.D. in Psychiatric Services 2012*

[i]Estimated 10% of American Veterans of the Gulf war are diagnosed with PTSD – The Nebraska Department of Veterans' Affairs, Post-traumatic Stress Disorder – http://www.ptsd.ne.gov/what-is-ptsd.html

[j]The US DoD counted the number of new PTSD cases annual in all services but did not divide the index trauma of these cases between combat and noncombat or between OIF and OEF. Fischer, H. *U.S. Military Casualty Statistics: Operation New Dawn, Operation Iraqi Freedom, and Operation Enduring Freedom.* Congressional Research Service. 2013. www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA590694

[k]Total number of US Army soldiers admitted worldwide for alcoholism and drug addiction, 1942–45 – p. 216 – *Hospitalization and Disposition, Norman Brill in Neuropsychiatry in WWII, Medical Department US Army V. 1*

[l]Forty-five percent of interviewed general sample of US Army-enlisted men returning in Sept. 1971 used any drug in Vietnam – DRUG USE BY U.S. ARMY ENLISTED MEN IN VIETNAM: A FOLLOW-UP ON THEIR RETURN HOME, Lee Robins et al., Table 2. Journal of Epidemiology, April, 1974, Vol. 99(4). – http://aje.oxfordjournals.org/content/99/4/235.full.pdf+html

[m]Includes disease [4]

[n]Department of Defense Personnel and Procurement Statistics, Statistical Information and Analysis Department, OIF at http://siadapp.dmdc.osd.mil/personnel/CASUALTY/oif-total.pdf

[o]Department of Defense Personnel and Procurement Statistics, Statistical Information and Analysis Department, OEF at http://siadapp.dmdc.osd.mil/personnel/CASUALTY/wotsum.pdf

[p]Nam Vet: Making Peace with Your Past, Chuck Dean, WordSmith Publishing (February 11, 2000)

[q]US Army suicides highest since Gulf War, Kristen Roberts, 2007 – http://www.reuters.com/article/2007/08/16/us-usa-army-suicide-idUSN1641660320070816

civilian counterparts [8, 9]. It is possible that volunteering for military service may enhance resilience to traumatic events as members are more committed to a military lifestyle and more fully supportive of the military mission. Reports suggest that individuals experience better outcomes following traumatic events if they believe their combat experiences served a higher purpose [10, 11].

Operational Tempo

The stability of the Cold War era allowed for a more predictable military career for most service members. Personal and family responsibilities could be anticipated and planned for without serious disruption by frequent or extended deployments. Beginning with the Persian Gulf War in 1990–1991

and continuing through current conflicts, however, the nature of military service became more unpredictable. Uncertainty of tour length, limited time spent in garrison (dwell time), and instability of garrison location have all been shown to be stressors associated with modern warfare [12].

Mental Health Advisory Team (MHAT) reports in Iraq and Afghanistan have consistently shown that longer deployments are related to a variety of risk factors and behavioral health indices. The longer a soldier has been in theater, the more likely he or she is to accumulate combat experiences. Multiple deployments are also a risk factor for a variety of well-being indices. NCOs on their second and third (or more) deployments have been shown to have more psychological problems and more use of medications. Multiple deployments also result in a greater intent to divorce and separate. Specifically, those on their second deployment report a significantly higher likelihood of divorce intent than those on their first deployment [13].

In some cases these psychological effects of deployment may be self-limited however, and survey data has demonstrated that mental health problems following a 1-year deployment begin to return to pre-deployment levels after approximately 2 years at home station and essentially reset after 3 years at home [14]. This is important to consider, as the changing nature of war has led to increased frequency of deployment, longer deployments, and shorter "dwell time" in garrison and at home. This dwell time is important, as events that occur during this time may help or hinder the service member in preparing for future or repeated deployments.

Public Interest

The extent to which the nation endorses the military mission and supports the troops can also have an impact on the mental health of service members both serving in combat and after returning from war [15]. Whereas during Vietnam public opinion had a profound negative impact on returning soldiers and veterans, more recent conflicts have seen greater public support both for the military mission and for the troops themselves – although with continued variation over time.

A small portion of society is executing today's wars, and much of the population remains largely unengaged, which may contribute to feelings of isolation among soldiers and veterans. While this may play a smaller role than it did post-Vietnam, it still may represent a risk factor for certain groups such as reservists and National Guard who return to homes, jobs, and communities without the support of military colleagues [2].

With the evolution of modern warfare and the stressors surrounding combat, both the traumatic events that service members are exposed to and the ways in which they perceive those events have changed over time. Research has shown that life events can have a direct impact on individual's health and well-being [16–19]. Understanding the interplay between these exposure events and individual responses is important for developing appropriate training and intervention strategies to mitigate the potential negative effects associated with combat and war.

Pre-deployment Stressors

For most of the last half of the twentieth century, the oppressive but comparatively stable conditions of the Cold War made it possible to maintain military personnel and rotation policies that fostered a fairly predictable career pattern for most American service members. Within reasonable limits, personal and family concerns could be anticipated, planned, and managed in the context of a military career that would probably not require extended deployment or combat. Researchers have identified several factors that likely contribute to the stress of modern military service, including unpredictability of "tour" length (deployment period), limited time spent in garrison (home base), and instability of garrison location [20].

Combat Stressors, Distress, Disorders, and Behaviors

Phases of Stress Response

The emotional and behavioral responses after combat and disaster occur in four phases. The first phase consists of strong emotions, including feelings of disbelief, numbness, fear, and confusion. These are often normal emotional responses to an extraordinary event. The second phase may last from weeks to months and involves efforts at adaptation to the new environment. Intrusive memories in the form of flashbacks or nightmares as well as hyperarousal may emerge during this phase. Somatic symptoms such as insomnia, fatigue, dizziness, headaches, and nausea are also common. The third phase is marked by feelings of disappointment and resentment if hopes for restoration of the pre-trauma emotional and physical environment are not met. The final reconstruction phase may last for years as survivors attempt to rebuild their lives and social and occupational identities. Individuals progress through these phases at different rates and may develop symptoms at different times in response to the same event [1].

Different people will react differently in a combat environment or when exposed to a traumatic event such as a man-made or natural disaster. All people will experience some

level of emotional distress in such an environment. A smaller proportion of the population will go on to have behavioral changes that may be dysfunctional, and only a much smaller subset of those exposed will develop a psychological disorder. These reactions are illustrated in Fig. 1.1.

Distress

Distress-related symptoms are universally experienced during a disaster or in the midst of combat. Health providers must be careful not to reinforce a view that the symptoms constitute a disease, as they represent normal responses that are common and usually transient. In the context of ongoing battle, the perception that one is ill can itself lead to impaired functioning and may increase long-term disability [1].

Disorders

Exposure to traumatic events during combat may result in well-defined psychiatric illnesses in certain individuals. Post-traumatic stress disorder (PTSD) is one such condition that has received a great deal of attention in combat and disaster situations. The Diagnostic and Statistical Manual Fifth Edition (DSM-5) defines PTSD as an exposure to a threat to physical integrity with a resulting emotional response involving helplessness, horror, or fear. Associated symptoms include re-experiencing phenomena such as flashbacks and nightmares; hyperarousal including insomnia, hypervigilance, and increased startle; and emotional numbing or avoidance behavior resulting in social or occupational dysfunction. If these symptoms are transient (less than 1month), they are classified as acute stress disorder, and after 1 month the diagnosis of PTSD is made. Other disorders that may result from exposure to traumatic events are illustrated in Table 1.2.

Soldiers in combat are a unique population that experience recurrent and ongoing stressors unknown to other parts of society. These events result in a variety of somatic and emotional responses that do not fully match the specific constellation of symptoms seen in other psychiatric disorders. *Battle fatigue* and *operational stress* are two terms often used to refer to these more vague symptoms including fatigue, GI distress, tremulousness, perceptual disturbances such as depersonalization and derealization, and a decreased ability to cope. These symptoms may be exacerbated by traumatic exposure, sleep deprivation, loss of social supports, injury, starvation, heat exhaustion, or cold injury [1]. Somatic complaints are a frequent finding among soldiers and veterans.

While the majority of soldiers and veterans exhibit significant resilience in the face of trauma and growth as a result of their military service, many develop significant psychological and behavioral problems related to their war experience. The ongoing war in Iraq and Afghanistan has led to high rates of posttraumatic stress, PTSD, depression, suicide, comorbid concussions, TBIs, substance abuse, anxiety, and other combat-related mental and behavioral health needs. Stigma associated with these problems and other barriers to care further complicate these problems. War veterans also show increased risk of physical health problems and early death [2]. Recent research indicates that the psychological effects of repeated traumatic event exposure are cumulative and that between 10% and 20% of combat veterans in the current conflicts in Iraq and Afghanistan develop PTSD [21–23].

Suicidal Behaviors

Suicide has been of increasing concern in the wars in Iraq and Afghanistan. Since 2005, suicide rates in the Army have climbed steadily and are now about double the prewar rate (20 per 100,000). For decades, service members committed

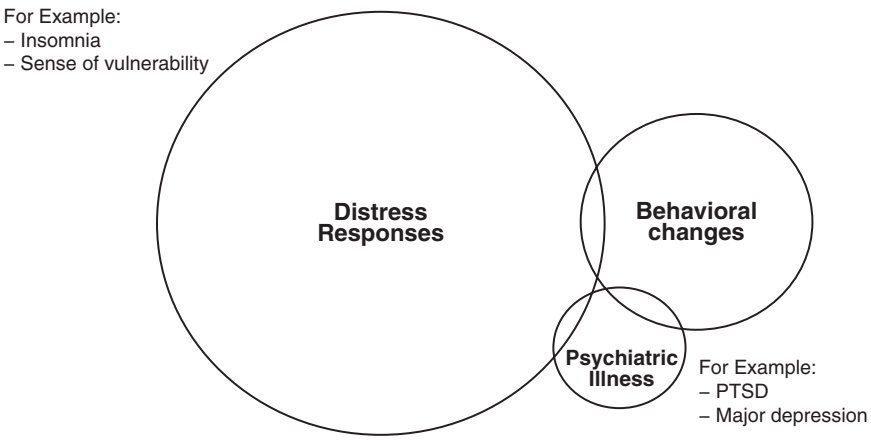

Fig. 1.1 Reactions after exposure to war (Source: Center for the Study of Traumatic Stress)

Table 1.2 Psychological responses to war and disaster: associated mental disorders and symptoms

Mental disorders
Acute stress disorder
Posttraumatic disorder
Generalized anxiety disorder
Panic disorder
Major depressive disorder
Brief psychotic episode
Adjustment disorders
Alcohol abuse and dependence
Substance abuse and dependence
Symptoms
Anger and irritability
Fear
Restlessness
Concentration and attention difficulties
Sadness
Insomnia (with or without nightmares)
Somatic complaints (headaches, gastrointestinal distress, musculoskeletal pain)
Increased alcohol and tobacco use
Diminished interest in activities

suicide more infrequently than their civilian counterparts, but in 2008 the suicide rate in the US Army reached a 28-year high and exceeded the rate in the age-matched general population [24]. Possible contributors to this rise in suicide include the stressors associated with prolonged war – multiple deployments, longer separation from family supports, increased combat exposure, more available fatal means in combat theater, and elevated rates of mental disorders such as PTSD [2]. Veterans who screen positive for PTSD have been found to be four times more likely to experience suicidal ideation as those without PTSD [25]. PTSD also substantially increases the risk of suicide attempts even after adjusting for depression, and the risk for completed suicide can be up to 9.8 times greater than in those without [26–29].

Accidents and Injuries

It is likely that under the stress of war service members are at greater risk for accidental injury. Soldiers who experienced more violence or human trauma have demonstrated greater risk-taking behaviors than those who were less exposed [30]. Vietnam veterans with PTSD have been shown to have a more than twofold risk of all-cause mortality including external causes such as homicides, suicides, and accidents [31].

Since 2007, there have been at least 32 documented cases of accidental drug overdoses in warrior transition units helping soldiers deal with physical and psychological injuries after deployment [32]. While suicide was ruled out in all of these cases, these suspicious injuries highlight the types of accidents and behavior-related injuries that may increase during times of war. This is part of a larger problem in the United States that has led the Centers for Disease Control and Prevention to declare an epidemic of prescription drug overdoses in recent years [33].

Aggression and Violence

There is some evidence that combat experience may contribute to an increased propensity for aggression and violence. This may also be due to PTSD, substance abuse, or other mental problems. Veterans of Iraq and Afghanistan who screened positive for PTSD or sub-threshold PTSD were more likely to report significantly greater anger, hostility, and aggression [34]. Estimates of domestic violence point to slightly higher rates among active-duty members as compared with their civilian counterparts, and several high-profile cases have involved the murder of a spouse by their soldier husband [35]. These findings are even more notable among veterans diagnosed with PTSD, substance abuse, or other psychiatric illness [36].

Stress on Relationships

War can strain even strong, previously healthy relationships. The long-term physical separation necessitated by deployment is often difficult, especially for young couples and those with young children. Soldiers who are informed of family stressors, such as illness or financial problems while in theater, may not be able to assist their families from afar, resulting in feelings of inadequacy, helplessness, and depression. Relationship problems, especially infidelity or break-ups, have been implicated in suicides both in the military and civilian population [2].

Terrorism and Fears of Exposure

Terrorism relies on the creation of fear or terror to undermine society's confidence in its government and leaders. As such, fear, anxiety, and a sense of chaos are the goals of terrorism. Mitigating the emotional effects of terrorism therefore is crucial to any successful war on terrorism.

In the United States, the terrorist attacks on the Pentagon and the World Trade Center and the distribution of anthrax-tainted mail resulted in widespread fear and uncertainty in the American public. These events resulted in neuropsychiatric

syndromes in many survivors of the attacks and their relatives [1].

Exposure

As noted previously, unexplained physical syndromes are a common sequela of combat. At times these unusual constellations of symptoms have been attributed to undetected neurological or chemical exposures, such as with Agent Orange, depleted uranium, or other toxic exposures. Gulf War syndrome presents a more recent example of a variety of symptoms attributed to an unknown exposure. The consistent appearance of these syndromes, affecting people in various ways, after wars or other military operations points to the likelihood that psychosocial factors contribute to etiology [1].

Numerous studies have examined the effects of handling remains on military personnel and disaster workers, with overall findings suggesting increased acute and long-term psychological distress and psychiatric disorders associated with recovery and identification of human remains [37–41]. In recent years, Mortuary Affairs soldiers have deployed repeatedly both to war zones and to the sites of natural and man-made disasters. During the Persian Gulf War, mortuary workers who had not experienced combat still exhibited posttraumatic symptoms including intrusion and avoidance even when other factors were controlled [42, 43].

Post-deployment Stressors

Injured Service Members

Over 47,000 soldiers, sailors, Marines, and airmen have been injured in Operations Iraqi Freedom and Enduring Freedom [44]. While modern military medicine has allowed many service members to survive wounds that would have previously been fatal, more and more service members are left with prolonged physical disability. Veterans with significant limitations in physical activity have higher rates of suicide than those without such limitations and likely suffer increased rates of psychiatric illness and adjustment difficulties [45]. TBI is a common injury in modern warfare that has been shown to have varied psychological and behavioral consequences.

As nearly half of service members are married, many of these injured military members return to spouses and children where the disruption to family life can be substantial [46]. Research on civilian families has suggested that children of disabled parents are at greater risk for behavior problems and children of parents with traumatic brain injury (TBI) experience increased acting out behavior and emotional problems [47, 48]. In the military population, combat-injured families that experience higher levels of pre-injury distress or ongoing disruption may be at greater risk for poorer child outcomes. Reducing family disruption post-injury or providing additional support during the disruption may help prevent child distress [49].

Reintegration/Screening

A major concern for returning soldiers is the detection and management of emerging PTSD and other distress symptoms, which persist and disrupt social, occupational, or interpersonal functioning. The process for reintegrating soldiers and screening for potential adjustment problems has continued to evolve during the operations in Iraq and Afghanistan [2].

Family Adjustment/Relationships

Upon return from deployment, some soldiers have a difficult time readjusting to their noncombat life, and spouses/partners have trouble relating to their soldier experiences of war including any psychological difficulties that have arisen [2]. The divorce rate among service members has been steadily increasing throughout the course of the current wars [50].

The National Vietnam Veterans Readjustment Study showed that one third of veterans with PTSD perpetrated domestic violence in the previous year – three times the rate of the general public and veterans without PTSD. Rates were even higher in veterans with substance abuse problems or who had been hospitalized for psychiatric reasons [36].

Importance of Sleep and the Impact of Sleep Disturbances

In the pre-deployment period, units will frequently train harder and longer in preparation for combat [51, 52]. The mantra of "we train how we fight" can lead to an increased operational tempo that leads to mental disorders which negatively impacts sleep [53]. Yet good sleep is critical for promoting both memory consolidation and emotion regulation and could potentially be protective for PTSD [54, 55], while sleep disturbances may increase the development of PTSD after experiencing potentially traumatic events. For example, survivors of motor vehicle accidents had higher rates of PTSD and depression if their sleep was impaired in 2 weeks leading up to the accident [56]. During deployment, when sleep disturbances are potentially at their highest, this could not only negatively affect troops' battle readiness [57, 58] but also increase rates of PTSD compared to troops who might

have better opportunities to sleep. Here, the question about sleep is the level at which the extinction of conditioned fear can occur. Extinction learning is perhaps the most significant emotional memory for adapting to significant stressors, so that previous triggers cease to induce negative behaviors and emotions [59, 60].

In the post-deployment period, extinction learning becomes even more critical if treatment for mental disorders is to be effective. For example, exposure therapy is a common psychotherapy for the treatment of PTSD, and if good sleep influences the generalization of extinction memory [60, 61], then, as part of the exposure therapy, we need to consider promoting sleep hygiene in an attempt to promote extinction memory consolidation that competes with the negative affect associated with traumatic memories [62].

Conclusion

Twenty-first-century conflicts show no signs of reductions in any of the emotional and behavioral impacts that warfighters have experienced throughout history. In fact, as technology increasingly removes men and women further and further away from direct contact with the enemy, as more and more warriors survive previously fatal injuries, and as asymmetric battles change the tactics used in conflicts, it only becomes more certain that these invisible wounds of war will continue to afflict our military service members. We must be vigilant and prepared to treat these injuries acutely as well as during a much longer period of healing.

References

1. Benedek DM, Ursano RJ, Holloway HC. Military and disaster psychiatry: chapter 28.9. In: Sadock BJ, Sadock VA, editors. Comprehensive textbook of psychiatry, vol. II. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2005. p. 2426–35. 2005.
2. Ursano RJ, et al. Posttraumatic stress disorder and traumatic stress: from bench to bedside, from war to disaster. Ann N Y Acad Sci. 2010;1208:72–81.
3. Shephard B. A war of nerves: soldiers and psychiatrists in the twentieth century. Cambridge, MA: Harvard University Press; 2001.
4. Department of Veteran Affairs. America's wars. Cited 29 Aug 2016. Available from: https://www.va.gov/opa/publications/factsheets/fs_americas_wars.pdf.
5. Defense Casualty Analysis System. Cited 29 Aug 2016. 2016. Available from: https://www.dmdc.osd.mil/dcas/pages/casualties.xhtml.
6. Iraq by the numbers. (2011). Available from: http://dpc.senate.gov/docs/fs-112-1-36.pdf.
7. Mastroianni GR et al. Chapter 3: the stresses of modern war. In Biobehavioral resilience to stress. CRC Press; 2008. p. 43–55.
8. Huffman AH, S.C.P. Military life: the psychology of serving in peace and combat. In: Britt TW, Adler AB, Castro CA, editors. The military family. Westport: Praeger Security International; 2006. p. 115–37.
9. Segal DR, M.W.S America's military population. In: Population Bulletin. 2004. p. 3–40.
10. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol. 2000;68(5):748–66.
11. Watson PJ, Shalev AY. Assessment and treatment of adult acute responses to traumatic stress following mass traumatic events. CNS Spectr. 2005;10(2):123–31.
12. Bell DB, Bartone J, Bartone BT, Schumm WR, Gade PA. USAREUR family support during operation joint endeavor: summary report. Alexandria: U.S. Army Research Institute for the Behavioral and Social Sciences; 1997.
13. Joint Mental Health Advisory Team 7 (J-MHAT 7), Operation Enduring Freedom 2010, Afghanistan. Joint Mental Health Advisory Team 7; 2011.
14. Mental health advisory team report (MHAT) VI, Operation Iraqi Freedom 07–09, report. In Army medicine reports. Mental Health Advisory Team VI; 2009.
15. Johnson DR, et al. The impact of the homecoming reception on the development of posttraumatic stress disorder. The West Haven Homecoming Stress Scale (WHHSS). J Trauma Stress. 1997;10(2):259–77.
16. Rabkin JG, Struening EL. Live events, stress, and illness. Science. 1976;194(4269):1013–20.
17. Rahe RH. Epidemiological studies of life change and illness. Int J Psychiatry Med. 1975;6(1–2):133–46.
18. Rahe RH, Arthur RJ. Life change and illness studies: past history and future directions. J Hum Stress. 1978;4(1):3–15.
19. Rahe RH, et al. Social stress and illness onset. J Psychosom Res. 1964;54:35–44.
20. Bell D, Bartone J, Bartone BT, Schumm WR, Gade PA. USAREUR family support during operation joint endeavor: summary report. Alexandria: U.S. Army Research Institute for the Behavioral and Social Sciences; 1997.
21. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA. 2007;298(18):2141–8.
22. Williams SL, et al. Multiple traumatic events and psychological distress: the South Africa stress and health study. J Trauma Stress. 2007;20(5):845–55.
23. Hoge CW, et al. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351(1):13–22.
24. Kuehn BM. Soldier suicide rates continue to rise: military, scientists work to stem the tide. JAMA. 2009;301(11):1111. 1113
25. Jakupcak M, et al. Posttraumatic stress disorder as a risk factor for suicidal ideation in Iraq and Afghanistan War veterans. J Trauma Stress. 2009;22(4):303–6.
26. Gradus JL, et al. Posttraumatic stress disorder and completed suicide. Am J Epidemiol. 2010;171(6):721–7.
27. Nock MK, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. PLoS Med. 2009;6(8):e1000123.
28. Nock MK, et al. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(8):868–76.
29. Wilcox HC, Storr CL, Breslau N. Posttraumatic stress disorder and suicide attempts in a community sample of urban american young adults. Arch Gen Psychiatry. 2009;66(3):305–11.
30. Killgore WD, et al. Post-combat invincibility: violent combat experiences are associated with increased risk-taking propensity following deployment. J Psychiatr Res. 2008;42(13):1112–21.
31. Boscarino JA. Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. Ann Epidemiol. 2006;16(4):248–56.
32. McGarry, ATAB. Accidental overdoses alarm military officials. Air Force Times; 2010.

33. Paulozzi L, Baldwin G, Franklin G, Kerlikowske RG, Jones CM, Ghiya N, Popovic T. CDC grand rounds: prescription drug overdoses – a U.S. epidemic. MMWR Morb Mortal Wkly Rep. 2012;61(1):10–3.
34. Jakupcak M, et al. Anger, hostility, and aggression among Iraq and Afghanistan War veterans reporting PTSD and subthreshold PTSD. J Trauma Stress. 2007;20(6):945–54.
35. Marshall AD, Panuzio J, Taft CT. Intimate partner violence among military veterans and active duty servicemen. Clin Psychol Rev. 2005;25(7):862–76.
36. Jordan BK, et al. Problems in families of male Vietnam veterans with posttraumatic stress disorder. J Consult Clin Psychol. 1992;60(6):916–26.
37. Bryant RA, Harvey AG. Posttraumatic stress reactions in volunteer firefighters. J Trauma Stress. 1996;9(1):51–62.
38. Fullerton CS, et al. Psychological responses of rescue workers: fire fighters and trauma. Am J Orthop. 1992;62(3):371–8.
39. Marmar CR, et al. Stress responses of emergency services personnel to the Loma Prieta earthquake Interstate 880 freeway collapse and control traumatic incidents. J Trauma Stress. 1996;9(1):63–85.
40. McCarroll JE, Ursano RJ, Fullerton CS. Symptoms of PTSD following recovery of war dead: 13–15-month follow-up. Am J Psychiatry. 1995;152(6):939–41.
41. Ursano RJ, McCarroll JE, Fullerton CS. In: Ursano EARJ, editor. Textbook of disaster psychiatry. New York: Cambridge University Press; 2007.
42. McCarroll JE, et al. Effects of exposure to death in a war mortuary on posttraumatic stress symptoms. J Nerv Ment Dis. 2001;189(1):44–8.
43. McCarroll JE, et al. Somatic symptoms in Gulf War mortuary workers. Psychosom Med. 2002;64(1):29–33.
44. Casualty status. Department of Defense; 2012.
45. Sher L. Suicide in war veterans: the role of comorbidity of PTSD and depression. Expert Rev Neurother. 2009;9(7):921–3.
46. Cozza SJ, Chun RS, Polo JA. Military families and children during operation Iraqi freedom. Psychiatr Q. 2005;76(4):371–8.
47. LeClere FBA, Kowalewski BM. Disability in the family: the effects on children's well-being. J Marriage Fam. 1994;56:457–68.
48. Pessar LF, et al. The effects of parental traumatic brain injury on the behaviour of parents and children. Brain Inj. 1993;7(3):231–40.
49. Cozza SJ, et al. Combat-injured service members and their families: the relationship of child distress and spouse-perceived family distress and disruption. J Trauma Stress. 2010;23(1):112–5.
50. Jelinek P. Military divorces edge up again in 9th year of war. Washington, DC: The Associated Press; 2009.
51. Seelig AD, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. Sleep. 2010;33(12):1615–22.
52. Price M, Gros DF, Strachan M, Ruggiero KJ, Acierno R. Combat experiences, pre-deployment training, and outcome of exposure therapy for post-traumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom veterans. Clin Psychol Psychother. 2013;20(4):277–85.
53. Kessler RC, Heeringa SG, Stein MB, Colpe LJ, Fullerton CS, Hwang I, et al. Thirty-day prevalence of DSM-IV mental disorders among nondeployed soldiers in the US Army: results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). JAMA Psychiatry, 2014. 2014;71(5):504–13.
54. Koffel E, Polusny MA, Arbisi PA, Erbes CR. Pre-deployment daytime and nighttime sleep complaints as predictors of post-deployment PTSD and depression in National Guard troops. J Anxiety Disord. 2013;27(5):512–9.
55. Mellman TA, Pigeon WR, Nowell PD, Nolan B. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. J Trauma Stress. 2007;20(5):893–901.
56. Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. Sleep. 2010;33(1):69–74.
57. Lieberman HR, Bathalon GP, Falco CM, Kramer FM, Morgan CA 3rd, Niro P. Severe decrements in cognition function and mood induced by sleep loss, heat, dehydration, and undernutrition during simulated combat. Biol Psychiatry. 2005;57(4):422–9.
58. Lieberman HR, Niro P, Tharion WJ, Nindl BC, Castellani JW, Montain SJ. Cognition during sustained operations: comparison of a laboratory simulation to field studies. Aviat Space Environ Med. 2006;77(9):929–35.
59. Hermans D, Craske MG, Mineka S, Lovibond PF. Extinction in human fear conditioning. Biol Psychiatry. 2006;60(4):361–8.
60. Pace-Schott EF, Germain A, Milad MR. Effects of sleep on memory for conditioned fear and fear extinction. Psychol Bull. 2015;141(4):835–57.
61. Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. Biol Mood Anxiety Disord. 2015;5(1):1–19.
62. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther. 2008;46(1):5–27.

Combat-Related Post-traumatic Stress Disorder: Prevalence and Risk Factors

2

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Post-traumatic stress disorder (PTSD) is associated with employment across a range of high-risk occupations. Although prevalence rates for the general population have been estimated to be 4.7% in terms of symptoms in the past 12 months, and 8.3% in terms of lifetime prevalence [42], rates in high-risk occupations are substantially higher. For example, the rates of PTSD in police officers were estimated to be 13% [68], while the rates of PTSD in firefighters were estimated to be 17% [13]. More recently, Perrin et al. [60] compared the prevalence of PTSD across different occupations involved in rescue and recovery work at the World Trade Center site. The overall prevalence of PTSD among rescue and recovery workers 2–3 years after the disaster was 12.4% but ranged from 6.2% for police to 21.2% for unaffiliated volunteers. Perrin et al. [61] concluded that workers and volunteers in occupations least likely to have had prior disaster training or experience were at greatest risk of PTSD, underscoring the importance of occupational context in terms of PTSD risk.

Just like emergency service personnel, military personnel are also exposed to significant dangers that can elevate their risk of PTSD and related outcomes. The rates themselves vary depending on the assessment context, the extent of combat-related events, and a range of unit and demographic factors. This chapter details the prevalence of combat-related PTSD taking these variables into account. These estimates are important for predicting the psychological toll that military service may have in order to (1) anticipate mental health resource needs in target populations, (2) document personal or occupational variables that may drive the development of PTSD symptoms, and (3) identify opportunities for training and early intervention that might reduce the likelihood of service members experiencing PTSD.

Besides addressing prevalence, this chapter also frames the discussion of combat-related PTSD within an occupational health model. Using such a model has ramifications for understanding the symptoms, risk factors, and moderating variables associated with the development of combat-related PTSD. We also address the link between PTSD and sleep problems.

First, however, we note that while the focus of this chapter is on combat-related PTSD, other types of military experiences can be associated with PTSD risk. For example, events that occur during the course of military service such as sexual assault, training accidents, and unrelated personal life experiences may contribute to the risk of PTSD (e.g., [80]). Furthermore, deployment-related events on noncombat operations such as peacekeeping or humanitarian missions may also be associated with the risk of PTSD (e.g., [50, 52]). PTSD estimates appear to vary depending on the level of threat that service members experience on these operations. Many of the experiences that appear to drive the development of PTSD during noncombat operations (such as exposure to personal threat, atrocities, and death) may also occur in combat operations. Whether encountered in combat or noncombat operations, exposure to these events are regarded as part of the occupation. Service members are trained for these events and, to some extent, expected to encounter such events as part of their professional responsibilities.

Other key outcomes are also important to acknowledge when addressing the mental health sequelae associated with high-risk occupations. These outcomes include alcohol misuse [83], anger problems [77], risk-taking [3], relationship difficulties [66], particular emotional problems associated with guilt or grief [3, 79], other mood or anxiety disorders [29, 77], and sleep problems [51, 69]. Many of these problems overlap with PTSD in terms of symptoms and in terms of risk factors.

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Taking this backdrop of additional problems associated with combat deployment into account, diagnostic criteria for PTSD are briefly reviewed, and prevalence estimates are discussed below.

Post-traumatic Stress Disorder

PTSD has a set of diagnostic criteria as defined by the fifth edition of the *American Psychiatric Association*: *Diagnostic and Statistical Manual of Mental Disorders* [6]. To be diagnosed with PTSD, individuals must have been exposed to actual or threatened death, serious injury, or sexual violation and have symptoms from each of the four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. Finally, the diagnosis requires that these symptoms need to be present for at least 1 month and need to cause significant distress or problems in daily functioning. There is some controversy over these criteria on how they diverge from the fourth edition of the *DSM* (*DSM-IV*; [6]). At least one study has shown that overall prevalence may be somewhat lower or comparable under the *DSM-5* criteria [42]. In a study of service members, Hoge, Riviere, Wilk, Herrell, and Weathers [30] found that while overall prevalence was similar, about 30% of soldiers who met criteria by one definition did not meet criteria by the other.

The *DSM-IV* criteria differs from the *DSM-5* criteria in several ways; the *DSM-IV* has less specific exposure criteria; requires the individual to have responded to the event with intense fear, helplessness, or horror; and has three symptom clusters (reexperiencing, avoidance, and hyperarousal), rather than four. To date, most of the recent research on PTSD has relied on the diagnostic criteria delineated in the *DSM-IV* (or the prevailing criteria at the time of the research).

Prevalence Estimates for Vietnam and the Gulf War

The principal study of PTSD prevalence among US Vietnam veterans was conducted more than a decade after the war ended. The National Vietnam Veterans Readjustment Study (NVVRS) surveyed more than 1,000 veterans and conducted in-depth diagnostic interviews with a subsample of 260 veterans. This multimethod approach was used in combination to develop current and lifetime prevalence rates of PTSD [47]. According to the NVVRS, approximately 15% of male and 9% of female Vietnam veterans met the criteria for current PTSD. Furthermore, the NVVRS-estimated prevalence of lifetime PTSD was approximately 31% for males and 27% for females [47].

Dohrenwend et al. [17] reexamined the NVVRS data years later to address criticisms of the original analysis. In their reanalysis of a subsample of NVVRS veterans who had been interviewed in the original study, Dohrenwend et al. examined external evidence of exposure to combat-related events as well as degree of functional impairment and possible symptom exaggeration to calculate adjusted PTSD rates. Although the adjusted rates were lower than previously estimated, the rates remained substantial with 9.1% of veterans meeting criteria for current PTSD and 18.7% of veterans meeting criteria for lifetime prevalence. Thus, even using more sophisticated techniques (including cross-referencing news reports of combat), the rates of PTSD in Vietnam veterans remain significant.

Elevated PTSD rates in Vietnam veterans are not unique to the United States. For example, studies of PTSD rates in Vietnam veterans from Australia yielded similar estimates [60]. In an analysis of structured clinical interviews conducted with Australian Vietnam veterans, PTSD rates were estimated at 12% current and 21% lifetime prevalence. In addition, Canadians who served in Vietnam with the US military reported similar or higher rates of PTSD than their US counterparts [72].

The risk of PTSD can vary, however, by the nature of the conflict. For example, in a large survey study of more than 3,000 Gulf War veterans from the United States, rates of exceeding criterion on the Mississippi Scale for Combat-Related PTSD [40] ranged from 3% to 8% depending on the time of assessment [85]. In another study, Kang et al. [38] estimated the prevalence of PTSD in Gulf War veterans compared to their non-Gulf War veteran counterparts using the PTSD Checklist (PCL, Weathers et al.) [82] 5–6 years after the war. Approximately 12% of Gulf War veterans reported PTSD compared to 4% of non-Gulf veterans. Similarly, Lee and colleagues reported that 12% of the 3,000 British veterans who sought advice from the Gulf Veterans' Medical Assessment Programme were clinically diagnosed with PTSD47 [48]. Finally, prevalence estimates were also calculated for Australian veterans of the Gulf War. In their analysis of structured interviews with 1,871 veterans, Ikin et al. [32] reported rates of new-onset PTSD were 5.4%. Taken together, estimated PTSD prevalence rates were lower following the Gulf War than the Vietnam War, demonstrating the impact that the nature of the conflict had on subsequent adjustment of veterans.

Prevalence Estimates for Afghanistan and Iraq

More recent estimates of combat-related PTSD have been conducted with service members who deployed to Iraq and Afghanistan. Just as in the case of estimating PTSD

prevalence with Vietnam veterans, there are several variables that affect these estimates following deployment to Iraq and Afghanistan. For example, the sample studied, the assessment methodology (clinical interviews versus self-report measures), and the timing of data collection can all influence resulting prevalence estimates (see [52, 66] for a discussion of methodological issues associated with PTSD measurement).

Population-based studies arguably provide the most reliable estimates of PTSD prevalence. To that end, Smith et al. [71] used data from the Millennium Cohort Study to assess the prevalence of PTSD using the PCL with a strict definition of PTSD (defined as scoring at least 50 on the PCL and according to the *DSM-IV* algorithm). In this prospective survey of more than 50,000 US service members who deployed to Iraq or Afghanistan, individual responses were not anonymous, but confidentiality was assured. The prevalence rate of *new-onset* PTSD was in the range of 7.6–8.7% for deployers who reported any level of combat exposure, 1.4–2.1% for deployers who did not report combat exposure, and 2.3–3.0% for non-deployers.

Boulos and Zamorski [11] reported on results of structured interviews with Canadian Armed Forces personnel and found an estimated PTSD prevalence rate of 7.7% among those who had deployed to Afghanistan in the past year, compared to 3.2% who had not. These results were comparable to those reported by the Millennium Cohort Study.

Other studies have yielded different estimates using anonymous methods, targeting maneuver units, and surveying individuals at a different point in the deployment cycle. For example, PTSD prevalence rates are higher in studies that focus on deployed service members from maneuver units compared to post-deployment studies that focus on the population as a whole. Specifically, the US Army's Mental Health Advisory Teams (MHATs) document PTSD prevalence in maneuver units deployed to Iraq and Afghanistan (e.g., [36]). From the anonymous surveys collected in Afghanistan as part of the Joint Mental Health Advisory Team mission conducted in 2010, the raw estimate of PTSD using the strict definition was 15.1%.

In post-deployment studies using methods similar to the MHAT, the Land Combat Study also estimated PTSD rates using both the strict definition and a broader definition (which relied solely on the DSM-IV algorithm of symptom reporting). Soldiers from US brigade combat teams returning from Afghanistan during a period of relatively moderate combat levels had a PTSD prevalence of 6.2% (using the strict definition) and 11.5% (using the broad definition; [29]). In contrast, soldiers from brigade combat teams returning from Iraq during a period of relatively high combat levels had a PTSD prevalence of 12.9% (using the strict definition) and 18.1% (using the broad definition; [29]).

Impact of Assessment Strategy on Estimated Rates

Estimates can vary depending on the timing of the survey and type of data collected. In terms of timing, Milliken et al. [58] analyzed population-based clinical data of more than 100,000 soldiers and found that rates of suspected PTSD varied depending on whether the mandated health assessment was conducted at reintegration during the Post-Deployment Health Assessment (PDHA) or 3–6 months later (as part of the Post-Deployment Health Reassessment [PDHRA] program). Among active duty personnel surveyed during the PDHA time frame, 6.2% met the cutoff criterion of 3 or more on the measure of PTSD (PC-PTSD; [64]), whereas 9.2% met criterion during the PDHRA time frame. This increase in rates in the early post-deployment period confirmed what Bliese et al. [9] reported based on results of a post-deployment screen using the PCL with a matched sample of more than 500 soldiers. Although not all studies have found this increase with Gulf War veterans (e.g., [56]), Wolfe et al. [85] also found an increase in PTSD reporting when comparing the first week after returning from deployment to 18–24 months later in Gulf War veterans.

Rates of US soldiers returning from Iraq surveyed as part of the Land Combat Study between 2004 and 2007 showed an interesting contrast over a 9 month period. Using the strict definition established by Hoge et al. [29], Thomas et al. [77] reported that 14.8% of active duty soldiers exceeded criteria at 3 months post-deployment and 16.6% exceeded the cutoff at 12 months post-deployment. National Guard rates demonstrated an even greater increase over time, with rates of soldiers exceeding PTSD cutoff scores rising from 14.7% at 3 months post-deployment to 24.6% at 12 months post-deployment.

These results not only highlight the importance of timing but also of the type of population being assessed [77]. Although there may be an initial optimism associated with returning home, rates may increase as the difficulties associated with transitioning from combat become more distressing, and, as exemplified by the National Guard rates reported by Thomas and colleagues, the support from the occupational context may falter when service members adjust to civilian life [15]. Analysis of the increased PTSD risk faced by National Guard troops returning from the Gulf War [85] supports this contention.

While there is consistency in rates increasing over time and in the heightened rates found in National Guard units, the type of data collected also influences the rates reported. As mentioned previously, non-anonymous surveys that may have consequences for a service member's medical record [58, 71] generally appear to yield lower estimates than anonymous surveys [29, 77] although these comparisons are confounded by the type of sample being assessed (population sample versus brigade combat team).

Warner et al. [81] directly addressed the issue of anonymous survey versus medical record assessment on PTSD rates. In their study, a subset of 1,712 soldiers completing the mandated PDHA also agreed to participate in an anonymous survey. Comparisons between the subsample and the larger sample of more than 3,500 soldiers from the same brigade demonstrated no key demographic or deployment history differences. When rates of exceeding criterion on the PC-PTSD (in this case, scoring 3 or higher) were compared, 3.3% of the brigade exceeded criterion for PTSD on the non-anonymous PDHA, whereas 7.7% of the subset exceeded criterion on the anonymous version of the same survey. This study highlights the importance of understanding the context of the assessment and the potential benefits of anonymity when estimating the burden of mental health distress in a population. It should be noted, however, that it is not simply an issue of anonymity but rather anonymity confounded with intent to follow-up with medical services. That is, in this example, not only does the PDHA use personal identifying information, but the consequences of exceeding cutoff criterion include potential follow-up with a medical provider and inclusion of the results in one's medical record.

These kinds of differences in assessment strategies can lead to apparent rate differences that may be misleading. The importance of considering both strategy and sample characteristics is exemplified by contrasting the approaches to the UK and US estimates. On the surface, US estimates appear to contrast sharply with published estimates of PTSD in the UK military. In a non-anonymous, population-wide survey in 2005–2006 of more than 4,700 UK veterans of the 2003 Iraq War, Hotopf et al. [31] reported that 4% of the UK veterans exceeded a cutoff of 50 on the PCL. This rate was substantially lower than the 15.9–17.5% estimate provided by Thomas et al. [77] using the same cutoff criterion although based on anonymous surveys of US maneuver units 3–12 months after deployment to Iraq. However, the UK veterans had shorter deployments, experienced less combat, and were older than their US counterparts, all key factors in determining risk for combat-related PTSD.

In a follow-up study, Iversen et al. [35] interviewed 821 individuals from the initial UK sample several years later after the service members had experienced additional combat deployments to Iraq and Afghanistan. Using PC-PTSD scores that allowed for comparison to US rates reported by Milliken et al. [58], 6.1% of active duty soldiers and 7.0% of army reservists scored three or more, roughly similar to the US active duty rates. Interestingly, the UK research with these large-scale data sets has also demonstrated a similar (though modest) pattern of increasing PTSD rates over the course of the post-deployment period [19]. Thus, even if the actual estimates differ, the patterns appear to hold constant.

In an effort to directly address the divergence between the US and UK estimates of PTSD in service members, an international team combined equivalent data collected following the same deployment to Iraq, during the same time period, with similar unit types, and controlled for demographic variables such as gender and rank as well as combat exposure, using the same combat exposure items [74]. Of interest here is that the US and UK rates of PTSD did not differ significantly from one another once potential confounders were controlled for in the analysis. Moreover, controlling for potential covariates, the UK rates of alcohol problems indicated higher rates of alcohol use problems than in the United States.

In another demonstration of the importance of methodology, Engelhard et al. [18] assessed PTSD prevalence using the PTSD Symptom Scale (PSS, [20]) and structured clinical interviews with approximately 400 Dutch soldiers after a 4-month deployment to Iraq. PTSD estimates using the PSS were higher than estimates based on structured clinical interviews, underscoring the importance of assessment technique in deriving PTSD rates. Using the more conservative PSS cutoff score, between 0% and 17% of the Dutch soldiers scored above cutoff depending on which units were surveyed; cohorts differed in terms of when their rotation occurred and in terms of level of unit training. Differences based on when a unit is in theater are important due to potential differences in terms of the levels of combat they experience.

In a meta-analysis summarizing 28 PTSD studies with veterans of Iraq and Afghanistan, Kok et al. [46] addressed the variability in PTSD rates as outlined above and identified key military variables such as type of unit, deployment phase, and amount of combat exposure that can influence these rates. By taking the military-relevant variables into account, Kok and colleagues concluded there is remarkable consistency in the reported rates (5.5% in military population samples and 13.2% in operational infantry units), underscoring the importance of considering the occupational context. See Table 2.1 for a summary of the methodological choices that need to be considered when determining PTSD rates in the military.

Table 2.1 Methodological considerations for determining PTSD prevalence in the military

Factor	Description
Study design	Anonymity, consequence for medical record
Sample	Combat arms vs. population
Measurement	Interview vs. survey; DSM-IV vs. DSM-5 criteria
Timing	Immediate vs. delayed post-deployment
Service type	Active duty vs. national guard

Combat Experiences

As the various studies reviewed above demonstrate, there is consistency across these studies in linking combat experiences to increased risk for PTSD. The overall association between the degree of combat exposure and PTSD was identified in the NVVRS [47] and was later confirmed in an examination of external evidence corroborating combat exposure [17]. Studies with service members in the Gulf War [85] and in the wars in Iraq and Afghanistan have also confirmed this relationship [29, 77]. For example, in the Millennium Cohort Study, deployed personnel who reported combat exposures had close to four times the risk of new-onset PTSD compared to those who did not report combat exposure [71], although this relationship is not necessarily universal across military occupational specialties [73].

This robust relationship between combat exposure and PTSD warrants a further examination of specific combat exposure variables. There are several different ways of categorizing combat exposure variables, without a consistent method or approach reported in the literature. One method is to assess specific individual experiences (e.g., Pietrzak et al. [62]). Another method categorizes a list of combat exposure variables into rational categories (e.g., [21, 83]). A third method uses exploratory factor analyses to categorize combat exposure variables (e.g., [41]). While factor analysis can be used to identify distinct categories, the factors may reflect how frequently events occur in addition to identifying meaningful relationships among the events. Regardless of the method selected, there is little consistency in terms of which combat experiences are the most toxic with the possible exception of exposure to atrocities.

Early work by Breslau and Davis [12] found a link between amount of combat experiences and PTSD in a sample of 69 Vietnam veteran psychiatric inpatients. Specifically, they found a link with the items "buddy killed in action," "separated from unit," "witnessed atrocities," and "participated in atrocities," but the individual items "under enemy fire," "combat patrol/dangerous duty," "surrounded by the enemy," and "wounded" were not significantly correlated with PTSD diagnosis. It is also important to note that there was also a strong relationship between participation in atrocities and PTSD, even after controlling for overall combat exposure. That is, regardless of the number of combat stressors reported, *participating* in atrocities conferred a strong risk of receiving a diagnosis of PTSD (but not for other psychiatric disorders like panic disorder, major depression, or a manic episode). In a separate study of 85 psychiatric inpatients (84 of whom were Vietnam veterans), the association between atrocities and PTSD was confirmed [24].

The lack of association between being wounded and PTSD was further explored in a study of 90 veterans of the war in Croatia from 1991 to 1993 [16]. In this interview study, soldiers who sustained nondisabling injuries were more likely to report PTSD than were soldiers who sustained disabling injuries or active duty soldiers who were not injured. The authors note that both groups of injured soldiers received injuries from the same kinds of combat-related events.

Other studies have attempted to organize a wide range of combat-related events into discrete categories. In an examination of NVVRS data, King et al. [43] followed a rational approach to categorize four war zone stressors: (1) traditional combat (e.g., firing a weapon, seeing dead Americans), (2) atrocities-abusive violence (e.g., observing events that raise questions of morality, involvement in terrorizing civilians), (3) perceived threat (e.g., the individual thinking he/she would not survive the situation or were in danger of being wounded/killed), and (4) malevolent environment (which included a degree of subjective assessment regarding difficult living conditions, perceived helplessness, and futility). Clinical psychologists and graduate students were used to sort the list of combat-related events into the four categories. In terms of association with PTSD, malevolent environment appeared to be the strongest; traditional combat was the weakest.

Fontana and Rosenheck [21] also used data from the NVVRS and examined the association of different types of combat exposure with benefits and liabilities. In contrast to King et al. [43], Fontana and Rosenheck categorized five types of combat exposure: (1) fighting, (2) killing, (3) perceived threat to self, (4) death/injury of others, and (5) atrocities. These categorizations were developed based on a review of common content by the authors. Each of these categories were highly correlated with PTSD (rs = 0.35–0.46), and the relationship between combat exposure and PTSD was mediated by perceptions of benefits (patriotic beliefs, self-improvement, and solidarity with others) and liabilities associated with combat.

In a later structural equation analysis, Fontana and Rosenheck [22] explicitly discussed how the various exposure categories are so intercorrelated that it is difficult to identify unique contributions of any one factor to the risk of PTSD. By testing for mediation, however, they were able to identify some relationships between combat exposure and PTSD. For example, they found that battlefield conditions fully mediated the impact of fighting on PTSD. Indeed, insufficiency of resources had a strong, direct relationship to

PTSD (much like "malevolent environment" described by [43]). Furthermore, killing was strongly related to PTSD, and exposure to atrocities did not have a significant and unique association to PTSD once other variables (such as killing) were accounted for in the model. The relationship between personal threat and PTSD was also suppressed when other combat exposure categories were entered in the model.

Subsequently, Wilk et al. [83] had military experts sort a list of 33 combat exposure items into Fontana and Rosenheck's [21] five categories. In addition, Wilk and colleagues also added a category to reflect positive experiences associated with combat exposure. In this analysis, which focused on alcohol misuse (not PTSD) and adjusted for demographics and unit cohesion, all six combat exposure categories were correlated with alcohol misuse (when tested in separate models). When psychiatric problems (including PTSD) were controlled for, threat to oneself and witnessing atrocities remained significant correlates of alcohol misuse as measured by a two-item screen. These results are consistent with earlier work highlighting the importance of atrocities as a risk factor for post-deployment adjustment. In an integrated model testing all of the combat exposure categories simultaneously, personal threat was still correlated with alcohol misuse, in contrast to the PTSD analysis reported by Fontana and Rosenheck [22]. Using the same categorization as Wilk et al. [83], Adler et al. [3] found a significant positive correlation over time between these six combat exposure categories and PCL scores (again, when tested in separate models).

Although not specifically examining PTSD, Killgore et al. [41] studied the relationship between different types of combat experiences and risk-taking propensity among a sample of veterans from Operation Iraqi Freedom. In contrast to the categorization approach described above, these researchers factor analyzed the list of combat exposure items and identified seven categories: violent combat exposure, US human trauma exposure, having survived a close call, having a buddy killed/injured, having killed enemy, having killed friendly/nonhostile forces, and pride in mission. While these categories were labeled differently, they are essentially similar to those proposed by Fontana and Rosenheck [21], with the exception of Killgore and colleague's delineation between US human trauma and buddy injured/killed. In contrast, King et al. [43] had fewer categories and combined fighting, killing, and exposure to death into one category.

Regardless of which model is used, the most consistent finding appears to be that atrocities is associated with negative mental health, but there is less consistency regarding any of the other categories (e.g., [21, 22, 41, 83]). Other studies have found some consistency in terms of the relationship between killing and PTSD. In a series of studies on the association of killing to PTSD symptoms, Maguen and colleagues have repeatedly found that after controlling for other combat exposures, killing accounts for a significant but small amount of variance in PTSD symptoms. This relationship was found using NVVRS interview data [53], surveys with Gulf War veterans [55], and post-deployment screening data with US veterans of the Iraq war [54]. Taken together with other studies (e.g., [12, 22]), there appears to be some convergence that combat-related killing is associated with PTSD, but the degree to which it is a principal driver of combat-related PTSD or the degree to which other variables mediate its impact remains unclear.

It is also important to acknowledge the way in which combat stressors are defined. While most of the studies cited in this section have assessed exposure to potentially traumatic events, studies have also indicated *that the malevolent environment*, or nontraumatic stressors associated with the deployment environment, is also an important risk factor [78]. In one study, for example, service members reported that these kinds of nontraumatic stressors were actually more stressful than combat experiences [28]. Interian, Kline, Janal, Glynn, and Losonczy [33] also found that nontraumatic stressors related to the home front were linked with higher levels of PTSD. Despite the undisputed significance of combat-related traumatic events in predicting PTSD, these nontraumatic stressors also represent an independent risk factor for the development of PTSD. Given that these nontraumatic stressors may be easier for organizations to address, they provide an important perspective on the risk of developing PTSD.

In summary, the majority of studies seem to demonstrate a complex relationship between combat experiences and PTSD. Rather than one particular type of experience predicting PTSD, it may be the overall environment and the way in which these events are interpreted that result in PTSD. Another possibility is that it is the sheer number of events, rather than the different categories, that account for PTSD. Few studies have examined the curvilinear nature of PTSD but, as Adler et al. [2] reported, there may be a point at which the relationship between combat events and PTSD rises exponentially. That is, there may be a tipping point or threshold linked to the sheer number of combat-related demands whereby the service member develops PTSD rather than a specific category of exposure that drives PTSD symptoms. Perhaps it is more useful, therefore, to examine moderators of the combat exposure-PTSD link rather than identify specific combat-related experiences that place service members at risk.

Variables Moderating the Combat Exposure-PTSD Link

Several studies have examined variables that influence the combat exposure-PTSD link, through a direct association, mediation, or moderation. These variables include preexist-

ing psychological problems [14, 34], demographic variables like junior rank and younger age [34, 85], as well as variables measured either during deployment or upon return home, such as lack of social support [34, 76], low levels of psychological hardiness [76], low use of problem-focused coping (e.g., [70]), hostile unit climate (e.g., [23]), and low morale [34]. Similarly, Jones et al. [37] found that greater unit cohesion, high morale, and good leadership were all associated with lower levels of PTSD among UK Armed Forces personnel surveyed during their deployment to Afghanistan. Furthermore, specific leader behaviors addressing operational stress (e.g., "encourages soldiers to seek help for stress-related problems," "intervenes when a soldier displays stress reactions such as anxiety, depression or other behavioral health problem") were associated with fewer PTSD symptoms [4]. This relationship held even after controlling for generally good leadership, rank, and combat exposure. Note that while there is also evidence that gender influences the combat exposure-PTSD relationship, examining the impact of gender is beyond the scope of this chapter (for reviews of gender and combat-related PTSD, see [39, 43, 85]).

In an analysis of NVVRS data, results of structural equation modeling demonstrated the importance of hardiness as a personal resource as well as social support during the homecoming period in predicting PTSD [44]. Postwar stressful life events also accounted for PTSD symptoms, primarily through the lack of support and hardiness. Interestingly, these variables served as mediators but not moderators of the combat exposure-PTSD relationship. Thus, the impact of combat exposure (traditional combat, atrocities-abusive violence, perceived threat, and malevolent environment) was not exacerbated by low levels of hardiness or lack of social support, but their impact on PTSD occurred indirectly through the absence of these resources. Those high in hardiness appeared to seek out support and do better in terms of PTSD.

Building on the results of the NVVRS data, Vogt et al. [80] studied US veterans returning from Iraq and Afghanistan to identify risk factors for PTSD symptoms. Risk pathways from King et al. [45] were replicated, including the importance of pre-deployment risk factors (childhood family functioning and stressors), warzone stressors (combat exposure, perceived threat, and concerns about relationship disruptions during deployment), and postwar variables (stressors and social support). In particular, the perception of threat mediated the relationship between combat exposure and PTSD symptoms. The importance of cognitive appraisal has been replicated in other studies as well (e.g., [57]).

The goal of the foregoing discussion has been to provide a sense of the breadth of risk factors associated with the development of combat-related PTSD and the kinds of methodological issues associated with identifying these risk factors. While not exhaustive, this discussion provides a basis from which to understand that there are preexisting risk factors, risk factors associated with the deployment context, and risk factors that are evident at post-deployment as well. Table 2.2 provides a summary of some of the risk factors discussed in this chapter.

Table 2.2 Selected risk factors for combat-related PTSD across deployment phase

Deployment phase	Risk factors
Preexisting	Mental health problems, history of problems in childhood family
	Junior rank/age
	Sleep problems
	Inadequate training
Deployment	Overall combat exposure
	Participation in atrocities
	Threat to self, exposure to death/injury, killing
	Malevolent environment/battlefield conditions/ nontraumatic deployment stressors
	Wounded status[a]
	Low levels of unit cohesion and morale
	Low levels of good/supportive leadership
	Low levels of problem-focused coping
Post-deployment	Sleep problems
	Inadequate support (from unit, leadership, and family)
	Traits (e.g., lack of hardiness)
	Coping (e.g., low levels of problem-focused coping)

[a]Note that wounded status has not been consistently identified as a predictor of PTSD

As discussed previously, the specific combat event itself may be less critical than how the individual interprets that event. However, to date, the research has addressed the role of individual cognitive processing of events and has not examined the shared processing of events by military units. Bliese et al. [10] have discussed the importance of considering unit-level characteristics in understanding unit-by-unit differences in the relationship between combat exposure and PTSD. Just as the individual's cognitive processing appears to influence the impact of events on their mental health, so too may the military unit's processing as a whole affect the group's adjustment.

There are different elements that may affect group-level processing, from shared perceptions of unit cohesion, level of training, and leadership to shared perceptions of loss, betrayal, and social support. More research is needed, however, to clarify how unit-level processing of events influences the relationship between combat experiences and PTSD. For example, it may be that consistency of perceptions across the unit is as predictive of adjustment as actual ratings of those perceptions. As Bliese and Britt [8] found in their analysis of survey data from US soldiers deployed to Haiti, while the

overall group perception of leadership quality was a significant moderator of the relationship between work stressors and outcomes such as morale and depression, group consensus about the quality of unit leadership was also a significant moderator of that relationship. This finding demonstrates the potential power of the group's perception to impact a range of military-related mental health variables. Kok et al. [46] have also emphasized that understanding the military context is critical for identifying underlying patterns of PTSD.

PTSD and Sleep

At this point, we have reviewed the topics of diagnosis, prevalence, risk factors, and moderators associated with PTSD. One variable that is important to consider across all four of these topics is sleep. In terms of diagnosis, sleep problems are included in the DSM-5 criteria for PTSD [7]. Specifically, having traumatic nightmares is one of the symptoms in the intrusion symptom domain, and sleep disturbance is one of the symptoms in the domain of alterations in arousal and reactivity. Although sleep problems are included as part of the symptom picture of PTSD, sleep problems themselves are a relatively frequent problem reported by service members (e.g., [2, 69]) and are also correlated with PTSD [59, 69, 75, 84].

Not only is there an association between sleep problems and PTSD, sleep problems may be a precursor to the development of combat-related PTSD. For example, predeployment sleep problems serve as predictors of post-deployment mental health symptomatology in service members, including PTSD [25, 86]. In addition, Wright et al. [87] found that sleep problems reported at 4 months postdeployment were a risk factor in the development of PTSD (and depression) symptoms 8 months later. In contrast, PTSD (and depression symptoms) did not predict the development of sleep problems over time, providing support for the premise that sleep problems could serve as an early warning indicator of mental health problems. Not only are sleep problems indicators of increased risk and chronicity of PTSD, but sleep problems may affect the efficacy of evidence-based therapies for PTSD as well (see [26] for review).

Identifying the role of sleep in the development of PTSD is important because it offers two key avenues for intervention. First, it is possible that addressing sleep problems early may reduce the risk of subsequent PTSD symptomatology, although to date no early interventions have demonstrated the efficacy of this approach. Second, reporting sleep problems may be less stigmatizing than reporting other more traditional mental health symptoms. Thus, evaluating sleep problems may be a way to identify service members who can benefit from care in a way that is more acceptable to service members. Understanding this larger context is important in order to provide treatment in a way that is consistent with the occupational culture of the military.

Occupational Health Model of PTSD

Understanding the dynamics of combat and PTSD within an occupational context is different from understanding how an individual victim of a potentially traumatic event develops PTSD. In the case of the individual victim, the traumatic event is typically unexpected, and the individual is not trained to respond. In the case of high-risk occupations, PTSD symptoms can be reconceptualized using an occupational health model [15].

The occupational health model of PTSD assumes that individuals in high-risk occupations are not passive victims of potentially traumatic events; these events are encountered as part of the occupation for which they are trained, and the individual may be an active participant in these events. As exemplified by Perrin et al. [61], experienced emergency rescue personnel reported fewer PTSD symptoms in the wake of responding to the World Trade Center disaster than did rescue volunteers. Professional experience, identity, group support, and training may be critical protective factors.

Indeed, training is an essential component of the occupational health model. In the case of the military, for example, service members who rated their training and deployment preparation highly reported fewer mental health problems following deployment to Iraq and Afghanistan [63]. Furthermore, Adler et al. [1] found that service members reported that their training "kicked in" when they were confronted with a combat-related event like a firefight. Even though they reported symptoms of PTSD, they did not report the subjective peri-traumatic response of feeling helpless, horrified, or afraid (a *DSM-IV* criterion for PTSD that was dropped by *DSM-5*).

In an occupational health approach, the context of the event and the presence of group support are also important. Combat-related events typically occur to cohesive teams that provide normative information about how to respond as well as essential support to each other. These teams also have a strong expectation that they will look out for one another and that leaders will also look out for their unit members. This group perspective provides an important source of strength and support.

In addition, PTSD symptoms may occur in a different pattern than those that occur in response to an individual trauma. For example, some symptoms, such as hypervigilance, may occur prior to a specific combat-related event in response to training. The occupational health model also suggests that some symptoms are adaptive combat-related skills that can

be used to help service members adjust to combat and are not necessarily dysfunctional in a combat environment. For example, anger can help focus an individual's response and enhance performance during a combat deployment, but it is not particularly helpful in terms of relationship building following deployment. When service members transition home, these symptoms can become problematic, interfere with adjustment to noncombat missions, and may even increase as the supportive structures change with less unit contact or after an individual leaves the military.

Overall, the occupational health model can account for the presence of psychological reactions prior to exposure to potentially traumatic events, widen the domain of reactions typically considered (such as anger, guilt, grief, risk-taking, and potential benefits associated with deployment), and suggest different potential symptom trajectories. The occupational health model also proposes a basis for understanding the importance of variables that can reduce the impact of combat-related events on service member mental health.

By conceptualizing symptoms as part of the occupational context, the occupational health model can also suggest new avenues of research. As mentioned previously, unit-based cognitive appraisal should be examined to understand the role of shared interpretations of events in the development of PTSD. In addition, cognitive appraisal training should be studied as a method for helping service members and their leaders manage the demands of combat (e.g., [80]). Or early intervention effort and as part of the US Army's resilience training program [65].

These training techniques, however, should not just be evidence informed but should also be evidence based. While some post-deployment early intervention techniques have been validated (e.g., [2]), more research needs to be conducted on using evidence-based techniques within the military [49]. Not all techniques based on civilian research are necessarily a good fit for the military context and may need to be adapted. These adapted interventions should be designed to leverage strengths in military culture, including the tradition of taking care of one another and meeting training standards. By integrating these characteristics into an intervention package, evidence-based military mental health training programs can be designed and implemented to be optimally effective in reducing the link between combat exposure, PTSD, and other post-deployment mental health problems.

Future Directions

Given the devastating consequences of PTSD in service members returning from combat coupled with the impact it has on their families, it is important to capitalize on three emerging trends. First, the field should take a public health perspective in understanding PTSD. While emphasizing treatment is important, it is equally important to understand the role of early interventions in reducing symptomatology. Although early interventions may not be easily studied with individual victims of trauma, studies can be conducted with groups that are at high risk for exposure to occupationally related traumatic events. Service members, like other high-risk occupations in the emergency services sector, are uniquely prepared to place themselves in harm's way. As such, studies can be conducted to validate prevention programs designed to reduce the negative impact of occupationally related traumatic stressors on individuals.

Second, given that sleep is implicated as an early warning indicator both prior to exposure and in the immediate aftermath of exposure to potentially traumatic events, future research should focus on establishing an occupational culture that considers sleep a "critical item of resupply," a resource to be safeguarded and managed, much like water is considered a critical supply item to prevent dehydration. Unique sleep interventions, including the use of personal monitoring devices and personalized feedback, may prove to be a mechanism to improve sleep habits among service members who may otherwise be tempted to shortchange their sleep [5].

Third, leaders should be trained in sleep management and encouraged to prioritize the sleep of their teams, taking into account scheduling, sleeping conditions, and the work culture. Recent work [27] suggests that relatively simple approaches such as these may be associated with better outcomes and as such presents an interesting focus for future research.

To the extent that future research on PTSD targets sleep, organizations like the military may benefit not only from a reduction in symptoms but also an increase in performance that would otherwise be jeopardized as a result of chronic sleep problems. Future research should capitalize on high-risk occupations like the military in order to incorporate prospective designs, test early interventions, and leverage existing support provided by unit members and unit leadership.

References

1. Adler AB, Wright KM, Bliese PD, Eckford R, Hoge CW. A2 diagnostic criterion for combat-related posttraumatic stress disorder. J Trauma Stress. 2008;21(3):301–8. doi:10.1002/jts.20336.
2. Adler AB, Bliese PD, McGurk D, Hoge CW, Castro CA. Battlemind debriefing and battlemind training as early interventions with soldiers returning from Iraq: randomization by platoon. J Consult Clin Psychol. 2009;77(5):928–40. doi:10.1037/a0016877.
3. Adler AB, Britt TW, Castro CA, McGurk D, Bliese PD. Effect of transition home from combat on risk-taking and health-related

behaviors. J Trauma Stress. 2011;24(4):381–9. doi:10.1002/jts.20665.
4. Adler AB, Saboe KN, Anderson J, Sipos ML, Thomas JL. Behavioral health leadership: new directions in occupational mental health. Curr Psychiatry rep. 2014;16(10):484. doi:10.1007/s11920-014-0484-6.
5. Adler AB, Gunia BC, Bliese PD, Kim PY, LoPresti ML. Using actigraphy feedback to improve sleep insoldiers: an exploratory trial. Sleep Health. 2017;3(2):126–31. doi:10.1016/j.sleh.2017.01.001.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM- IV. 4th ed. Washington, DC: American Psychiatric Association; 1994.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Association; 2013.
8. Bliese PD, Britt TW. Social support, group consensus and stressor-strain relationships: social context matters. J Organ Behav. 2001;22(4):425–36. doi:10.1002/job.95.
9. Bliese PD, Wright KM, Adler AB, Cabrera O, Castro CA, Hoge CW. Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. J Consult Clin Psychol. 2008;76(2):272–81. doi:10.1037/0022-006X.76.2.272.
10. Bliese PD, Adler AB, Castro CA. Research-based preventive mental health care strategies in the military. In: Adler AB, Bliese PD, Castro CA, editors. Deployment psychology: evidence-based strategies to promote mental health in the military. Washington, DC: American Psychological Association; 2011. p. 103–24.
11. Boulos D, Zamorski MA. Contribution of the mission in Afghanistan to the burden of past-year mental disorders in Canadian Armed Forces Personnel, 2013. Can J Psychiatry. 2016;61(1 suppl):64S–76S. doi:10.1177/0706743716628857.
12. Breslau N, Davis GC. Posttraumatic stress disorder: the etiologic specificity of wartime stressors. Am J Psychiatry. 1987;144(5):578–83.
13. Bryant RA, Harvey AG. Posttraumatic stress in volunteer firefighters. Predictors of distress. J Nerv Ment Dis. 1995;183(4):267–71.
14. Cabrera OA, Hoge CW, Bliese PD, Castro CA, Messer SC. Childhood adversity and combat as predictors of depression and post-traumatic stress in deployed troops. Am J Prev Med. 2007;33(2):77–82. S0749-3797(07)00235-8 [pii]. doi:10.1016/j.amepre.2007.03.019.
15. Castro CA, Adler AB. Reconceptualizing combat-related posttraumatic stress disorder as an occupational hazard. In: Adler AB, Bliese PD, Castro CA, editors. Deployment psychology: evidence-based strategies to promote mental health in the military. Washington, DC: American Psychological Association; 2011. p. 217–42.
16. Delimar D, Sivik T, Korenjak P, Delimar N. The effect of different traumatic experiences on the development of post-traumatic stress disorder. Mil Med. 1995;160(12):635–9.
17. Dohrenwend BP, Turner JB, Turse NA, Adams BG, Koenen KC, Marshall R. The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science. 2006;313:979–82. doi:10.1126/science.1128944.
18. Engelhard IM, van den Hout MA, Weerts J, Arntz A, Hox JJ, McNally RJ. Deployment-related stress and trauma in Dutch soldiers returning from Iraq. Prospective study. Br J Psychiatry. 2007;191:140–145. 191/2/140 [pii]. doi:10.1192/bjp.bp.106.034884.
19. Fear NT, Jones M, Murphy D, Hull L, Iversen AC, Coker B, et al. What are the consequences of deployment to Iraq and Afghanistan on the mental health of the UK armed forces? A cohort study. Lancet. 2010;375(9728):1783–1797. S0140–6736(10)60672–1 [pii]. doi:10.1016/S0140-6736(10)60672-1.
20. Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J Trauma Stress. 1993;6(4):459–73. doi:10.1002/jts.2490060405.
21. Fontana A, Rosenheck R. Psychological benefits and liabilities of traumatic exposure in the war zone. J Trauma Stress. 1998;11(3):485–503. doi:10.1023/A:1024452612412.
22. Fontana A, Rosenheck R. A model of war zone stressors and posttraumatic stress disorder. J Trauma Stress. 1999;12(1):111–26. doi:10.1023/A:1024750417154.
23. Fontana A, Litz B, Rosenheck R. Impact of combat and sexual harassment on the severity of posttraumatic stress disorder among men and women peacekeepers in Somalia. J Nerv Ment Dis. 2000;188(3):163–9.
24. Ford JD. Disorders of extreme stress following war-zone military trauma: associated features of posttraumatic stress disorder or comorbid but distinct syndromes? J Consult Clin Psychol. 1999;67(1):3–12.
25. Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, et al. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. Sleep. 2013;36(7):1009–18. doi:10.5665/sleep.2798.
26. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatr. 2013;170(4):372–82. doi:10.1176/appi.ajp.2012.12040432.
27. Gunia BC, Sipos ML, LoPresti ML, Adler AB. Sleep leadership in high-risk occupations: an investigation of soldiers on peacekeeping and combat missions. Mil Psychol. 2015;27(4):197–211. doi:http://dx.doi.org/10.1037/mil0000078
28. Heron EA, Bryan CJ, Dougherty CA, Chapman WG. Military mental health: the role of daily hassles while deployed. J Nerv Ment Dis. 2013;201(12):1035–9. doi:10.1097/NMD.0000000000000058.
29. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351(1):13–22. doi:10.1056/NEJMoa040603.
30. Hoge CW, Riviere LA, Wilk JE, Herrell RK, Weathers FW. The prevalence of post-traumatic stress disorder (PTSD) in US combat soldiers: a head-to-head comparison of DSM-5 versus DSM-IV-TR symptom criteria with the PTSD checklist. Lancet Psychiatry. 2014;1(4):269–77. doi:10.1016/S2215-0366(14)70235-4.
31. Hotopf M, Hull L, Fear NT, Browne T, Horn O, Iversen A, et al. The health of UK military personnel who deployed to the 2003 Iraq war: a cohort study. Lancet. 2006;367(9524):1731–1741. S0140–6736(06)68662–5 [pii]. doi:10.1016/S0140-6736(06)68662-5.
32. Ikin JF, Sim MR, Creamer MC, Forbes AB, McKenzie DP, Kelsall HL, et al. War-related psychological stressors and risk of psychological disorders in Australian veterans of the 1991 Gulf War. Br J Psychiatry. 2004;185:116–26. doi:10.1192/bjp.185.2.116185/2/116. [pii].
33. Interian A, Kline A, Janal M, Glynn S, Losonczy M. Multiple deployments and combat trauma: do homefront stressors increase the risk for posttraumatic stress symptoms? J Trauma Stress. 2014;27(1):90–7. doi:10.1002/jts.21885.
34. Iversen AC, Fear NT, Ehlers A, Hacker Hughes J, Hull L, Earnshaw M, et al. Risk factors for post-traumatic stress disorder among UK Armed Forces personnel. Psychol Med. 2008;38(4):511–522. S0033291708002778 [pii]. doi:10.1017/S0033291708002778.
35. Iversen AC, van Staden L, Hacker Hughes J, Browne T, Hull L, Hall J, et al. The prevalence of common mental disorders and PTSD in the UK military: using data from a clinical interview-based study. BMC Psychiatry. 2009;9(68) doi:10.1186/1471-244X-9-68.
36. Joint Mental Health Advisory Team 7. Joint Mental Health Advisory Team 7 (J-MHAT 7): operation enduring freedom 2010, Afghanistan (2010). Retrieved from http://www.armymedicine.army.mil/reports/mhat/mhat_vii/J_MHAT_7.pdf.
37. Jones N, Seddon R, Fear NT, McAllister P, Wessely S, Greenberg N. Leadership, cohesion, morale, and the mental health of UK Armed

Forces in Afghanistan. Psychiatry. 2012;75(1):49–59. doi:10.1521/psyc.2012.75.1.49.
38. Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War veterans: a population-based survey of 30,000 veterans. Am J Epidemiol. 2003;157(2):141–8. doi:10.1093/aje/kwf187.
39. Katz LS, Cojucar G, Davenport CT, Pedram C, Lindl C. Post-deployment readjustment inventory: reliability, validity, and gender differences. Mil Psychol. 2010;22:41–56. doi:10.1080/08995600903249222.
40. Keane TM, Caddell JM, Taylor KL. Mississippi scale for combat-related posttraumatic stress disorder: three studies in reliability and validity. J Consult Clin Psychol. 1988;56(1):85–90.
41. Killgore WDS, Cotting DI, Thomas JL, Cox AL, McGurk D, Vo AH, et al. Post-combat invincibility: violent combat experiences are associated with increased risk-taking propensity following deployment. J Psychiatr Res. 2008;42(13):1112–21. doi:10.1016/j.jpsychires.2008.01.001.
42. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. J Trauma Stress. 2013;26(5):537–47. doi:10.1002/jts.21848.
43. King DW, King LA, Gudanowski DM, Vreven DL. Alternative representations of war zone stressors: relationships to posttraumatic stress disorder in male and female Vietnam veterans. J Abnorm Psychol. 1995;104(1):184–95.
44. King LA, King DW, Fairbank JA, Keane TM, Adams GA. Resilience-recovery factors in post-traumatic stress disorder among female and male Vietnam veterans: hardiness, postwar social support, and additional stressful life events. J Pers Soc Psychol. 1998;74(2):420–34.
45. King DW, King LA, Foy DW, Keane TM, Fairbank JA. Posttraumatic stress disorder in a national sample of female and male Vietnam veterans: risk factors, war-zone stressors, and resilience-recovery variables. J Abnorm Psychol. 1999;108(1):164–70. doi:10.1037//0021-843X.108.1.164.
46. Kok BC, Herrell RK, Thomas JL, Hoge CW. Posttraumatic stress disorder associated with combat service in Iraq or afghanistan: reconciling prevalence differences between studies. J Nerv Ment Dis. 2012;200(5):444–50. doi:10.1097/NMD.0b013e318253231200005053-201205000-00012. [pii]
47. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, et al. Trauma and the Vietnam war generation: report of findings from the National Vietnam Readjustment Study. New York: Mazel; 1990.
48. Lee HA, Gabriel R, Bolton JP, Bale AJ, Jackson M. Health status and clinical diagnoses of 3000 UK Gulf War veterans. J R Soc Med. 2002;95(10):491–7.
49. Lester PB, McBride S, Bliese PD, Adler AB. Bringing science to bear: an empirical assessment of the comprehensive soldier fitness program. Am Psychol. 2011;66(1):77–81. doi:10.1037/a0022083.
50. Litz BT, Gray MJ, Boltan EE. Posttraumatic stress disorder following peacekeeping operations. In: Britt TW, Adler AB, editors. The psychology of the peacekeeper: lessons from the field. Westport: Praeger; 2003. p. 243–58.
51. Luxton DD, Greenburg D, Ryan J, Niven A, Wheeler G, Mysliwiec V. Prevalence and impact of short sleep duration in redeployed OIF soldiers. Sleep. 2011;34(9):1189–95. doi:10.5665/sl eep.1236.
52. Maguen S, Suvak M, Litz BT. Predictors and prevalence of post-traumatic stress disorder among military veterans. In: Adler AB, Castro CA, Britt TW, editors. Military life: the psychology of serving in peace and combat, Operational Stress, vol. 2. Westport: Praeger Security International; 2006. p. 141–69.
53. Maguen S, Metzler TJ, Litz BT, Seal KH, Knight SJ, Marmar CR. The impact of killing in war on mental health symptoms and related functioning. J Trauma Stress. 2009;22(5):435–43. doi:10.1002/jts.20451.
54. Maguen S, Lucenko BA, Reger MA, Gahm GA, Litz BT, Seal KH, et al. The impact of reported direct and indirect killing on mental health symptoms in Iraq war veterans. J Trauma Stress. 2010;23(1):86–90. doi:10.1002/jts.20434.
55. Maguen S, Vogt DS, King LA, King DW, Litz BT, Knight SJ, Marmar CR. The impact of killing on mental health symptoms in Gulf War veterans. Psychol Trauma Theory Res Practice Policy. 2011;3(1):21–6. doi:10.1037/a0019897.
56. McCarroll JE, Ursano RJ, Fullerton CS. Symptoms of PTSD following recovery of war dead: 13–15-month follow-up. Am J Psychiatry. 1995;152(6):939–41.
57. McCuaig Edge HJ, Ivey GW. Mediation of cognitive appraisal on combat exposure on psychological distress. Mil Psychol. 2012;24(1):71–85. doi:10.1080/08995605.2012.642292.
58. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA: J Am Med Assoc. 2007;298(18):2141–8. doi:10.1001/jama.298.18.2141.
59. Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. Sleep. 2013;36(2):167–74. doi:10.5665/sleep.2364.
60. O'Toole BI, Marshall RP, Grayson DA, Schureck RJ, Dobson M, Ffrench M, et al. The Australian Vietnam Veterans Health Study: III. psychological health of Australian Vietnam veterans and its relationship to combat. Int J Epidemiol. 1996;25(2):331–40.
61. Perrin MA, DiGrande L, Wheeler K, Thorpe L, Farfel M, Brackbill R. Differences in PTSD prevalence and associated risk factors among World Trade Center disaster rescue and recovery workers. Am J Psychiatry. 2007;164(9):1385–1394. 164/9/1385 [pii]. doi:10.1176/appi.ajp.2007.06101645.
62. Pietrzak RH, Whealin JM, Stotzer RL, Goldstein MB, Southwick SM. An examination of the relation between combat experiences and combat-related posttraumatic stress disorder in a sample of Connecticut OEFOIF Veterans. J Psychiatr Res. 2011;45(12):1579–84. doi:10.1016/j.jpsychires.2011.07.010.
63. Price M, Gros DF, Strachan M, Ruggiero KJ, Acierno R. Combat experiences, pre-deployment training, and outcome of exposure therapy for post-traumatic stress disorder in operation enduring Freedom/Operation Iraqi Freedom veterans. Clin Psychol Psychother. 2012; doi:10.1002/cpp.1768.
64. Prins A, Ouimette P, Kimerling R, Cameron RP, Hugelshofer DS, Shaw-Hegwer J, et al. The primary care PTSD screen (PC-PTSD): development and operating characteristics. Prim Care Psychiatry. 2003;9(1):9–14. doi:10.1185/135525703125002360.
65. Reivich KJ, Seligman ME, McBride S. Master resilience training in the U.S. Army. Am Psychol. 2011;66(1):25–34. doi:10.1037/a0021897.
66. Richardson LK, Frueh BC, Acierno R. Prevalence estimates of combat-related post-traumatic stress disorder: critical review. Aust N Z J Psychiatry. 2010;44(1):4–19. doi:10.3109/00048670903393597.
67. Riviere LA, Merrill JC. The impact of combat deployment on military families. In: Adler AB, Bliese PB, Castro CA, editors. Deployment psychology: evidence-based strategies to promote mental health in the military. Washington, DC: American Psychological Association; 2011. p. 125–49.
68. Robinson HM, Sigman MR, Wilson JP. Duty-related stressors and PTSD symptoms in suburban police officers. Psychol Rep. 1997;81(3 Pt 1):835–45.
69. Seelig AD, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. Sleep. 2010;33(12):1615–22.
70. Sharkansky EJ, King DW, King LA, Wolfe J, Erickson DJ, Stokes LR. Coping with Gulf War combat stress: mediating and moderating effects. J Abnorm Psychol. 2000;109(2):188–97.

71. Smith TC, Ryan MA, Wingard DL, Slymen DJ, Sallis JF, Kritz-Silverstein D. New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: prospective population based US military cohort study. BMJ: British Medical Journal. 2008;336(7640):366–371. bmj.39430.638241.AE [pii]. doi:10.1136/bmj.39430.638241.AE.
72. Stretch RH. Psychosocial readjustment of Canadian Vietnam veterans. J Consult Clin Psychol. 1991;59(1):188–9.
73. Sundin J, Fear NT, Iversen A, Rona RJ, Wessely S. PTSD after deployment to Iraq: conflicting rates, conflicting claims. Psychol Med. 2010;40(3):367–382. doi: S0033291709990791 [pii]. doi:10.1017/S0033291709990791.
74. Sundin J, Herrell RK, Hoge CW, Fear NT, Adler AB, Greenberg N, et al. Mental health outcomes in US and UK military personnel returning from Iraq. Br J Psychiatry. 2014;204(3):200–7. doi:10.1192/bjp.bp.113.129569.
75. Swinkels CM, Ulmer CS, Beckham JC, Buse N, Calhoun PS. The Association of Sleep Duration, Mental Health, and Health Risk Behaviors among U.S. Afghanistan/Iraq era veterans. Sleep. 2013;36(7):1019–25. doi:10.5665/sleep.2800.
76. Taft CT, Stern AS, King LA, King DW. Modeling physical health and functional health status: the role of combat exposure, posttraumatic stress disorder, and personal resource attributes. J Trauma Stress. 1999;12(1):3–23. doi:10.1023/A:1024786030358.
77. Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch Gen Psychiatry. 2010;67(6):614–23. doi:10.1001/archgenpsychiatry.2010.54.
78. Thomas JL, Britt TW, Odle-Dusseau H, Bliese PB. Dispositional optimism buffers combat veterans from the negative effects of warzone stress on mental health symptoms and work impairment. J Clin Psychol. 2011;67:866–80.
79. Toblin RL, Riviere LA, Thomas JL, Adler AB, Kok BC, Hoge CW. Grief and physical health outcomes in U.S. soldiers returning from combat. J Affect Disord. 2012;136(3):469–475. S0165-0327(11)00715-4 [pii]. doi:10.1016/j.jad.2011.10.048.
80. Vogt D, Smith B, Elwy R, Martin J, Schultz M, Drainoni ML, Eisen S. Predeployment, deployment, and postdeployment risk factors for posttraumatic stress symptomatology in female and male OEF/OIF veterans. J Abnorm Psychol. 2011;120(4):819–831. 2011-13218-001 [pii]. doi:10.1037/a0024457.
81. Warner CH, Appenzeller GN, Grieger T, Belenkiy S, Breitbach J, Parker J, et al. Importance of anonymity to encourange honest reporting in mental health screening after combat deployment. Arch Gen Psychiatry. 2011;68(10):1065–71. doi:10.1001/archgenpsychiatry.2011.112.
82. Weathers FW, Litz BT, Herman DS, Huska JA, & Keane TM. The PTSD Checklist (PCL): reliability, validity, and diagnostic utility. Paper presented at the Annual meeting of the International Society for Traumatic Stress Studies, San Antonio;1993.
83. Wilk JE, Bliese PD, Kim PY, Thomas JL, McGurk D, Hoge CW. Relationship of combat experiences to alcohol misuse among U.S. soldiers returning from the Iraq war. Drug Alcohol Depend. 2010;108:115–21. doi:10.1016/j.drugalcdep.2009.12.003.
84. Williams SG, Collen J, Orr N, Holley AB, Lettieri CJ. Sleep disorders in combat-related PTSD. Sleep Breath. 2015;19(1):175–82. doi:10.1007/s11325-014-0984-y.
85. Wolfe J, Erickson DJ, Sharkansky EJ, King DW, King LA. Course and predictors of posttraumatic stress disorder among Gulf War veterans: a prospective analysis. J Consult Clin Psychol. 1999;67(4):520–8.
86. Wright KM, Britt TW, Bliese PD, Adler AB. Insomnia severity, combat exposure and mental health outcomes. Stress Health. 2010:1–9. doi:10.1002/smi.1373.
87. Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol. 2011;67(12):1240–58. doi:10.1002/jclp.20845.

Sleep as a Mediator of mTBI and PTSD

3

Dante Picchioni and Thomas J. Balkin

Introduction

The frequently comorbid relationship between post-traumatic stress disorder (PTSD) and post-concussion syndrome (PCS) has been described and discussed extensively (e.g., [50]), and the fact that there is significant overlap in the symptomology of these disorders has generated considerable discussion and speculation regarding the nature of both (e.g., [9]). Indeed, it has been pointed out that the extent of this overlap, and the nonspecific nature of those symptoms common to both diagnoses, has essentially made it impossible to place any confidence in efforts to differentially screen for these disorders in a post hoc manner (e.g., in military personnel returning from deployment; see [16]).

Of course, the potential utility of determining whether, and the extent to which, various symptoms directly reflect lingering effects of mTBI events vs. the effects of PTSD could be important if it turned out that such information usefully informs and guides treatment strategies and/or future research. But to date, the utility of differential diagnoses has not been demonstrated empirically. In fact, even the legitimacy of the concept of PCS as a distinct clinical entity has been called into question by findings such as those reported by Dean et al. [11], who found that 34% of individuals who had not previously experienced a head injury nevertheless reported PCS symptoms – making them indistinguishable from the 31% of patients who had previously experienced a head injury and who similarly reported experiencing PCS symptoms.

It has been suggested that the relatively high prevalence of "neurological abnormalities" in veterans with PCS [43] implies an increased likelihood that the syndrome is indeed the lingering effects of a physical insult to the brain [42]. Similarly, the finding that veterans with PCS symptoms (regardless of whether they also have PTSD) exhibit relatively reduced metabolic activity in cerebellum, pons, and temporal lobe [36] has been offered as evidence that a persistent physiological brain injury was most likely a causal factor (although they concede that the presence of lingering brain injury does not preclude the possibility that comorbid PTSD might also be contributing to observed symptoms).

The problem with such reasoning is that it depends on the presumption that such neurological and metabolic findings reflect causal factors that are exclusively (or at least primarily) within the realm of "physical injury" – i.e., that such findings "tip the scales" toward an increased likelihood that there has, in fact, been a primary, physical insult to the brains of affected individuals. But this is not necessarily the case. There is a wealth of data showing that psychological stressors can result in both functional and physiological changes to the brain (e.g., [27, 41]). It is beyond the scope of this chapter to review this large (and ever-expanding) body of literature. But it is clear that the preponderance of evidence generally precludes the notion that that one can, based on the presence of functional and/or physical changes to the brain alone, reliably determine the nature (i.e., physical vs. psychological) of the precipitating insult nor the basis of overt symptoms.

As a case in point, it is useful to consider recent findings that have been invoked to suggest that N-acetylaspartate (NAA) may prove useful as a biomarker of mTBI: because mTBI is, by definition, a condition specifically characterized by a set of symptoms in the absence of gross, overt physical brain damage (i.e., or at least the absence of damage detectable with standard brain imaging techniques like CAT and structural MRI), it has been suggested that mTBI/PCS is a

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"functional" disorder characterized, for example, by mitochondrial (metabolic) dysfunction. Such dysfunction can result in reduced whole-brain levels of NAA, the levels of which are considered to generally reflect reduced neuronal "wellness" (e.g., see [48]). Indeed, reduced NAA levels have been reported in a variety of neurological disorders including (but not limited to) Alzheimer's disease, HIV-related dementia, glial brain tumors and meningiomas (see review by Rigotti et al. [39]), and subcortical ischemic vascular dementia, epilepsy, amyotrophic lateral sclerosis, and even in cognitively impaired but non-demented elderly (suggesting that NAA reductions may be an early marker of Alzheimer's disease – for review, see [46]).

But, interestingly, reduced NAA levels (at least in some brain regions including hippocampus and anterior cingulate) have also been reported in PTSD patients [47]. Similarly, in patients diagnosed with Gulf War syndrome, reduced NAA has been found in the pons and basal ganglia [18]. And although Weiner et al. [57] recently failed to replicate the latter finding when they assessed regional NAA levels in a sample of Gulf War syndrome patients (despite an elevated rate of comorbid PTSD in their sample), these studies, considered together, clearly show that reduced NAA levels do not necessarily suggest brain damage resulting exclusively from disease or physical trauma. In other words, although NAA may be a sensitive marker of such insults, it is not necessarily a marker that is specific to such insults – and it is therefore (like "neurological abnormalities") unlikely to prove useful as a biomarker that will help differentiate PCS from PTSD.[1]

To make matters more complicated (i.e., to make it even more difficult to envision development of an NAA measurement-based tool that could potentially aid in the differential diagnoses of neurological (including mTBI) and psychological disorders), it has been reported that sleep deprivation also results in reduced NAA levels [54]. This, of course, complicates matters by virtue of the fact that sleep disturbance (and thus sleep loss) is a symptom of both mTBI/PCS and PTSD – making it possible that some or all of the variance of NAA levels in PTSD and mTBI/PCS is attributable not to some direct effect of these disorders but rather to the effect of a symptom shared by both disorders: sleep disturbance.

[1]Nevertheless, assessment of NAA levels may ultimately prove useful for management of concussion, especially if, as hypothesized by Vagnozzi et al. [55], it is found that NAA mediates (or at least serves as a marker of) increased vulnerability to subsequent mTBI events (the so-called second-impact syndrome). If this proves to be the case, then the duration of the rest period following an mTBI event (e.g., the post-injury period during which athletes are sidelined and soldiers are restricted to limited duty) might be extended considerably (relative to current practice – generally, a 1-week hiatus from activity) since NAA levels typically fail to recover to normal levels until about 30 days post-injury.

Symptom Overlap

As depicted in Fig. 3.1, the overlap of PTSD and PCS symptoms is considerable, with many of the shared symptoms being fairly generic. For example, mood disturbance, difficulty concentrating, and fatigue are symptoms of a myriad of other medical conditions including chronic fatigue syndrome, fibromyalgia, and hypothyroidism, to name but a few. But the most generic of these shared symptoms may be "sleep disturbance" – a complaint that is virtually ubiquitous among medical/psychiatric conditions and is common even among individuals with no known medical/psychiatric conditions. For example, it has been estimated that approximately one in five Americans are at least intermittently affected by bouts of insomnia [53].

Perhaps because sleep disturbance/insomnia is so common among clinical and nonclinical populations alike, the potential importance of this symptom – i.e., the central role that sleep/sleep disturbance may play in expression/exacerbation of various disorders and specific symptoms of those disorders (not to mention "recovery from" those disorders) – is generally underappreciated. Therefore, the aim of this chapter is to increase cognizance of the potential role that sleep disturbance plays in the expression of both "shared" symptoms and some of the relatively "unique" symptoms of mTBI/PCS and PTSD (see Fig. 3.2).

Sleep and Symptoms Common to mTBI/PCS and PTSD

Fatigue

Perusal of the scientific literature reveals that the word "fatigue" is used liberally as a hypothetical construct generally reflecting both subjective feelings of malaise and lethargy and objective evidence of reduced capacity for mental and/or physical performance. It has also sometimes been used as a synonym for sleepiness. For the purpose of this chapter, a conceptualization similar to that proposed by Balkin and Wesensten [2] is used: fatigue is a physiologically based deficit in subjective inclination and mental/physical capacity to continue performance of a task that varies as a function of work (the product of "time on task" and workload). And although fatigue can be exacerbated by sleepiness, it is an entity that is clearly distinct from sleepiness – as evidenced by the fact that it can be reversed by simple rest (time off task). This is illustrated in Fig. 3.3 (adapted from [58]).

As depicted in Fig. 3.3, response speed on a 10-min psychomotor vigilance task (PVT; see [12]) was measured every 2 h during a 40-h period of total sleep deprivation. Fatigue ("time-on-task") effects were clearly evident as

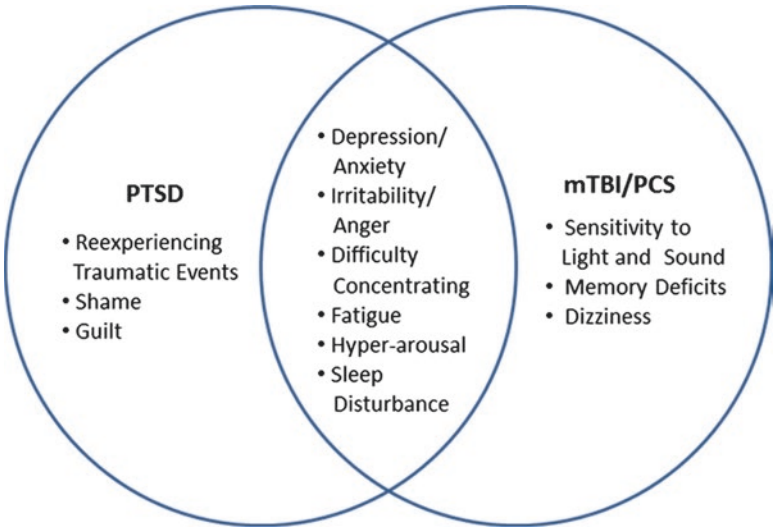

Fig. 3.1 Overlap of PTSD and mTBI/PCS symptoms

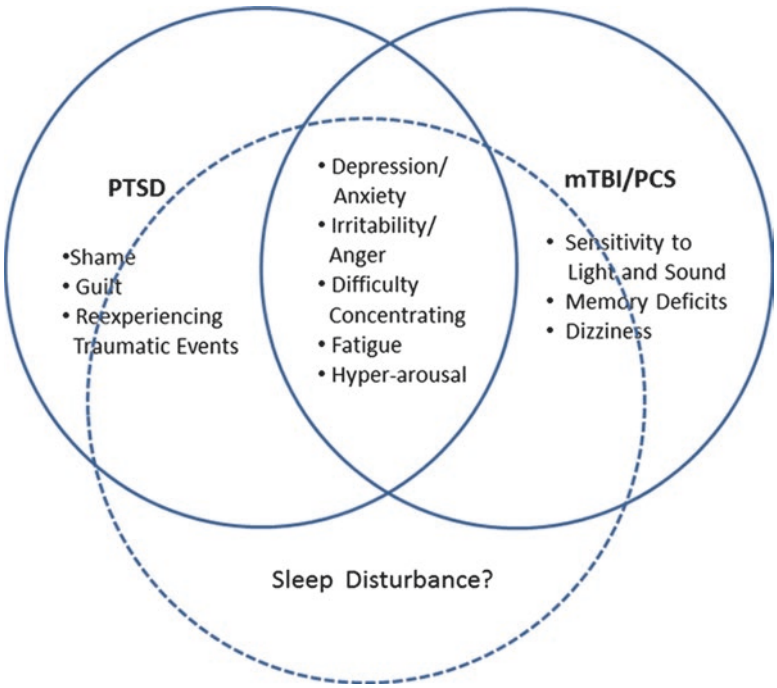

Fig. 3.2 Overlap of PTSD and mTBI/PCS symptoms with the effects of sleep loss

mean RT speed declined within each 10-min test session but then recovered (at least partially) by the time the next test session was initiated (despite the fact that there was no intervening sleep). That sleepiness actually interacts with fatigue effects is clearly evidenced by (a) the finding that the slope of performance decline within the 10-min PVT tends to steepen as sleep loss is extended (e.g., compare initial performance (at 0800 h on day 1) with performance 24 h later), and (b) there is a clear circadian rhythm of performance that corresponds to the circadian rhythm of alertness [58].

Clearly, these results show that sleepiness interacts with "fatigue" even when the latter is rather narrowly operationally defined as "time on task on a reaction time test." Therefore, to the extent that the definition of fatigue in such literature specifically subsumes the concept of "sleepiness" (e.g., [2]) or regardless of the extent to which the definition of fatigue is left nebulous, one can be confident in the assertion that sleepiness interacts with fatigue and serves to confound efforts to specify fatigue as a pathological symptom (of PTSD and/or mTBI/PCS) independent of "sleep disturbance."

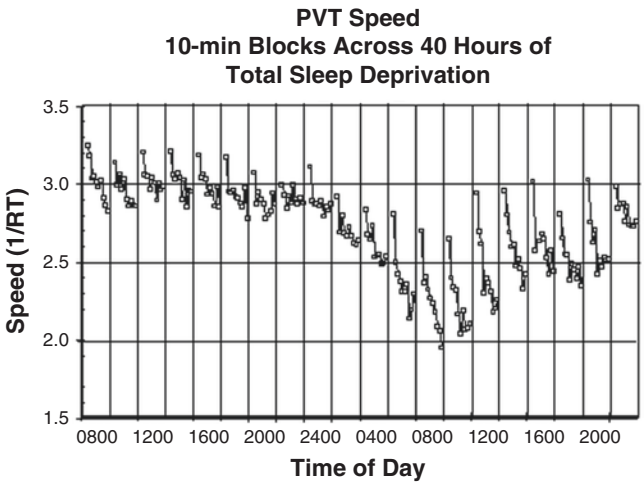

Fig. 3.3 Mean reaction time performance (speed) is depicted for each minute of a 10-min psychomotor vigilance test (PVT), administered every 2 h across 40 h of continuous wakefulness – depicting the interaction between sleepiness and fatigue (time-on-task) effects (Adapted from [58])

Insomnia

The hyperarousal symptom cluster for PTSD includes difficulty falling or staying asleep [1]. The research criteria for post-concussion disorder list "disordered sleep" as one of the symptoms that must occur shortly after the trauma and that must last for at least 3 months [1]. "Disordered sleep" is very vague because there are many ways normal sleep physiology can be disrupted. A specific sleep disorder that is common to both PTSD and TBI (especially mild TBI) is insomnia. Approximately 30% of TBI patients report insomnia that meets diagnostic criteria, and this number grows considerably if reports of insomnia that fall short of meeting full diagnostic criteria are also counted [34]. Approximately 44% of PTSD patients report difficulty falling asleep and approximately 91% report difficulty staying asleep [31].

Depression

PTSD and TBI are both highly comorbid with depression. Because insomnia is essentially chronic, partial sleep deprivation, it is likely that to a significant extent the depression experienced by these patient groups has been precipitated by, or at least exacerbated by, inadequate sleep [21]. Indeed, it has been found that insomnia precedes the initial occurrence of depression [17], it precedes the reoccurrence of depression [35], and it is predictive of depression [37, 61].

On the other hand, it is important to note that the effects of sleep loss are not always, nor exclusively, deleterious. For a subgroup of depressed patients, acute, total sleep deprivation has been shown to have a transient antidepressant effect (i.e., that is reversed by subsequent recovery sleep). Similarly, it has been observed that in some bipolar patients, sleep disruptions may trigger episodes of mania rather than lethargy [24]). Such paradoxical reactions to sleep loss serve to demonstrate the extent to which individual differences exist and can potentially complicate efforts to discern the role of sleep/sleep disturbance plays in the pathogenesis of PTSD, PCS, depression, and other various disorders.

Difficulty Concentrating

In the present chapter, "concentration" refers to the ability, by dint of will, to maintain appropriate mental focus on specific external stimuli. In the case of a student, that focus may be on written text, with "adequate concentration" evidenced by comprehension of the written material, consolidation of that material into memories, and integration of those memories into existing knowledge schemas. For a truck driver, adequate concentration would be evidenced by appropriate handling of his/her vehicle in accordance with extant weather, road, and traffic conditions; adequate attention to navigation and dashboard gauges; and the ability to recognize and avoid potential hazards as they develop up the road. Of course, the amount of sleep needed to maintain nominally adequate concentration varies by task and by individual.

But as any college student who ever "pulled an all-nighter" can attest, "difficulty concentrating" is a hallmark consequence of sleep loss. Despite concerted effort to maintain focus and make sense of written text, the sleepy student experiences progressively greater difficulty studying across the night: first, reading becomes a chore in which paragraphs and sometimes pages are read but not absorbed, written words fail to coalesce into meaningful sentences, and the mind – faced with this paucity of meaningful information from the external world (i.e., the written page) – inclines toward reverie, eventually succumbing to frank sleep onset.

It is therefore not surprising that "difficulty concentrating" has also long been recognized by the scientific community as a consequence of sleep loss. For example, in his seminal work to determine the factors that make a neurocognitive performance test sensitive to sleep loss, Wilkinson [59] identified several factors, including "duration" (the longer the test, the more sensitive to sleep loss) and "inherent interest" in the test material (the more interesting/engaging the test material, the more "stimulating" and thus resistant to the effects of sleep loss). Thus, those qualities or parameters of a test that make concentration on that test easier (i.e., short duration and interesting content) also make that test relatively insensitive to the effects of sleep loss – indirect but compelling evidence that sleep loss impacts our ability to concentrate.

Sleepiness is currently thought to be characterized by "state instability" [13] – i.e., it is wakefulness made tenuous by repeated incursions of sleep-promoting processes (see [14]). As described by Olofsen et al. [33], the physiological basis of "state instability" is a flip/flop switch [of the sort proposed by Saper et al. [44]], in which sleep-promoting

neurons in the ventral lateral preoptic nucleus are reciprocally inhibited by monoaminergic wake-promoting neurons. Sleep results when sleep-promoting neuronal activity is preponderant (exerting pressure on one end of the flip/flop switch) and wakefulness ensues when wake-promoting cell activity is preponderant (exerting pressure at the other end of the flip/flop switch). State instability increases as activity levels of these two cell groups approach equilibrium, essentially balancing the pressure on both sides of the switch. The resulting instability of the flip/flop switch causes rapid fluctuations between ascendant sleep- and wake-promoting processes.

Since sleepiness is an unstable brain state characterized by rapid, transitory fluctuations between sleep- and wakefulness-promoting mechanisms, it is not difficult to understand why sleepiness is characterized by "difficulty concentrating," since by its very nature concentration would be presumed to involve and require continuous engagement of wake-promoting processes (so as to facilitate the continuous focus on external stimuli over time).

Hyperarousal

In addition to insomnia, one of the hallmarks of PTSD is general hyperarousal (as exemplified by an exaggerated startle response). TBI patients do not show an exaggerated startle response. In fact, if anything, they have a sort of emotional blunting, since it has been shown that they do not display the normal startle potentiation that results from viewing stimuli with a negative emotional valence [30, 45]. This is an interesting observation because patients with narcolepsy display a similar absence of startle potentiation following presentation of unpleasant stimuli [25]. Finally, it is important to point out that hyperarousal is more likely to contribute to insomnia and subsequent excessive daytime sleepiness than vice versa. In fact, sleep deprivation in healthy controls generally blunts the startle response [28].

Sleep and Symptoms of mTBI/PCS

Excessive Daytime Sleepiness

Excessive daytime sleepiness is a common complaint in mTBI patients [34]. For 25% of these patients, the subjective complaint of sleepiness is substantiated by objective measures [3]. And the finding that TBI patients tend to have low levels of hypocretin/orexin in their cerebrospinal fluid (e.g., [40]) suggests that the pathophysiology of TBI-related sleepiness may be similar to that of narcolepsy.

One of the symptoms of PTSD is difficulty falling or staying asleep, and the full diagnostic criteria for insomnia include subjective impairment in daytime function/alertness. However, as measured by the multiple sleep latency test (MSLT; see [10]), PTSD patients do not display objective signs of sleepiness [6, 23]. This is not surprising because it is likely that hyperarousal – a problem that contributes to nighttime sleep disturbance – likewise interferes with daytime sleepiness testing on the MSLT, so that mean sleep onset latencies in these patients do not accurately reflect the underlying level of sleep deficit. Nevertheless, similar to TBI patients, PTSD patients have low levels of hypocretin/orexin in their cerebrospinal fluid [51], an observation that is consistent with the notion that PTSD, like mTBI, may share pathophysiological underpinnings with narcolepsy.

Memory Deficits

Chief among the cognitive symptoms of mTBI that are important to consider within the context of sleep are those relating to memory. Evidence is mounting that memory consolidation is facilitated by – and may for some types of memory in fact be dependent upon – adequate sleep [56]. The relevant evidence comes from an ever-expanding number of studies designed to measure sleep-dependent improvement in performance on a variety of declarative and procedural memory tasks [15]. Although alternative explanations for positive results from such studies remain possible – e.g., it has been suggested that at least some of the salutary effects of sleep may simply be "passive protection from interference" (i.e., deficits resulting from acquisition of new, nontarget learning/memories during the intervening period between initial acquisition of the target material and testing for that material) – such alternative explanations are becoming less tenable as evidence from various laboratories continues to mount. For example, the finding by Marshall et al. [29] that experimental enhancement of slow wave EEG activity during sleep enhances next-day performance on memory tests clearly suggests that sleep does, in fact, play an active role in memory consolidation – i.e., something above and beyond what occurs passively as a result of freedom from interference.

Memory deficits (both retrograde and anterograde amnesia) can result from mTBI events, and recent evidence suggests that at least some aspects of resulting deficits (e.g., in declarative memory) are mediated by impaired medial temporal lobe function (e.g., see [52]). It has also been shown that PCS patients tend to experience difficulty forming new memories, perhaps as a secondary effect of deficits in short-term (working) memory (the ability to maintain and manipulate multiple pieces of information simultaneously) [19]. Individuals with PTSD have likewise been shown to experience short-term memory deficits [7].

As with the other symptoms of these disorders, the question becomes whether the memory deficits are specific to each disorder or whether they are (at least partially) attributable to the sleep disturbance that characterizes both disorders. If impaired memory formation is caused by deficits in encoding or retrieval, the link is easy to establish.

Disordered sleep would lead to excessive daytime sleepiness, which would lead to deficits in concentration, and this in turn would lead to a decreased ability to form a strong memory trace during encoding or a decreased ability to recall the memory during retrieval.

On the other hand, if memory impairments are the result of deficits in consolidation, the link becomes more difficult to establish because few studies have measured long-term memory in these patients across delay periods greater than 24 h. Although there are as yet no relevant studies for PTSD or TBI, investigators from one study did establish sleep-dependent memory consolidation deficits in patients with insomnia [32], which is itself a frequently reported symptom of both PTSD and mTBI.

Sleep and Symptoms of PTSD

Hyperarousal and Irritability

It is currently thought that PTSD may be a disorder characterized by contextual fear conditioning and that abnormal hippocampal (memory) functioning in PTSD results in (a) generalization of the fear (stress) response to inappropriate (nonthreatening) environments along with (b) an impaired capacity for extinguishing fear responses [38]. Functional brain imaging studies of PTSD patients have provided evidence that is consistent with such hypotheses, revealing elevated activity in the amygdala (reflecting elevated emotional responsivity), reduced activity in prefrontal regions (mediating executive mental functions and providing inhibitory feedback to limbic regions including the amygdala), and abnormal activity in the hippocampus (mediating memory consolidation – sometimes found to be abnormally elevated and sometimes abnormally reduced in PTSD patients, depending upon the particular study situation).

Because (a) it is known that memory for emotion-laden events is enhanced (i.e., compared to emotion-neutral events; see [8]) and because sleep loss has been shown to result in disinhibition of the amygdala and hyperresponsiveness to emotional stimuli [62], it is reasonable to hypothesize that sleep-deprived individuals may be especially vulnerable to development of PTSD. That is, it is possible that sleep loss-induced deactivation of prefrontal cortices results in a disinhibited, hyperreactive amygdala that, by virtue of a relatively exaggerated fear response, contributes to development of PTSD by making subjectively bad experiences worse. Such heightened reactivity to aversive stimuli could contribute to the strength (and thus resistance to extinction) of those memories that subsequently form the basis of reexperiencing in PTSD patients.

As a corollary, it is therefore also reasonable to hypothesize that well-slept individuals, by virtue of their less reactive amygdalae, may be more resilient to stressors/less likely to develop PTSD since the memories of stressful events are likely to have been formed with relatively less emotional valence. Further study is needed to determine whether sleep quality/duration mediates the likelihood of developing PTSD and/or mediates the process(es) by which recovery from PTSD is affected.

Reexperiencing Traumatic Events

In a sense, the "reexperiencing of traumatic events" that occurs in PTSD can be considered akin to "perseveration" – the (sometimes) pathological, persistent repetition of a word, gesture, or act. Perseveration is commonly observed in obsessive-compulsive disorder, schizophrenia, dementia, and brain injury. Perseveration can be classified as the absence of set-shifting, which is an executive function that can be measured with the Wisconsin Card Sort Task, Trail-Making Test, and Color Trails Test. Typically, patients with prefrontal brain damage have relatively little difficulty learning the initial rule associated with these tasks, but they experience difficulty subsequently switching to a new rule set. Such deficits in set-shifting are also observed in PTSD patients who were victims of domestic violence [49] and in PTSD resulting from combat exposure that occurred decades before testing [4].

Some investigators have found that sleep deprivation increases perseverative errors [20, 22, 60], although others have failed to find such an effect [5, 26]. In one study, designed primarily to measure the effects of 24 h of acute, total sleep deprivation on odor identification accuracy [26], a set-shifting task (the Color Trails Test) was included to help ensure that any observed changes in odor identification were a primary effect of sleep loss, rather than a reflection of more general decrements in cognitive performance. In this study, significant impairments in odor identification were observed, but there were no significant effects of sleep loss on set-shifting, per se. The authors suggested that these results reflected the differential sensitivity of the ventromedial prefrontal cortex (which is involved in odor identification) vs. the dorsolateral prefrontal cortex (which is more involved in set-shifting) to sleep loss. However, in a study specifically designed to measure the effects of sleep loss on higher-order cognitive performance using a complex marketing game called "Masterplanner," there was clear evidence of increasing perseveration (i.e., inappropriately continuing to market a product for which market conditions had changed unfavorably) as duration of sleep deprivation increased [20].

To the extent that such findings reflect insomnia-induced deficits in PTSD and TBI, it is possible that the perseveration-like symptoms (in fact, *each* of the sleep-mediated symptoms mentioned in this chapter) may to a significant extent be improved directly by simply improving the patients' sleep. In addition, it is reasonable to hypothesize that the

general improvement in cognitive ability and emotional regulation that accrues with improved sleep would, at the very least, have the beneficial effect of improving amenability to treatments like cognitive behavioral therapy.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders-text revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
2. Balkin TJ, Wesensten NJ. Differentiation of sleepiness and mental fatigue effects. In: Ackerman PL, editor. Cognitive fatigue. Washington, DC: American Psychological Association; 2011. p. 47–66.
3. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. Brain. 2007;130:1873–83.
4. Beckham JC, Crawford AL, Feldman ME. Trail making test performance in Vietnam combat veterans with and without posttraumatic stress disorder. J Trauma Stress. 1998;11:811–9.
5. Binks PG, Waters WF, Hurry M. Short-term total sleep deprivations does not selectively impair higher cortical functioning. Sleep. 1999;22:328–34.
6. Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch Gen Psychiatry. 2004;61:508–16.
7. Brewin CR. The nature and significance of memory disturbance in posttraumatic stress disorder. Annu Rev Clin Psychol. 2011;7:203–27.
8. Brown R, Kulik J. Flashbulb memories. Cognition. 1977;5(1):73–99.
9. Bryant R. Post-traumatic stress disorder vs traumatic brain injury. Dialogues Clin Neurosci. 2011;13(3):251–62.
10. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep. 1986;9:519–24.
11. Dean PJ, O'Neill D, Sterr A. Post-concussion syndrome: prevalence after mild traumatic brain injury in comparison with a sample without head injury. Brain Inj. 2012;26(1):14–26.
12. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple, visual RT task during sustained operations. Behav Res Methods Instrum Comput. 1985;17:652–5.
13. Doran SM, Van Dongen HPA, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. Arch Ital Biol. 2001;139:253–67.
14. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol. 2005;25:117–29.
15. Ellenbogen JM, Payne JD, Stickgold R. The role of sleep in declarative memory consolidation: passive, permissive, active or none? Curr Opin Neurobiol. 2006;16:716–22.
16. Fear NT, Jones E, Groom M, Greenberg N, Hull L, Hodgetts TJ, Wessely S. Symptoms of post-concussional syndrome are non-specifically related to mild traumatic brain injury in UK armed forces personnel on return from deployment in Iraq: an analysis of self-reported data. Psychol Med. 2009;39(8):1379–87.
17. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? J Am Med Assoc. 1989;262:1479–84.
18. Haley RW, Marshall WW, McDonald GG, Daugherty MA, Petty F, Fleckenstein JL. Brain abnormalities in Gulf war syndrome: evaluation with 1H MR spectroscopy. Radiology. 2000;5(3):807–17.
19. Hall RC, Hall RC, Chapman MJ. Definition, diagnosis, and forensic implications of postconcussional syndrome. Psychosomatics. 2005;46:195–202.
20. Harrison Y, Horne JA. One night of sleep loss impairs innovative thinking and flexible decision making. Organ Behav Hum Decis Process. 1999;78:128–45.
21. Harvey AG. Insomnia: symptom or diagnosis? Clin Psychol Rev. 2001;21:1037–59.
22. Herscovitch J, Stuss D, Broughton R. Changes in cognitive processing following short-term cumulative partial sleep deprivation and recovery oversleeping. J Clin Neuropsychol. 1980;2:301–19.
23. Hurwitz TD, Mahowald MW, Kuskowski M, Engdahl BE. Polysomnographic sleep is not clinically impaired in Vietnam combat veterans with chronic posttraumatic stress disorder. Biol Psychiatry. 1998;44:1066–73.
24. Kasper S, Wehr TA. The role of sleep and wakefulness in the genesis of depression and mania. L'Encéphale. 1992;18(Spec 1):45–50.
25. Khatami R, Birkmann S, Bassetti CL. Amygdala dysfunction in narcolepsy-cataplexy. J Sleep Res. 2007;16:226–9.
26. Killgore WD, McBride SA. Odor identification accuracy declines following 24 h of sleep deprivation. J Sleep Res. 2006;15:111–6.
27. Knapman A, Kaltwasser SF, Martins-de-Souza D, Holsboer F, Landgraf R, Turck CW, Czisch M, Touma C. Increased stress reactivity is associated with reduced hippocampal activity and neuronal integrity along with changes in energy metabolism. Eur J Neurosci. 2012;35(3):412–22.
28. Lin C, Yang C. The effect of 24-hour sleep deprivation on startle responses associated with emotion-provoking pictures [abstract]. Sleep. 2004;27:A171.
29. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444:610–3.
30. Neumann DR, Hammond F, Norton J, Blumenthal T. Using startle to objectively measure anger and other emotional responses after traumatic brain injury: a pilot study. J Head Trauma Rehabil. 2011;26(5):375–83.
31. Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatr. 1998;155:929–33.
32. Nissen C, Kloepfer C, Nofzinger EA, Feige B, Voderholzer U, Riemann D. Impaired sleep-related memory consolidation in primary insomnia: a pilot study. Sleep. 2006;29:1068–73.
33. Olofsen E, Van Dongen HPA, Mott CG, Balkin TJ, Terman D. Current approaches and challenges to development of an individualized sleep and performance prediction model. Open Sleep J. 2010;2010(3):24–43.
34. Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil. 2009;24:155–65.
35. Perlis ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. J Affect Disord. 1997;42:209–12.
36. Peskind ER, Petrie EC, Cross DJ, Pagulayan K, McCraw K, Hoff D, Hart K, Yu CE, Raskind MA, Cook DG, Minoshima S. Cerebrocerebellar hypometabolism associated with repetitive blast exposure mild traumatic brain injury in 12 Iraq war Veterans with persistent post-concussive symptoms. NeuroImage. 2011;54(1):S76–82.
37. Picchioni D, Cabrera OA, McGurk D, Thomas JL, Castro CA, Balkin TJ, Hoge CW. Sleep symptoms as a partial mediator between combat stressors and other mental health symptoms in Iraq war veterans. Mil Psychol. 2010;22:340–55.
38. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future (review). Biol Psychiatry. 2006;60(4):376–82.
39. Rigotti DJ, Inglese M, Gonen O. Whole-brain N-acetylaspartate as a surrogate marker of neuronal damage in diffuse neurologic disorders. Am J Neuroradiol. 2007;28(10):1843–9.

40. Ripley B, Overeem S, Fujiki N, Nevsimalova S, Uchino M, Yesavage J, Nishino S. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. Neurology. 2001;57:2253–8.
41. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. Ann N Y Acad Sci. 2012;261(1):88–96.
42. Ruff RL, Riechers RG, Ruff SS. Relationships between mild traumatic brain injury sustained in combat and post-traumatic stress disorder. F1000 Med Rep. 2010;2:64.
43. Ruff RL, Ruff SS, Wang XF. Headaches among operation Iraqi freedom/operation enduring freedom veterans with mild traumatic brain injury associated with exposures to explosions. J Rehabil Res Dev. 2008;45(7):941–52.
44. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437:1257–63.
45. Saunders JC, McDonald S, Richardson R. Loss of emotional experience after traumatic brain injury: findings with the startle probe procedure. Neuropsychology. 2006;20:224–31.
46. Schuff N, Meyerhoff DJ, Mueller S, Chao L, Sacrey DT, Laxer K, Weiner MW. N-acetylaspartate as a marker of neuronal injury in neurodegenerative disease. Adv Exp Med Biol. 2006;576:241–62.
47. Schuff N, Neylan TC, Fox-Bosetti S, Lenoci M, Samuelson KW, Studholme C, Kornak J, Marmar CR, Weiner MW. Abnormal N-acetylaspartate in hippocampus and anterior cingulate in post-traumatic stress disorder. Psychiatry Res. 2008;162(2):147–57.
48. Signoretti S, Lazzarino G, Tavazzi B, Vagnozzi R. The pathophysiology of concussion. PM&R. 2011;3(10, Supplement 2):S359–68.
49. Stein MB, Kennedy CM, Twamley EW. Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. Biol Psychiatry. 2002;52:1079–88.
50. Stein MB, McAllister TW. Exploring the convergence of post-traumatic stress disorder and mild traumatic brain injury. Am J Psychiatr. 2009;166(7):768–76.
51. Strawn JR, Pyne-Geithman GJ, Ekhator NN, Horn PS, Uhde TW, Shutter LA, Geracioti TD. Low cerebrospinal fluid and plasma orexin-A (hypocretin-1) concentrations in combat-related posttraumatic stress disorder. Psychoneuroendocrinology. 2010;35:1001–7.
52. Stulemeijer M, Vos PE, van der Werf S, van Dijk G, Rijpkema M, Fernandez G. How mild traumatic brain injury may affect declarative memory performance in the post-acute stage. J Neurotrauma. 2010;27(9):1585–95.
53. Trans-NIH Sleep Research Coordinating Committee. National sleep disorders research plan. U.S. Department of Health and Human Services. Washington, DC: National Institute of Health; 2003. http://www.nhlbisupport.com/sleep/research/research-a.htm
54. Urrila AS, Hakkarainen A, Heikkinen S, Huhdankoski O, Kuusi T, Stenberg D, Häkkinen AM, Porkka-Heiskanen T, Lundbom N. Preliminary findings of proton magnetic resonance spectroscopy in occipital cortex during sleep deprivation. Psychiatry Res. 2006;147(1):41–6.
55. Vagnozzi R, Signoretti S, Cristofori L, Alessandrini F, Floris R, Isgrò E, Ria A, Marziale S, Zoccatelli G, Tavazzi B, Del Bolgia F, Sorge R, Broglio SP, McIntosh TK, Lazzarino G. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. Brain. 2010;133(11):3232–42.
56. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. Neuron. 2004;44:121–33.
57. Weiner MW, Meyerhoff DJ, Neylan TC, Hlavin J, Ramage ER, McCoy D, Studholme C, Cardenas V, Marmar C, Truran D, Chu PW, Kornak J, Furlong CE, McCarthy C. The relationship between Gulf war illness, brain N-acetylaspartate, and post-traumatic stress disorder. Mil Med. 2011;176(8):896–902.
58. Wesensten NJ, Belenky G, Thorne DR, Kautz MA, Balkin TJ. Modafinil vs. caffeine: effects on fatigue during sleep deprivation. Aviat Space Environ Med. 2004;75(6):520–5.
59. Wilkinson RT. Sleep deprivation. In: Edholm OG, Bacharach AL, editors. The physiology of human survival. London., 1965: Academic; 1965. p. 399–430.
60. Wimmer F, Hoffmann RF, Bonato RA, Moffitt AR. The effects of sleep deprivation on divergent thinking and attention processes. J Sleep Res. 1992;1:223–30.
61. Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol. 2011;67:1240–58.
62. Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep – a prefrontal amygdala disconnect. Curr Biol. 2007;17(20):R877–8.

Gender Differences in Sleep and War Zone-Related Post-traumatic Stress Disorder

4

Kristine Burkman and Shira Maguen

Introduction

The number of women currently entering the US Armed Forces and the scope of their involvement in combat operations are unprecedented. Women comprise 14.5% of active duty and 18% of National Guard and Reserve personnel [1]. In addition to their increasing numbers, women are now eligible to serve in all positions within the military, including combat occupations, which put them at greater risk for exposure to combat and other military-related stressors. The mental health impact of serving in a war zone, particularly the development of post-traumatic stress disorder (PTSD), has been widely studied among male combat veterans. However, the increasing number and variety of roles among female military personnel serving in Operation Enduring Freedom (OEF, principally in Afghanistan), Operation Iraqi Freedom (OIF, principally in Iraq), and Operation New Dawn (OND, principally in Iraq) [2] allows a more comprehensive examination of gender differences in mental health outcomes related to serving in a war zone.

Numerous individual and environmental risk factors may influence whether exposure to trauma results in PTSD or other mental health problems. Although women in the general population have higher prevalence rates of PTSD than men [3], studies among military personnel and veterans report mixed results in the rates of PTSD and associated mental health outcomes [4–8]. Further examination of specific differences in symptom presentation among men and women exposed to traumatic events may reveal underlying mechanisms associated with the development of PTSD.

Studies among men and women exposed to civilian traumas (e.g., motor vehicle accidents, natural disasters, and terrorist attacks) indicate men and women respond differently immediately following a traumatic event [9–12]. Individual and trauma-related characteristics such as cognitive appraisal of traumatic events, neurobiology of stress response, and coping styles following traumatic events have been hypothesized to contribute to gender differences seen in PTSD [13]. Gender differences in executive functioning and verbal memory following trauma have significant PTSD treatment implications.

In this chapter, we will review the types and extent of trauma exposure military personnel face in the war zone and associated mental health outcomes. We will also examine how men and women differ in the development of specific post-traumatic stress disorder symptoms, particularly sleep disruption, following a traumatic event. Biological, cognitive, and social mechanisms of these gender differences will be explored, and implications for PTSD treatment will be discussed.

Exposure to War Zone Stressors

Exposure to combat stressors places military personnel at risk of developing PTSD and other mental health problems following deployment to a war zone [14–16]. Although direct combat (e.g., being attacked or ambushed, being fired on or firing upon enemies) is most commonly associated with war zone stressors, there are several other stressors encountered during deployments including exposure to the aftermath of battle (e.g., handling remains), perceived threat (e.g., incoming mortar, IED explosions), and difficult living and working environment (e.g., heat exposure, sexual harassment or assault). Historically, men have reported significantly higher rates of exposure to combat stressors than women [3, 17]. However, trends in combat exposure among military personnel are changing as women assume a greater number and variety of roles in combat [18]. Preliminary studies among OEF/OIF/OND cohorts demonstrate a closing gender gap in overall level of exposure, as well as significant gender differences among specific combat stressors experienced [5, 8, 19].

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Level of Exposure

On average, women deployed to Iraq and Afghanistan experience less combat exposure than their male counterparts [3, 20, 21]. Nonetheless, women serving in OEF/OIF/OND conflicts experience substantial levels of combat exposure. A recent study among women deployed to Iraq found that 29% reported experiencing low combat exposure, 12% reported experiencing moderate combat exposure, and 3% reported experiencing high levels of combat [20]. Another study found that approximately three-quarters of women deployed to Iraq experienced at least one or more combat experiences [22], which is comparable with studies conducted with primarily male samples [23]. Consequently, women are facing more dangerous situations in combat, which is reflected in recent findings that to date, 1,027 women have been wounded in action and 166 killed while deployed in support of OEF/OIF/OND [2].

Type of Exposure

As the number of women serving in war zones has increased, researchers have examined gender differences among specific types of stressors experienced. Findings from a large sample of active duty men and women deployed to Iraq suggest that men are more likely to report being in fire fights (47% versus 36%, respectively) or report shooting or directing fire at the enemy (15% versus 7%). Conversely, 38% of women reported being involved in handling human remains compared to 29% of men, likely as a result of more female serving in medical roles [19]. Similarly, a recent study found that men were more likely than women to endorse exposure to direct combat as part of a post-deployment screening [5]. Although men reported higher rates of direct combat exposure, 31% of women reported exposure to death, 9% reported witnessing killing, 7% reported injury in the war zone, and 4% reported killing in war.

Military Sexual Trauma

In addition to combat stressors, female military personnel may be at increased risk for military sexual trauma (MST) during deployment, including experiences of sexual harassment and sexual assault. While men are also exposed to MST, women generally confer a much higher risk of exposure to these types of interpersonal traumas during their military service [18, 24]. For example, Maguen and colleagues found that among active duty soldiers returning from deployment, 12% of women reported experiencing MST as compared to 1% of men [5]. This is consistent with rates reported by Kimerling and colleagues, who found that among OEF/OIF/OND veterans seeking care at a VA medical facility, 15% of female veterans reported experiencing MST whereas less than 1% of male veterans seeking care reported MST [25].

Evidence suggests that exposure to sexual assault while in the military poses a greater risk for negative mental health outcomes as compared with nonsexual trauma in the military or sexual trauma as a civilian. Kang and colleagues found that among a sample of Gulf War veterans, experiences of combat exposure and sexual assault during deployment were both strong predictors of PTSD; however, sexual assault emerged as a stronger predictor [26]. Another study found that sexual trauma experienced during military service was more strongly associated with adverse mental health outcomes like PTSD than was sexual trauma experienced before or after military service [27]. MST has also been associated with greater risk for development of anxiety disorders, depression, and substance use disorders [25, 28, 29].

Additional Risk Factors for PTSD

There is a growing body of literature examining risk and resiliency factors associated with interpersonal relationships in the development of PTSD and other mental health problems among OEF/OIF/OND veterans [14, 18, 30]. Researchers have examined primarily three areas including (1) relationships prior to military service such as childhood family environment, (2) relationships between service members while deployed such as unit cohesion, and (3) relationships following military such as intimate relationships, parenting, and general social support. Additionally, multiple deployments to a war zone has become increasingly common among US military troops, which introduce a unique set of stressors that OEF/OIF/OND veterans have been facing such as personnel turnover within combat units between deployments and long periods of time away from family and friends over the span of several years. There are significant differences in how men and women in the US military are exposed to and manage these risk factors.

Prior Trauma

Research with military populations has demonstrated that the experience of multiple traumatic events across the life span can have a cumulative negative effect on veteran's post-deployment adjustment and well-being [31]. In their review of studies examining premilitary trauma, Zinzow and colleagues (2007) found that women were more likely than men to endorse trauma prior to military service, with 81–93% of female veterans reporting a history of at least one lifetime trauma. Nearly half of female veterans report a history of

childhood physical or sexual abuse [31]. It has been well established among general population samples that early childhood adverse events, often within the family environment, can lead to the development of poor coping skills and difficulties with emotion regulation [32]. Given the high rate of interpersonal trauma experience by women entering the military, they may be at higher risk for revictimization or more likely to make internalized attributions as to why they have experienced military-related trauma which may place them at higher risk for developing PTSD [18].

Deployment Relationships

Unit cohesion and positive appraisals of military service have been found to decrease the odds of developing PTSD post-deployment [4, 30], as has the perception of support from fellow service members and confidence in military leadership [21]. In a sample of service members deployed to the Gulf War, women reported lower perceptions of social support from fellow service members [24, 33]. Among OEF/OIF/OND cohorts, sexual and gender-based harassment while deployed has been associated with higher risk for developing depressive symptoms [14]. Perception of support from fellow military personnel may be particularly critical, when strong unit cohesion has been found to engender confidence and promote adaptive problem solving when under attack [34]. Preliminary evidence in this area suggests that among women deployed to war zones, exposure to combat trauma may be exacerbated by the perceived lack of support from colleagues. A more comprehensive examination of working relationships among military personnel deployed to a war zone is warranted to further understand the potential protective effects of group cohesion, support, and strong leadership in the deterrence of negative mental health outcomes.

Post-deployment Interpersonal Functioning

Long months of separation from family and loved ones while deployed can create significant additional stress for men and women serving in war zones. Concerns about family and relationship problems are more strongly associated with post-deployment mental health for women service members than their male counterparts [24]. Although similar proportions of women (38%) and men (44%) in the military are parents, women are three times more likely to be a single parent and five times more likely to be married to another service member who is also eligible for deployment [35]. Previous research has shown that women who are single parents are more likely to report depressive symptoms and poor family functioning than women who are partnered in the period following deployment [36].

The presence of a supportive intimate partner may play a crucial role in coping with post-deployment stressors. Skopp and colleagues found that women who perceived greater decrements in intimate relationship strength were more likely to screen positive for PTSD, given higher levels of combat exposure [30]. However, the same interaction was not found among women with lower combat exposure or men regardless of combat exposure level suggesting that the perceived loss of relationship intimacy may exacerbate PTSD associated with high combat exposure among women. Another recent study found that while the presence of post-deployment stressors increased the risk of post-traumatic stress disorder symptoms among both men and women, post-deployment social support mediated the relationship between post-deployment stressors and the development of PTSD among women [8]. Taken together, it appears that interpersonal relationships following deployment may be particularly influential in the development of mental health symptoms among women.

Gender Differences in Mental Health Outcomes

The reported prevalence of mental health disorders, including PTSD, following deployment to a war zone varies widely across studies [37]. Ramchand and colleagues found significant differences in overall prevalence rates based on sample selection (treatment seeking vs. nontreatment seeking) and how PTSD and other mental health disorders were operationally defined [37]. Estimates of PTSD among active military personnel returning from combat deployment in Iraq and/or Afghanistan range from 4.6% to 24.5% using a four-item screen [5, 15, 23] and 6.2–31% using a 17-item self-report checklist assessing whether DSM-IV diagnostic criteria is met [4, 7, 16, 38–40]. Among OEF/OIF/OND veterans enrolled in the VA healthcare system, approximately 13–21.8% received a diagnosis of PTSD [41–43]. Despite the growing literature on the prevalence of PTSD among OEF/OIF/OND veterans post-deployment, few studies have examined gender differences.

Studies that have included women have found elevated rates of mental health disorders, including PTSD, yet results have been mixed. A nationally representative, longitudinal study of OEF/OIF/OND service members found that baseline rates of PTSD and other anxiety disorders were higher in females than males, whereas substance use disorders were more prevalent in males [6]. Another large study of OEF/OIF/OND veterans found that females were more likely to screen positive for PTSD and depression than male veterans [7]. A third study of OEF/OIF/OND veterans enrolled in VA care found that female veterans received depression diagnoses more frequently than male veterans, who were more fre-

quently diagnosed with PTSD and substance use disorder diagnoses [28]. These findings are supported by a fourth study among UK troops [44] that also found men were much more likely to endorse substance abuse and women were more likely to endorse depressive symptoms following deployment. However, some studies have found that female personnel were more likely than were their male counterparts to report depression, but no gender differences were found in the prevalence of PTSD [4, 5].

Other studies have specifically examined gender differences in combat exposure and mental health outcomes following deployment. Women who experienced low levels of combat were more likely to screen positively for PTSD and depression than their male counterparts with low exposure [20, 44]. This is consistent with studies of female veterans from previous eras who had significantly less combat exposure [45]. Interestingly, there were no differences in mental health outcomes between men and women in the medium combat condition, and there were too few women in the high combat condition to make meaningful comparisons [20]. Skopp et al. found that female soldiers with higher combat exposure more likely to screen positive for PTSD, as compared with their male counterparts [30]. Luxton et al. replicated and extended these findings; female soldiers with higher combat exposure were more likely to screen positive for both PTSD and depression than their male counterparts [46]. However, Woodhead and colleagues found that among soldiers exposed to high levels of combat, there were no gender differences among PTSD [44]. Similarly, in a large cohort study (N = 4,684 matched subjects) of US military members who were followed between 2001 and 2008, researchers found that 6.7% of women and 6.1% of men developed PTSD and that there were no significant gender differences for the likelihood of developing PTSD or for PTSD severity scores among women and men who reported combat experience and among those who did not [47].

Multiple studies suggest minimal gender differences in the expression of PTSD following deployment to a war zone [4, 21, 44]. Maguen and colleagues found that while male OEF/OIF/OND military personnel did report greater exposure to combat experiences, there were no gender differences with respect to PTSD symptoms [5]. Similarly, another study found that male and female veterans did not differ in the association between combat-related stressors and several mental health outcomes [8]. However, Maguen et al. found significant gender differences in types of combat-related stressors experienced among OEF/OIF/OND military personnel; men reported higher levels of direct combat experiences whereas women reported higher levels of exposure to MST [5].

Although exposure to MST puts both men and women at increased risk for developing PTSD [25, 28], evidence suggests a stronger association between MST and PTSD in female veterans. Gender differences regarding the association between MST and depression and MST and alcohol/drug abuse have been mixed [25, 28, 48]. However, one recent study found that female veterans with PTSD and MST were more likely to receive a comorbid diagnosis of depression, anxiety, or eating disorders, whereas male veterans with PTSD and MST were more likely to receive comorbid substance use disorder diagnoses [28].

What still remains to be investigated, however, is whether specific post-traumatic stress disorder symptoms are manifested differently in men versus women following specific traumatic events. Additional information about how men and women initially respond to trauma, and how those responses may predict subsequent outcomes, may be particularly helpful in tailoring treatment interventions.

Gender Differences in PTSD Symptomatology

In addition to understanding whether women are more or less vulnerable than men in developing combat-related PTSD following deployment, it may be valuable to examine whether women manifest PTSD symptoms differently than their male counterparts. Peritraumatic responses have been found to be strong predictors in whether people will go on to develop PTSD [49]. Examining gender differences in initial responses to traumatic events may inform why existing literature among civilians finds women are more likely than men to develop PTSD following a traumatic event [3, 50]. In a broad review of the literature, we found five studies among civilian samples examining differences in post-traumatic stress disorder symptoms following motor vehicle accidents (MVAs), natural disasters, and terrorist attacks. Consistent with existing literature, women in the following studies reported higher overall level of distress and number of symptoms, including greater problems with initiating and maintaining sleep. However, findings regarding gender differences among specific post-traumatic stress disorder symptoms are mixed.

Civilian Traumatic Experiences

One study examining the development of PTSD following a MVA found that women did not differ from men in meeting the overall reexperiencing criterion for a diagnosis of PTSD [9]. However, women were 4.7 times more likely than men to meet overall avoidance criteria and 3.8 times more likely to meet overall arousal criterion. Specific symptoms such as intense feelings of distress in situations similar to the MVA and physical reactivity to memories of the MVA were signifi-

cantly more common in women. Similarly, avoiding thoughts and situations associated with the accident, loss of interest in significant activities, and a sense of foreshortened future, as well as trouble sleeping, difficulty concentrating, and exaggerated startle response were also more common among women. Interestingly, gender differences remained even after controlling for overall symptom severity, prior trauma, peritraumatic dissociation, major depression or other anxiety disorders beside PTSD, and passenger injury.

In a second study, Bryant and colleagues found that women were more likely than men to meet criteria for acute stress disorder (ASD) immediately following a MVA [10]. Furthermore, meeting criteria for ASD was better predictor of developing PTSD 6 months following the accident among women as compared with men (93% versus 57%, respectively). Specifically, women were more likely to endorse peritraumatic dissociative symptoms (27% versus 10%) and avoidance symptoms (48% versus 37%), which is consistent with the previous study. However, unlike the previous study, Bryant and colleagues found that women were also more likely than men to meet reexperiencing symptoms (55% versus 34%) and men were somewhat more likely to endorse arousal symptoms than women (80% versus 76%) [10].

In a third study among survivors of MVAs, Irish and colleagues collected both self-report and objective data (e.g., heart rate and urinary cortisol levels) assessing levels of distress in the hospital immediately following the accident, and again at 6 weeks and 6 months [11]. Women reported higher levels of overall distress, specifically in the perception of threat at the time of the accident, which is consistent with the previous two studies [9, 10]. Also consistent with previous findings, women were more likely than men to report peritraumatic dissociation immediately following the accident, which was predictive of developing post-traumatic stress disorder symptoms 6 month later. As a result of higher overall level of distress immediately following the accident and a higher level of peritraumatic dissociation, women were more likely than men to develop post-traumatic stress disorder symptoms at 6 months following the MVA. Interestingly, no gender differences were found among objective measures of distress (e.g., heart rate and urinary cortisol levels), which poses the question whether certain symptoms are more or less influenced by biology (i.e., physiological response to threat) or culture (i.e., expression of emotion, behavior).

Gender differences in the expression of PTSD symptoms have been hypothesized to be influenced by culturally defined roles and rules of masculinity and femininity. In a study among hurricane survivors, Norris and colleagues hypothesized that participants from cultures that adopted more traditional views of masculinity and femininity would endorse greater differences in their report of PTSD symptoms [12]. Data was collected 6 months following Hurricane Andrew (Miami; White $n = 135$; Black $n = 135$) in 1992 and 6 months following Hurricane Pauline (Acapulco; $N = 200$) in 1997. Gender differences were most prominent in the Mexican sample; women reported higher scores on overall level of PTSD, intrusive, avoidant, arousal, and remorse symptoms. White women reported higher scores on overall level of PTSD and all other scales except remorse. Gender differences were attenuated among the Black sample; women reported higher scores on overall level of PTSD, intrusive, and arousal symptoms. Interestingly, sex differences in arousal symptoms were equal in all three culture groups, which support the earlier hypothesis that arousal symptoms following trauma are more likely to be influenced by biological vs. cultural factors.

A study of traumatic responses to the Loma Prieta earthquake (California, 1989) found similar results; women are more likely than men to report higher levels of intrusions and avoidance following a traumatic event [51]. Women also reported a higher level of distress at the time of the earthquake. When asked an open-ended question about how long the earthquake lasts, women reported significant longer periods of time than men. Items related to hyperarousal were not included in the measure of post-traumatic stress disorder symptoms used in this study (Impact of Events) [52], so it is unclear whether gender differences would have been found. However, similar to the previous study examining responses to hurricanes [12], it appears that women are more likely to express distress following a natural disaster and have a more distressed experience of the event itself.

Two studies have examined differences in how men and women respond to terrorist attacks [53, 54]. Following the 2001 terrorist attack on the Pentagon, Grieger and colleagues gathered self-report data from 77 active duty military and civilian employees in order to explore differences in how men and women initially responded to the attack and subsequent coping behaviors [53]. Women were found to have more peritraumatic dissociation and lower perceived levels of safety and were 5.6 times more likely to develop PTSD following the attack. Similarly, a study following terror attacks that occurred during the Al-Aqsa Intifada among Israeli citizens found that women reported a higher number of trauma-related symptoms and greater occupational impairment from those symptoms. Women also reported a greater number of dissociative symptoms than men, which has been a consistent finding across studies [9, 10, 12, 51, 54].

Across civilian studies, women consistently report a greater number of post-traumatic stress disorder symptoms and higher levels of distress following traumatic incidents. Although women are more likely to report dissociative symptoms following exposure to trauma, gender differences among avoidant, hyperarousal, and remorse symptoms remain mixed [10–12, 51]. It is also unclear whether findings from primarily civilian samples could be applied to a military population.

Sleep

Another approach to identifying gender differences in the symptomatology of PTSD is to examine differences in key areas of distress associated with posttraumatic stress reactions, such as sleep. In a review of 20 studies examining polysomnographically measured sleep abnormalities among the general population, Kobayshi and colleagues found that men showed poorer sleep continuity and lighter sleep compared to women [55]. Men also demonstrated lower sleep efficiency, greater percentage of stages 1 and 2 sleep, shorter REM latency, lower percentage of REM sleep, and more sleep-related respiratory problems. There is limited ability to examine gender differences in studies of polysomnographically measured sleep abnormalities in PTSD, given such studies have typically been conducted with exclusively or predominately male samples [55]. However Otte et al. conducted a study assessing objective sleep in women with PTSD and found that patients with PTSD slept less and had more stage 1 sleep compared to healthy controls [56]. Patients with PTSD also had more REM sleep in both studies [56, 57], but the difference was larger among the women with PTSD [57] than what was reported among men with PTSD [56].

Two recent polysomnographic studies specifically examined gender differences in sleep problems among individuals with PTSD. In one study, men ($N = 22$) and women ($N = 13$) were evaluated within 1 month of exposure to trauma and then again 2 months following the event. Researchers found that women with PTSD were more likely to experience wake after sleep onset than their male counterparts with PTSD [58]. Additionally, while not statistically significant due to sample size, both men and women with PTSD were found to have shorter duration of REM sleep and more frequent REM segments than healthy controls. The combination of shorter yet more frequent REM segments with the wake after sleep onset pattern found in women may place them at increased risk for developing PTSD after exposure to trauma.

Richards and colleagues did not find significant differences in wake after sleep onset between men ($N = 19$) and women ($N = 21$) with PTSD ($N = 40$) [59]. However, they found that compared to men with PTSD, women with PTSD had significantly more total sleep time. Compared to controls ($N = 43$), individuals with PTSD had less slow-wave sleep and total sleep time, although these findings were significantly more pronounced in men with PTSD than women with PTSD. Women with PTSD were also found to have significantly greater REM sleep than female controls, where men with PTSD showed less REM sleep than male controls, though not at statistically significant levels [59].

Quality of sleep is influenced by biological, psychological, and environmental factors that vary between men and women. The gender differences found in sleep patterns among individuals with PTSD, along with the gender differences found in symptom profiles among survivors of MVAs, natural disasters, and terrorist attacks, raise numerous questions about the mechanisms underlying various responses to traumatic events.

Potential Mechanisms Explaining Gender Differences

Although several studies among military personnel suggest minimal difference between men and women in the development of PTSD following combat exposure [4, 5, 14, 21], a broader review of literature suggest men and women may experience and respond to traumatic reviews differently [9, 10, 12]. A number of individual and trauma-related characteristics have been hypothesized to contribute to gender differences in PTSD [13] including differences in appraisal of traumatic events, neurobiology of stress response, coping styles following traumatic events, and response to PTSD treatment.

Cognitive Appraisal

It has been hypothesized that gender differences in risk for developing PTSD may be explained by initial appraisal of traumatic events [60]. Women have been found to be more attentive to danger cues than their male counterparts [61–63], which may underlie findings that women report higher overall perception of threat in traumatic events [11, 51, 53, 54, 64]. Interestingly, men who are exposed to trauma report higher levels of perceived control [65], which is associated with lower risk for development of PTSD. For example, in a study among survivors of MVAs, Delahanty and colleagues found that perceived loss of control, or attributing the responsibility of the accident to others, was significantly higher among female participants [68]. This study also found that the perception of loss of control was associated with higher risk of developing PTSD.

Additional research of cognitive appraisals of traumatic events among military personnel may help clarify mixed findings on gender differences in the development of PTSD following exposure to combat. In a recent study among men and women deployed to Iraq and Afghanistan, Woodhead and colleagues found that women reported experiencing fewer traumatic incidents than men, and yet a substantial proportion of women endorsed feeling their life was threatened by others (74.8%) while deployed as compared with men (87.5%) [44]. Gender differences between objective level of combat experienced and perceived level of threat while deployed may be partially explained by findings among civilian samples, which suggest women are more

aware of threatening stimuli and therefore more likely to appraise a situation as dangerous [11, 62].

Appraisal of threat may be influenced by limits of control, in that with appropriate training and authority to respond to danger, individuals perceive situations as less dangerous than if they were unprepared and ill-equipped. Prior to December 2015, women were prohibited from serving in certain combat occupations and were more likely to serve in supportive roles while on deployment, such as drivers or medical personnel. In a prospective study of the National Guard troops deployed to Iraq, Kline and colleagues found that there were no differences in combat exposure between men and women but that women were more likely to develop PTSS following deployment and that women reported lower levels of perceived military preparedness and unit cohesion than their male counterparts [66]. Perception of control may be particularly salient in incidents of military sexual trauma, where aspects of the military environment, such as survivors' perception that they cannot escape the situation or their attacker, concern that reporting the incident might result in negative consequences, and feeling of betrayal that they would be victimized by fellow service members may all contribute to negative mental health outcomes [18].

Neurobiological Correlates

Sex differences in biology may also play an important role in how men and women respond to traumatic events. A review of studies examining neurobiological correlates of PTSD found that women are particularly vulnerable to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (i.e., stress response system) following exposure to early and chronic interpersonal abuse [13]. Women entering the military are more likely than men to have experienced early and chronic interpersonal abuse [31], which may heighten their overall sensitivity to stress response. This may also help explain why despite lower rates of objective exposure to combat experiences, a substantial proportion of women deployed to Iraq and Afghanistan reported feeling in danger [44]. If a relatively higher proportion of female military personnel have experienced early chronic stress, it follows that they may be more likely to not only experience a stress response but also take a longer time to return to "homeostasis" or their resting state.

Abnormal acquisition of fear conditioning has been posited as a mechanism for development of PTSD. Inslicht and colleagues examined fear conditioning among individuals with PTSD and found that women had greater skin conductance responses than men, suggesting greater fear acquisition in women with PTSD [67]. This finding was in contrast to previous studies among healthy controls that found no difference in fear acquisition between men and women or found that female healthy controls were less likely to experience fear conditioning than male healthy controls. Greater fear acquisition among women with PTSD may indicate a specific preexisting vulnerability or may point to a phenomenon that emerges in a sex-dependent manner after the development of PTSD. This phenomenon may partially explain why women, particularly those with histories of past traumas, may be more likely than their male counterparts to report feeling in danger while deployed.

Women are also more likely to produce oxytocin following a traumatic event, which, in conjunction with the female stress hormone estrogen, produces a calming effect and plays a pivotal role in mediating stress responses [69]. Higher levels of oxytocin are associated with increased sense of attachment or "bonding" to others and a faster hypothalamic-pituitary-adrenal (HPA) axis recovery in women after an acute stressor in a laboratory experiment [69]. If women are "hard wired" to seek out social support following traumatic events, which higher levels of oxytocin may suggest, the presence of meaningful relationships and the lack thereof may have a unique influence in the development of post-traumatic stress disorder symptoms among women. For example, studies among OEF/OIF/OND military personnel found that interpersonal relationships (e.g., intimate relationship, perceived social support) moderate the relationship between trauma exposure and the development of PTSD among women but not men [14, 30].

Coping Styles

Gender differences in post-traumatic stress disorder symptoms may also be attributed to how men and women are socialized to response to stress. In general, women tend to adopt a more passive or avoidant coping style, whereas men adopt a more instrumental or active coping styles [13]. Given passive coping styles are associated with higher risk of developing PTSD, it would follow that women have a higher vulnerability to develop PTSD. However, women in the military may adopt more androgynous or masculine gender roles, which reduce the influence of gender-specific coping styles like avoidance [12, 70]. This may help explain why there is limited evidence of gender differences in the development of PTSD following deployment to a war zone [4, 21, 44]. This may also explain why findings of specific coping behaviors among military and veteran samples diverge from civilian literature. Problematic drinking following trauma is considered an avoidant coping behavior, and among general population samples, women are at higher risk for developing substance abuse following trauma [13, 53]. However, among military and veteran samples, men consistently reported higher levels of alcohol abuse as compared to women [6, 28, 44]. Taken together, there is evidence to suggest that traditional coping styles, which rely on adherence to traditional gender roles, may not apply to military and veteran samples.

Response to Treatment

Additional research has examined gender differences in response to treatment of PTSD, with implications for how men and women organize information and regulate emotional memories. PTSD has been found to be associated with impaired executive functioning, like difficulty planning, limited cognitive flexibility, poor impulse control, and problems with selective attention and working memory [71, 72]. In a large review of the literature examining the relationship between executive functioning and PTSD, Polak and colleagues found that men with PTSD performed worse on tasks of executive functioning compared to men without PTSD, whereas there were no differences in executive functioning found between women with PTSD and gender-matched healthy controls [73]. Adequate executive functioning is crucial in participation of common PTSD interventions, such as medication therapy and cognitive behavioral therapies (CBT), where remembering to follow a medication regimen or recall emotional experiences is necessary for successful treatment. Evidence that men with PTSD tend to have more problems with executive functioning than their female counterparts may suggest that men be less likely to fully benefit from some of the PTSD treatments offered.

In a randomized controlled trial of CBT for PTSD among adult survivors of MVAs and nonsexual assaults, participants were assigned to an exposure-only group (i.e., imaginal and in vivo) or an exposure-based treatment with cognitive restructuring group (i.e., imaginal and in vivo exposure, daily thought records, Socratic questioning) [74]. There were no differences in PTSD symptoms between treatment groups immediately following treatment. However, at the 6-month follow-up visit, men in the exposure-only group reported more severe PTSD symptoms than women in the exposure-only group and then both men and women in the exposure-based treatment with cognitive restructuring group [74]. Findings from this study suggest that men have reduced maintenance gains following exposure treatment as compared with women; however, those gains are more likely to be maintained if exposure therapy is combined with cognitive restructuring.

These findings are consistent with evidence that women recall emotional memories and retain extinction memories better than men [43, 75], which may facilitate emotional processing and long-term treatment gains. Also, men are less likely than women to discuss their emotional or cognitive experience with others [76] and are more likely to believe that expressing emotion, talking about the event, or reaching out for support are signs of "weakness" [77] which will only further inhibit the necessary emotional processing and cognitive restructuring associated with successful treatment outcomes.

Taken together, there is growing evidence to suggest that cognitive, biological, behavioral, and emotional factors may explain observed differences in how men and women perceive, experience, and respond to traumatic events. Such gender differences may also play a role in efficacy of PTSD treatment. Additional assessment of trauma history, cognitive style, emotional processing, and behavioral coping skills may increase successful treatment engagement and treatment efficacy among common interventions such as CBT.

Summary

The increasing role of women in combat operations has allowed a more comprehensive examination of how gender may impact the response to traumatic events in the war zone. Although men continue to report higher levels of exposure to combat, women report substantial exposure to deployment stressors and are at higher risk for certain traumatic experiences like military sexual trauma. Numerous factors influence the relationship between trauma exposure and subsequent post-traumatic stress disorder symptoms. For example, women are more likely to have experienced trauma prior to enter the military, which may increase their overall sensitivity to traumatic stress. Women are also more likely to perceive higher levels of threat and feel less in control during the traumatic event, which also increases the likelihood of developing PTSD.

Identifying gender differences in the prevalence of PTSD following combat is difficult given differences in methods across studies, but overall, minimal differences have been found. There is some evidence that women are at higher risk for developing depressive symptoms following combat exposure, whereas men are more likely to engage in problematic substance use. Quality of relationships following deployment appears to play an important role for women, where decreased closeness among intimate relationships increases women's risk of developing PTSD, and perceived social support mediates the relationship between combat exposure and subsequent PTSD.

Findings from civilian populations point to differences in how men and women initially respond to trauma. Women generally report higher levels of overall distress, a greater number of post-traumatic stress disorder symptoms, and more peritraumatic dissociation. Additionally, while both men and women with PTSD have significant problems with sleep, gender appears to play an important role in the type of sleep problems experienced. Findings of gender differences among avoidant and hyperarousal symptoms are mixed. Expression of post-traumatic stress disorder symptoms also appears to be influenced by culture, where greater differences are seen among cultures with more traditional gender roles. It is unclear whether similar gender differences in

symptom profiles following traumatic events would be found among military populations, where men and women may be less likely to assume traditional gender roles.

Men and women appear to perceive, respond, and cope with trauma differently. Cognitive, biological, behavioral, and emotional factors influence the development of PTSD, and differences observed between genders provide valuable information in how to better tailor assessment and treatment for men and women who have been exposed to combat trauma.

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References

1. Manning L. Women in the military: where they stand. 8th ed. Washington, DC: Women's Research and Education Institute; 2013.
2. Department of Defense. Defense casualty analysis system. (n.d.). Retrieved 18 Oct 2016 from http://www.dmdc.osd.mil/dcas/pages/casualties.xhtml.
3. Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol Bull. 2006;132(6):959–92.
4. Lapierre CB, Schweglen AF, LaBauve BJ. Posttraumatic stress and depression symptoms in soldiers returning from combat operations in Iraq and Afghanistan. J Trauma Stress. 2007;20(6):933–43.
5. Maguen S, Luxton DD, Skopp NA, Madden E. Gender differences in traumatic experiences and mental health in active duty soldiers redeployed from Iraq and Afghanistan. J Psychiatr Res. 2012;46(3):311–6.
6. Riddle JR, Smith B, Corbeil TE, Engel CC, Wells TS, Hoge CW, et al. Millennium cohort: the 2001–2003 baseline prevalence of mental disorders in the U.S. military. J Clin Epidemiol. 2007;60:192–201.
7. Tanielian T, Jaycox LH, editors. Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery. Santa Monica: the RAND Corporation; 2008.
8. Vogt D, Vaughn R, Glickman ME, Schultz M, Drainoni M, Elwy R, et al. Gender differences in combat-related stressors and their association with postdeployment mental health in a nationally representative sample of U.S. OEF/OIF veterans. J Abnorm Psychol. 2011;120(4):797–806.
9. Fullerton CS, Ursano RJ, Epstein RS, Crowley B, Vance K, Kao T-C, et al. Gender differences in posttraumatic stress disorder after motor vehicle accidents. Am J Psychiatry. 2001;158:1486–91.
10. Bryant RA, Harvey AG. Gender difference in the relationship between acute stress disorder and posttraumatic stress disorder following motor vehicle accidents. Aust N Z J Psychiatry. 2003;37:226–9.
11. Irish LA, Fischer B, Fallon W, Spoonster E, Sledjesk EM, Delahanty DL. Gender differences in PTSD symptoms: an exploration of peritraumatic mechanisms. J Anxiety Disord. 2011;25:209–16.
12. Norris FH, Perilla JL, Ibanez GE, Murphy AD. Sex differences in symptoms of posttraumatic stress: does culture play a role? J Trauma Stress. 2001;14:7–28.
13. Olff M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. Psychol Bull. 2007;133(2):183–204.
14. Vogt D, Smith B, Elwy R, Martin J, Schultz M, Drainoni ML, et al. Predeployment, deployment, and post-deployment risk factors for posttraumatic stress symptomatology in female and male OEF/OIF veterans. J Abnorm Psychol. 2011;120(4):819–21.
15. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA. 2006;295(9):1023–32.
16. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351:13–22.
17. King DW, King LA, Gudanowski DM, Vreven DL. Alternative representations of war zone stressors: relationships to posttraumatic stress disorder in male and female Vietnam veterans. J Abnorm Psychol. 1995;104(1):184–96.
18. Street AE, Vogt D, Dutra L. A new generation of women veterans: stressors faced by women deployed to Iraq and Afghanistan. Clin Psychol Rev. 2009;29:685–94.
19. Hoge CW, Clark JC, Castro CA. Commentary: women in combat and the risk of post-traumatic stress disorder and depression. Int J Epidemiol. 2007;36(2):327–9.
20. Mental Health Advisory Team (MHAT-IV). Operation Iraqi freedom 05–07. (n.d.) Retrieved 20 Dec 2010, from, http://www.armymedicine.army.mil/reports/mhat/mhat_iv/mhat-iv.cfm.
21. Rona RJ, Fear NT, Hull L, Wessely S. Women in novel occupational roles: mental health trends in the UK armed forces. Int J Epidemiol. 2007;36(2):319–26.
22. Dutra L, Grubbs K, Greene C, Trego L, McCartin T, Kloezeman K, Morland L. Women at war: implications for mental health. J Trauma Dissociation. 2011;12:25–37.
23. Milliken CS, Auchterloine JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA. 2007;298(18):2141–8.
24. Vogt D, Pless AP, King LA, King DW. Deployment stressors, gender, and mental health outcomes among Gulf war I veterans. J Trauma Stress. 2005;18(3):272–84.
25. Kimerling R, Street AE, Pavao J, Smith MW, Cronkite RC, Holmes TH, et al. Military-related sexual trauma among VHA patients returning from Afghanistan and Iraq. Am J Pub Health. 2010;100:1409–12.
26. Kang H, Dalager N, Mahan C, Ishii E. The role of sexual assault on the risk of PTSD among Gulf war veterans. Ann Epidemiol. 2005;15(3):191–5.
27. Himmelfarb N, Yeager D, Mintz J. Posttraumatic stress disorder in female veterans with military and civilian sexual trauma. J Trauma Stress. 2006;19(6):837–46.
28. Maguen S, Cohen B, Ren L, Bosch J, Kimerling R, Seal K. Gender differences in military sexual trauma and mental health diagnoses among Iraq and Afghanistan veterans with posttraumatic stress disorder. Womens Health Issues. 2012;22(1):e61–6.
29. Hankin CS, Skinner KM, Sullivan LM, Miller DR, Frayne S, Tripp TJ. Prevalence of depressive and alcohol abuse symptoms among women VA outpatients who report experiencing sexual assault while in the military. J Trauma Stress. 1999;12(4):601–12.
30. Skopp NA, Reger MA, Reger GM, Mishkind MC, Raskind M, Gahm GA. The role of intimate relationships, appraisals of military service, and gender on the development of posttraumatic stress symptoms following Iraq deployment. J Trauma Stress. 2011;24(3):277–86.
31. Zinzow HM, Grubaugh AL, Monnier J, Suffoletta-Maierle S, Frueh BC. Trauma among female veterans: a critical review. Trauma Violence Abuse. 2007;8(4):384–400.
32. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Marks JS. Relationship of childhood abuse and house-

hold dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE) study. Am J Prev Med. 1998;14:245–58.
33. Rosen LN, Wright K, Marlowe D, Bartone P, Gifford RK. Gender differences in subjective distress attributable to anticipation of combat among U.S. Army soldiers deployed to the Persian Gulf during operation desert storm. Mil Med. 1999;164(11):753–7.
34. Griffin J, Vaitkus M. Relating cohesion to stress, strain, disintegration, and performance: an organizing framework. Mil Psychol. 1999;11(1):27–55.
35. Joint Economic Committee. Helping military moms balance family and longer deployments. Senator Charles Schumer (Chair) and Congresswoman Carolyn Maloney (Vice Chair). Washington, DC; 2007.
36. Kelley ML, Herzog-Simmer PA, Harris MA. Effects of military induced separation on parenting stress and family functioning of deploying mothers. Mil Psychol. 1994;6:125–38.
37. Ramchand R, Schell TL, Karney BR, Osilla KC, Burns RM, Caldarone LB. Disparate prevalence estimates of PTSD among service members who served in Iraq and Afghanistan: possible explanations. J Trauma Stress. 2010;23(1):59–68.
38. Kolkow TT, Spira JL, Morse JS, Grieger TA. Post-traumatic stress disorder and depression in health care providers returning from deployment to Iraq and Afghanistan. Mil Med. 2007;172(5):451–5.
39. Smith TC, Ryan MA, Wingard DL, Slymen DJ, Sallis JF, Kritz-Silverstein D. New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposure: prospective population based US military cohort study. Br J Med. 2008;336(7640):366–71.
40. Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch Gen Psychiatry. 2010;67(6):614–23.
41. Erbes C, Westermeyer J, Engdahl B, Johnsen E. Post-traumatic stress disorder and service utilization in a sample of service members from Iraq and Afghanistan. Mil Med. 2007;172(4):359–63.
42. Seal KH, Bertenthal D, Miner CR, Sen S, Marmar C. Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veteran Affairs facilities. Arch Intern Med. 2007;167(5):476–82.
43. Segal SK, Cahill L. Endogenous noradrenergic activation and memory for emotional material in men and women. Psychoneuroendocrinology. 2009;34:1263–71.
44. Woodhead C, Wessely S, Jones N, Fear NT, Hatch SL. Impact of exposure to combat during deployment to Iraq and Afghanistan on mental health by gender. Psychol Med. 2012;42(9):1–12. [Epub ahead of print].
45. King DW, King LA, Foy DW, Keane TM, Fairbanks JA. Posttraumatic stress disorder in a national sample of female and male Vietnam veterans: risk factors, war-zone stressors, and resilience-recovery variables. J Abnorm Psychol. 1999;108:164–70.
46. Luxton DD, Skopp NA, Maguen S. Gender differences in depression and PTSD symptoms following combat exposure. Depress Anxiety. 2010;27:1027–33.
47. Jacobson IG, Donoho CJ, Crum-Cianflore NF, Maguen S. Longitudinal assessment of gender differences in the development of PTSD among US military personnel deployed in support of the operations in Iraq and Afghanistan. J Psychiatr Res. 2015;68:30–6.
48. Kimerling R, Gima K, Smith MW, Street A, Frayne S. The veterans health administration and military sexual trauma. Am J Public Health. 2007;97:2160–6.
49. Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull. 2003;129(1):52–73.
50. Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR. Sex differences in posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54:1044–8.
51. Anderson K, Manuel G. Gender differences in reported stress response to the Loma Prieta earthquake. Sex Roles. 1994;3:725–33.
52. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209–18.
53. Grieger TA, Fullerton CS, Ursano RJ. Posttraumatic stress disorder, alcohol use, and perceived safety after the terrorist attack on the pentagon. Psychiatr Serv. 2003;54:1380–2.
54. Solomon Z, Gelkopf M, Bleich A. Is terror gender-blind? Gender differences in reaction to terror events. Soc Psychiatry Psychiatr Epidemiol. 2005;40:947–54.
55. Kobayashi I. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
56. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C, et al. Delta sleep response to metyrapone in post-traumatic stress disorder. Neuropsychopharmacology. 2003;28:1666–76.
57. Otte C, Lenoci M, Metzler T, Yehuda R, Marmar RC, Neylan CT. Effects of metyrapone on hypothalamic-pituitary-adrenal axis and sleep in women with post-traumatic stress disorder. Biol Psychiatry. 2007;61:952–6.
58. Kobayashi I, Mellman TA. Gender differences in sleep during the aftermath of trauma and the development of posttraumatic stress disorder. Behav Sleep Med. 2012;10(3):180–90.
59. Richards A, Metzler TJ, Ruoff LM, Inslicht SS, Rao M, Talbot LS, Neylan TC. Sex differences in objective measures of sleep in posttraumatic stress disorder and healthy control subjects. J Sleep Res. 2013;22(6):679–87.
60. Norris FH, Friedman MJ, Watson PJ, Byrne CM, Diaz E, Kaniasty K. 60,000 disaster victims speak: part I. An empirical review of the empirical literature, 1981–2001. Psychiatry. 2002;65:207–39.
61. Kemp AH, Silberstein RB, Armstrong SM, Nathan PJ. Gender differences in the cortical electrophysiological processing of visual emotional stimuli. NeuroImage. 2004;21:632–46.
62. McClure EB, Monk CS, Nelson EE, Zarahn E, Leibenluft E, Bilder RM, et al. A developmental examination of gender differences in brain engagement during evaluation of threat. Biol Psychiatry. 2004;55:1047–55.
63. Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. Biol Psychiatry. 2002;52:318–27.
64. Mak AS, Blewitt K, Heaven PCL. Gender and personality influences in adolescent threat and challenge appraisals and depressive symptoms. Pers Individ Dif. 2004;36:1483–96.
65. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull. 2004;130:355–91.
66. Kline A, Ciccone DS, Weiner M, Interian A, St. Hill L, Facla-Dodson M, et al. Gender differences in the risk and protective factors associated with PTSD: a prospective study of National Guard troop deployed to Iraq. Psychiatry. 2013;76(3):256–72.
67. Inslicht SS, Metzler TJ, Garcia NM, Pineles SL, Milad MR, Orr SP, Marmar CR, et al. Sex differences in fear conditioning in posttraumatic stress disorder. J Psychiatr Res. 2013;47(1):64–71.
68. Delahanty DL, Herberman HB, Craig KJ, Hayward MC, Fullerton CS, Ursano RJ, et al. Acute and chronic distress and posttraumatic stress disorder as a function of responsibility for serious motor vehicle accidents. J Consult Clin Psychol. 1997;65:560–7.
69. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RAR, Updegraff JA. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. Psychol Rev. 2000;107:411–29.
70. Cheng C. Processes underlying gender-role flexibility: do androgynous individuals know more or know how to cope? J Pers. 2005;73:645–73.

71. Koso M, Hansen S. Executive function and memory in post-traumatic stress disorder: a study of Bosnian war veterans. Eur Psychiatry. 2006;21:167–73.
72. Meewisse ML, Nijdam MJ, de Vries GJ, Gersons BP, Kleber RJ, van der Velden PG, et al. Disaster-related posttraumatic stress symptoms and sustained attention: evaluation of depressive symptomatology and sleep disturbances as mediators. J Trauma Stress. 2005;18:299–302.
73. Polak AR, Witteveen AB, Reitsma JB, Olff M. The role of executive function in posttraumatic stress disorder: a systematic review. J Affect Disord. 2012; doi:10.1016/j.jad.2012.01.001.
74. Felmingham KL, Bryant RA. Gender differences in the maintenance of response to cognitive behavior therapy for posttraumatic stress disorder. J Consult Clin Psychol. 2012; doi:10.1037/a0027156.
75. Milad MR, Zeidan MA, Contero A, Pitman RK, Klibanski A, Rauch SL, et al. The influence of gonadal hormones on conditioned fear extinction in healthy humans. Neuroscience. 2010;168:652–8.
76. Dindia K, Allen M. Sex differences in self-disclosure: a meta-analysis. Psychol Bull. 1992;112(1):106–24.
77. McClean CP, Anderson ER. Brave men and timid women? A review of the gender differences in fear and anxiety. Clin Psychol Rev. 2009;29:496–505.

Part II

Rack Time: Some Perspectives on Sleep and the Deployment Cycle from a Military Psychologist

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> A typical day at boot camp began with reveille at 0400 hours. We tumbled out of our sacks in the chilly dark and hurried through shaves, dressing, and chow. The grueling day ended with taps at 2200. At any time between taps and reveille, however, the DI might break us out for rifle inspection, close-order drill, or for a run around the parade ground over the sand by the bay. This seemingly cruel and senseless harassment stood me in good stead later when I found that war allowed sleep to no man. – E.B. Sledge, excerpt from *With the Old Breed, at Peleliu and Okinawa*.

There are many facets of life that one contemplates before their first deployment to a combat zone, but sleep is often overlooked. Instead, thoughts turn to whether or not one will display sufficient courage and fortitude under fire while still executing the mission and supporting their comrades. Most struggle with the impending separation from spouses, children, friends, and loved ones. A few may confront crises of confidence in the adequacy of their training and technical abilities. Many simply lament the impending loss of basic daily comforts such as the ability to choose when and where one eats and uses the toilet. In sleep and the deployment cycle, no one really thinks or talks about it, that is, until they begin their deployment.

Poor sleep often starts at pre-deployment training and is perceived as a compression of time in conjunction with saying good-bye to loved ones, attempts to savor the final days and hours of liberty, and copious travel. Consequently, it is not uncommon to start a deployment in a state of sleep deprivation. Receiving, staging, onward movement, and integration (RSOI) compounds the problem with flights across multiple time zones and sleeping in transient quarters filled with hundreds of strangers arriving and departing at all hours of the day, all punctuated with fixed chow times that seem to provide the only stability in a chaotic life moment. Many service members may recall these transitions more as dream states of mixed consciousness full of emotions that evolve from the sadness of separation to the anxious anticipation of being "boots-on-ground." The one academic model which seems to resonate with this experience is the 3P model of sleep health problems [1] which notes the role of the pre-deployment phase in predisposing one to acute sleep problems on deployment. One wonders, why is this model not more often discussed in pre-deployment briefs?

As for deployment, sleep becomes a desperately sought commodity; some would even consider it a luxury. As reviewed by Pruiksma and Peterson (this volume), an in-theater survey of Army personnel deployed to Iraq and Afghanistan indicated 32 % of respondents had high or very high concerns about insufficient sleep, with a mean sleep duration of 5.6 h. This average coincides with additional data provided by 3175 Sailors deployed to Afghanistan

after 2009, of which 67 % reported 6 or fewer hours of sleep per day and an average sleep time of 5.9 h [4].

Combat deployments bring exposure to ambushes by the enemy, planned assaults on enemy positions, the random barrage of "indirect" enemy rocket fire, and an omnipresent threat of improvised explosive devices, all experiences with an intuitive link to poor sleep and easily portrayed in books and film. What is less well-known and more difficult to portray to those who have never deployed are the self-inflicted wounds to sleep health. These wounds are incurred by an assortment of cuts, starting with poorly designed work schedules that have pushed service members to their functional limits, a situation often involving manning shortfalls. There is a struggle between competing interests during the precious little downtime that forces a choice between sleep and communication with family, exercise, or simply doing one's laundry and eating. Another cut is inflicted by the design and placement of field quarters and sleeping tents next to loud generators, airfields, and a failure to separate day and night sleepers. The key point here is that kinetic "guns and bombs" combat does not explain all the sleep health problems associated with deployment. For example, Taylor and colleagues (2014) reported that either having a sleep deficit or getting less than 6 h of sleep was a better predictor of PTSD risk (univariate OR, respectively, 11.39, 12.84) than being in the highest category of self-reported combat exposure (univariate OR = 9.77) for Sailors deployed to Afghanistan. Therefore, poor sleep on deployment, whether it is linked primarily to combat or factors such as operational tempo and environment, can have serious psychological consequences that extend into post-deployment.

The "redeployment" RSOI can impart just as much circadian disruption and emotional intensity as the initial journey into theater; thus, one must face the many challenges of reintegration into society, family, jobs, and the hard, lonely internal work of psychologically integrating the deployment experience into one's identity while suffering from months of poor sleep and an intense circadian disruption. For many, the post-deployment transition is the most difficult part of the deployment-cycle experience. One commonly perceived, yet understudied, post-deployment phenomenon that deserves attention is the use of alcohol to self-medicate insomnia stemming from months of poor sleep intensified by the circadian disruption of the flight home. The end result may be alcohol dependency that exacerbates or becomes the diathesis stressor for underlying psychopathologies. The longitudinal study of sleep and its potential pathogenic role in the transition from deployment to post-deployment will be challenging but deserve attention.

From a methodological standpoint, much of the research investigating deployments to Iraq and Afghanistan often fails to consider the diversity of missions and locales that fall under the rubric of "combat deployment." For instance, the MHAT sample cited by Pruiksma and Peterson may have been comprised of traditional "combat" maneuver soldiers serving in isolated outposts like those in the Korengal and Kunar river valleys of Afghanistan. Meanwhile, the Navy sample [4] was constituted primarily by Sailors in support roles with much less time "outside-the-wire" and concentrated in places like Bagram Airfield in Afghanistan (even the Navy sample had stark differences between types of deployments and exposure to hostile threats). Despite these differences, both the MHAT and Navy samples reported similarly inadequate amounts of sleep. Poor deployment sleep extends from remote, rustic, temporary combat outposts to the densely packed metropolises of seemingly permanent forward operating bases (FOBs); thus no one deployment subpopulation should be ignored when studying sleep problems in deployed veterans. Likewise, there may be important differences in the etiology and sequela of sleep health problems imparted by these different deployment types.

Why is sleep disruption pervasive throughout the deployment cycle? Though combat exposure may not be universal during a combat-zone deployment, the self-inflicted environmental factors seem widespread, and here I speculate why. Sleep is a casualty of deployment logistical complexity. Many aspects of deployment that affect sleep such as flight schedules, the placement and composition of sleep quarters, work schedules, manpower, and the rotation of troops in and out of theater are so complex that their execution requires computerized, multivariate, algebraic analysis developed by teams of highly trained engineers. Another brutal reality is that the objectives of the mission take precedence over human factors such as the fatigue of the troops (aviation being one of the few exceptions). In fairness, the inability to incorporate the human limits of sleep into military operational planning is not an intentional omission on the part of military planners or leadership. Rather, it is a situation better attributed to the sheer vastness of the combat enterprise in places like Iraq and Afghanistan and the innate limitation of human cognitive capacity that, in tandem, force "human factors" such as sleep to take a back seat in the congested cognitive landscape of

planners who must sort through more salient competing logistical and operational considerations. It is therefore an essential function of experts working in and for the Department of Defense (DoD) to possess the training and background in sleep health that will enable them to (a) identify factors that contribute to poor sleep health, (b) raise the issue to the conscious awareness of task-saturated planners and leaders, and (c) work collaboratively to find solutions that are commensurate with mission execution, a model embraced by the Navy Mobile Care Team [2].

The chapters in this volume provide some of the background that will be necessary to advance the cause of sleep health in deployment. As challenging as it may be to integrate concerns about sleep health into operational military planning and logistics, I am confident that doing so will not only improve the effectiveness of the force and enhance the chance for mission success but also reduce the prevalence of long-term health problems associated with deployment-related sleep difficulties and improve the quality of life for service members, veterans, and their families. Although sleep may not be the first concern that comes to mind when preparing for deployment, it quickly becomes a topic you cannot ignore, as it is infused into every aspect of the deployment experience. Whether one is struck by the prevalence of exhausted, bloodshot eyes, mounds of energy drink cans, and short tempers on deployment or examines their stress control surveys to find that poor sleep is a more powerful predictor of PTSD than combat, the words of Marine Private Sledge's observation from World War II continues to resonate: war allows sleep to no one.

References

1. Bramoweth AD, Germain A. Deployment-related insomnia in military personnel and veterans. Curr Psychiatr Rep. 2013;15:401. doi:10.1007/s11920-013-0401-4.
2. Campbell JS, Koffman RL. Ecological systems of combat and operational stress: theoretical basis for the U.S. Navy Mobile Care Team in Afghanistan. Mil Behav Health. 2015;2(4):316–26. doi:10.1080/21635781.2014.963761.
3. Pruiksma and Peterson (2017). Vermetten E, Germain A, Neylan TC, editors. In: Sleep and combat-related post traumatic stress disorder. Springer, New York
4. Taylor MK, Hilton SM, Campbell JS, Beckerley SE, Shobe KK, Drummond SP. Prevalence and mental health correlates of sleep disruption among military members serving in a combat zone. Mil Med. 2014;179(7):744–51. doi:10.7205/MILMED-D-13-00551.
5. Sledge EB. With the old breed, at Peleliu and Okinawa. Novato: Presidio Press; 1981.

The Role of Sleep in the Health and Resiliency of Military Personnel

5

Stacey Young-McCaughan, Alan L. Peterson, and Mona O. Bingham

Introduction

Although restful sleep is recognized as essential for good health, it is puzzling that so little is known about this activity, especially as it relates to psychological resiliency. Sleep is a naturally occurring circadian behavior that is believed to be a restorative process essential for normal metabolic function [1–3]. Sleep is an essential component of both physical and psychological functioning that promotes health as well as resilience to adversity. This is especially true in the military, where sleep deprivation can have profound negative consequences on both individual performance and unit functioning.

There are myriad characteristics of military service that disrupt normal sleep including early work start times and late work stop times, long work hours, irregular work schedules, and caffeine, tobacco, and alcohol use. During deployments, additional distracters and sources of disruption from normal sleep include hazardous working conditions, extreme temperatures, loud noises, continuous operations, irregular and changing work schedules, and an overall lack of control over the sleeping environment [4–6]. One of the most common observations of service members both during and following deployment is disturbed sleep [7]. Over the past 10 years of continuous military operations in Iraq and Afghanistan, the issue of sleep disturbance has become more urgent, especially when considered with other behavioral health concerns such as posttraumatic stress, anxiety, depression, and suicide [8].

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Review of the Literature

Normal Sleep and the Impact of Sleep Disturbance

Sleep is a naturally occurring circadian behavior that is believed to be a restorative process essential for body restitution, facilitation of motor function, and consolidation of learning and memory [3]. There are five distinct stages of sleep. Stages 1, 2, 3, and 4 are collectively called non-rapid eye movement (NREM) sleep. The fifth stage is labeled REM sleep. Each of the sleep stages occurs several times during normal sleep in cycles lasting approximately 90 min [3]. During NREM sleep, the EEG becomes progressively more synchronized and temperature drops, as do heart rate, blood pressure, and respiratory rate. REM sleep is characterized by the sudden onset of an asynchronous EEG pattern. Very little muscle movement occurs during REM sleep, except for muscle twitches of the face and the eyes. Sleepers awakened from REM sleep typically report dreaming. Some of the most commonly used terms in the assessment and treatment of sleep disorders are included in Table 5.1.

Sleep deprivation can have profound negative consequences. Humans deprived of sleep for more than 48 h experience increasing levels of fatigue and irritability, have increased difficulty concentrating, and undergo a deterioration of motor coordination [3]. Symptoms of sleep deprivation can be very similar to symptoms associated with psychiatric disorders, including lack of self-care, poor work initiative, lapses of attention, impaired judgment, and withdrawal. The chance for errors and accidents increases. Illusions and hallucinations are possible. Neurological signs of abnormal eye movements and speech can also occur. Seizure threshold is lowered and psychotic episodes are possible [3]. When recovering from sleep deprivation, the

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Table 5.1 Causes of sleep disturbance unique to military deployment

Adverse sleeping environments of limited and uncomfortable space, excessive noise (e.g., from generators, aircraft operations, or explosions), temperature extremes, ambient light, and noxious fumes and smells
Stress related to combat including a realistic or perceived threat to life or of injury
High operation tempo (OPTEMPO)
The need for instant alertness to respond to an attack or when called to duty
Nighttime duties
Excessive and ill-timed use of caffeine, tobacco, and alcohol that can disrupt sleep
The concurrent use of multiple medications to control symptoms of stress and/or to promote sleep which, counterintuitively, lead to more disturbed sleep
Stress related to family issues at home
Continuous high sensory input from televisions, computers, phones, video games, and other electronic devices

amount of time spent in the various stages of sleep is altered. Initially, stage 4 sleep predominates. On succeeding nights, REM sleep rebounds. Stage 4 sleep is believed to be the most important stage in restoring normal daytime functioning [3].

The primary symptoms of insomnia include difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and non-restorative or poor quality of sleep. In civilian populations, research studies have estimated that approximately 30% of adult samples drawn from different countries report one or more of the symptoms of insomnia [9]. If perceived daytime impairment or distress due to insomnia is added to the case definition, prevalence estimates decline to approximately 10%. Insomnia has been associated with higher rates of illness and decreased quality of life [10–13]. Disturbed sleep is also associated with poor job performance, including difficulty performing duties and increased rates of work-related accidents [11, 14]. Even more concerning, especially for the military, is the observation in civilian populations that the frequency of nightmares has been directly related to the risk of suicide [15]. One study [16] estimated health costs for young adults with insomnia to be $1253 greater than for individuals without insomnia.

Incidence and Impact of Sleep Disturbance in the Military

The nature of military service has a unique impact on sleep. A study of US military personnel indicated that the rate of insomnia has increased dramatically since the start of Operation Enduring Freedom in 2001 [17]. The study population included all service members in the active component of the army, navy, air force, marine corps, or coast guard between 1 January 2000 and 31 December 2009. For study purposes, insomnia was defined as two or more ambulatory visits within 90 days of each other or a hospitalization including one of five different insomnia ICD-9 codes. The crude incident rate for insomnia was calculated by the number of cases per 10,000 person-years. From 2000 to 2009, the crude incidence rate of insomnia in the US military increased from 7 to 136 cases per 10,000. The incidence rates increased for all service branches, but the greatest increase by far was in the army (from 7 to 226 cases per 10,000). In addition, the evaluation of individual cases of insomnia from before to after deployment revealed that the incidence rates for insomnia increased more than 250% in the army. Interestingly, the incidence rate of insomnia between 2000 and 2009 was higher for military health-care occupations (12–205 per 100,000) as compared to combat military occupations (4–145 per 100,000). The primary limitation of this study is that it is based on ICD-9 codes from ambulatory visits or hospitalizations rather than population samples. Whether the overall rate of insomnia in the military population as a whole is different from the rate in civilian populations is not clear.

The 2008 Department of Defense Survey of Health Related Behaviors [18] of 28,546 army, navy, marine corps, air force, and coast guard personnel indicated that only one quarter (24%) reported sleeping 7 or more hours per night in the past 6 months. The Walter Reed Army Institute for Research recommends that military service members obtain 7–8 h of good quality sleep every 24-h period to sustain operational readiness [19]. According to these guidelines, 75% of the respondents to the Defense Survey of Health Related Behaviors are getting too few hours of sleep.

Data from the Millennium Cohort Study provides additional information on sleep in US military personnel [20]. A survey of 41,225 military personnel from all US branches of service, including the Reserve and National Guard, indicated that service members report sleeping an average of 6.5 h per night. However, between 20 and 30% of the study cohort reported trouble sleeping over the past month. The primary limitation of the sleep data from the Millennium Cohort Study is that sleep habits were measured using two questions from the Posttraumatic Stress Disorder Checklist – Civilian (PCL-C) and the one question from the Patient Health Questionnaire (PHQ) related to anxiety. Potentially, Millennium participants may have answered thinking of their sleep in relation to PTSD and anxiety rather than their sleep in general.

During deployment, reports of sleep disturbance increase. One study evaluated 156 air force personnel deployed in 2001 to an undisclosed bare-base environment in support of Operation Enduring Freedom [6]. The results indicated that 74% reported their quality of sleep was significantly worse in the deployed environment, 40% had a sleep efficiency less than 85%, and 42% took longer than 30 min to fall asleep.

The Mental Health Advisory Team (MHAT) Reports V [21] and VI [22] do not specifically report sleep habits during deployment to Operation Enduring Freedom or Operation Iraqi Freedom, but they do report the use of sleeping medications. Nine percent of soldiers serving in Afghanistan reported using sleeping medications [21]. A similar number of soldiers serving in Iraq as part of maneuver units (8%) reported using sleeping medications. However, 14% of soldiers serving in support and sustainment units reported using sleeping medications [22]. This was a statistically significant difference, even after controlling for gender, rank, and time in theater. Support and sustainment units include medical personnel who were identified by the Armed Forces Health Surveillance Center [17] to have higher rates of insomnia as compared to combat occupations.

The Joint Mental Health Advisory Team 7 (J-MHAT 7) [4] specifically assessed reasons for sleep disruption in army soldiers and marines deployed to Afghanistan in 2010. One-third of soldiers (33%) and almost 40% of marines (38%) reported not getting enough sleep, a slight increase from previous reports (29% of soldiers in the 2009 MHAT VI report, 25% of marines in the 2006 MHAT IV report, and 22% of marines in the 2008 MHAT V report). Reasons cited for poor sleep were similar between the soldiers and marines and included poor sleep environment (33% soldiers and 47% marines), nighttime duties (30% soldiers and 47% marines), high operations tempo (17% soldiers and 27% marines), stress related to personal life (11% soldiers and 13% marines), stress related to combat (10% soldiers and 16% marines), and off-duty leisure such as video games and movies (4% soldiers and 5% marines). Eleven percent of the soldiers and 7% of the marines reported taking medications for sleep. They also reported heavy caffeine use, with 60% of the soldiers who reported taking sleeping medications also reporting that they consumed at least one energy drink per day. In contrast, only 43% of the soldiers who did not report taking sleeping medications reported consuming at least one energy drink per day. One of the recommendations from this report was to include sleep hygiene and discipline training as part of predeployment training and to identify small unit leaders to be responsible for ensuring opportunities for sleep unique to the unit location and circumstances.

Stressors documented during deployment that prompt behavioral health intervention include sleep disturbance [5]. Sleep disturbance was one of the top five stressors during deployment and was the principle "other" behavioral health diagnoses recorded in almost 30% of individuals receiving care the first half of 2008 [23].

Upon redeployment, sleep disturbance often continues. In an electronic record review of 1887 predominantly navy and marine personnel, 41% of those who had been deployed to Iraq or Afghanistan reported sleep problems as compared with 25% of those who had been deployed elsewhere [7]. However, like the Millennium Cohort Study, sleep was assessed using the navy's Post-Deployment Health Assessment Test (PDHAT), which includes all the questions from the PTSD Checklist – Military. Similarly, in the Millennium Cohort Study, individuals who had been deployed reported decreased sleep duration as compared with individuals who had never been deployed [20]. Other variables significantly associated with trouble sleeping included female gender, lower reported general health, and reported mental health symptoms [20].

Findings from a study of 130 injured service members with extremity trauma sustained during service in Operation Enduring Freedom or Operation Iraqi Freedom indicated that 71% reported sleep disturbance three or more nights per week (S. Young-McCaughan, C. M. Miaskowski, M. O. Bingham, C. A. Vriend, A. Inman, J. Menetrez, unpublished data, 2011). Sleep disturbance was more prevalent than pain (average pain ≥5 and/or worst pain ≥7 reported by 55% of sample), depression (Center for Epidemiologic Studies Depression Scale ≥16 reported by 52% of the sample), anxiety (Spielberger Anxiety Scale ≥46 reported by 27% of the sample), and PTSD (PTSD Checklist – Military ≥50 reported by 19% of the sample) (Young-McCaughan et al. unpublished data 2011).

Repeated deployments have been a commonplace for conflicts in support of combat operations following 9/11 [24]. In one study [25], approximately 40% of the over 1.3 million service members who have ever been deployed had been deployed at least twice, 12% had been deployed at least three times, 4% had been deployed at least four times, and 1% had been deployed at least five times. This same report documented sleep disorders as one of the most common conditions to increase following second and third deployments.

Sleep disturbance often affects more than just the individual. In a study of 45 male Operation Enduring Freedom/Operation Iraqi Freedom veterans, reports of sleep problems predicted lower marital and relationship satisfaction [26]. Together, sleep disturbance and sexual problems predicted 29% of the variance in relationship satisfaction.

Sleep disturbance is consistently reported as most prevalent in service members with posttraumatic stress [27–29]. In one study of 2863 soldiers redeploying from service in Iraq [28], 71% of the 432 individuals reporting symptoms of PTSD on the Patient Health Questionnaire (PHQ) also reported sleep disturbance. In contrast, of the 2180 individuals not reporting symptoms of PTSD, only 26% reported sleep disturbance. The specific type of sleep disturbance is not queried with the PHQ. The report by 26% of those without symptoms of PTSD of sleep disturbance is more than three times greater than that reported in a study of 21,244 Gulf War veterans [27]. In the Gulf War veterans, only 8% of 1605 otherwise healthy individuals reported sleep disturbance, but 64% of the 1096 individuals with PTSD reported

sleep disturbance. The variability in reports of sleep disturbance could be related to the conflict (Gulf War or Operation Enduring Freedom/Operation Iraqi Freedom), military status (active duty or retired), and comorbid medical and psychiatric conditions, as well as the questionnaire used to elicit this information.

Several military programs have been developed to evaluate and treat sleep disorders in garrison and during deployments. Two in-garrison military studies indicated that insomnia can be successfully treated using cognitive behavior therapy delivered in a psychoeducational group format [30] as well as in an integrated behavioral health format in a primary care setting [31]. The Walter Reed Army Institute of Research (WRAIR) has developed a sleep management system to assess and address sleep issues before and during deployments [32]. The program, developed prior to the Iraq and Afghanistan conflicts, includes the following six elements: (1) actigraphy measurement of soldier sleep in garrison and in theater, (2) a mathematical model to predict an individual soldier's cognitive readiness as a function of his or her sleep, (3) guidelines for the use of stimulants, (4) guidelines for behavioral strategies to promote sleep, (5) guidelines for pharmacological strategies to promote sleep, and (6) guidelines and tools for monitoring performance in real time in operational environments.

Psychological Resiliency in the Military

Resiliency is traditionally a term used in mechanical engineering to describe the physical property of a material to absorb energy and change shape and then return to the original shape or position, either immediately or over time. More recently, the concept has been applied to adaptive responses to psychological stress. There is a great deal of variability in the understanding of psychological resilience, both in civilian and military populations [33]. One definition of psychological resiliency is a "dynamic process encompassing positive adaptation within the context of significant adversity" [34].

Understanding and promoting resilience is of great importance to the US military as it seeks to mediate the psychological stress of the ongoing conflicts in Iraq and Afghanistan [35–37]. Yet relatively little is known of the mechanisms for resilience, factors that contribute to psychological resilience to adversity encountered as part of military duty, or means to promote resiliency in service members [33]. In a group of 328 US air force medical personnel deploying to Iraq, psychological resilience (as assessed with the Connor-Davidson Resilience Scale) was significantly correlated ($P < 0.05$) with low predeployment stress, positive military experiences, and positive affect [38]. Sleep was not assessed in this study. Conducting a secondary analysis using data collected from 1632 male and female veterans of Vietnam, King and his colleagues [39] identified social support and hardiness as two key factors contributing to postwar resilience and recovery. Again, sleep was not assessed.

Despite a rudimentary understanding of psychological resilience and the factors that support resilience, the American military has instituted a variety of programs to promote resilience for service members. In 2007, the Battlemind training system was mandated to all US army units [40]. Battlemind training focuses on ten combat skills taking a cognitive and skills-based approach to focus on safety, relationships, and common physical, social, and psychological reactions to combat [41]. In a randomized controlled trial comparing stress education to Battlemind debriefing to small group Battlemind training (18–45 individuals) to large group Battlemind training (126–225 individuals), small group Battlemind training participants with high combat exposure reported fewer posttraumatic stress symptoms and sleep problems as compared to the stress education group [41]. Now known as resilience training, the Battlemind program provides training and information targeting all phases of the soldier deployment cycle, life cycle, and support system and "offers strength-based, positive psychology tools to aid Soldiers, Leaders, and Families in their ability to grow and thrive in the face of challenges and bounce back from adversity" [42].

In 2009, the Chairman of the Joint Chiefs of Staff, Admiral Michael Mullen, commissioned the Consortium for Human and Military Performance (CHAMP), working with scientists and leaders from the Uniformed Services University of the Health Sciences (USU), Samueli Institute, and the Institute for Alternative Futures to develop a comprehensive framework of Total Force Fitness (TFF) to promote resilience [43, 44]. The program uses a mind-body framework with eight domains of total fitness including physical [45], psychological [46], behavioral and occupational [47], medical and environmental [48], nutritional [49], spiritual [50], social [51], and family [52]. This work, now signed by the Chairman of the Joint Chiefs of Staff into policy, has resulted in a renewed emphasis on promoting resilience for military individuals, families, and communities before, during, and after deployments. The army at Fort Hood, Texas, operationalized Total Force Fitness, establishing the first multimodal, integrative program dedicated to integrating the body, mind, and spirit to produce a balanced lifestyle. The program was described by the Fort Hood and III Corps Deputy Commanding General as representing "a fundamental shift in focus toward holistic well-being and resiliency" [53]. How Total Force Fitness will be further implemented across the services is now being discussed [43]. Sleep is addressed in the physical, psychological, behavioral and occupational,

and medical and environmental domains as either a key component of fitness or as an indicator of poor functioning. Although the actual efficacy of this program in increasing resiliency is not known, a program evaluation of Total Force Fitness is proposed that includes the assessment of sleep patterns [54].

In 2011, the University of Pennsylvania program "Comprehensive Soldier Fitness" was mandated across the US Army. The program consists of four components including online self-assessment, an online self-help training, training of master resilience trainers, and mandatory resilience training at every army leader school [35]. Cornum and her colleagues [55] acknowledged the challenge of sleep deprivation during deployment, but it is not apparent that promoting restful sleep is a component of the program. Multiple assessments of the program are ongoing [56].

Model Including Sleep as Essential for Psychological Resilience

Some research suggests that restful sleep is an essential ingredient for achieving and maintaining psychological resilience during military deployments. In a study testing the stress buffering effects of self-engagement in soldiers deployed to Bosnia as part of Operation Joint Guard (OJG), Britt and Bliese [57] found that hours of sleep accounted for 14% of the variance in psychological distress. Fewer sleep problems were considered a positive outcome in testing Battlemind training [41]. But, while a better and more comprehensive understanding of military resilience is emerging from current programs and ongoing research, only a few authors have deliberately considered sleep as a component of resilience [32, 41, 47, 55, 57].

From the previous reviews of sleep and resilience in military personnel, sleep can be conceptualized as a base physiological requirement for resiliency similar to how air, food, and water are conceptualized as base physiological requirements for the attainment of higher levels of functioning (e.g., safety, love and belonging, esteem, and self-actualization) in Maslow's hierarchy of needs [58]. Animal laboratory research has documented death from total sleep deprivation in rodent models [59]. Although there are no reports of human death from sleep deprivation, it is thought to be a life-sustaining physiological requirement. The authors propose that the progressive requirements for military resiliency are physiological, psychological, knowledge and skills, and social support (see Fig. 5.1), with sleep being one of the basic physiological requirements for success at sequential tasks. Examples of research suggesting that these are essential elements for psychological resilience are presented below.

Physiological Needs

Maslow [58] conceptualized physiological needs as those required for human survival: air, food, and water. At its most base requirement, human behavior is focused on achieving physiologic homeostasis, and these needs must be addressed at some level before higher needs can be addressed. For a model of resilience, the base physiological needs beyond air, food, and water might be sleep, nutrition, and physical fitness. Cross-sectional studies have demonstrated that physically active individuals are less likely to develop psychological stress disorders [60]. One study evaluating reactions to the stress of extreme military training of survival, evasion, resistance, and escape (SERE) noted that service members more aerobically fit were less likely to report distress following the training [61].

Psychological Needs

Psychological needs that promote resilience could include optimism, hardiness, and an affiliation with military culture. Bonanno [62] has worked with a wide variety of individuals who have suffered trauma and loss including the death of a spouse, rape, the September 11th attack on the World Trade Center towers in New York City, and the Balkan Civil War. He has identified characteristics of resilient individuals including hardiness, self-enhancing biases, positive emotion, laughter, and repression of the trauma as a coping mechanism. Similar findings have been observed by others in civilian [63–65] and military populations [39].

Knowledge and Skills

Knowledge and skills that seem essential to resilience include individual and unit training, competence in successfully completing essential tasks, and understanding of the mission. The military focuses on training core skills that can be applied to a rapidly changing and potentially dangerous environment. The ability to "adapt and overcome" adversity is highly valued. However, an overall understanding of the mission and the role an individual plays in the unit's smallest to largest elements and the application of knowledge and skills to that mission is critical to psychological resilience [36].

Social Support

Social support in the military that promotes resilience is typified by confidence and trust in leadership, unit cohesion, a team approach to mission, and cultural confidence. In behav-

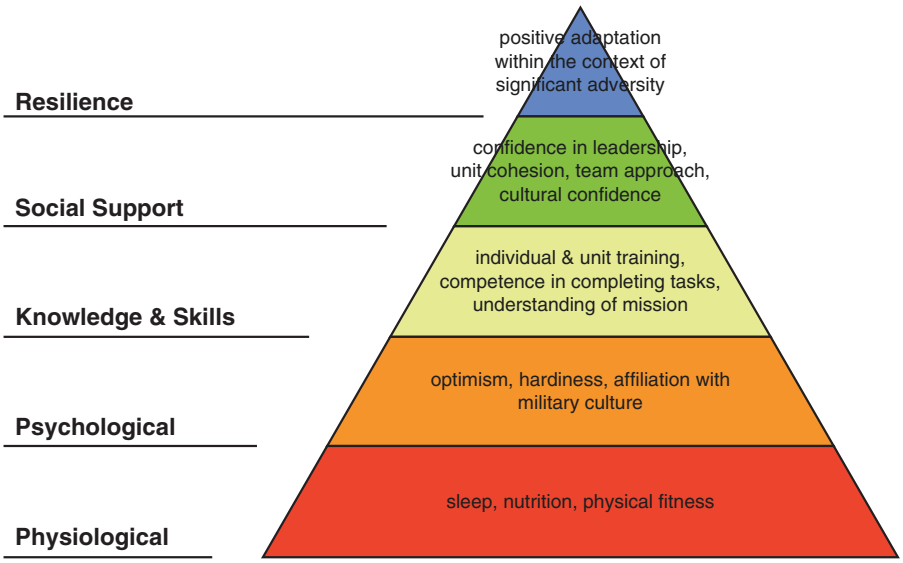

Fig. 5.1 Model of military resilience. The progressive requirements for military resiliency based upon Maslow's hierarchy of needs [58]. Sleep is one of the physiological requirements for success at succeeding tasks

ioral health surveys conducted in the Iraq and Afghanistan theaters of operation, unit cohesion was identified as a protective factor for solider well-being [21, 66]. Confidence in leadership, especially under conditions of high combat exposure, has also been identified as playing a role in promoting resilience [22]. Following deployment, lower unit support and post-deployment social support have been associated with decreased resilience and psychosocial functioning as well as increased posttraumatic stress and depressive symptoms [67].

Resilience

Maslow's end-state was self-actualization [58]. The end-state of the currently proposed model is resilience or positive adaptation within the context of significant adversity. Similar to Maslow's hierarchy, specific physiological, psychological, knowledge and skills, and social support needs must be addressed before resilience can be realized.

The proposed model clearly delineates base considerations such as sleep, which have often been overlooked in the understanding and study of psychological resilience. However, the proposed model does not incorporate the processing and the interpretation of new experiences. Neither does this model capture the interaction between genes and the environment or the effects of these interactions on resiliency.

Gaps in the Understanding of Sleep in Health and Resilience in the Military

With continued military deployments around the world, psychological resiliency is emerging as an essential and key feature of a healthy force. Gaps in the understanding of military resilience, specifically as related to sleep, include assessment of both sleep and resilience and a better understanding of sleep and sleep disturbance in the military in both times of combat operation and recovery in garrison.

Assessment of Resilience

The Connor-Davidson Resilience Scale (CD-RISC) is one of the most widely used measures of resilience [68, 69]. It includes ten questions asking individuals to rate themselves on the ability to adapt and deal with change, appreciate humor, cope with stress, bounce back after hardships, achieve goals, stay focused under pressure, not be easily discouraged, and handle unpleasant feelings. The Connor-Davidson Resilience Scale does not include an assessment of sleep.

The Response to Stressful Experiences Scale (RSES) [70], another measure of resilience, also does not include an assessment of sleep. The RSES is a 22-item questionnaire developed by a team of experts at the National Center for PTSD to assess trait-related cognitive, emotional, and behavioral resilience [70]. It asks participants to assess how well each statement describes them, both during and after stressful events in their lives. Psychometric testing in 1014 active-duty, reserve, and veteran groups showed that the instrument has sound internal consistency as well as good test-retest reliability over 7 days. The instrument correlated positively with the Connor-Davidson Resilience Scale as well as unit cohesion and post-deployment support. The Response to Stressful Experiences Scale correlated negatively with psychological symptom distress as assessed with the Patient Health Questionnaire-9, posttraumatic stress as assessed with the PTSD Checklist – Military (PCL-M), and overall mental health as assessed with the Minnesota Multiphasic Personality Inventory-2 Neuroticism, thus demonstrating concurrent validity. Factor analysis revealed a six-factor

model of resilience including subscales for active coping, meaning-making, cognitive flexibility, spirituality, self-efficacy, and restoration. The Response to Stressful Experiences Scale does not include an assessment of sleep.

The assessment of sleep should be considered for inclusion in any future revisions to the Connor-Davidson Resilience Scale or to the Response to Stressful Experiences Scale, as well as in the development of new measures.

Natural History, Types, and Causes of Sleep Disturbance in the Military

Seemingly not enough is known about the natural history, types, and causes of sleep disturbance in the military or how this compares with civilian populations. Sleep disturbance unique to military service includes the impact of deployment, redeployment, and physical injury on sleep. The opportunities to control the sleep environment are certainly very different in the military. The Walter Reed Army Institute of Research (WRAIR) supports a program of research focused on sleep deprivation and methods to deal with sleep debt in the support of continuous operations [32]. Anecdotal reports from Iraq and Afghanistan suggest that continuous operations are not the primary deterrent to restful sleep; rather, service members report difficulty sleeping during times they are allowed to sleep. Seemingly, a greater emphasis needs to be placed on promoting sleep under adverse conditions.

There are myriad reasons why military members find it difficult to sleep (see Table 5.1). Many of these reasons were endorsed by soldiers and marines participating in the J-MHAT 7 survey [4]. It is unclear how deployment contributes to sleep disturbance beyond what is known of sleep disturbance in civilian populations or service members in garrison. Neither is it known how best to intervene for specific combat-related sleep disturbances. Typical sleep hygiene interventions (such as going to bed and awaking at the same time, keeping the temperature between 60 and 70 °F/16 and 21 °C, and eliminating ambient light), sleep restriction/stimulus control behaviors (such as using bed only for sleep and getting out of bed after 30 min if unable to sleep), and relaxation therapies (such as guided relaxation, meditation, and yoga) are neither easily accepted in the macho military culture nor often easily used in a combat environment.

Conclusion

The role sleep plays in the health and resiliency of military personnel is just beginning to be recognized. Perhaps because sleep is an integral part of everyday activities and because periodic sleep disturbance is a common occurrence, the unique contribution of restful sleep to both health and wellness is not routinely considered. Military service members face unique challenges to sleep, especially during deployments. A better understanding of the types and causes of sleep disturbance in military members and the development of sleep interventions tailored to military men and women are essential in promoting resilience in the military.

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References

1. Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press; 1993.
2. Pressman MR, Orr WC. Understanding sleep: the evaluation and treatment of sleep disorders. Washington, DC: American Psychological Association; 1997.
3. Ropper AH, Samuels MA. Sleep and its abnormalities. In: Adams RD, Victor M, editors. Principles of neurology. 9th ed. New York: McGraw-Hill Medical; 2009.
4. Joint Mental Health Advisory Team 7. Joint Mental Health Advisory Team 7 (J-MHAT-7) Report, Operation Enduring Freedom 2010, Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of The Surgeon General United States Army Medical Command and the Office of the Command Surgeon HQ, USCENTCOM and the Office of the Command Surgeon U.S. Forces Afghanistan. Published February 22, 2011. Accessed 9 Feb 2017.
5. Moore BA, Krakow B. Characteristics, effects, and treatment of sleep disorders in service members. In: Freeman SM, Moore BA, Freeman A, editors. Living and surviving in Harm's way: a psychological treatment handbook for pre- and post-deployment of military personnel. New York: Routledge; 2009. p. 281–306.
6. Peterson AL, Goodie JL, Satterfield WA, Brim WL. Sleep disturbance during military deployment. Mil Med. 2008;173(3):230–5.
7. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U. S. service members returning from military deployments. Mil Med. 2010;175(10):759–62.
8. Armed Forces Health Surveillance Center. Mental disorders and mental health problems, active component, U.S. Armed Forces, January 2000–December 2009. MSMR. 2010;17(11):6–13.
9. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7–S10.
10. Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. J Fam Pract. 2002;51(3):229–35.

11. Léger D, Guilleminault C, Bader G, Lévy E, Paillard M. Medical and socio-professional impact of insomnia. Sleep. 2002;25(6):621–5.
12. Léger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. Psychosom Med. 2001;63(1):49–55.
13. Satei MJ, Pigeon WR. Identification and management of insomnia. Med Clin North am. 2004;88(3):567–96.
14. Pilcher JJ, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. Sleep. 1996;19(4):318–26.
15. Tanskanen A, Tuomilehto J, Viinamaki H, Vartiainen E, Lehtonen J, Puska P. Nightmares as predictors of suicide. Sleep. 2001;24(7):845–8.
16. Ozminkowski R, Wang S, Walsh J. The direct and indirect costs of untreated insomnia in adults in the United States. Sleep. 2007;30(3):263–73.
17. Armed Forces Health Surveillance Center. Insomnia, active component, U.S. Armed Forces, January 2000–December 2009. MSMR. 2010;17(5):12–5.
18. Bray RM, Pemberton MR, Hourani LL, et al. 2008 Department of Defense survey of health related behaviors among active duty military personnel. Research Triangle Park: RTI International; 2009.
19. Mental Health Advisory Team IV. Mental Health Advisory Team IV (MHAT-IV) Report, Operation Iraqi Freedom 05–07. http://armymedicine.mil/Pages/Mental-Health-Advisory-Team-IV-Information.aspx. Report to the Office of the Surgeon Multinational Force-Iraq and the Office of The Surgeon General United States Army Medical Command. Published November 17, 2006. Accessed 9 Feb 2017.
20. Seelig AD, Jacobson IG, Smith B, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. Sleep. 2010;33(12):1615–22.
21. Mental Health Advisory Team V. Mental Health Advisory Team V (MHAT-V) Report, Operation Iraqi Freedom 06–08: Iraq; Operation Enduring Freedom 8: Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multi-National Force-Iraq and the Office of the Command Surgeon and the Office of The Surgeon General United States Army Medical Command. Published February 14, 2008. Accessed 9 Feb 2017.
22. Mental Health Advisory Team VI. Mental Health Advisory Team VI (MHAT-VI) Report, Operation Iraqi Freedom 07–09. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multi-National Corps-Iraq and the Office of The Surgeon General United States Army Medical Command. Published May 8, 2009. Accessed 9 Feb 2017.
23. Hung B. Behavioral health activity and workload in the Iraq theater of operations. US Army Med Dep J. 2008:39–42.
24. Belasco A; Congressional Research Service. The cost of Iraq, Afghanistan, and other Global War on Terror operations since 9/11. http://www.fas.org/sgp/crs/natsec/RL33110.pdf. Published March 29, 2011. Accessed 16 Jan 2012.
25. Armed Forces Health Surveillance Center. Associations between repeated deployments to OEF/OIF/OND, October 2001–December 2010, and post-deployment illnesses and injuries, active component, U.S. Armed Forces. MSMR. 2011;18(7):2–11.
26. Goff BSN, Crow JR, Reisbig AMJ, Hamilton S. The impact of individual trauma symptoms of deployed soldiers on relationship satisfaction. J Fam Psychol. 2007;21(3):433–353.
27. Engel CC, Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for Gulf War-related health concerns. Psychosom Med. 2000;62(6):739–45.
28. Hoge CW, Terhakopian A, Castro CA, Messer SC, Engel CC. Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. Am J Psychiatry. 2007;164(1):150–3.
29. Lewis V, Creamer M, Failla S. Is poor sleep in veterans a function of post-traumatic stress disorder? Mil Med. 2009;174(9):948–51.
30. Hryshko-Mullen A, Broeckl L, Haddock CK, Peterson AL. Behavioral treatment of insomnia: the Wilford Hall insomnia program. Mil Med. 2000;165(3):200–7.
31. Goodie JL, Isler WC, Hunter CL, Peterson AL. Using behavioral health consultants to treat insomnia in primary care: a clinical case series. J Clin Psychol. 2009;65(3):294–304.
32. Wesensten NJ, Belenky G, Balkin TJ. Sleep loss: implications for operational effectiveness and current solutions. In: Britt TW, Castro CA, Adler AB, editors. Military performance, Military Life: The Psychology of Serving in Peace and Combat, vol. 1. Westport: Praeger Security International; 2006. p. 81–107.
33. McGeary DD. Making sense of resilience. Mil Med. 2011;176(4):1–2.
34. Luthar SS, Cicchetti D, Becker B. The construct of resilience: a critical evaluation and guidelines for future work. Child Dev. 2000;71(3):543–62.
35. Casey GW Jr. Comprehensive soldier fitness: a vision for psychological resilience in the U.S Army. Am Psychol. 2011;66(1):77–81.
36. Meredith LS, Sherbourne CD, Gaillot S, et al. Promoting psychological resilience in the U.S. military. Santa Monica: Rand Corp; 2011.
37. Peterson AL, Cigrang JA, Isler W. Future directions: trauma, resilience, and recovery research. In: Freeman SM, Moore BA, Freeman A, editors. Living and surviving in harm's way: a psychological treatment handbook for pre- and post-deployment of military personnel, vol. 2009. New York: Routledge; 2009. p. 467–93.
38. Maguen S, Turcote DM, Peterson AL, et al. Description of risk and resilience factors among military medical personnel before deployment to Iraq. Mil Med. 2008;173(1):1–9.
39. King DW, King LA, Foy DW, Keane TM, Fairbank JA. Posttraumatic stress disorder in a national sample of female and male Vietnam veterans: risk factors, war-zone stressors, and resilience-recovery variables. J Abnorm Psychol. 1999;108(1):164–70.
40. Adler A. Information paper: Battlemind resilience training research accomplishments. U.S. Army Medical Department Web site: https://www.resilience.army.mil/about.html. Published May 19, 2009. n.d.. Accessed 5 Mar 2011.
41. Adler AB, Bliese PD, McGurk D, Hoge CW, Castro CA. Battlemind debriefing and Battlemind training in early interventions with soldiers returning from Iraq: randomization by platoon. J Consult Clin Psychol. 2009;77(5):928–40.
42. Resilience training. U.S. Army Medical Department Web site. https://www.resilience.army.mil. Accessed 13 Jan 2012.
43. Land BC. Current Department of Defense guidance for Total Force Fitness. Mil Med. 2010;175(8 Suppl):3–5.
44. Mullen M. On Total Force Fitness in war and peace. Mil Med. 2010;175(8 Suppl):1–2.
45. Roy TC, Springer BA, McNulty V, Butler NL. Physical fitness. Mil Med. 2010;175(Suppl 8):14–20.
46. Bates MJ, Bowles S, Hammermeister J, et al. Psychological fitness. Mil Med. 2010;175(8 suppl):21–38.
47. Bray RM, Spira JL, Olmsted KR, Hout JJ. Behavioral and occupational fitness. Mil Med. 2010;175(8 Suppl):39–56.
48. O'Connor FG, Deuster PA, DeGroot DW, White DW. Medical and environmental fitness. Mil Med. 2010;175(8 Suppl):57–64.
49. Montain SJ, Carvey CE, Stephens MB. Nutritional fitness. Mil Med. 2010;175(8 Suppl):65–72.
50. Hufford DJ, Fritts MJ, Rhodes JE. Spiritual fitness. Mil Med. 2010;175(8 Suppl):73–87.
51. Coulter I, Lester P, Yarvis J. Social fitness. Mil Med. 2010;175(8 Suppl):88–96.
52. Westphal RJ, Woodward KR. Family fitness. Mil Med. 2010;175(8 Suppl):97–102.

53. Parks R. Resilience program at Fort Hood changes name, no impact to services. Fort Hood Sentinel. April 28, 2011. http://www.forthoodsentinel.com/story.php?id=6472. Accessed 13 Jan 2012.
54. Walter JA, Coulter I, Hilton L, Adler AB, Bliese PD, Nicholas RA. Program evaluation of Total Force Fitness in the military. Mil Med. 2010;175(8 Suppl):103–9.
55. Cornum R, Matthews MD, Seligman MEP. Comprehensive soldier fitness: building resilience in a challenging institutional context. Am Psychol. 2011;66(1):77–81.
56. Lester PB, McBride S, Bliese PD, Adler AB. Bringing science to bear: an empirical assessment of the Comprehensive Soldier Fitness Program. Am Psychol. 2011;66(1):77–81.
57. Britt TW, Bliese PD. Testing the stress-buffering effects of self engagement among soldiers on a military operation. J Pers. 2003;71(2):245–65.
58. Maslow AH. A theory of human motivation. Psychol Rev. 1943;50(4):370–96.
59. Everson CA, Bergmann BM, Rechtschaffen A. Sleep deprivation in the rat: III. Total sleep deprivation. Sleep. 1989;12(1):13–21.
60. Martinsen EW. Physical activity in the prevention and treatment of anxiety and depression. Nord J Psychiatry. 2008;62(Suppl 47):25–9.
61. Taylor MK, Markham AE, Reis JP, et al. Physical fitness influences stress reactions to extreme military training. Mil Med. 2008;173(8):738–42.
62. Bonanno GA. Loss, trauma and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? Am Psychol. 2004;59(1):20–8.
63. Butler L, Koopman C, Azarow J, et al. Psychological predictors of resilience after the September 11, 2001 terrorist attacks. J Nerv Ment Dis. 2009;197(4):266–73.
64. Campbell-Sills L, Cohan SL, Stein MB. Relationship of resilience to personality, coping, and psychiatric symptoms in young adults. Behav Res Ther. 2006;44(4):585–99.
65. Tugade MM, Fredrickson BL, Barrett LF. Psychological resilience and positive emotional granularity: examining the benefits of positive emotions on coping and health. J Pers. 2004;72(6):1161–90.
66. Dickstein BD, McLean CP, Mintz J, et al. Unit cohesion and PTSD symptom severity in Air Force medical personnel. Mil Med. 2010;175(7):482–6.
67. Pietrzak RH, Johnson DC, Goldstein MB, et al. Psychosocial buffers of traumatic stress, depressive symptoms, and psychosocial difficulties in veterans of Operation Enduring Freedom and Iraqi Freedom: the role of resilience, unit support, and postdeployment social support. J Affect Disord. 2010;120(1–3):188–92.
68. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the Connor-Davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience. J Trauma Stress. 2007;20(6):1019–28.
69. Connor KM, Davidson JRT. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety. 2003;18(2):76–82.
70. Johnson DC, Polusny MA, Erbes CR, et al. Development and initial validation of the response to stressful experiences scale. Mil Med. 2011;176(2):161–9.

Sleep Disturbance During Military Deployment

6

Kristi E. Pruiksma and Alan L. Peterson

Some of the earliest historical reports from the military battlefield highlight the potential impact of combat stress on psychological and physical functioning [1]. Although historical reports specifically describing battle-related sleep problems are limited, it is believed that sleep disturbance in and around the military battlefield has been commonplace throughout history. For example, in battlefield settings where there is a risk of attack by the enemy at night, the need to remain vigilant while attempting to achieve some level of restorative sleep is likely to lead to intermittent and erratic sleep patterns. Oftentimes, identified military personnel are assigned to stand watch at night, while others are allowed to sleep. Presumably, those who had to stand watch on the night shift are at risk of sleep disturbance the following day as they attempt to sleep while daytime military operations are occurring. In addition, the pressure to remain awake and alert while standing watch is immense. Service members who fall asleep while standing watch endanger the entire military unit and face harsh punishment up to and including death by firing squad. It is rather easy to conceptualize how these pressures to sleep or remain awake at random times can lead to chronic sleep disturbance, sleep deprivation, and insomnia during sustained operations.

However, controlled research on sleep problems during military deployments has been limited. The vast majority of our knowledge about normal sleep, sleep disorders, and insomnia comes from studies conducted in civilian settings. A comprehensive review of the behavioral sleep medicine literature is beyond the scope of the current chapter. However, the leading model of insomnia [2] provides a basic framework from which to consider factors contributing to sleep disturbance during military deployment (also see Bramoweth and Germain [3] for a delineation of this model as it applies to insomnia in military personnel and veterans). This model outlines three primary factors contributing to sleep disruption and insomnia: predisposing factors, initiating factors, and perpetuating factors. Predisposing factors are factors that exist prior to deployment that can set the stage for sleep disruption during deployment such as family stressors, financial difficulties, elevated physiological arousal, family history, gender, genetics, and age. Precipitating factors are those situational stressors unique to the war zone and deployed setting. These factors will be reviewed in depth in this chapter. Perpetuating factors are those factors that maintain insomnia and sleep disturbance even after the removal of the initiating factors. These can include poor sleep behaviors and unhealthy beliefs about sleep.

Sleep Disturbance During Deployments to Iraq and Afghanistan

Considerable research has now been conducted to evaluate sleep disturbance during deployments in and around Afghanistan in support of Operation Enduring Freedom (OEF) as well as in and around Iraq as part of Operation Iraqi Freedom (OIF) and Operation New Dawn (OND). The first study to collect data to evaluate sleep disturbance during deployments was conducted by the senior author of this chapter (ALP) soon after September 11, 2001 during a deployment in support of Operation Enduring Freedom (OEF) [4]. The study evaluated self-reported symptoms of sleep disturbance and insomnia in a group of 156 US Air Force personnel deployed to an undisclosed location in support of OEF during October–November 2001. The military

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participants were deployed to establish a "tent city" air base to support flying operations throughout the OEF theater. Sleeping quarters consisted primarily of TEMPER (Tent, Extendable, Modular, Personnel) tents at a bare-base location. Daytime temperatures often exceeded 120 °F (49 °C), and the majority of the military construction projects occurred during nighttime hours. Most of the participants were male (83%), married (60%), and enlisted personnel (84%), and the mean age was 29.2 years.

Because there was not an available measure to assess sleep disturbance and insomnia during military deployments, the study investigator developed a Military Deployment Survey of Sleep to assess these factors. The survey was a 21-item self-report instrument empirically derived from questions used in previous sleep studies with additional questions specifically related to military deployment. Surveys were completed voluntarily and anonymously an average of 33 days after arrival at the deployed location.

The results indicated that the majority of participants (74%) rated their subjective sleep quality as significantly worse in the deployed setting than it was to prior to deployment. The average sleep efficiency was 83%, which is below the 85% threshold used for the classification of insomnia. Overall, about 40% of the participants had a sleep efficiency of less than 85%. Additionally, the average sleep onset latency was 32 min, which is greater than the 30-min threshold for insomnia, and about 40% of participants overall had a sleep onset latency of greater than 30 min. The average total sleep time was about 6.5 h, and almost 15% of participants had a total sleep time of less than 4.5 h. Approximately 25% of participants experienced a wakening after sleep onset or early morning awakening of greater than 30 min.

Data regarding sleep during deployment also have been collected through the Millennium Cohort Study, a large-scale, longitudinal study of health in service members [5]. Utilizing this data, Seelig et al. [6] (discussed further in Chap. 47 of this book) compared self-reported sleep among service members who had never been deployed, were currently deployed, or had returned from deployment. Deployed service members reported significantly shorter sleep duration and were more likely to report trouble sleeping than members who had never deployed, but they reported similar rates of sleep problems as those with previous deployments. The relationship between deployment and sleep difficulties was significantly mediated by exposure to combat and mental health symptoms such as post-traumatic stress disorder (PTSD), depression, anxiety, and panic symptoms.

Luxton et al. [7] also found a significant relationship between short sleep duration and mental health problems including suicide attempts, depression, PTSD, panic, and high-risk health behaviors such as tobacco and alcohol use among service members returning from deployment. Findings from these studies are consistent with Spielman's model of insomnia [2] and demonstrate both how sleep difficulties can be initiated by precipitating events (deployment, combat trauma exposure, etc.) and how they can persist after the precipitating event has ended due to perpetuating factors (e.g., development of poor sleep habits).

Taylor et al. [8] analyzed data from the Behavioral Needs Assessment Survey collected from 3175 US Navy personnel deployed to Afghanistan and had findings consistent with those noted above. They examined subjective sleep characteristics and relationships of sleep to mental health symptoms and found that participants reportedly obtained an average of 5.9 h of sleep per day despite requiring 6.8 h to feel rested, with 56% being classified as sleep deficient. They also found that disrupted sleep was associated with depression, PTSD, and generalized anxiety disorder.

Mental Health Advisory Team Reports

A considerable amount of the data on sleep disturbance and insomnia during deployments in support of OEF and OIF come from the Mental Health Advisory Team (MHAT) reports. Nine MHAT reports have been published between 2003 and 2013.

MHAT-I

The initial MHAT report [9] was chartered by the US Army Surgeon General in July 2003. Its mission was to assess mental health issues in US Army soldiers deployed to Iraq. The participants included 756 soldiers, 82% of whom had engaged in combat. A number of the participants were behavioral health providers who were surveyed on factors related to behavioral health practice in Iraq. The initial MHAT did not include any specific questions to assess sleep or insomnia in deployed participants. However, 33% of psychiatrists surveyed in 2003 indicated that additional sleeping medications would be helpful for treating patients in Iraq.

MHAT-II

Similar to the first MHAT report, the MHAT-II report [10] did not have any measures of sleep or insomnia. However, the MHAT-II did highlight the importance of getting adequate sleep. Specifically, the report stated, "Leaders should emphasize the importance of not scheduling additional duties during downtime and should assure that Soldiers get sufficient rest to maintain optimal cognitive acuity (generally 7–8 hours sleep per 24-hour period)" [10] (p. 20).

MHAT-III

The third MHAT (MHAT-III) report [11] was the first to ask specifically about sleep. The MHAT-III surveyed a total of 1124 soldiers at 13 forward operating bases in Iraq during OIF 04–06 deployment periods. The results indicated that 43 soldiers (3.8%) reported using sleep medications.

MHAT-IV

The fourth MHAT (MHAT-IV) report [12] assessed the mental health of deployed US service members from August to October 2006. The participants included both US Army soldiers (N = 1320) and marines (N = 447) during OIF 05–07 deployment periods. The surveys were anonymous and also included behavioral health, primary care, and unit ministry team surveys. Focus group interviews were also conducted with the participants. The MHAT-IV results indicated that 12% of soldiers and 5% of marines reported taking medication for a mental health, combat stress, or sleep problem during the deployment. However, the medications given for sleep were not separated from those given for mental health problems or combat stress. The behavioral health providers interviewed indicated that the sleep medications Lunesta, Ambien, Sonata, and Strattera were needed but not available during this deployment period.

MHAT-V

The fifth Mental Health Advisory Team (MHAT-V) report [13] was the first MHAT report to include assessments of US military personnel deployed to both theaters of operation in Iraq (OIF 06–08; N = 2295) and Afghanistan (OEF 8; N = 699). It was also the first MHAT report to have a major emphasis on sleep and included assessment measures of (1) sleep deprivation, (2) sleep and behavioral health problems, (3) sleep and performance, and (4) medications for sleep disturbance. It also provided a Soldier Combat and Well-Being Model and provided six recommendations for sleep management during deployments.

Sleep Deprivation

The MHAT-V survey [13] assessed sleep as a means to examine the relationships between sleep deprivation in the combat zone and reports of behavioral health and performance. For US soldiers deployed to Iraq in 2007, 32% reported high or very high concern that they were not getting enough sleep. For those deployed to Afghanistan in 2007, 34% reported concerns about not getting enough sleep. This was a statistically significant increase from the 21% of soldiers reporting similar concerns in Afghanistan during 2005. Soldiers deployed to OIF and OEF reported an average of 5.6 h of sleep per day. This was about an hour less than the 6.4 h of sleep that the soldiers reported that they thought they needed to feel well rested. Both of these values are less than the 7–8 h of sleep per night that has been recommended by the Walter Reed Army Institute of Research as being necessary to maintain optimal cognitive functioning [13] (Appendix F).

Sleep and Behavioral Health Problems

The MHAT-V [13] also assessed the relationship between sleep and behavioral health problems (see Fig. 6.1). The report noted that the relationship between these two factors is correlational, and it is not known whether sleep problems contribute to behavioral health problems or vice versa. The MHAT-V data indicated that, for enlisted male soldiers (E-1 to E-4) who reported no problems with sleep deprivation, only about 12% endorsed symptoms of depression, anxiety, or acute stress. However, for those soldiers who reported 2 h of sleep deprivation, about twice as many (23%) endorsed symptoms of depression, anxiety, or acute stress.

Sleep and Performance

The MHAT-V [13] also assessed the impact of stress and emotional problems on work performance (accidents and making mistakes) as a function of sleep deprivation. Six percent of soldiers deployed to OEF reported they had an accident or made mistakes during the deployment due to sleepiness. Almost 25% of OEF soldiers reported falling

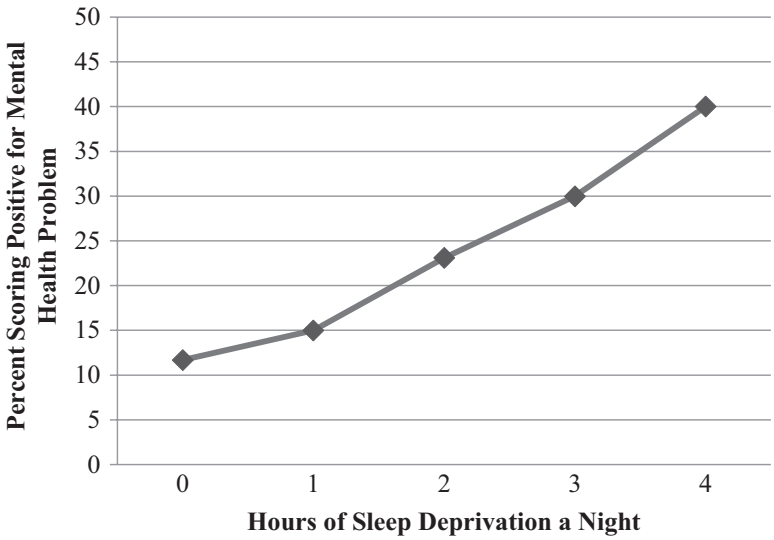

Fig. 6.1 Adjusted percent for male E1–E4 soldiers in theater for 9 months (Reprinted with permission from the Mental Health Advisory Team V [13])

asleep during convoys. Interestingly, the results were different for officers and enlisted personnel. Junior enlisted personnel who reported sleep deprivation also reported increases in sleep-related mistakes and accidents. However, sleep-deprived officers reported a slight decrease in reported accidents and mistakes. The MHAT-V authors interpreted this finding to suggest that officers may underestimate the degree to which sleep deprivation is associated with performance declines.

Medications for Sleep Disturbance

Approximately 16% of soldiers deployed to Iraq during the time of the MHAT-V survey and 17% of those deployed to Afghanistan reported taking mental health medications, and about half of these medications were for sleep [13]. Primary care providers surveyed as part of MHAT-V (N = 135) reported significant increases in the number of medications prescribed for sleep, depression, and anxiety relative to the MHAT-IV. About half (52%) of MHAT-V primary care providers indicated that they prescribed medications for sleep problems on a weekly basis, as compared to 30% surveyed as part of MHAT-IV ($P < 0.001$). The MHAT-V authors hypothesize that this increase may be related to two factors. First, multiple deployments and an increased length of deployments may have contributed to more soldiers seeking care for sleep problems. Second, the Army Medical Department developed and disseminated the "Respect.Mil" program in an attempt to improve primary care providers' ability to identify and treat behavioral health problems with medications. The dissemination of programs like Respect.Mil in the US Army may have allowed deployed primary care providers to be more comfortable with treating sleep and behavioral health problems. It should be noted that the integration of behavioral health providers into military primary care settings for the treatment of insomnia and other behavioral health problems has been used for the past decade as a means to help overcome the stigma of specialty mental health treatment [14–16].

A Model for Soldier Combat and Well-Being

The MHAT-V report [13] provided a Soldier Combat and Well-Being Model that includes sleep disturbance as one of the major risk factors for negatively impacting behavioral health and performance (see Fig. 6.2). This model was adapted from a model previously published by Bliese and Castro [17]. The model assumes that the behavioral health and performance of soldiers is influenced by both environmental factors (e.g., trauma exposure) and individual-level risk factors (e.g., sleep quality). The model includes (1) risk factors (e.g., combat exposure, deployment experiences, etc.), (2) protective factors (e.g., training, willingness to seek care, etc.), and (3) behavioral health status and performance indices.

MHAT-V Recommendations for Sleep Management

The MHAT-V report highlights that sleep problems and sleep deprivation are manageable risk factors [13]. As such, the report includes specific recommendations for sleep management, and Appendix F of the MHAT-V report outlines the Combined Arms Doctrine Directorate on Sleep Management written by the Walter Reed Army Institute of Research. Topics covered in the Sleep Management Doctrine include sleep deprivation, sleeping in the operational environment, maintaining performance during sustained or continuous operations, caffeine countermeasures, work schedules, night shift work, time zone travel, specific sleep loss effects, determining sleep loss in the operational environment, and common misconceptions about sleep and sleep loss. The MHAT-V report provides six specific recommendations for sleep management [13] (pp. 101–102):

1. Sleep recommendation: Ensure leaders at all levels develop and monitor work cycle programs that provide adequate sleep time based on the Combined Arms Doctrine Directorate (CADD) on sleep management.
2. Sleep recommendation: Ensure leaders at all levels encourage soldiers to seek treatment for sleep problems.
3. Sleep recommendation: Ensure officers know that sleep deprivation is cumulative and that their cognitive performance is highly susceptible to the effects of sleep deprivation. Finally, while much is known about sleep, there are also large gaps in research. Three areas that continue to be important from a research perspective are:
4. Sleep recommendation: Conduct research on the role of sleep and sleep problems in behavioral health problems such as acute stress and PTSD.
5. Sleep recommendation: Conduct research on ways to unobtrusively monitor sleep and provide performance estimates for individuals and groups.
6. Sleep recommendation: Investigate the efficacy of sleep aids as well as agents that might be used to safely maintain performance under short-term periods of sleep deprivation.

MHAT-VI

The MHAT-VI reports of OIF [18] and OEF [19] followed a format similar to MHAT-V, with the goals of assessing soldier behavioral health, examining behavioral health care delivery in OIF and OEF, and providing further recommendations for sustainment and improvement to command leadership. The MHAT-VI reports included a few notable changes from previous reports. First, platoons were randomly selected for data collection. Second, the assessments were conducted with two distinct samples: maneuver units and support and sustainment units. These distinct units might also be described as combatants versus noncombatants [20]. Third, the MHAT-VI reports examined trends

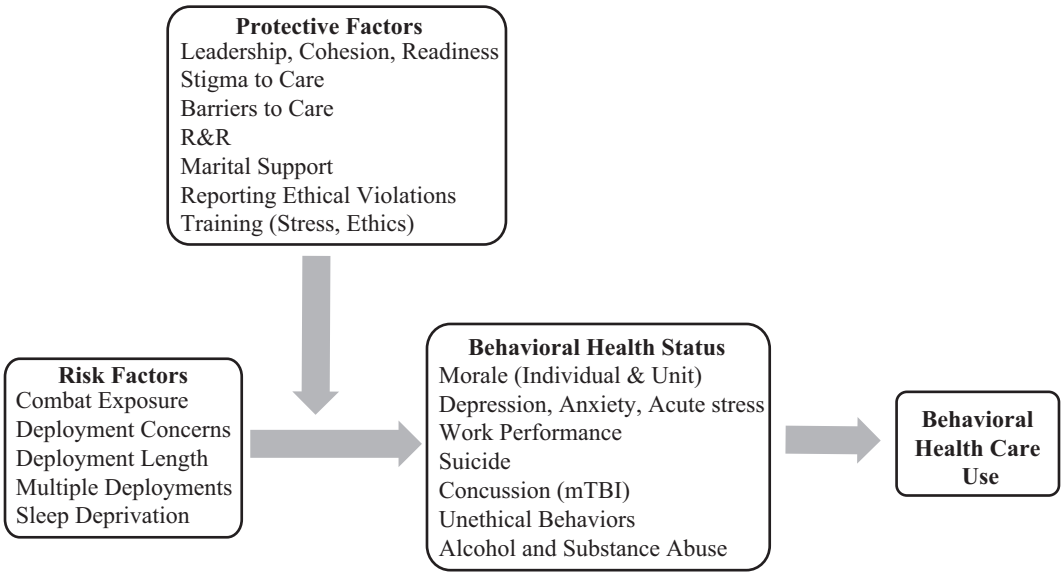

Fig. 6.2 Soldier Combat and Well-Being Model. Model in the Mental Health Advisory Team V Report [13] adapted from original publication by P. B. Bliese and C. A. Castro [17] (Reprinted with permission from the MHAT-V and Praeger Publishers)

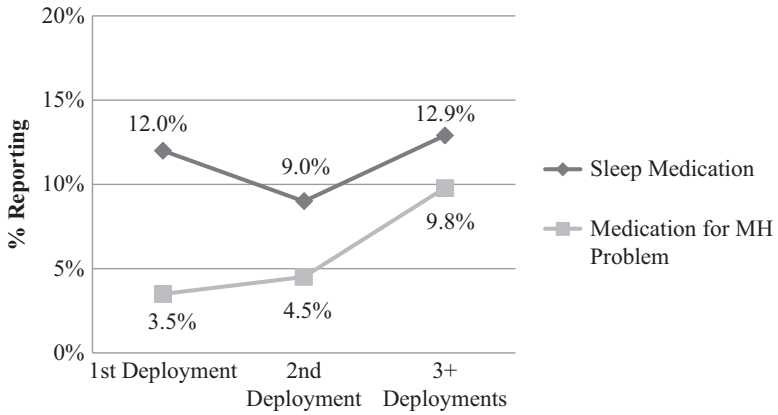

Fig. 6.3 Multiple deployments and medication use (Reprinted with permission from the Mental Health Advisory Team IV [12])

across the previous MHAT reports. However, as noted previously, the early MHAT reports included little data specifically about sleep. However, the degree to which the sleep management recommendations were implemented from MHAT-V to MHAT-VI was included. In addition, the MHAT-VI reports were the first to assess sleep medication use separate from medication use for a mental health or combat stress problem.

A total of 1260 soldiers from maneuver platoons and 1182 soldiers from support or sustainment platoons completed surveys in OIF (December 2008–March 2009) [18]. In OEF (April 2009–June 2009), 638 soldiers from maneuver platoons and 744 soldiers from support or sustainment platoons completed surveys [19]. Behavioral health providers also completed surveys, and focus groups were also conducted.

Medication Use

During deployments, substantially more soldiers report taking medications for sleep than for behavioral health conditions such as depression, anxiety, and acute stress. Specifically, in the OEF population, 9.2% of maneuver platoons and 13.5% of support and sustainment platoons reported sleep medication use compared to rates of 2.9% and 6.4% for behavioral health medication use [19]. Rates in the OIF population were similar, with 8.1% of maneuver platoons and 13.5% of support and sustainment platoons reporting sleep medication use compared to rates of 4.8% and 5.1% for behavioral health medication use [18]. In contrast to behavioral health medication use, rates of sleep medication use did not tend to increase with the number of deployments (see Fig. 6.3). Rates essentially started high and remained high, whereas rates for behavioral health dramatically increased at the third deployment and beyond.

Rates of medication use also appear to differ by platoon type, with support and sustainment platoons reporting significantly higher rates of sleep medication use than the maneuver platoon (13.5% vs. 8.1%) [18]. This difference was found after controlling for rank, time in theater, and gender. Both the support and sustainment platoons reported lower rates than civilian samples of young adults. For example, Johnson and colleagues [21] found that 24.7% of male individuals in the 1996 Detroit Area Survey reported taking prescription sleep aids in the previous year.

It is unclear if the differential rates between sleep medication use and other behavioral health medication use reported here are associated with limited medication availability. In Afghanistan, 73% of providers with prescriptive privileges reported inadequate psychiatric medication availability, and 90% reported that procedures for ordering prescriptions were unclear [19]. The report does not specify if medications specifically for sleep are more readily available than medications used for other conditions such as depression or anxiety.

Sleep and Deployment Concerns

Soldiers were asked about noncombat-related concerns regarding deployment, including not getting enough sleep. Across the MHAT reports conducted from 2005 to 2009, the percentage of service members reporting a concern about sleep deprivation ranged from 23.4 to 35.9% [19]. Sleep deprivation was less of a concern relative to other items such as deployment length, lack of privacy or personal space, lack of time off for personal time, and boring or repetitive work. Although the percentage of service members reporting concern about sleep deprivation did not necessarily increase over time, the rank order of the sleep item tended to rise from the 9th top concern to the 6th top concern. The reason for this is unclear but could possibly be related to increased awareness about the importance of sleep or wear over time as a large number of soldiers experience multiple deployments. Furthermore, when OEF soldiers included in the MHAT-VI were asked to rate the intensity of their concerns (from 1, "very low trouble or concern," to 5, "very high trouble or concern") for the same items, not getting enough sleep was the highest-rated concern for maneuver units but not for support units. This data suggested that for those soldiers who endorsed sleep deprivation as a concern, they rated this concern very highly.

Sleep Management Recommendations

As previously noted, the MHAT-V recognized the important role of sleep in military operations in the deployed setting and included six recommendations to address sleep management for both OEF and OIF soldiers [13] (pp. 101–102). MHAT-VI found that the recommendations were largely in the process of being implemented [18]. Specifically, the Combined Arms Doctrine Directorate on Sleep Management was incorporated into leadership courses to ensure that leaders allow adequate sleep time in work cycles. Sleep management information was also incorporated into the senior leader Battlemind training to inform leaders of the cumulative effects of sleep deprivation on cognitive performance and to encourage soldiers to seek treatment for sleep problems. Evidence suggested that Battlemind training administered post-deployment effectively reduced sleep problems [22]. However, the extent to which leaders implemented sleep-related information during deployment was unclear. The MHAT-VI report [18] also highlighted that funding through the US Army Medical Research and Material Command (MRMC) was provided for research in the following areas recommended by MHAT-V: (1) the role of sleep in behavioral health problems, (2) methods for unobtrusively monitoring sleep and performance estimates, and (3) the efficacy of sleep aids and agents used to maintain performance under sleep deprivation.

Joint-MHAT-7

The previous MHAT reports (MHAT-I through MHAT-VI) were supported by the Office of the Surgeon General of the Army. The Joint MHAT-7 report [23] was also supported by the Office of the Surgeon General of the Army, with additional support from the offices of the Surgeons' General of the Navy and Air Force and the Office of the Medical Officer of the Marine Corp. As a result, J-MHAT-7 includes samples of Air Force and Navy personnel and a larger sample of marines than the previous reports. In all, 911 soldiers in the Army maneuver unit platoons completed the survey, as did 335 marines. The J-MHAT-7 report did not indicate the number of Air Force and Navy personnel surveyed. Similar to MHAT-VI, survey data was collected from a cluster sample of randomly selected platoons. J-MHAT-7 further expanded data available regarding sleep during deployment by including items about caffeine use and factors related to sleep disruption.

Medication Use and Energy Drinks

Rates of medication use in the J-MHAT-7 report [23] largely replicated rates found in previous MHAT reports. Forty-five percent of providers identified sleep aids as the most commonly prescribed medications. It was also found that 60% of the sample who took sleep medications also drank at least one energy drink per day, compared to just 43% of the sample who were not taking sleep medications. This difference was statistically significant. Data collected from J-MHAT-7 was further analyzed by the Centers for Disease Control and Prevention [24], which found that 44.7% of service members consumed at least one energy drink per day. Service members who drank three or more energy drinks per day were also more likely to report sleeping less than 4 h per day, sleep

disruption due to stress and illness, and falling asleep during briefings or on guard duty. Although a direction of causality could not be determined (i.e., do sleep problems result in caffeine use or vice versa), it is likely that for some service members, regular caffeine use to promote alertness serves as a perpetuating factor that can contribute to continued sleep difficulties after deployment. The finding that service members who take sleep medications also rely on energy drinks during the day also suggests that sleep medications may not be providing an adequate amount of sleep, resulting in increased daytime sleepiness.

Sleep and Deployment Concerns

In the marine sample collected for the J-MHAT-7, concerns about sleep significantly increased compared to previous MHAT reports [23]. Specifically, 37.7% reported concern about not getting enough sleep during deployment compared to 25.4% in the MHAT-IV and 22.0% in the MHAT-V. Difficulties communicating back home and concern about continuous operations were the only other items to show a significant increase. The reasons for these increases are unclear. One possibility is that service members were being provided with more education regarding sleep, which may have resulted in more concern about sleep. Whether this concern translated into steps to improve sleep hygiene is unknown.

Factors Impacting Sleep

In the marine sample, 61.2% reported experiencing sleep disruption at least half of the time in the previous month, and 46.7% attributed this to environmental factors [23]. Soldiers and marines who reported this level of sleep disruption were queried about the frequency that several factors impacted sleep (see Fig. 6.4). In both samples, the primary factors were nighttime duties (29.5% of soldiers and 47.4% of marines) and poor sleep environment (33.1% of soldiers and 46.7 of marines). In a focus group, one behavioral health provider commented, "In a lot of cases you find that day and night workers are mixed in the same tent. Mixing these shifts can disrupt sleep for anyone, but primarily for light sleepers" [23] (p. 79). The surge also likely exacerbated the impact of poor sleep environment on sleep difficulties. One service member described this issue stating, "You want to throw 20 people into a 10 man tent and have us live like that for the past 9 months....REALLY?" [23] (p. 23).

Sleep Management Recommendations

Based on the finding that service members with sleep difficulties also had higher rates of energy drink consumption, the committee suggested considering the "merits of freely accessible energy drinks" in the deployed setting [23]. The US Army Research Institute of Environmental Medicine is currently conducting a survey of caffeine use in theater. The committee also recommended that sleep hygiene training be incorporated in pre-deployment training with an emphasis on instructing leaders to implement procedures to improve sleep hygiene based on unique circumstances for that unit. Thus, effective implementation of procedures to improve sleep continued to be identified as a concern for military personnel in the deployed setting.

Joint-MHAT-8

Similar to Joint-MHAT-7, the Joint-MHAT-8 report [25] was supported by the Office of the Surgeons' General of the Army, Navy, and Air Force along with the Office of the Medical Officer of the Marine Corps. In addition, the Joint-MHAT-8 was supported by the US Joint Staff Surgeon, the Office of the Command Surgeon, the US Army Central Command (USCENTCOM), and the Office of the Surgeon General, US Forces Afghanistan (USFOR-A). To ensure comparability across years, the Joint-MHAT-8 utilized similar cluster sampling of randomly selected maneuver unit platoons. A total of 619 surveys completed by soldiers and 212 surveys completed by marines were included in the analyses. Continuing the trend from previous MHAT reports, additional items assessing sleep were included in Joint-MHAT-8 to specifically assess leadership and sleep.

Overall, sleep-related findings in J-MHAT-8 were consistent with J-MHAT-7. The most notable changes were a decrease in medication use for sleep in the Army sample (6.4% in J-MHAT-8 vs 11.3% in J-MHAT-7). This was not the case for the marines, who reported a slight increase in sleep medication use (11.2% in J-MHAT-8 vs 7.1% in J-MHAT-7). There was also a significant decrease in nighttime duties being a frequent reason for sleep problems for the marine sample (30% in J-MHAT-8 vs 49% for J-MHAT-7) but not the Army sample (37% in J-MHAT-8 vs 31% for J-MHAT-7). The reasons for these changes are unknown but may be due to military branch-specific deployed operational duty requirements.

Leadership and Sleep

J-MHAT-8 was the first to include items to assess support of helpful sleep habits from noncommissioned officers (NCOs). Soldiers and marines endorsed the following items at a frequency level of "sometimes, often, or always," respectively: "encourage extra sleep before missions" (62% and 63%), "consider sleep an important planning factor" (56% and 49%), "encourage service members to get to sleep on time" (50% and 35%), "ensure service members have a good sleeping environment" (47% and 33%), "support appropriate use of prescription sleep meds" (25% and 18%), and "ask service members about their sleeping habits" (25% and 13%). Interestingly, sleep leadership was significantly associated with perceived combat readiness as evidenced by endorsement of the following statements: "I think my platoon would

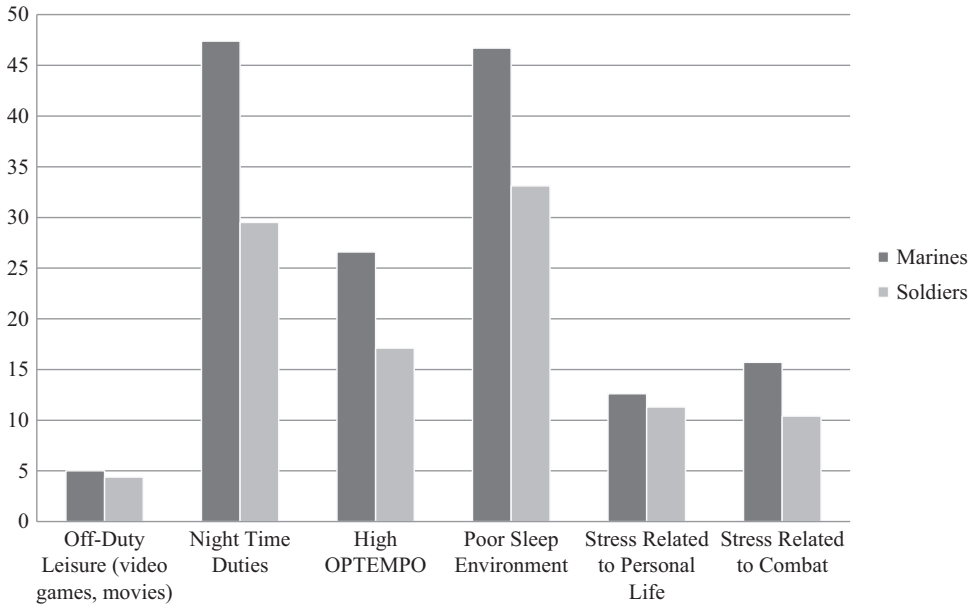

Fig. 6.4 Sleep problems during the last month: "How Often Have the Following Interfered with Your Sleep?" (Adapted and reprinted with permission from the Joint Mental Health Advisory Team 7 [23])

do/did an excellent job in combat"; "I think the level of training in my platoon is high"; and "I have real confidence in my platoon's ability to perform its mission." When leaders encouraged service members to get extra sleep before missions or considered sleep an important planning factor, soldiers' and marines' reports of combat readiness were significantly higher.

Recommendations

Based on its findings, the J-MHAT-8 gave the following recommendations related to sleep: "Incorporate sleep hygiene discipline into pre-deployment training. Emphasize that small unit leaders are responsible for implementing sleep discipline and mitigating factors that lead to poor sleep environments" [25] (p. 6).

MHAT-9

MHAT-9 for OEF [26] was directed by the Chief of Staff of the Army and, unlike the previous Joint MHAT reports, included only soldiers in the Army with a specific emphasis on small unit officer leadership. A total of 849 surveys collected from 39 maneuver platoons were included in the analyses.

Compared to the previous reports, the sleep-related findings for MHAT-9 were similar to those found in previous reports with regard to factors that impact sleep (e.g., nighttime duties, poor sleep environment, high OPTEMPO, etc.); behavioral health, accidents, and mistakes; and medications. There was a slight decrease in the percent of soldiers reporting significant concerns about sleep, with 27% endorsing this concern for MHAT-9 compared to 34% in J-MHAT-8.

Recommendations

As a result of these findings, the MHAT-9 team included the following three recommendations related to sleep, which are consistent with previous recommendations in other MHAT reports: "Continue efforts to educate leaders on importance of sleep and enforcing sleep standards; require leaders to become familiar with FM 6-22.5, Combat and Operational Stress Control Manual for Leaders and Soldiers, which provides guidance on sleep; hold leaders accountable for the sleep environment in their command" [26] (p. 6).

Summary

Sleep problems are a common event during military deployment and are significant concerns for service members as well as their military leaders. The primary initiating factors for sleep disturbance appear to be deployment-related environmental factors such as loud noises, uncomfortable sleeping conditions, variable sleep schedules, and exposure to combat trauma. Service members deployed to OIF and OEF reported an average of about 5.5 h of sleep per night [13]. This was about an hour less than the amount of sleep that the service members reported that they thought they needed and 1.5–2.5 h less than the 7–8 h of sleep per night recommended by the Walter Reed Army Institute of Research [13] (Appendix F). However, a limitation of this report is that it fails to highlight the individual differences that exist in normal sleep duration. In the most comprehensive epidemiological study of normal sleep conducted to date, Lichstein and colleagues [27] found that there is a normal distribution of sleep duration. Additionally, negative health consequences

have been reported in both short and long sleepers [28]. Although 7–8 h of sleep may be optimal for a large percentage of the population, there is also a sizeable proportion who can function quite adequately with less sleep, and there are some who require considerably more than 7–8 h.

A noteworthy percentage of US military service members deployed to Iraq and Afghanistan have been prescribed sleep medications. In the OEF population, 9.2% of maneuver platoons and 13.5% of support and sustainment platoons reported using sleep medications. Rates in the OIF population were similar, with 8.1% of maneuver platoons and 13.5% of support platoons using these medications [18]. It is interesting to note that in both the OEF and OIF populations, sleep medication use was found to be higher in the noncombatant units (support and sustainment platoons) than in the combatant units (maneuver platoons) [18]. These differences were found even after controlling for rank, time in theater, and gender. It is interesting to note that previous studies have found that deployed noncombatant personnel may also be at greater risk of developing PTSD [29, 30]. Previous research has also suggested that differences in these groups may be due to the fact that noncombatants do not receive the same level of training and mental preparation for exposure to combat-related traumatic events [20].

A primary limitation of the use of sleep medications is the potential for side effects (e.g., grogginess, slowed cognitive processing, slowed reaction time), which may have major implications for military personnel, especially during deployments that may require individuals to awaken quickly and respond immediately to an ambush, mortar or rocket attack, or other emergency situation. Efforts to minimize sleep disturbance and insomnia during deployment using behavioral approaches continue to be developed. However, the extent to which these efforts are feasible and effective in a deployed setting is yet to be examined.

A number of recommendations to improve sleep management were made in MHAT-VI [19]. Although the J-MHAT-7 report [23] suggested that the previous sleep recommendations were largely in the process of being implemented, some research suggests otherwise. For example, one study of military officers who had recently returned from deployment ($N = 49$) found that 80% were not briefed on sleep management [31]. Furthermore, 73.9% reported that their unit never or rarely encouraged and monitored naps; 66.7% reported that their unit never or rarely designated dark and quiet areas for rest; 50% reported that their unit never or rarely enforced sleep schedules; and 36.4% reported that their unit never or rarely worked in shifts. In addition, the feasibility of the Combined Arms Doctrine Directorate Sleep Management training is unclear. For instance, the training states, "Soldiers require 7 to 8 hours of good quality sleep every 24-hour period to sustain operational readiness" [13] (p. 130). Obtaining this duration of sleep may not be feasible at some forward operating bases and combat outposts.

Efforts to improve sleep among military personnel serving in deployed locations may result in improvements in the short term (e.g., work performance, cognitive functioning) and also in the long term. Evidence indicates that sleep difficulties reported by service members are also associated with the development of mental health difficulties such as PTSD and depression [32, 33]. Additional research is needed to further expand the current knowledge base on sleep disturbance during military deployment. As highlighted by the MHAT-V report [13], research is needed on (1) how sleep and sleep problems may contribute to psychological health problems such as acute stress and PTSD, (2) new approaches for the unobtrusive monitoring of sleep during deployments, and (3) the efficacy of behavioral and pharmacological approaches to sleep management in deployed settings. There are a number of uncontrolled case reports of successful use of a variety of approaches to treat sleep problems in deployed settings, including biofeedback for insomnia [34], imagery rehearsal therapy for nightmares [35], and prazosin for nightmares [36]. However, large-scale, prospective clinical trials are needed to evaluate the use of both behavioral and medication treatments for sleep disturbance in deployed settings.

References

1. Ritchie EC, Ivany CG. Combat and operational behavioral health: an update to an old history. In: Ritchie EC, Bradley JC, Grammer GG, et al., editors. Combat and operational mental health. San Antonio: The Borden Institute; 2011. p. 3–7.
2. Bramoweth AD, Germain A. Deployment-related insomnia in military personnel and veterans. Curr Psychiatry Rep. 2013;15(10):1–8.
3. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am. 1987;10(4):541–53.
4. Peterson AL, Goodie JL, Satterfield W, Brim W. Sleep disturbance during military deployment. Mil Med. 2008;173(3):230–5.
5. Ryan MA, Smith TC, Smith B, for the Millennium Cohort Study Team, et al. Millennium cohort: enrollment begins a 21-year contribution to understanding the impact of military service. J Clin Epidemiol. 2007;60(2):181–91.
6. Seelig AD, Jacobson IG, Smith B, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. Sleep. 2010;33(12):1615–22.
7. Luxton DD, Greenburg D, Ryan J, Niven A, Wheeler G, Mysliwiec V. Prevalence and impact of short sleep duration in redeployed OIF soldiers. Sleep. 2011;34(9):1189–95.
8. Taylor MK, Hilton SM, Campbell JS, Beckerley SE, Shobe KK, Drummond SP. Prevalence and mental health correlates of sleep disruption among military members serving in a combat zone. Mil Med. 2014;179(7):744–51.
9. Mental Health Advisory Team. Mental Health Advisory Team (MHAT) Report, Operation Iraqi Freedom (OIF). http://armymedicine.mil/Pages/Reports.aspx. Report to the U.S. Army Surgeon General & HQDA G-1. Published December 16, 2003. Accessed 3 Nov 2016.
10. Mental Health Advisory Team II. Mental Health Advisory Team II (MHAT-II) Report, Operation Iraqi Freedom (OIF-II). http://armymedicine.mil/Pages/Reports.aspx. Report to The U. S. Army Surgeon General. Published January 30, 2005. Accessed 3 Nov 2016.

11. Mental Health Advisory Team III. Mental Health Advisory Team III (MHAT-III) Report, Operation Iraqi Freedom 04–06. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multinational Force-Iraq and the Office of The Surgeon General United States Army Medical Command. Published May 29, 2006. Accessed 3 Nov 2016.
12. Mental Health Advisory Team IV. Mental Health Advisory Team IV (MHAT-IV) Report, Operation Iraqi Freedom 05–07. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multinational Force-Iraq and the Office of The Surgeon General United States Army Medical Command. Published November 17, 2006. Accessed 3 Nov 2016.
13. Mental Health Advisory Team V. Mental Health Advisory Team V (MHAT-V) Report, Operation Iraqi Freedom 06–08: Iraq; Operation Enduring Freedom 8: Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multi-National Force-Iraq and the Office of the Command Surgeon and the Office of The Surgeon General United States Army Medical Command. Published February 14, 2008. Accessed 3 Nov 2016.
14. Goodie JL, Isler WC, Hunter CL, Peterson AL. Using behavioral health consultants to treat insomnia in primary care: a clinical case series. J Clin Psychol. 2009;65(3):294–304.
15. Hunter CL, Peterson AL. Primary care psychology training at Wilford Hall Medical Center. Behav Ther. 2001;24(10):220–2.
16. Isler WC, Peterson AL, Isler D. Behavioral treatment of insomnia in primary care settings. In: James L, Folen R, editors. The primary care consultant: the next frontier for psychologists in hospitals and clinics. Washington, DC: American Psychological Association; 2005. p. 121–51.
17. Bliese PB, Castro CA. The Solider Adaptation Model (SAM): applications to peacekeeping research. In: Britt TW, Adler AB, editors. The psychology of the peacekeeper: lessons from the field. Westport: Praeger; 2003. p. 185–204.
18. Mental Health Advisory Team VI. Mental Health Advisory Team VI (MHAT-VI) Report, Operation Iraqi Freedom 07–09. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Surgeon Multi-National Corps-Iraq and the Office of The Surgeon General United States Army Medical Command. Published May 8, 2009. Accessed 3 Nov 2016.
19. Mental Health Advisory Team VI. Mental Health Advisory Team VI (MHAT-VI) Report, Operation Enduring Freedom 2009, Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of the Command Surgeon U.S. Forces Afghanistan and the Office of The Surgeon General United States Army Medical Command. Published November 6, 2009. Accessed 3 Nov 2016.
20. Peterson AL, Wong V, Haynes M, Bush A, Schillerstrom JE. Documented combat-related mental health problems in military noncombatants. J Trauma Stress. 2010;23(6):674–81.
21. Johnson EO, Roehrs T, Roth T, Breslau N. Epidemiology of alcohol and medication as aids to sleep in early adulthood. Sleep. 1998;21(2):178–86.
22. Adler AB, Bliese PD, McGurk D, Hoge CW, Castro CA. Battlemind debriefing and battlemind training as early interventions with soldiers returning from Iraq: randomization by platoon. J Consult Clin Psychol. 2009;77(5):928–40.
23. Joint Mental Health Advisory Team 7. Joint Mental Health Advisory Team 7 (J-MHAT-7) Report, Operation Enduring Freedom 2010, Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of The Surgeon General United States Army Medical Command and the Office of the Command Surgeon HQ, USCENTCOM and the Office of the Command Surgeon U.S. Forces Afghanistan. Published February 22, 2011. Accessed 3 Nov 2016.
24. Centers for Disease Control and Prevention. Energy drink consumption and its association with sleep problems among U.S. service members on a combat deployment – Afghanistan, 2010. MMWR. 2012;61(44):895.
25. Joint Mental Health Advisory Team 8. Joint Mental Health Advisory Team 8 (J-MHAT-8) Report, Operation Enduring Freedom 2012, Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of The Surgeon General United States Army Medical Command and Office of the Command Surgeon, Headquarters, US Army Central Command (USCENTCOM), and Office of the Surgeon General, US Forces Afghanistan (USFOR-A). Published August 12, 2013. Accessed 3 Nov 2016.
26. Mental Health Advisory Team 9. Mental Health Advisory Team 9 (MHAT-9) Report, Operation Enduring Freedom (OEF) 2013, Afghanistan. http://armymedicine.mil/Pages/Reports.aspx. Report to the Office of The Surgeon General United States Army Medical Command and Office of the Command Surgeon, Headquarters, US Army Central Command (USCENTCOM), and Office of the Surgeon General, US Forces Afghanistan (USFOR-A). Published October 10, 2013. Accessed 3 Nov 2016.
27. Lichstein KL, Durrence HH, Riedel BW, Taylor DJ, Bush AJ. Epidemiology of sleep: age, gender, and ethnicity. Mahwah: Erlbaum; 2004.
28. Knutson KL, Turek FW. The U-shaped association between sleep and health: the 2 peaks do not mean the same thing. Sleep. 2006;29(7):878–9.
29. Martin CB. Routine screening and referrals for PTSD after returning from Operation Iraqi Freedom in 2005,US Armed Forces. MSMR. 2007;14(6):2–7.
30. Smith TC, Ryan MA, Wingard DL, Slyman DJ, Sallis JF, Kritz-Silverstein D. New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: prospective populations based US military cohort study. BMJ. 2008. 2008;336(7640):366–71.
31. Miller NL, Shattuck LG, Matsangas P. Sleep and fatigue issues in continuous operations: a survey of U.S. Army officers. Behav Sleep med. 2011;9(1):53–65.
32. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. Mil Med. 2010;175(10):759–62.
33. Picchioni D, Cabrera OA, McGurk D, et al. Sleep symptoms as a partial mediator between combat stressors and other mental health symptoms in Iraq war veterans. Mil Psychol. 2010;22(3):340–55.
34. McLay RN, Spira JL. Use of a portable biofeedback device to improve insomnia in a combat zone, a case report. Appl Psychophysiol Biofeedback. 2009;34(4):319–21.
35. Moore BA, Krakow B. Imagery rehearsal therapy for acute posttraumatic nightmares among combat soldiers in Iraq. Am J Psychiatry. 2007;164(4):683–4.
36. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. J Trauma Stress. 2010;23(5):645–8.

Sleep and Fatigue Issues in Military Operations

7

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Introduction

Sleep is unquestionably a critical commodity for humans, yet research indicates a growing sleep debt prevalent in many segments of society. Performance and health have been shown to be profoundly affected by lack of sleep; we ignore the need for sleep at our peril. Research conducted at the Naval Postgraduate School over the past two decades has demonstrated that members of our military service are chronically sleep deprived. Many of them have insufficient opportunities to sleep due to long work hours and operational commitments. Travel across time zones with its resultant jetlag is common. In addition, because of the 24/7 nature of the military mission, opportunities for sleep often occur during circadian-misaligned time periods. Military sleeping conditions are less than ideal, further exacerbating a chronic sleep debt.

This chapter focuses on the unique challenges of obtaining adequate sleep in military settings and the consequent effects on performance and health. We first provide an overall background on normal sleep and general requirements for sleep in humans. We then examine the relationship between insufficient sleep, circadian misalignment, fatigue, and human performance. We present recent studies of sleep in military personnel in operational settings. These studies assess the nature and extent of sleep issues in those populations, examine the factors that cause sleep problems, and address the somewhat unique challenges of sleeping in military operational environments. In the last section, we provide a brief overview of fatigue countermeasures and alertness aids that are currently used in the military.

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Normal Sleep

Sleep is a biological imperative [61], a vital requirement for life. Horne defined sleep as "the rest and recovery from the wear and tear of wakefulness" [36]. A consensus report of sleep experts suggests that adults should sleep on average 7 or more hours per night on a regular basis to promote optimal health [78]. However, young adults, individuals recovering from sleep debt, and individuals with illnesses may require more sleep – even 9 or more hours per night. The propensity to sleep is modulated by two processes: the homeostatic and the circadian (*circa*, about; *dies*, day) processes [12]. The homeostatic process increases the need for sleep according to prior wakefulness. In contrast, the circadian process modulates the human sleep and wakefulness behavior in an approximately 24.50-h to 25-h sinusoidal pattern [36, 42]. The phase of the circadian clock can be slowly aligned with the external environment by the individual's behavioral patterns like mealtimes, daytime sounds, and environmental light [19].

When humans receive an adequate amount of quality sleep at the right time of the day, sleep is considered sufficient and the individual feels well-rested [11, 23]. If any of the three factors associated with recuperative sleep (i.e., timing, duration, and quality) are not met, however, the individual does not feel alert and may report feeling tired or fatigued. Sleep is best when received during the biological night [24, 25], but may be insufficient when desynchronized from the circadian clock, for example, when an individual sleeps during the biological "day." This situation may result in circadian misalignment [8]. Partial sleep deprivation (PSD) occurs when humans receive less sleep than is needed; total sleep deprivation (TSD) is when the individual is not allowed to sleep at all. Sleep deprivation is also associated with increased sleep inertia, a transitional state from wake to sleep in which the individual has lowered arousal and reduced cognitive functioning [75]. Upon awakening, sleep-deprived individuals experience sleep inertia ranging from a

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minute to 4 h in duration, dependent on the specific effects being measured [16, 75]. Sleep inertia, however, rarely exceeds 30 min in the absence of major sleep deprivation.

Effects of Insufficient Sleep

Insufficient sleep affects humans in various ways, degrading both cognitive and physical performance and increasing the need for sleep and the propensity to fall asleep. Consequently, sleep-deprived individuals may unintentionally fall asleep while working or driving [3]. Sleep and circadian rhythmicity are major determinants of human physiological functions and behavioral expression, both at an individual and team level [7]. Inadequate sleep negatively impacts learning through declarative and working memory, the qualitative reorganization of memory and the quantitative strengthening of new memories [13, 43]. Sleep deprivation affects vigilance performance by increasing lapses in attention [9, 10, 77], deteriorates mood and affect [26], challenges the integration of emotion and cognition to guide moral judgments [40], and impairs real-world decision-making tasks which involve unique and unfamiliar circumstances [33]. Furthermore, risk preference within a decision-making context is moderated by sleep deprivation [46]. Sleep has also been associated with creativity, innovative thinking, and strategic planning [18, 32].

Sleep deprivation is also associated with degraded physical performance and motor activities. For example, postural equilibrium, sensorimotor coupling, and physical and athletic performance (e.g., speed and endurance) deteriorate with insufficient sleep and circadian misalignment [2, 57, 73]. From an occupational health perspective, inadequate sleep is considered a potential risk factor for work injuries [76], while chronic sleep problems have confirmed serious health consequences. Lastly, we should note that chronic sleep deprivation, such as that encountered by individuals who engage in shiftwork, may have deleterious effects on long-term brain functioning and innate circadian rhythms [28, 50, 52]. Monk and colleagues suggested that chronic exposure to shiftwork may scar the circadian system because individuals are required to sleep at circadian-misaligned times [51]. This "circadian scarring"may have serious implications, including long-term disruption of natural sleep patterns.

The association between sleep and well-being, however, extends beyond the effects already described. Chronic sleep problems may affect health with the development of sleep-related disorders and other pathological conditions. For example, suppression of the immune system has been associated with inadequate sleep. Research findings have shown the deleterious effect of poor sleep on adaptive and innate immunity and on the increased risk of infectious disease [39]. Figure 7.1 shows the multifaceted effects of poor sleep. Grouped together, the short-term effects of poor sleep are predominantly associated with performance, while long-term inadequate sleep may result in poor health outcomes.

Sleep in the Military

The population of individuals who serve in the US military is comprised of officers and enlisted personnel who are relatively young in age. Demographically, the average age of officers is 35, while the average age of enlisted personnel is approximately 27 years of age. Nearly one-half (48.8%) of the enlisted personnel are 25 years old or younger in contrast to 13.3% of the officers ("2012 Demographics: Profile of the Military Community," [1]). This demographic structure highlights the increased need for good-quality sleep for these younger individuals, which, according to a recent consensus report, may be 9 or more hours of sleep per night to promote optimal health [78]. Despite this physiological need, however, it is well documented that individuals who serve in the military continually experience sleep deprivation and elevated fatigue levels [47, 48]. All three components of good sleep (timing, duration, and quality) are challenged in the military environment. During the last two decades, numerous studies conducted at the Naval Postgraduate School have documented the sleep patterns of active duty service members (e.g., [47]). Figure 7.2 shows the average daily sleep duration of 6,366 active duty service members assessed in 33 studies with data collected during military operations, during training and education, and during deployments and combat missions. Each data point represents the average daily sleep duration for each population in the corresponding study. From this diagram, the extent of sleep deprivation across all these environments and studies is evident. Most averages are below the 7-h sleep criterion for good health, while none exceeds the approximately 8-h criterion for full cognitive functioning [4].

Numerous factors affect sleep patterns in military operational environments. The predominant stressors include factors exogenous to the individual per se, that is, factors associated with the environment in which the service member is required to live and work. Service members have limited opportunities to sleep at their preferred time due to operational commitments [64–66, 68, 70, 71]. The problem of circadian misalignment is further exacerbated by artificial lighting conditions in work environments, by natural sunlight received at circadian inappropriate times, and by shiftwork [5, 35, 49, 54, 60].

Shiftwork is a common practice in the military because almost all operational military units, especially when deployed, are required to function 24/7. The shift schedule that is selected depends on the organizational culture, the

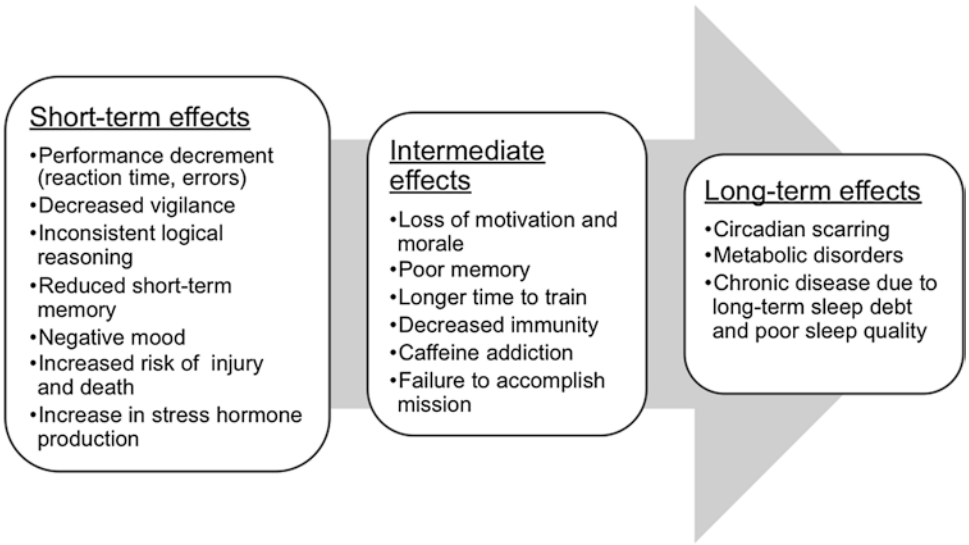

Fig. 7.1 Consequences of poor sleep practices

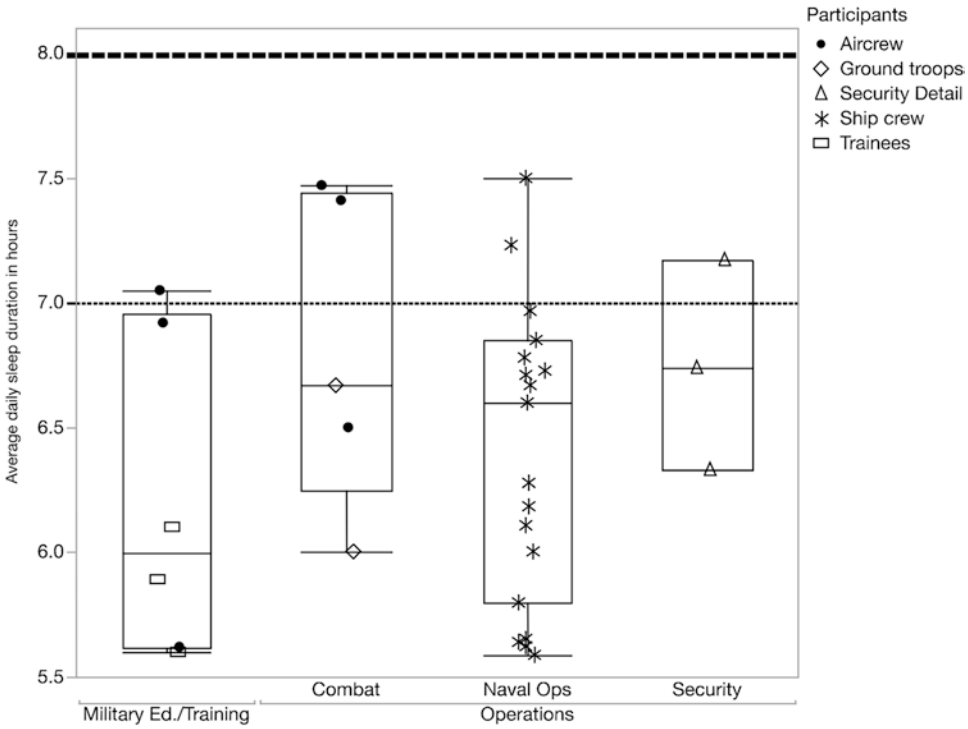

Fig. 7.2 Average daily sleep duration in various military environments

prior experience of the command leadership, and the availability of qualified personnel to stand watch. Depending on the shift (or in military parlance, "watch") itself and other daily activities in which the individual and military unit are involved, a number of fixed and rotating watch systems are commonly used. Some of these schedules result in days that are other than 24 h in length. For example, the length of the day for an individual on a 5-h on watch and 10-h off watch ("5/10 or 5 and dime") schedule can be considered either 15 or 30 h in length [65, 68]; the 5-h on/15-h off ("5/15") schedule results in a 20-h day. Studies on naval vessels have revealed how some of these traditional watch schedules used

at sea result in sleep deprivation, fragmented sleep, suboptimal performance, and worrisome levels of alertness [55, 59, 62]. It is noteworthy that the typical workday of active duty service members includes much more than just standing watch. Other duties and responsibilities may prolong the work day by 50% or more, with some crewmembers on US Navy ships working up to 15 h per day [30, 34, 44, 67].

The poor quality of sleeping conditions [45] leads to elevated levels of fatigue and affects morale as measured by self-reported mood states [14, 65, 68–70] and cognitive performance as measured by psychomotor vigilance tests. Studies conducted on multiple US Navy (USN) ships show the deleterious effect of sleep deprivation and circadian misalignment on psychomotor vigilance, with increased average reaction times and variability [14, 62, 64–66, 68–70]. The need to remain awake for long periods of time while deprived of sleep leads service members to consume large amounts of caffeinated beverages – to include energy drinks [63]. When taken in large quantities, caffeine affects sleep, making it difficult to fall asleep when opportunities are present [63, 74]. Even when there are opportunities to sleep, service members often have to sleep in berthing compartments which may not be optimal for good sleep. For example, our studies on USN ships have shown that noise from within or outside the berthing compartment, temperature conditions (both too hot or too cold), light, and environmental motion are some of the factors reported as disturbing sleep [62, 68, 70].

These sleep-disrupting factors can be classified as first-order effects in the sense that the existence of the stressors constitutes the cause of sleep pattern disruption. Combined with stressful life events, being away from home for extended periods of time, and combat exposure, military service members experience increased levels of occupational stress [31]. This second-order effect often results in further diminishment of sleep [41, 68]. It is no surprise that exposure to the often harsh military environment and living conditions affects the overall health of military personnel. Post-traumatic stress disorder (PTSD), depression, anxiety, and sleep disorders are the most common psychological and neurological injuries among service members [53].

An additional comment is appropriate regarding the "superhuman" appearance attributed to many military service members – also called the "myth of the warrior" Shay [72]. Especially in operationally critical and dangerous conditions, adopting this attitude may be beneficial to members of the military profession, allowing them to accomplish their mission in the face of serious adversity. However, this same characteristic can become a problem when active duty military personnel deny their own need for sleep and replenishment. Research has shown that individuals who are sleep-deprived commonly fail to accurately assess their own level of sleepiness [27, 37]; they are largely unaware of their increasing cognitive deficits [77]. Therefore, sleep-deprived individuals may overestimate their ability to overcome the detrimental effects of sleepiness. Silimarly, when forced to perform while fatigued, military members are often inaccurate judges of their own limitations. This problem is further exacerbated by the widespread belief among service members that motivation may be the answer to overcoming tiredness, despite research findings demonstrating that motivation can only partially compensate for changes in performance due to sleep deprivation [56].

Overall, numerous factors contribute to poor sleep in the military operational environment. The diagram in Fig. 7.3 shows these factors clustered into three categories: psychological/pathological, environmental, and organizational.

Countermeasures for Insufficient Sleep

Historically, the need to remain alert and the need to sleep whenever opportunities present themselves have been approached using pharmacologic and non-pharmacologic countermeasures and interventions. The optimization of performance through the implementation of best practices to retain/restore alertness, however, begins well before the actual operations commence. First, service members should be made aware of their biological need for sleep and how sleep deprivation affects them. Second, before operations begin, service members should be allowed, whenever possible, to bank sleep, i.e., to accrue sleep "in excess" as a reserve [6, 58]. To the extent possible, mission planners should take into account human alertness by using existing sleep and performance models to predict best and worst periods of performance [38], allowing planners to weigh risks and optimize shiftwork.

During operations, commanding officers should implement a sleep schedule for their unit. Even though long periods of sleep are not possible in the operational environment, "prophylactic naps" have been demonstrated to increase alertness [29]. The habitability of sleeping spaces should also be considered as a way to improve sleep, and enhanced lighting conditions may improve the alertness of sleep-deprived service members [20]. Because of the importance of having alert warfighters/service members, military organizations and law enforcement agencies have issued regulations and guidelines regarding fatigue management (e.g., [22]). In conjunction with these approaches, pharmacologic interventions may also be beneficial when appropriately implemented in the field to enhance performance by improving alertness [79] or to facilitate getting sleep when needed [15]. The pharmacologic and non-pharmacologic approaches to improve alertness and help service members sleep when needed are shown in the Fig. 7.4.

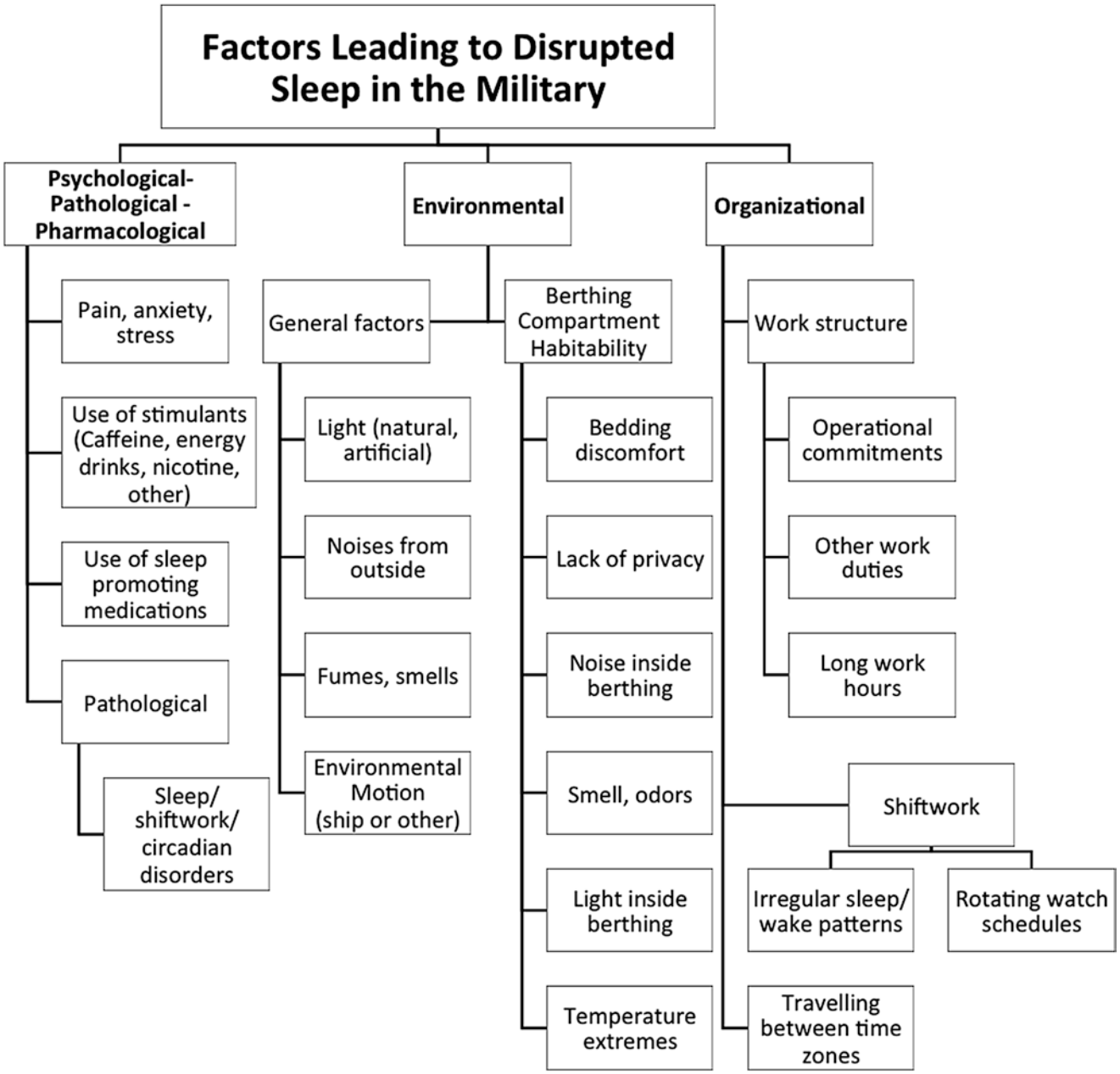

Fig. 7.3 Factors leading to disturbed sleep in the military

Conclusions

The military operational environment is notorious for its unpredictable nature. Service members are often challenged by irregular, or in some cases, unforeseen, operational duties, and long work hours. It is not surprising that active duty service members are chronically fatigued because they cannot get as much sleep as they need due to operational commitments and erratic schedules. These problems are further exacerbated by an increase in operational tempo (OPTEMPO), i.e., the pace of military operations, which has been excessive over the past two decades [21]. Service members not only have limited opportunities to sleep due to operational commitments, but they also find it difficult to sleep when they have spare time because their sleep opportunities often occur during circadian-misaligned time periods. They also experience chronic circadian desynchrony and low quality of sleep-related habitability factors in their sleeping compartments. Sleep, however, remains a critical requirement for

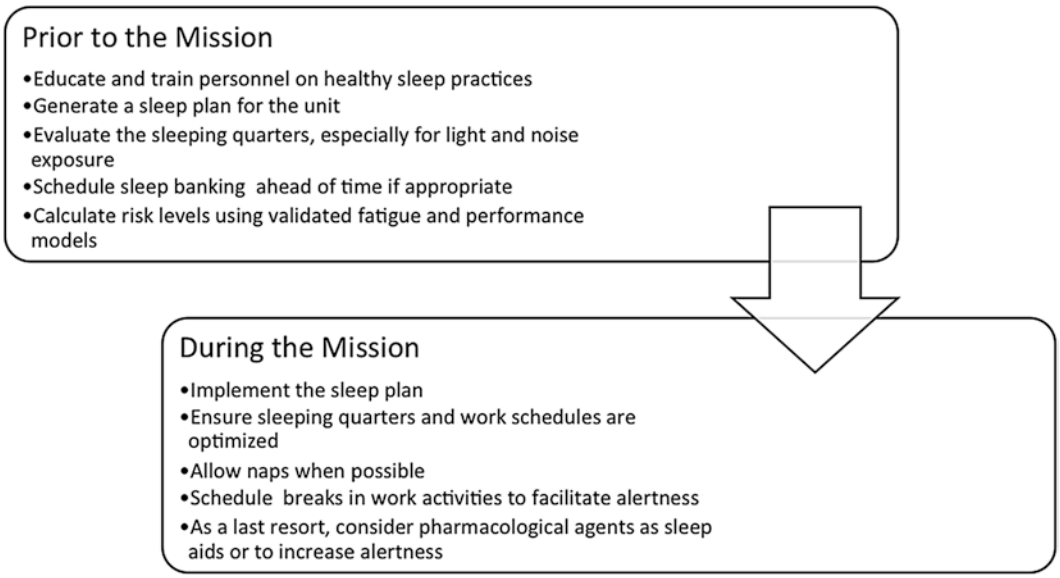

Fig. 7.4 Pharmacologic and non-pharmacologic approaches to improve alertness and help service members sleep

humans. Performance and health are both affected by insufficient sleep. Long-term effects include insomnia and circadian scarring, which are common "hidden wounds" in military veterans. The military, like other organizations that require shiftwork, needs to embrace the importance of sleep health [17] and implement sleep hygiene practices as an inexpensive approach to optimizing operational performance, increasing personnel retention, and minimizing long-term health costs both for active duty service members and veterans.

References

1. Demographics: Profile of the Military Community. (2014). Retrieved 12 Jul 2014, from http://www.militaryonesource.mil/12038/MOS/Reports/2012_Demographics_Report.pdf.
2. Aguiar SA, Barela JA. Sleep deprivation affects sensorimotor coupling in postural control of young adults. Neurosci Lett. 2014;574:47–52.
3. Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Work organisation and unintentional sleep: results from the WOLF study. Occup Environ Med. 2002;59:595–600.
4. Anch AM, Browman CP, Mitler M, Walsh JK. Sleep: a scientific perspective. Englewood Cliffs: Prentice-Hall; 1988.
5. Arendt J, Middleton B, Williams P, Francis G, Luke C. Sleep and circadian phase in a ship's crew. J Biol Rhythm. 2006;21(3):214–21.
6. Arnal PJ, Sauvet F, Leger D, Van Beers P, Bayon V, Bougard C, et al. Benefits of sleep extension on sustained attention and sleep pressure before and during total sleep deprivation and recovery. Sleep. 2015;38(12):1935–43.
7. Baranski J, Thompson M, Lichacz FMJ, McCann C, Gil V, Pastó L, Pigeau R. Effects of sleep loss on team decision making: motivational loss or motivational gain? Hum Factors. 2007;49(4):646–60.
8. Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry. 2014;26(2):139–54. doi:10.3109/09540261.2014.911149.
9. Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. J Sleep Res, 2003;12:1–12.
10. Belenky GL, Thorne DR, Thomas ML, Redmond DP, Sing HC, Wesensten NJ, Balkin TJ. The effects of 7 days of sleep restriction or augmentation on performance and subsequent recovery. J Sleep Res. 2002;11(Suppl. 1):17.
11. Bin YS. Is sleep quality more important than sleep duration for public health? Sleep. 2016;39(9):1629–30.
12. Borbély A. Two process model of sleep regulation. Hum Neurobiol. 1982;1:195–204.
13. Broughton RJ, Ogilvie RD. Sleep, arousal, and performance. Boston: Birkhauser; 1992.
14. Brown S, Matsangas P, Shattuck NL. Comparison of a circadian-based and a forward rotating watch schedules on sleep, mood, and psychomotor vigilance performance Paper presented at the Human Factors and Ergonomics Society (HFES) Annual Meeting, Los Angeles, CA. 2015.
15. BUMED. Performance maintenance during continuous flight operations: a guide for flight surgeons (NAVMED P-6410): U.S. Navy Bureau of Medicine and Surgery. 2000.
16. Burke TM, Scheer FAJL, Ronda JM, Czeisler CA, Wright KP. Sleep inertia, sleep homeostatic and circadian influences on higher-order cognitive functions. J Sleep Res. 2015;24(4):364–71. doi:10.1111/jsr.12291.
17. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep. 2014;37(1):9–17.
18. Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC. REM, not incubation, improves creativity by priming associative networks. PNAS. 2009;106(25):10130–4.
19. Cajochen C, Chellappa SL, Schmidt C. Circadian and light effect on human sleepiness-alertness. In: Garbarino S, Nobili L, Costa G, editors. Sleepiness and human impact assessment. Milan: Springer; 2014. p. 9–22.
20. Caldwell JA, Mallis MM, Caldwell JL, Paul MA, Miller JC, Neri DF, Aerospace Medical Association Fatigue Countermeasures Subcommittee of the Aerospace Human Factors Committee. Fatigue countermeasures in aviation. Aviat Space Environ Med. 2009;80(1):29–59.

21. Castro CA, Adler AB. Operations Tempo (OPTEMPO): preface to the special issue. Mil Psychol. 2005;17(3):131–6.
22. Combat and operational stress control manual for leaders and soldiers – field manual No. 6-22.5. Washington, DC: Department of the Army; 2009.
23. Czeisler CA. Duration, timing and quality of sleep are each vital for health, performance and safety. Sleep Health. 2015;1(1):5–8.
24. Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci. 1995;15:3526–38.
25. Dijk DJ, Edgar DM. Circadian and homeostatic control of wakefulness and sleep. In: Turek FW, Zee PC, editors. Regulation of sleep and wakefulness. New York: Marcel Dekker; 1999. p. 111–47.
26. Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. Sleep. 1997;20(4):267–77.
27. Drake CL, Roehrs T, Burduvali E, Bonahoom A, Rosekind MR, Roth T. Effects of rapid versus slow accumulation of eight hours of sleep loss. Psychophysiology. 2001;38(6):979–87.
28. Drake CL, Wright KP. Shift work, shift-work disorder, and jet lag. In: Kryger MH, Roth T, Dement WC, editors. Principles and practices of sleep Medicine. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 784–98.
29. Driskell JE, Mullen B. The efficacy of naps as a fatigue countermeasure: a meta-analytic integration. Hum Factors. 2005;47(2):360–77.
30. Green KY. A comparative analysis between the Navy standard workweek and the actual work/rest patterns of sailors aboard U.S. Navy frigates (Master's thesis). Naval Postgraduate School, Monterey, CA. 2009.
31. Harms PD, Krasikova DV, Vanhove AJ, Herian MN, Lester PB. Stress and emotional well-being in military organizations. In: Perrewé PL, Rosen CC, Halbesleben JRB, editors. The role of emotion and emotion regulation in job stress and well being (Vol. 11). Emerald Group Publishing Ltd., Bingley, West Yorkshire, 2013. p. 103–32
32. Harrison Y, Horne JA. One night of sleep loss impairs innovative thinking and flexible decision making. Organ Behav Hum Decis Process. 1999;78(2):128–45.
33. Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. J Exp Psychol. 2000;6(3):236–49.
34. Haynes LE. A comparison between the Navy standard workweek and the actual work and rest patterns of U.S. Navy sailors (Master's thesis). Naval Postgraduate School, Monterey, CA. 2007.
35. Horn WG, Thomas TL, Marino K, Hooper TI. Health experience of 122 submarine crewmembers during a 101-day submergence. Aviat Space Environ Med. 2003;74(8):858–62.
36. Horne JA. Why we sleep. New York: Oxford University Press; 1988.
37. Horne JA. Sleepiness as a need for sleep: when is enough, enough? Neurosci Biobehav Rev. 2010;34:108–18.
38. Hursh SR, Redmond DP, Johnson ML, Thorne DR, Belenky G, Balkin TJ, et al. Fatigue models for applied research in warfighting. Aviat Space Environ Med, 2004;75(3 Suppl):A44–53. discussion A54–A60.
39. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol. 2015;66:143–72. doi:10.1146/annurev-psych-010213-115205.
40. Killgore WD, Killgore DB, Day LM, Li C, Kamimori G, Balkin T. The effects of 53 hours of sleep deprivation on moral judgment. Sleep. 2007;30(3):345–52.
41. Kim E-J, Dimsdale JE. The effect of psychosocial stress on sleep: a review of polysomnographic evidence. Behav Sleep Med. 2007;5(4):256–78.
42. Klein DC, Morre RY, Reppert SM, editors. Suprachiasmatic nucleus: the mind's clock. New York: Oxford University Press; 1991.
43. Landmann N, Kuhn M, Piosczyk H, Feige B, Baglioni C, Spiegelhalder K, et al. The reorganisation of memory during sleep. Sleep Med Rev. 2014;18(6):531–41.
44. Mason DR. A comparative analysis between the Navy standard workweek and the work/rest patterns of sailors aboard U.S. Navy cruisers (Master's thesis). Naval Postgraduate School, Monterey, CA. 2009.
45. Matsangas P, Shattuck NL. Sleep quality in crewmembers of US Navy ships while underway. Sleep. 2016;39(Abstract Supplement):A98–9.
46. McKenna BS, Dickinson DL, Orff HJ, Drummond SPA. The effects of one night sleep deprivation on known-risk and ambiguous-risk decisions. J Sleep Res. 2007;16:245–52.
47. Miller NL, Matsangas P, Kenney A. The role of sleep in the military: implications for training and operational effectiveness. In: Laurence JH, Matthews MD, editors. The Oxford handbook of military psychology. New York: Oxford University Press; 2012. p. 262–81.
48. Miller NL, Matsangas P, Shattuck LG. Fatigue and its effect on performance in military environments. In: Hancock PA, Szalma JL, editors. Performance under stress. 1st ed. Burlington: Ashgate Publishing; 2008. p. 231–50.
49. Miller NL, Nguyen JL. Working the nightshift on the USS John C. Stennis: implications for enhancing warfighter effectiveness. Paper presented at the Human Systems Integration Symposium (HSIS) 2003: Enhancing Human Performance in Naval & Joint Environments, Vienna, VA. 2003.
50. Monk TH, Buysse DJ, Billy BD, Fletcher ME, Kennedy KS. Polysomnographic sleep and circadian temperature rhythms as a function of prior shift work exposure in retired seniors. Healthy Aging Clin Care Elder. 2013;5:9–19.
51. Monk TH, Buysse DJ, Billy BD, Fletcher ME, Kennedy KS, Begley AE, et al. Shiftworkers report worse sleep than day workers, even in retirement. J Sleep Res. 2013;22:201–8.
52. Mysliwiec V, Matsangas P, Baxter T, Shattuck NL. An unusual circadian rhythm in an active duty service member. Sleep and Biological Rhythms. 2015;14(1):113–5.
53. Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. Sleep. 2013;36(2):167–74.
54. Nguyen JL. The effects of reversing sleep-wake cycles on sleep and fatigue on the crew of USS JOHN C. STENNIS. Monterey: Naval Postgraduate School; 2002.
55. Paul MA, Ebisuzaki D, McHarg J, Hursh SR, Miller JC. An assessment of some watch schedule variants used in Canadian Patrol Frigates, Technical Report Report No. DRDC Toronto TR 2012-078. Toronto: Defence Research and Development; 2012.
56. Pigeau R, Angus B, O'Neil P. Vigilance latencies to aircraft detection among NORAD surveillance operators. Hum Factors. 1995;37(3):622–34.
57. Reilly T, Edwards B. Altered sleep–wake cycles and physical performance in athletes. Physiol Behav. 2007;90(2):274–84.
58. Rupp TL, Wesensten JN, Bliese PD, Balkin T. Banking sleep: realization of benefits during subsequent sleep restriction and recovery. Sleep. 2009;32(3):311–21.
59. Rutenfranz J, Plett R, Knauth P, Condon R, De Vol D, Flethcher N, et al. Work at sea: a study of sleep, and circadian rhythms in physiological and psychological functions, in watchkeepers on merchant vessels. Int Arch Occup Environ Health. 1988;60(5):331–39.
60. Sallinen M, Kecklund G. Shift work, sleep, and sleepiness – differences between shift schedules and systems. Scand J Work Environ Health. 2010;36:121–33.
61. Savage VM, West GB. A quantitative, theoretical framework for understanding mammalian sleep. Proc Natl Acad Sci Proc Natl Acad Sci U.S.A. 2007;104(3):1051–6.
62. Shattuck NL, Matsangas P. Work and rest patterns and psychomotor vigilance performance of crewmembers of the USS Jason Dunham:

a comparison of the 3/9 and 6/6 watchstanding schedules, Technical Report Report no. NPS-OR-14-004. Monterey: Naval Postgraduate School; 2014.
63. Shattuck NL, Matsangas P. Caffeinated beverage consumption rates and reported sleep in a U.S. Navy ship. Proc Hum Factors Ergon Soc Annu Meet. 2015;59(1):696–700.
64. Shattuck NL, Matsangas P. A comparison of sleep and performance of U.S. Navy sailors on four different shiftwork schedules. Sleep. 2015;38(Abstract Supplement):A130.
65. Shattuck NL, Matsangas P. Operational assessment of the 5-h on/10-h off watchstanding schedule on a US Navy ship: sleep patterns, mood, and psychomotor vigilance performance of crew members in the nuclear reactor department. Ergonomics. 2015;59(5):657–64. doi:10.1080/00140139.2015.1073794.
66. Shattuck NL, Matsangas P. A six-month assessment of sleep during naval deployment: a case study of a commanding officer. Aerosp Med Hum Perform. 2015;86(5):1–5.
67. Shattuck NL, Matsangas P. Work and rest patterns in marine corps embassy security guard program: promoting health and wellness through informed work schedules, Technical Report No NPS-OR-16-001R. Monterey: Naval Postgraduate School; 2016.
68. Shattuck NL, Matsangas P, Brown S. A comparison between the 3/9 and the 5/10 watchbills, Technical Report Report No. NPS-OR-15-006. Monterey: Naval Postgraduate School; 2015.
69. Shattuck NL, Matsangas P, Moore J, Wegemann L. Prevalence of musculoskeletal symptoms, excessive daytime sleepiness, and fatigue in the crewmembers of a U.S. Navy ship, Technical Report No. NPS-OR-15-005. Monterey: Naval Postgraduate School; 2015.
70. Shattuck NL, Matsangas P, Powley EH. Sleep patterns, mood, psychomotor vigilance performance, and command resilience of watchstanders on the "five and dime" watchbill, Technical Report No. NPS-OR-15-003. Monterey: Naval Postgraduate School; 2015.
71. Shattuck NL, Waggoner LB, Young RL, Smith CS, Matsangas P. Shiftwork practices in the United States Navy: a study of sleep and performance in watchstanders aboard the USS Jason Dunham. Sleep. 2014;37(Abstract Supplement):A78.
72. Shay J. Ethical standing for commander self-care: the need for sleep. Parameters. 1998;28(2):93–105.
73. Simpson NS, Gibbs EL, Matheson GO. Optimizing sleep to maximize performance: implications and recommendations for elite athletes. Scand J Med Sci Sports. 2016; doi:10.1111/sms.12703.
74. Smith A. Effects of caffeine on human behavior. Food Chem Toxicol. 2002;40(9):1243–55.
75. Tassi P, Muzet A. Sleep inertia. Sleep Med Rev. 2000;4(4):341–53.
76. Uehli K, Mehta AJ, Miedinger D, Hug K, Schindler C, Holsboer-Trachsler E, et al. Sleep problems and work injuries: a systematic review and metaanalysis. Sleep Med Rev. 2014;18(1):61–73.
77. Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep. 2003;26(2):117–26.
78. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse DJ, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep. 2015;38(6):843–4.
79. Wesensten NJ, Belenky GL, Thorne DR, Kautz MA, Balkin TJ. Modafinil vs. caffeine: effects on fatigue during sleep deprivation. Aviat Space Environ Med. 2004;75(6):520–5.

Suicidal Behavior in Posttraumatic Stress Disorder: Focus on Combat Exposure

8

Yuriy Dobry and Leo Sher

Introduction

Suicidal behavior is a complex psychiatric, medical and social phenomenon that due to an alarming prevalence is approached by the clinical and scientific community as a significant public health problem. World Health Organization (WHO) reported that in the year 2000, more than 800,000 people died from suicide globally, with billions of dollars in associated economic cost [1]. It's a growing trend that has affected the societies of North American, European, Asian, and Australian continents alike [2–7]. For example, Kessler et al. [8] have demonstrated suicidal ideation, plans, and attempt in US adults to be approximately 13.5 %, 3.9%, and 4.6%, respectively, with 39.3% of attempts considered to be grave. Combat-exposed active military personnel and veterans are at an especially high risk of suicidal behavior and as a result have been under an intense scrutiny of clinical and military communities, as well as public policy makers [9–17].

Risk Factors for Suicidal Behavior

An emotionally and politically charged issue, an almost epidemic proportion of suicidal behavior in our society, including the military, has fueled extensive research into its mechanism and risk factors. Brent et al. [18] suggested that suicidal behavior is inherited independently of psychiatric disorders, a model supported by data from twin studies and analysis of genetically and culturally homogenous populations [19, 20]. Despite the challenge of predicting suicidal behavior, numerous psychological and demographic risk factors have been identified and described. For example, in a large survey representative of the US population, young age, female gender, being previously married, and low education level were all found to be associated with an increased risk of suicidal behavior [8]. Furthermore, suicidal ideation and plan appear to increase the risk of suicidal attempt [8, 21, 22], and young age, axis II psychiatric diagnoses, and a poor social support were all found to be associated with an increased risk of suicide reattempt [23].

A wide range of traumatic experiences including combat exposure, abuse, genocide, and natural catastrophes have also been shown to be associated with an elevated risk of suicidal behavior across different demographic groups [8, 13, 24–32]. Surprisingly, until recently, trauma and posttraumatic stress disorder (PTSD) received relatively little attention as an etiological factor of suicidal behavior, as most of the research has been focused on other axis I and II psychiatric diagnoses [8, 33]. Considering that the lifetime prevalence of PTSD diagnosis is approximately 1.3–7.8% in the general US population [33, 34], and up to 83% in the severely traumatized groups such as combat personnel or veterans [17, 32, 34–36], with up to 50% of PTSD subjects at an increased risk of suicidal behavior [13, 15, 21, 37, 38], trauma and PTSD should be at the top of research and clinical agendas (see Table 8.1). Additionally, the high degree of comorbidity between PTSD and multiple medical illnesses that carry an independent risk of suicidal behavior [39], such as traumatic brain injury (TBI) and cardiovascular and respiratory diseases [36, 40–42], and an urgency to rigorously investigate PTSD's role in suicidal behavior is evermore apparent.

Relationship Between PTSD and Suicidal Ideation

Numerous large studies representing North American, European, and South African general populations have demonstrated a robust correlation between PTSD and sui-

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Table 8.1 Suicidal behavior in the general and combat-exposed populations

Populations	Suicidal ideation/ suicidal ideation with plan	Suicide attempt	Death from suicide
General population [1–3]	13.5/3.9%	4.6%	0.015%
General population with chronic PTSD [38, 66]	38.3/8.5%	9.6%	0.4%
Veterans with PTSD [79]	44/36%	14%	0.6–11.8%
OEF/OIF returning veterans [15, 54, 126]	12.5% [54]–21/6% [15]	9% [19]	0.022% [126]

cidal ideation [3, 43, 44]. Even after Marshall et al. [45] applied partial diagnostic criteria to PTSD, a strong association emerged, with a proportion of subjects with suicidal ideation increasing from 9% with no PTSD symptoms to 33% for those with four PTSD symptoms. It is a correlation that appears to nearly equally affect patients with different demographic characteristics and traumatic experiences, evidenced by studies on sheltered women traumatized by domestic abuse, adolescents exposed to street or jail violence, and Israeli students exposed to the trauma of terrorism [46–51].

Numerous studies in combat veterans, active duty military, or police personal exposed to combat violence have also demonstrated a strong, positive association between PTSD and suicidal ideation [51]. Bell et al. [52] found that reexperiencing symptom cluster of PTSD was strongly associated with suicidal ideation in Vietnam combat veterans, and veterans of Iraq and Afghanistan wars carrying the diagnosis of PTSD were several times more likely to endorse suicidal ideation when compared to controls [53]. Veterans from the Operation Enduring Freedom and Operation Iraq freedom (OEF/OIF) who endorsed suicidal ideation were found to be more likely to suffer from symptoms of PTSD [54]. In the Norwegian peacekeepers, suicidal ideation jumped from 6% to 17% when PTSD symptoms were factored in the analysis [55], and Maia et al. [56] found police officers with a history of violent trauma exposure and full PTSD diagnosis to have a sevenfold increase in the lifetime prevalence of suicide ideation compared to a well-matched control group without PTSD.

PTSD and Suicide Attempt

Considering the high rate of suicidal ideation in traumatized subjects, it is not surprising that up to 29% of combat veterans and up to 40% of civilians diagnosed with PTSD will make a suicide attempt, some more than once [2, 57]. It's a behavioral trend observed and noted as early as 1950s when World War II veterans returned home [58]. Both Hyer et al. [11] and Hendin et al. [10] separately demonstrated that up to 20% of combat-exposed Vietnam veterans carrying a diagnosis of chronic PTSD attempted suicide, with persistent combat action and survival guilt as well as symptoms of depression mediating the self-destructive behavior. Brenner and colleagues [59] found that the risk of suicide attempt in veterans with PTSD is significantly higher than for controls and is further increased by a comorbidity with TBI.

Similarly, several large studies involving civilian subjects demonstrated a robust association between PTSD and the risk of suicide attempt compared to a demographically matched control groups [2, 8, 36, 60]. Sareen and colleagues [43], for example, found that PTSD was the only anxiety disorder independently correlated to suicide attempts, and the European Study of the Epidemiology of Mental Disorders (ESEMED) which analyzed 21,425 adults from six European countries found that 10.7% of subjects suffering from PTSD has attempted suicide [3].

Contribution of PTSD to Death from Suicide

Although established rates of suicidal ideation and attempts carry some utility in predicting death rates from suicide, data on specific population is the best tool for this task. For example, suicide rate among veterans with PTSD was found to be more than three times the rate in the general population expected by the Center for Disease Control and Prevention [61]. Bullman and colleagues [62] found increased risks of suicide in Vietnam veterans diagnosed with PTSD, when compared to the general population and veterans without PTSD, and Watanabe et al. [63] demonstrated that death from suicide in combat-exposed Vietnam marines exceeded that of demographically matched control group not exposed to combat action in Vietnam. Boscarino et al. [64] further showed that the risk of death from suicide in Vietnam combat veterans with PTSD is elevated, even after controlling effects of combat trauma, and Farbero and colleagues [65] demonstrated that veterans who died from suicide are more likely to experience PTSD symptoms in the past than matched veterans who died from motor vehicle accidents. A large nationwide Danish study found a high degree of association between PTSD and suicide, with comorbid depression further elevating the risk [66].

Interestingly, not every study demonstrated a positive correlation between PTSD and suicide rate. Krysinka et al. [67] reviewed 52 papers on the relationship between completed suicide rate and PTSD and found no positive association. A large Veteran Affairs National Registry for Depression study by Zivin and colleagues [68], for example, found suicide

rate among veterans diagnosed with PTSD to be lower compared to veteran group without the diagnosis. The discrepancy could potentially be accounted by differences in study designs, populations, treatment quality, and diagnostic tools and highlights the need to refine research methodology in the fields of suicide, PTSD, and trauma.

The Role of Comorbid Psychiatric Conditions in Suicidal Behavior of PTSD

Mood, anxiety, substance abuse, and personality disorders often co-occur with PTSD [52, 69–72], with some estimates that up to 99.8% of patients with PTSD carry another psychiatric diagnosis [8]. A comorbidity can both contribute to the suicidal behavior of combat-exposed as well as civilian patients and artificially inflate data on suicide rates in PTSD [12, 16] (see Table 8.2). The explanations for the high rate of co-occurrences vary from psychiatric disorders predisposing to trauma and PTSD, to depression, anxiety, and substance use disorders being the effect of PTSD symptoms. Additionally, certain symptom clusters of PTSD overlap with symptoms of common psychiatric diagnoses, and common biological and psychological factors are shared by both PTSD and other psychiatric disorders.

PTSD, Mood Disorders, and Suicidal Behavior

Lifetime PTSD, even subthreshold diagnosis, is strongly associated with mood disorders. The comorbidity is especially prominent with the major depressive disorder (MDD) and, with an exception of dysthymia, usually precedes the symptoms of depression [45, 73]. In the traumatic events of Oklahoma City bombing, a large proportion of victims with pre-disaster MDD developed PTSD, and a large proportion of victims with pre-event PTSD developed new-onset MDD, highlighting the complexity of the interaction between PTSD and depressive disorders [47, 74, 75]. Fullerton et al. [76] also found that preexisting MDD increases susceptibility to the development of acute and chronic PTSD, and Shalev with colleagues [77] demonstrated that up to 44.5% of people develop a comorbidity between PTSD and a major depressive disorder after a traumatic event, with a positive synergistic effect on suicidality and clinical impairment compared to either disorder alone.

Approximately 56–87% of individuals who commit suicide are diagnosed with MDD [78], but numerous well-controlled studies involving subjects traumatized by combat have demonstrated that comorbidity between PTSD and MDD increases suicidal behavior compared to either diagnosis alone [79–82]. Freeman et al. [56] showed that patients with chronic, combat-related PTSD and a history of suicide attempt were more likely to have suffered from comorbid symptoms of depression, and Wunderlich et al. [83] demonstrated that depression in young adults diagnosed with PTSD was a major contributor to the risk of suicide attempt.

Studies have also found a correlation between bipolar disorder and PTSD leading to an elevated risk of suicidal [84]. Lu and colleagues [85] demonstrated, for example, that history of bipolar illness interacts with trauma to increase the risk of developing PTSD and suicide attempt, and Lucas et al. [86] showed that patients with comorbid PTSD and bipolar type 1 disorder are at higher risk of suicide attempt than bipolar-only group or patients diagnosed with bipolar who have been exposed to trauma but without the diagnosis of PTSD.

PTSD, Primary Psychotic Disorders, and Suicidal Behavior

Trauma and PTSD also appear to increase the chance of suicidal behavior in patients with a psychotic disorder [87, 88].

Table 8.2 Relative risk of suicidal behavior in PTSD comorbid with different psychiatric disorders

PTSD + mood disorder	Risk of suicidal behavior	PTSD + anxiety disorder	Risk of suicidal behavior	PTSD + other disorders	Risk of suicidal behavior	Combination of disorders	Risk of suicidal behavior
Major depressive disorder	++	Alcohol abuse	+	Personality disorders	+	2 + disorders combined	+
Dysthymia	+	Alcohol dependence	+	TBI	+	3 + disorders combined	++
Mania	++	Drug abuse	+	Generalized anxiety disorder	+	4 + disorders combined	+++
Any mood disorder	++	Drug dependence	+	Panic disorder	+	5 + disorders combined	++++
		Any substance disorder	+	Any anxiety	+		
				PTSD	+		

+ represents an approximate degree of suicidal behavior risk. Table was constructed using data from [8, 12, 15]

Strauss et al. [89] found comorbid PTSD to be associated with a higher risk of suicide ideation and behavior in veterans with schizophrenia and schizoaffective disorders. Terrier and colleagues [90] showed that in response to the trauma of first psychotic episode, approximately 40% of patients developed PTSD with an increased risk of suicidal ideation. Finally, the same investigators also demonstrated that patients with schizophrenia suffering from comorbid PTSD showed elevated suicidal ideation, plan, and attempts compared to subjects without comorbid PTSD [85].

PTSD, Anxiety Disorders, and Suicidal Behavior

A number of large national representative studies have demonstrated that anxiety disorders are often comorbid with PTSD diagnosis, and the comorbidity appears to increase the risk of suicidal behavior [34, 45, 91–93]. Capron and colleagues [94] suggested that excessive sensitivity to anxiety symptoms of PTSD is associated with an increased rate of suicide attempt, and Hapke et al. [95] concluded that symptoms of anxiety predispose to the development of PTSD. Ferrada-Noli et al. [96] found that out of 149 refugee subjects traumatized by torture, 117 were diagnosed with PTSD. Out of the subjects positive for PTSD, 29% got labeled with another anxiety disorder, and the comorbid group demonstrated risk of suicidal attempt that was even higher than PTSD comorbid with depression group.

PTSD, Borderline Personality Disorder, and Suicidal Behavior

In a large study, Pietrzak and colleagues [97] reported that PTSD is frequently comorbid with several personality disorders, including the borderline personality disorder (BPD). Many other researchers have also validated this association, with estimates that nearly 60% of PTSD patients suffer from BPD [98, 99].

In exploring this relationship, Pagura and colleagues [100] suggested that despite being separated categorically by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), both BPD and PTSD share a relationship to trauma with higher risk of suicidal behavior as a result. Some studies even hypothesize that BPD should be viewed as part of a posttraumatic stress "syndrome" or complex PTSD [10, 101–105]. Oquendo and colleagues [81] suggested that the increased suicidal behavior in patients suffering from PTSD and depressive disorders is mediated by cluster B personality traits, while Bell et al. [52] showed that reexperiencing symptoms of trauma were predictive of suicidal behavior and overlap with experiences of patients with BPD.

Despite an incompletely understood mechanism, the co-occurrence of BPD and PTSD elevates the risk of suicidal behavior compared to either disorder alone [106, 107]. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Wave II, for example, showed that the comorbid group suffered from a higher psychiatric burden, a lower quality of life, and a higher rate of suicide attempts than either group alone [99]. A study by Harned and colleagues [108], however, suggested that comorbid PTSD and BPD in women actually lowered the suicide intent and lethality from suicide attempts, a controversial conclusion given the data that suggest otherwise.

PTSD and Alcohol and Drug Abuse Disorders

Data shows a strong association between trauma, PTSD, and illicit substance and alcohol use [60, 109], including in veteran and active military personnel. The National Comorbidity Survey, for example, found that subjects with an alcohol or drug use disorders were more likely to have co-occurring PTSD compared to controls [96], and the analysis of the Epidemiologic Catchment Area (ECA) data by Cottler et al. [110] found that individuals with a history of cocaine and opioid use were at increased risk of trauma exposure and PTSD, compared to controls.

Suicide rate in subjects with comorbid PTSD and substance dependence has also been shown to exceed either one of these disorders alone [111–113] and appears to vary with different disorders [114]. A study by Harned et al. [115] demonstrated that women diagnosed with PTSD and substance dependence are at higher risk of suicide as well as non-suicidal self-injury, and a large, retrospective, Australian study looking at the relationship between opioid dependence disorder and suicide attempt and ideation found that opioid-dependent subjects had higher rates of PTSD and BPD which were believed to raise rates of attempted suicide [116].

Longitudinal analysis of co-occurrence of PTSD and substance or alcohol suggests a mechanism behind this association. Brown et al. [73] demonstrated that PTSD often precedes substance and alcohol use disorders, most likely as a self-medication of PTSD symptoms, and Chapman et al. [46] as well as Pietrzak et al. [53] suggested that substance and alcohol abuse mediates an increased risk of suicidal behavior in traumatized patients. Data from a large Australian National Survey of Mental Health and Well-Being showed that patients with trauma and PTSD had a high rate of substance use disorder, most commonly alcohol. They showed that in 8.7% of the cases, trauma preceded the onset of substance use; for 33.8% the traumatic event occurred simultaneous to the onset of substance use disorder symptoms, suggesting that substance use could predispose to as well as complicate trauma and PTSD [111].

Trauma, PTSD, and Suicidal Behavior

Most of the subjects in civilian and military populations experience at least one traumatic event in their lifetime, but fewer than 10% develop PTSD [117], and even a smaller fraction engages in suicidal behavior [118]. PTSD, comorbid psychiatric disorders, trauma, or a combination of these factors could potentially mediate the association between trauma and suicidal behavior. Several well-controlled studies in civilian populations, including large, nationally representative data sets, have demonstrated that trauma leads to suicidal behavior with and without PTSD [119–122]. Numerous studies have shown that symptoms other than classic symptom clusters of PTSD are responsible for mediating suicidal behavior in subjects with PTSD. Several investigators, for example, demonstrated that instability in paternal relationship, combat guilt, and depression were predictive of suicide in Vietnam veterans with PTSD [10, 11], and Kotler et al. [37] suggested that posttraumatic symptoms of avoidance or intrusion were not significantly correlated with the suicide risk in subjects diagnosed with PTSD, but anger and impulsivity were.

Nelson and colleagues [123] showed combat trauma and not PTSD mediated that association between combat exposure and suicidal behavior in Canadian Forces personnel, and Kang and Bullman [13] found that suicidal behavior was directly proportional to the degree of combat trauma exposure.

Numerous studies also argue that it is in fact symptoms of PTSD that are responsible for suicidal behavior, in traumatized civilian as well as combat populations [46, 47, 50–52, 62, 96, 124–126]. For example, Cox and colleagues [124] isolated and characterized the group that developed PTSD after trauma exposure and demonstrated that symptoms of PTSD and not trauma experience was associated with suicide attempt, highlighting its role in the development of suicidal behavior.

Protective Factors, Management, and Future Research in PTSD and Suicidal Behavior

Social Support

Social support, both objective and perceived, appears to decrease the chances of PTSD as well as the risk of suicidal behavior in the civilian and the military populations [37, 123, 125, 127–129]. For OEF/OIF veterans diagnosed with PTSD, post-deployment social support system in the form of marriage, family, and friends and access to medical care as well as greater sense of purpose, control, leadership, and satisfaction with social safety net appeared protective against the risk of suicide [54, 130]. For example, being service connected to a VA hospital health-care system appears to decrease the risk of suicidal behavior in war veterans with PTSD [68].

Additionally, considering findings by Kessler and colleagues [8] that 90% of first suicide attempts happened rapidly after formation of ideation, research into appropriate ways of providing social support to high-risk war veterans should be a top priority. The US Department of Defense, for example, has started instituting ways of screening for PTSD, comorbid psychiatric disorder, and other suicide risk factors in returning veterans, with a goal of decreasing growing suicidal activity observed in returning combat personnel and veterans [131].

Coping Mechanisms

Coping mechanisms modulate the symptoms of PTSD and can be exploited to reduce the risk of suicidal behavior associated with it. A study by Amira and colleagues [132] has shown that the risk of suicide was significantly associated with decreased use of minimization, replacement, and mapping psychological strategies and significantly related to increased suppression in patients diagnosed with PTSD, suggesting that diminished ability to deal with trauma and emotional impairment increases the risk of suicidal behavior. Solomon et al. [133] demonstrated that veterans who used more problem-solving and less emotion- and distance-based coping mechanisms were less likely to manifest symptoms of PTSD. Finally, an innovative study that looked at approximately 15,000 subjects demonstrated that trauma and PTSD can actually function as a coping strategy and reduce the risk of suicidal behavior [134], exemplifying a novel application of psychotherapy to treat the symptoms of PTSD and lower suicidal behavior.

Psychotherapy

Sareen et al. [135] has shown that military personnel exposed to combat trauma endorsed increased need for mental health service, such as counseling and therapy, and Shalev et al. [136] demonstrated that immediate and delayed prolonged exposure cognitive behavioral therapy (CBT) prevented PTSD in some traumatized patients. Jakupcak and Varra [137] recommend identifying veterans with PTSD at high risk for suicide and treating them with CBT, arguably the most popular psychotherapy technique currently employed in this patient population [138]. Refinement of the current and

innovation of novel psychotherapeutic techniques to target the symptoms of PTSD, comorbid psychiatric conditions, and associated impairment, including suicidality, is a promising direction for future research. Psychodynamic psychotherapy, hypnotherapy, and eye movement desensitization and reprocessing [140] are all examples of psychotherapeutic techniques that hold a promise for patients with PTSD.

Pharmacology in PTSD

As discussed by Chen and colleagues [27], immediate psychopharmacological intervention might mitigate some aspects of the psychiatric impairment associated with trauma exposure and PTSD, including suicidal behavior. Numerous studies have supported the use of selective serotonin reuptake inhibitors (SSRIs) in treating the symptoms of PTSD and associated psychiatric morbidities, and the Federal Drug Administration (FDA) has even approved two members of its class, fluoxetine and paroxetine [139–140, 143]. Nagy et al. [144], for example, has demonstrated that fluoxetine is efficacious in reducing PTSD symptoms of reexperiencing, avoidance, and hyperarousal, and Zohar et al. [145] have shown sertraline to be effective in reducing anger and emotional dysregulation in combat-traumatized PTSD veterans. Data on efficacy of SSRIs in PTSD has been inconsistent, however. For example, Martenyi and colleagues [146] suggested that fluoxetine might not be efficacious in veteran with PTSD, and Shalev and colleagues [136] demonstrated that escitalopram might not be useful in preventing PTSD symptoms in traumatized patients. Finally, a small study using only male subjects, by Hetzberg and colleagues [82], did not find fluoxetine to be more effective than placebo in reducing symptoms of PTSD in combat veterans.

Other classes of antidepressants have demonstrated some efficacy in reducing symptoms of PTSD, including in combat veteran populations, but unfavorable side effects make these medications less popular than SSRIs [139, 142, 147]. Similarly, antipsychotics, anticonvulsants, and benzodiazepines are not commonly employed on long-term basis due to an unclear cost-benefit analysis of these medications [141, 148]. Scarcity of data on pharmacological interventions in combat-traumatized PTSD patients should fuel a search for novel biological targets for psychotropic agents such as monoamine, glutamate and endocannabinoid neurotransmitter systems, neuropeptides, and components of the HPA axis as well as other neuroactive endocrine factors [14, 147–151]. Successful treatment of PTSD may reduce suicidality in patients with PTSD.

Table 8.3 Strategies in preventing suicidal behavior in combat-exposed patients with PTSD

Increasing active personnel and veteran awareness of suicidal behavior
Pre-deployment screening for risk factors for suicidal behavior
Deployment screening for risk factors for suicidal behavior
Post-deployment screening for risk factors for suicidal behavior
Increasing mental health access
Reducing military stigmatization of mental health problems and services
Promoting unit cohesiveness and raising awareness
Educating military personnel, friends, families, community leaders on suicide, PTSD, and other psychiatric disorders
Addressing symptoms of comorbid psychiatric disorders
Psychopharmacology
Psychotherapy
Gun removal

Conclusion

Nationally managed mental health-care access for the military personnel and veterans traumatized in combat can improve the quality of life and reduce suicidal behavior in this patient population [152]. Keuhn correctly noted that the cultural and logistical barriers in the military often impede proper mental health-care delivery to a patient population, often with complex psychiatric presentation [13]. Zamorsky et al. [153] emphasized proper screening, improvement of mental health recourses, and awareness of psychological problems as the fundamental tactics in decreasing suicidality among military personnel and veterans. "The Joshua Omvig Veterans Suicide Prevention Act" of 2007 [126] and the US House of Representatives Committee on Veterans' Affairs [154] acknowledged the issue of the increasing suicidal behavior and its relationship to PTSD and offered several sensible approaches to stabilizing the worrisome trend of increasing rate of death from suicide in the military. Screening for psychiatric symptoms before, during, and post-deployment, training staff, increasing regular and emergency mental health-care access, and educating families and friends of veterans and active duty personnel on the risk factors of suicide are all examples of innovative approaches the military is undertaking in order to tackle the growing problem of self-destructive behavior in its ranks (see Table 8.3).

References

1. World report on violence and health. http://who.int/violence_injury_prevention/violence/world_report/en/index.html. Accessed 1st Jan 2012.
2. Bolton JM, Robinson J. Population-attributable fractions of Axis I and Axis II mental disorders for suicide attempts: findings from a representative sample of the adult, noninstitutionalized US population. Am J Public Health. 2010;100(12):2473–80.

3. Bernal M, Haro JM, Bernert S, et al. Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord. 2007;101((1)-33):27–34.
4. Bonneux LG, Huisman CC, de Beer JA. Mortality in 272 European regions, 2002–2004. An Update. Eur J Epidemiol. 2010;25(2):77–85.
5. Beautrais AL. Suicide in Asia. Crisis. 2006;27(2):55–7.
6. Australian Bureau of Statistics. http://www.abs.gov.au. Accessed 1st Jan 2012.
7. Leading causes of death reports. National center for injury prevention and control. www.cdc.gov/ncipc/wisquars/default.htm. Accessed 1st Jan 2012.
8. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the national comorbidity survey. Arch Gen Psychiatry. 1999;56:617–26.
9. McCarthy JF. Suicide mortality among patients receiving care in the veterans health administration health system. Am J Epidemiol. 2009;169(8):1033–8.
10. Hendin H, Haas AP. Suicide and guilt as manifestations of PTSD in Vietnam combat veterans. Am J Psychiatry. 1991;148:586–91.
11. Hyer L, McCranie EW, Woods MG, et al. Suicidal behavior among chronic Vietnam theatre veterans with PTSD. J Clin Psychol. 1990;46:713–21.
12. Ilen MA, Bohnert ASB, Ignacio RV, et al. Psychiatric diagnoses and risk of suicide in veterans. Arch Gener Psychiatry. 2010;67(11):152–1158.
13. Kuehn BM. Soldier suicide rates continue to rise: military, scientists work to stem the tide. JAMA. 2009;301(11):1111. 1113
14. Sher L. Suicide in war veterans: the role of comorbidity of PTSD and depression. Expert Rev Neurother. 2009;9(7):921–3.
15. Pietrzak RH, Russo AR, Ling Q, et al. Suicidal ideation in treatment-seeking Veterans of Operations Enduring Freedom and Iraqi Freedom: the role of coping strategies, resilience, and social support. J Psychiatr Res. 2011;45(6):720–6.
16. Guerra VS, Calhoun PS. Examining the relation between posttraumatic stress disorder and suicidal ideation in an OEF/OIF veteran sample. J Anxiety Disord. 2011;25(1):12–8.
17. Kang HK, Bullman TA. Risk of suicide among US veterans after returning from the Iraq or Afghanistan war zones. JAMA. 2008;300(6):652–3.
18. Brent DA, Bridge J, Johnson BA, et al. Suicidal behavior runs in families. Arch Gen Psychiatry. 1996;53(12):11145–52.
19. Roy A. Genetic and biologic risk factors for suicide in depressive disorders. Psychiatry Q. 1993;64(4):345–58.
20. Roy A, Segal NL, Sarchiapone M. Attempted suicide among living co-twins of twin suicide victims. Am J Psychiatry. 1995;152(7):1075–6.
21. Pearce CM, Martin G. Predicting suicide attempts among adolescents. Acta Psychiatr Scand. 1994;90(5):324–8.
22. Andrews JA, Lewinsohn PM. Suicidal attempts among older adolescents: Prevalence and co-occurrence with psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 1992;31(4):655–62.
23. Johnsson-Fridell E, Ojehagen A, Traskman-Bendz L. A 5- year follow-up study of suicide attempts. Acta Psychiatr Scand. 1996;93(3):151–7.
24. Gutierrez PM, Thakkar RR, Kuczen C. Exploration of the relationship between physical and/or sexual abuse, attitudes about life and death and suicidal ideation in young women. Death Stud. 2000;24(8):675–88.
25. Dahl S. Acute response to rape—a PTSD variant. Acta Psychiatr Scand Suppl. 1989;355:56–62.
26. Loncar M, Medved V, Jovanovic N, et al. Psychological consequences of rape on women in 1991–1995 war in Croatia and Bosnia and Herzegovina. Croat Med J. 2006;47(1):67–75.
27. Chen CC, Yeh TL, Yang YK, et al. Psychiatric morbidity and post-traumatic symptoms among survivors in the early stage following the 1999 earthquake in Taiwan. Psychiatry Res. 2001;105(1–2):13–22.
28. Vehid HE, Alyanak B, Eksi A. Suicide ideation after the 1999 earthquake in Marmara. Tohoku J Exp Med. 2006;208(1):19–24.
29. Clarke DE, Colantonio A, Rhodes A, et al. Differential experiences during the holocaust and suicidal ideation in older adults in treatment for depression. J Trauma Stress. 2006;19(3):417–23.
30. Fergusson DM, Woodward LJ, Horwood LJ. Risk factors and life processes associated with the onset of suicidal behavior during adolescence and early adulthood. Psychol Med. 2000;30(1):23–39.
31. Garrison CJ, Jackson KL, Addy CL, et al. Suicidal behaviors in young adolescents. Am J Epidemiol. 1991;133:1005–14.
32. Weiss DS, Marmar CR, Schlenger WE, et al. The prevalence of lifetime and partial post-traumatic stress disorder in Vietnam theater veterans. J Trauma Stress. 1992;5:365–76.
33. Davidson JRT, Stein DF, Shalev SY, et al. Posttraumatic stress disorder: acquisition, recognition, course, and treatment. J Neuropsychiatry Clin Neurosci. 2004;16(2):135–47.
34. Davidson JR, Hughes D, Blazer DG, et al. Posttraumatic stress disorder in the community: an epidemiological study. Psychol Med. 1991;21:713–21.
35. Scurfield RM. Posttraumatic stress disorder in Vietnam veterans. New York: Plenum Press; 1993. p. 285–95.
36. Sareen J, Cox BJ, Stein MB, et al. Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. Psychosom Med. 2007;69(3):242–8.
37. Kotler M, Iancu I, Efroni R, et al. Anger, impulsivity, social support and suicide risk in patients with posttraumatic stress disorder. J Nerv Ment Dis. 2001;189(3):162–7.
38. Tarrier N, Gregg L. Suicide risk in civilian PTSD patients predictors of suicidal ideation, planning and attempts. Soc Psychiatry Psychiatr Epidemiol. 2004;39(8):655–61.
39. Druss B, Pincus H. Suicidal ideation and suicide attempts in general medical illnesses. Arch Intern Med. 2000;160(10):1522–6.
40. Weisberg R, Bruce S, Machan J, et al. Nonpsychiatric illness among primary care patients with trauma histories and posttraumatic stress disorder. Psychiatr Serv. 2002;53(7):848–54.
41. Schnurr PP, Friedman MJ, Sengupta A, et al. PTSD and utilization of medical treatment services among male Vietnam veterans. J Nerv Ment Dis. 2000;188(8):496–504.
42. Bruce SE, Weisberg RB, Dolan RT, et al. Trauma and posttraumatic stress disorder in primary care patients. Prim Care Compan J Clin Psychiatry. 2001;3(5):211–7.
43. Sareen J, Houlahan T, Cox BJ, Asmundson GJG. Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. J Nerv Ment Dis. 2005;193(7):450–4.
44. Khasakhala L, Sorsdahl KR, Harder VS, et al. Lifetime mental disorders and suicidal behavior in South Africa. Afr J Psychiatry (Johannesbg). 2011;14(2):134–9.
45. Marshall RD, Olfson M, Hellman F, et al. Comorbidity, impairment and suicidality in subthreshold PTSD. Am J Psychiatry. 2001;158:1467–73.
46. Chapman JF, Ford JD. Relationships between suicide risk, traumatic experiences, and substance use among juvenile detainees. Arch Suicide Res. 2008;12(1):50–61.
47. Mazza JJ, Reynolds MW. Exposure to violence in young Inner-City adolescents: relationships with suicidal ideation, depression, and PTSD symptomatology. J Abnorm Child Psychol. 1999;27(3):203–213A.
48. Chemtob CM, Pat-Horenczyk R, Madan A, et al. Israeli adolescents with ongoing exposure to terrorism: suicidal ideation, posttraumatic stress disorder, and functional impairment. J Trauma Stress. 2011;24(6):756–9.
49. Chemtob CM, Madam A, Berger P, et al. Adolescent exposure to the World Trade Center attacks, PTSD symptomatology, and suicidal ideation. J Trauma Stress. 2011;24(5):526–9.

50. Weaver TL, Allen JA, Hopper E, et al. Mediators of suicidal ideation within a sheltered sample of raped and battered women. Health Care Women Int. 2007;28(5):478–89.
51. Famularo R, Fenton T, Kinscherff R, et al. Psychiatric comorbidity in childhood post traumatic stress disorder. Child Abuse Neg. 1996;20(10):953–61.
52. Bell JB, Nye EC. Specific symptoms predict suicidal ideation in Vietnam combat veterans with chronic post-traumatic stress disorder. Mil Med. 2007;172(11):1144–7.
53. Jakupcak M, Cook J, Imel Z, et al. Posttraumatic stress disorder as a risk factor for suicidal ideation in Iraq and Afghanistan War veterans. J Trauma Stress. 2009;4(22):303–6.
54. Pietrzak RH, Goldstein MB, Malley JC, et al. Risk and protective factors associated with suicidal ideation in veterans of Operations Enduring Freedom and Iraqi Freedom. J Affect Disorders. 2010;123(1–3):102–7.
55. Thoresen S, Mehlum L. Traumatic stress and suicidal ideation in Norwegian male peacekeepers. J Nerv Ment Dis. 2008;196:814–21.
56. Maia DB, Marmar CR, Metzler T, et al. Posttraumatic stress symptoms in an elite unit of Brazilian police officers: prevalence and impact on psychosocial functioning and on physical and mental health. J Affect Disord. 2007;97:241–5.
57. Freeman TW, Roca V, Moore WM. Comparison of chronic combat-related Posttraumatic Stress Disorder (PTSD) patients with and without a history of suicide attempt. J Nerv Ment Dis. 2000;188(7):460–3.
58. Simon W. Attempted suicides among veterans. J Nerv Ment Dis. 1950;111(6):451–68.
59. Brenner LA, Betthauser LM, Homaifar BY, et al. Posttraumatic stress disorder, traumatic brain injury, and suicide attempt history among veterans receiving mental health services. Suicide Life Threat Behav. 2011;41(4):416–23.
60. Anderson BA, Howard MO, Walker RD, et al. Characteristics of substance-abusing veterans attempting suicide: a national study. Psychol Rep. 1995;77:1231–42.
61. Drescher R, CS BTA, et al. Causes of death among male veterans who received residential treatment for PTSD. J Trauma Stress. 2003;16(6):535–43.
62. Bullman TA, Kang HK. Posttraumatic stress disorder and the risk of traumatic deaths among Vietnam veterans. J Nerv Ment Dis. 1994;182(11):604–10.
63. Watanabe KK, Kang HK. Military service in Vietnam and the risk of death from trauma and selected cancers. Ann Epidemiol. 1995;5(5):407–12.
64. Boscarino JA. External-cause mortality after psychologic trauma: the effects of stress exposure and predisposition. Compr Psychiatry. 2006b;47:503–14.
65. Farberow NL, Kang HK, Bullman TA. Combat experience and postservice psychosocial status as predictors of suicide in Vietnam veterans. J Nerv Ment Dis. 1990;178(1):32–7.
66. Gradus JL, Qin P, Lincoln AK, et al. Posttraumatic stress disorder and completed suicide. Am J Epidemiol. 2010;171(6):721–7.
67. Krysinska K, Lester D. Post-traumatic stress disorder and suicide risk: a systematic review. Arch Suicide Res. 2010;14(1):1–23.
68. Zivin K, Kim HM, McCarthy JF, et al. Suicide mortality among individuals receiving treatment for depression in the veterans affairs health system: associations with patient and treatment setting characteristics. Am J Public Health. 2007;97(12):2193–8.
69. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
70. Kozariæ-Kovaèiæ D, Dubravka KH, Grubišiæ-Iliæ M. Posttraumatic stress disorder and depression in soldiers with combat experiences. Croat Med J. 2001;42(2):165–70.
71. Brady KT, Killeen TK, Brewerton T, et al. Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry. 2000;61:22–32.
72. Warshaw MG, Massion AO, Peterson LG, et al. Suicidal behavior in patients with panic disorder: retrospective and prospective data. J Affect Disord. 1995;34(3):235–47.
73. Brown TA, Campbell LA, Lehman CL, et al. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol. 2001;110(4):585–99.
74. North CS, Nixon SJ, Shariat S, et al. Psychiatric disorders among survivors of the Oklahoma City bombing. JAMA. 1999;282(8):755–62.
75. Davis GC, Peterson EL, Schultz L. Psychiatric sequelae of posttraumatic stress disorder in women. Arch Gen Psychiatry. 1997;54(1):81–7.
76. Fullerton CS, Ursano RJ, Epstein RS, et al. Peritraumatic dissociation following motor vehicle accidents: relationship to prior trauma and prior major depression. J Nerv Ment Dis. 2000;188(5):267–72.
77. Shalev AY, Freedman S, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry. 1998;155(5):630–7.
78. Rihmer Z. Suicide risk in mood disorders. Curr Opin Psych. 2007;20(1):17–22.
79. Kramer TL, Lindy JD, Green BL, et al. The comorbidity of posttraumatic stress disorder and suicidality in Vietnam veterans. Suicide Life Threat. 1994;24(1):58–67.
80. Oquendo M, Friend JM, Halberstam B, et al. Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. Am J Psychiatry. 2003;160(3):580–2.
81. Oquendo M, Brent DA, Birmaher B, Greenhill L, Kolko D, Stanley B, Zelazny J, Burke AK, Firinciogullari S, Ellis SP, Mann JJ. Posttraumatic stress disorder comorbid with major depression: factors mediating the association with suicidal behavior. Am J Psychiatry. 2005;162(3):560–6.
82. Hertzberg MA, Feldman ME, Beckham JC, et al. Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans. Ann Clin Psychiatry. 2000;12(2):101–5.
83. Wunderlich U, Bronisch T, Wittchen HU. Comorbidity patterns in adolescents and young adults with suicide attempts. Eur Arch Psychiatry Clin Neurosci. 1998;248(2):87–95.
84. Dilsaver SC, Benazzi F, Akiskal HS. Post-traumatic stress disorder among adolescents with bipolar disorder and its relationship to suicidality. Bipolar Disord. 2009;9(6):649–55.
85. Weili L, Mueser KT, Rosenberg ST, et al. Correlates of adverse childhood experiences among adults with severe mood disorders. Psychiatr Serv. 2008;59(9):1018–26.
86. Lucas C, Quarantini Â, Miranda S, et al. The impact of comorbid posttraumatic stress disorder on bipolar disorder patients. J Affect Disord. 2010;123(1–3):71–6.
87. Cohen CI, Abdallah CG, Diwan S. Suicide attempts and associated factors in older adults with schizophrenia. Schizophr Res. 2010;119(1–3):253–7.
88. Tarrier N, Picken A. Co-morbid PTSD and suicidality in individuals with schizophrenia and substance and alcohol abuse. Soc Psychiatry Psychiatr Epidemiol. 2011;46(11):1079–86.
89. Strauss J, Calhoun P, Marx C, et al. Comorbid posttraumatic stress disorder is associated with suicidality in male veterans with schizophrenia or schizoaffective disorder. Schizophr Res. 2006;84(1):165–9.
90. Tarrier N, Khan S, Cater J, et al. The subjective consequences of suffering first episode psychosis: trauma and suicide behavior. Soc Psychiatry Psychiatr Epidemiol. 2007;42(1):29–35.
91. Pietrzak RH, Goldstein RB, Southwick SM, et al. Prevalence and Axis I comorbidity of full and partial posttraumatic stress dis-

order in the United States: results from Wave 2 of the National Epidemiologic Survey on alcohol and related conditions. J Anxiety Disord. 2011;25(3):456–65.
92. Brent DA, Perper JA, Moritz G, et al. Posttraumatic stress disorder in peers of adolescent suicide victims: predisposing factors and phenomenology. J Am Acad Child Adolesc Psychiatry. 1999;34(2):209–15.
93. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048–60.
94. Capron DW, Cougle JR, Ribeiro JD, et al. An interactive model of anxiety sensitivity relevant to suicide attempt history and future suicidal ideation. J Psychiatr Res. 2011;46(2):174–80. [Epub ahead of print]
95. Hapke U, Schumann A, Rumpf HJ, et al. Post-traumatic stress disorder: the role of trauma, pre-existing psychiatric disorders, and gender. Eur Arch Psychiatry Clin Neurosci. 2006;256(5):299–306.
96. Ferrada-Noli M, Asberg M, Ormstad K, et al. Suicidal behaviour after severe trauma, part 1: PTSD diagnoses, psychiatric comorbidity and assessments of suicidal behaviour. J Trauma Stress. 1998;11:103–12.
97. Pietrzak HR, Risë B, Goldstein SM, et al. Personality disorders associated with full and partial posttraumatic stress disorder in the U.S. population: results from Wave 2 of the National Epidemiologic Survey on alcohol and related conditions. J Psychiatr Res. 2011;45(5):678–86.
98. Zanarini MC, Frankenburg FR, Dubo ED, et al. Axis I comorbidity of borderline personality disorder. Am J Psychiatry. 1998;155(12):1733–9.
99. Pagura J, Steinb MB, Boltona JM, et al. Comorbidity of borderline personality disorder and posttraumatic stress disorder in the U.S. population. J Psychiatr Res. 2010;44(16):1190.
100. Brodsky BS, Mann JJ. Risk factors for suicidal behavior in borderline personality disorder. J Calif Alliance Ment Ill. 1997;8:27–8.
101. Zanarini MC, Gunderson JG, Marino MF, et al. Childhood experiences of borderline patients. Compr Psychiatry. 1989;30(1):18.
102. Goldman SJ, D'Angelo EJ, DeMaso DR, et al. Physical and sexual abuse histories among children with borderline personality disorder. Am J Psychiatr. 1992;149(12):1723.
103. Herman JL, Perry JC, van der Kolk BA. Childhood trauma in borderline personality disorder. Am J Psychiatr. 1989;146(4):490.
104. Herman JL. Complex PTSD: a syndrome in survivors of prolonged and repeated trauma. J Trauma Stress. 1992;5(3):377.
105. Heffernan K, Cloitre M. A comparison of posttraumatic stress disorder with and without borderline personality disorder among women with a history of childhood sexual abuse: etiological and clinical characteristics. J Nerv Ment Dis. 2000;188(9):589.
106. Nepon J, Pagura J, Sreen J. Limitations of report of suicidal behavior among women with co-occurring PTSD and borderline personality disorder. Am J Psychiatry. 2010;167(10):1152–4.
107. Nepon J, Belik SL, Bolton J, et al. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on alcohol and related conditions. Depress Anxiety. 2010;27(9):791–8.
108. Harned MS, Rizvi SL, Linehan MM. Impact of co-occurring posttraumatic stress disorder on suicidal women with borderline personality disorder. Am J Psychiatry. 2010;167(10):1210–7.
109. Mills KL, Teesson M, Ross J, et al. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of mental health and well-being. Am J Psychiatry. 2006;163(4):651–8.
110. Cottler LB, Compton WM, Mager D, et al. Posttraumatic stress disorder among substance users from the general population. Am J Psychiatry. 1992;149(5):664–70.
111. Creamer M, Burgess P, McFarlane AC. Post-traumatic stress disorder: findings from the Australian National Survey of mental health and well-being. Psychol Med. 2001;31(7):1237–47.
112. Moylan PL, Jones HE, Haug NA, et al. Clinical and psychosocial characteristics of substance-dependent pregnant women with and without PTSD. Addict Behav. 2001;26(3):469–74.
113. Najavits LM, Weiss RD, Shaw SR. A clinical profile of women with PTSD and substance dependence. Psychol Addict Behav. 1999;13:98–104.
114. Panagioti M, Gooding P, Tarrier N. Post-traumatic stress disorder and suicidal behavior: a narrative review. Clin Psychol Rev. 2009; 29(6):471–82.
115. Harned MS, Najavitsm LM, Weiss RD. Self-harm and suicidal behavior in women with comorbid PTSD and substance dependence. Am J Addict. 2006;15(5):392–5.
116. Maloney E, Degenhardt L, Darke S, et al. Suicidal behavior and associated risk factors among opioid-dependent individuals: a case–control study. Addiction. 2007;102(12):1933–41.
117. Stein MB, Walker JR, Hazen AL, et al. Full and partial posttraumatic stress disorder: findings from a community survey. Am J Psychiatry. 1997;154(8):1114–9.
118. Breslau N. The epidemiology of trauma, PTSD, and other posttrauma disorders. Trauma Violence Abuse. 2009;10(3):198–210.
119. Davidson JRT, Hughes DC, George LK, et al. The association of sexual assault and attempted suicide within the community. Arch Gen Psychiatry. 1996;53(6):550–5.
120. Stein DJ, Chiu WT, Hwang I, et al. Cross-national analysis of the associations between traumatic events and suicidal behavior: findings from the WHO World Mental Health Surveys. PLoS One. 2010;5(5):e10574.
121. Belik SL, Cox BJ, Stein MB, et al. Traumatic events and suicidal behavior: results from a national mental health survey. J Nerv Ment Dis. 2007;195(4):342–9.
122. Molnar B, Berkman L, Buka S. Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behavior in the US. Psych Med. 2001;31(6):965–77.
123. Nelson C, Cyr KS, Corbett B, et al. Predictors of posttraumatic stress disorder, depression, and suicidal ideation among Canadian Forces personnel in a National Canadian Military Health Survey. J Psychiatr Res. 2011;45(11):1483–8.
124. Wilcox HC, Storr CL, Breslau N. Posttraumatic stress disorder and suicide attempts in a community sample of urban American young adults. Arch Gen Psychiatry. 2009;66(3):305–11.
125. Boscarino JA. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. Psychosom Med. 1997;59(6):605–14.
126. Joshua Omvig Veterans Suicide Prevention Act Prevention Act. 38 USC 101 note. Public Law 110–110. Nov. 5, 2007.
127. Kaslow NJ, Thompson MP, Okun A, et al. Risk and protective factors for suicidal behavior in abused African American women. J Consult Clin Psychol. 2002;70(2):311–9.
128. Thoresen S, Mehlum L, Røysamb E, et al. Risk factors for completed suicide in veterans of peacekeeping: repatriation, negative life events, and marital status. Arch Suicide Res. 2006;10:353–63.
129. Veiel HO, Brill G, Haefner H, et al. The social supports of suicide attempters: the different roles of family and friends. Am J Community Psychol. 1998;16(6):839–61.
130. Jakupcak M, Vannoy S, Imel Z, Cook JW, et al. Does PTSD moderate the relationship between social support and suicide risk in Iraq and Afghanistan War Veterans seeking mental health treatment? Depress Anxiety. 2010;27(11):1001–5.
131. Quinlan JD, Guaron MR, Deschere BR, et al. Care of the returning veteran. Am Fam Physician. 2000;82(1):43–9.
132. Amira M, Kaplanb ZR, Efronia MK. Suicide risk and coping styles in posttraumatic stress disorder patients. Psychother Psychosom. 1999;68:76–81.
133. Solomon Z, Mikulincer M, Flum H. Negative life events, coping responses, and combat-related psychopathology: a prospective study. J Abnorm Psychol. 1988;97:302–7.

134. Bush NE, Skopp NA, McCann R, et al. Posttraumatic growth as protection against suicidal ideation after deployment and combat exposure. Mil Med. 2011;176(11):1215–22. (8)
135. Sareen J, Cox BJ, Afifi TO, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care findings from a large representative sample of military personnel. Arch Gen Psychiatry. 2007;64(7):843–52.
136. Shalev AY, Ankri Y, Israeli-Shalev Y, et al. Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach and Prevention Study. Arch Gen Psychiatry. 2011;69(2):166–76. [Epub ahead of print]
137. Jakupcak M, Varra EM. Treating Iraq and Afghanistan war veterans with PTSD who are at high risk for suicide. Cogn Behav Pract. 2011;18(1):85–97.
138. Harvey AG, Bryant RA, Tarrier N. Cognitive behavior therapy for posttraumatic stress disorder. Clin Psychol Rev. 2003;23(3):377–407.
139. Friedman MJ, Donnelly CL, Mellman TA. Pharmacotherapy for PTSD. Psychiatr Ann. 2003;33(1):157–62.
140. Foa EB, Keane TM, Friedman MJ. Guidelines for treatment of PTSD. J Trauma Stress. 2000;13(4):537–52.
141. Jeffreys M. Clinician's guide to medications for PTSD. http://www.ptsd.va.gov/professional/pages/clinicians-guide-to-medications-for-ptsd.asp. Accessed 1 Jan 2012.
142. Davidson J, Roth S, Newman E. Fluoxetine in post-traumatic stress disorder. J Trauma Stress. 1990;4(3):419–23.
143. Martin MA, Stein MB. Oxford handbook of anxiety and related disorders. San Diego: Oxford University Press; 2009. p. 404–11.
144. Nagy LM, Morgan CA, Southwick SM, et al. Open prospective trial of fluoxetine for posttraumatic stress disorder. J Clin Psychopharmacol. 1993;13(2):107–13.
145. Zohar J, Amital D, Miodownik C, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharmacol. 2002;22(2):190–5.
146. Martenyi F, Brown EB, Caldwell CD. Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study. J Clin Psychopharmacol. 2007;27(2):166–70.
147. Butterfield MI, Stechuchak KM, Connor KM, Davidson JRT, Wang C, MacKuen CL, Pearlstein AM, Marx CE. Neuroactive steroids and suicidality in posttraumatic stress disorder. Am J Psychiatry. 2005;162:2.
148. Baker DG, Nievergelt CM, Risbrough VB. Post-traumatic stress disorder: emerging concepts of pharmacotherapy. Expert Opin Emerg Drugs. 2009;14(2):251–72.
149. Oquendo MA, Echavarria G, Galfalvy HC, et al. Lower cortisol levels in depressed patients with comorbid post-traumatic stress disorder. Neuropsychopharmacology. 2003;28(3):591–8.
150. Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatry. 2001;62:41–6.
151. Kovacic Z, Henigsberg N, Pivac N, et al. Platelet serotonin concentration and suicidal behavior in combat related posttraumatic stress disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32(2):544–51.
152. Sher L. Preventing suicide in posttraumatic stress disorder. Aust N Z J Psychiatry. 2009;43(7):691–2.
153. Zamorski MA. Suicide prevention in military organizations. Int Rev Psychiatry. 2011;23(2):173–80.
154. Department of Veterans Affairs. The comprehensive VHA mental health strategic plan. Washington, DC: Department of Veterans Affairs; 2005.

Part III

Neuroscience PTSD and Sleep

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There are few clinical problems in the sleep medicine field that are more challenging to impact than the sleep difficulties experienced by individuals suffering from PTSD. They are instantly recognizable, unique in their presentation, and relatively impervious to change. In individuals with normal sleeping patterns prior to their traumatic exposure, a traumatic event can change a lifetime of sleep in those individuals affected. From that moment on, their ability to obtain what for others would seem to be commonplace is no longer obtainable.

That an isolated behavioral event associated with an extreme emotional reaction can leave such a lasting imprint on such a complex behavior as sleep, arousal, and dreaming implies some sort of permanent neurological trace in a fundamental cog of the working mind. In this manner, an experience alone, and without direct physical contact or perturbation, can have as long-lasting impact as if the individual had suffered an acute stroke where physical damage to a neuronal circuit has occurred. Critical to understanding what has happened requires a detailed understanding and investigation of the neural systems underlying these emotions, behaviors, and processes.

The chapters that follow begin this scientific journey and explanation, though further research is desperately needed to understand this complex of events and to clarify mechanisms by which they can be either protected against, the damage lessened, or once present, managed efficiently to sustain a meaningful life.

The individual chapters in this section follow the current windows into brain function available to the neuroscientist ranging from animal models of memory to genetic studies, functional and structural neuroanatomical approaches, and to the use of radioligands to study the neurochemistry of the disorder. As in the use of these techniques for many disorders, each has its strengths and limitations, and neurobiological models that can connect, span, and distil information across these multiple approaches are needed.

As these chapters demonstrate, extensive advances have been made in bridging the basic science of fear conditioning, a key construct for understanding PTSD, and the neurochemistry, genetics, and functional and structural alterations demonstrated in PTSD as a disorder. Alterations in the amygdala, the hippocampus, the prefrontal cortex, the anterior cingulate cortex and insula, as well as in the neurochemical alteration of their function, each of which can be linked to neurobiological mechanisms of fear conditioning, have been described. Still, bridges between these links and the mechanisms and treatment of the sleep disturbances unique to PTSD remain in their infancy. While less focused on results or conclusions in relation to

PTSD sleep disturbances, these authors outline exciting hypothetical models that can be tested in future studies. As sleep is among the most crippling of the disorders that PTSD patients face and clinicians loathe to overcome, these insights are a welcome addition to our knowledge base, and we should look forward to gleaning new insights as this work progresses.

Genetics of Post-traumatic Stress Disorder and Sleep Disturbance

9

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Introduction

Approximately 50% of military personnel returning from Afghanistan and Iraq (Operation Enduring Freedom and Operation Iraqi Freedom) have experienced combat [1]. For those who have served in Iraq, that number may be as high as 80% [2]. Given the nature of combat and the likelihood of experiencing a traumatic event during military service, it is not surprising the rate of post-traumatic stress disorder (PTSD) among veterans is relatively high when compared to civilians. Indeed, estimates suggest 11–30% of veterans who serve during periods of conflict ultimately develop PTSD [2–4], and the current prevalence of PTSD in OEF/OIF veterans has been estimated at 23% [5]. Among veterans with PTSD, sleep complaints are one of the most common concerns reported, often providing motivation for seeking treatment [6, 7]. Further, disruptions in sleep, particularly rapid eye movement (REM) sleep, can affect consolidation of extinction learning, a key ingredient to exposure-based PTSD treatment, in animal (e.g., [8]) and human studies [9, 10]. Recent prospective research shows that poor sleep may be a predictor of future PTSD symptoms (e.g., [11]), providing additional support for relationship between these phenotypes.

PTSD-related sleep disturbances consist of two distinct phenomena. First, individuals with PTSD frequently report concerns regarding their sleep quality, citing difficulties initiating or maintaining sleep. The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders [DSM-5] lists sleep difficulties in the PTSD symptom cluster describing changes in arousal and reactivity [Criterion E] [12]. Although poor sleep is not specific to PTSD, the likelihood of sleep difficulties is greatly enhanced among individuals suffering from PTSD [13, 14]. For example, Neylan and colleagues [13] examined the prevalence of sleep disturbances among a sample of Vietnam veterans with and without PTSD. Among veterans with PTSD, 44% reported frequent difficulties with sleep onset, compared to only 9% of veterans without PTSD and 6% of civilians without PTSD. Similarly, 91% of veterans with PTSD reported frequent difficulties remaining asleep throughout the night, compared to 63% of veterans without PTSD and 53% of civilians without PTSD.

A second sleep-related concern commonly reported among veterans with PTSD is recurrent nightmares [15, 16]. Although the content of nightmares varies, trauma-related nightmares often consist of repeatedly replaying the traumatic event over in one's dreams [17]. This reliving of the traumatic event is generally accompanied by a strong, negative emotional reaction. As such, the DSM-5 includes trauma-related nightmares in the intrusion symptom cluster for PTSD [Criterion B] [12]. Neylan and colleagues [13] reported that 52% of Vietnam veterans with PTSD experienced frequent nightmares, compared to 5% of veterans without PTSD and 4% of civilians without PTSD. Not only do these trauma-related nightmares cause significant distress among veterans with PTSD, they also negatively impact sleep quality due to frequent awakenings [18, 19].

Research elucidating the risk factors for PTSD and sleep difficulties has been increasing in the recent years. Both environmental and genetic (including epigenetic) factors play a role in posttrauma outcomes. The goals of this article are (1) to briefly review research methodologies utilized in psychiatric genetics, (2) to examine the existing evidence for quantitative and genomic variation that has been associated with increased risk for – or resilience to – PTSD in humans, (3) to

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provide a brief review of the genetically informed literature on sleep phenotypes and how this may be related to PTSD, and (4) to discuss future directions for genetic approaches in examining relationships between sleep and PTSD.

Genetic Methodology Overview

There are a number of approaches for investigating genetic influences on various outcomes (referred to as phenotypes in the genetic literature). A few primary approaches will be reviewed briefly here; the interested reader can see [20] for a more detailed account.

Quantitative genetic studies are concerned with determining the extent to which a particular disorder is heritable (i.e., a^2, the proportion of variance attributed to genes), has common environmental effects (i.e., c^2, the effect of environmental factors common to a pair of relatives), and has nonshared environmental effects (i.e., e^2, the effect of environmental factors unique to a particular individual). Quantitative genetic studies often rely on twin or adoption samples, in which the degree of phenotypic similarity between individuals with shared genes and/or environment (e.g., monozygotic versus dizygotic twins) may be determined.

Molecular genetic studies seek to identify variants in the human genome that differ among individuals with and without phenotypes of interest. The two most commonly studied forms of variation are single nucleotide polymorphisms (SNPs), which occur when a single nucleotide in the DNA sequence is altered to form different alleles (i.e., various forms of a genetic locus), and variable number tandem repeat (VNTR) polymorphisms, which are segments of repeated base pairs, forming alleles of different lengths. Recent focus in molecular genetics has been on copy number variation, in which one or more sections of DNA are altered and a loss or gain of DNA sequence results. Put simply, gene-finding efforts are aimed at the identification of sites across the genome where a form of an allele is present in a higher percentage of cases versus controls. Approaches used in molecular studies can be theory driven (i.e., candidate gene studies) or agnostic (i.e., genome-wide association studies; GWAS). While candidate studies involve theoretically based gene selection, GWAS take an agnostic approach and compare frequencies of hundreds of thousands of SNPs across the entire genome of cases to those of controls. GWAS are especially powerful when genetic variations with appreciable frequency in the population at large, but relatively low penetrance, are the major contributors to genetic susceptibility to common diseases. With the decreasing costs of sequencing and the introduction of the Psychiatric Genomics Consortium (see below for more details), GWAS have become important in the identification of key causal variants underlying psychiatric disorders.

Gene-environment interplay is particularly important to consider for disorders such as PTSD that are contingent on an environmental event. Gene-environment interplay involves investigating the relationships between various genetic and environmental factors as they relate to a particular phenotype and includes two primary approaches: gene-environment interaction and gene-environment correlation. *Gene-environment interactions* (GxE) can be thought of in terms of the genetic variation modifying the relationship between environmental exposure (e.g., a traumatic event) and the phenotype (e.g., PTSD) or the environment modifying the effect of genetic variation on an outcome. Common examples of GxE in the PTSD literature are that genotype may influence how someone responds to a trauma (i.e., whether or not they go on to develop PTSD) or that genetic variation may only influence the development of PTSD at a specific trauma threshold. As environmental influences (e.g., work schedule, stress, medication use) significantly affect sleep, GxE designs are also important for sleep phenotypes [21]. *Gene-environment correlation* (rGE), on the other hand, refers to the extent to which individuals create and influence their own environments [22]. In other words, rGE reflects the passive and active ways in which an individual's genotype influences their subsequent environment. For example, genetic variation may influence an individuals' likelihood of enlisting for military service, which in turn increases their chance of experiencing combat trauma, or genetic variation may predispose individuals to a higher amount of caffeine consumption, which can then affect sleep.

Epigenetic factors also have gained increased attention in the molecular genetic literature. First coined in 1940 by Waddington, epigenetics is the study of mitotically heritable (i.e., through mitosis), but reversible, changes in gene expression occurring without a change in the DNA sequence and brought about through alterations in DNA methylation and chromatin structure [23–25]. It represents an alternative and quicker mechanism by which an organism responds to challenges such as traumatic events, dietary states, or prolonged infection posed by the environment within its lifetime [26]. In the last two decades, three major areas of epigenetic studies have emerged: (i) histone modification that affects nucleosome structure, (ii) DNA methylation, and (iii) DNA modification through RNA interference.

Genetic Studies of PTSD

Twin Studies

As reviewed in detail by our team [27] and others [28], twin studies suggest risk for both trauma exposure and PTSD is partially explained by genetic factors in both veteran and civilian populations. Using a civilian sample, Kendler and

Baker [29] found the heritability of negative life events to be 39% and that for traumatic event exposure to be 36%. The heritability of PTSD is estimated to range from 30% [30, 31] to 70% [32], even after controlling for the genetic influences on trauma. Most recently, Wolf and colleagues [33] used a sample of veterans to examine the moderating effects of combat exposure on PTSD. They found that combat exposure severity significantly moderated both genetic and environmental influences on PTSD, such that associations were stronger for individuals with higher combat exposure [33]. Data from twin studies on PTSD indicate the majority of genes that affect risk for PTSD also influence risk for other psychiatric disorders and vice versa and this genetic risk may also be shared with sleep problems, though this is yet to be tested.

Molecular Genetic Studies

There is a large literature of molecular genetic studies of PTSD, which has grown immensely over the past 5 years. Over 100 candidate gene studies have been published to date, exploring a wide range of genes with potentially plausible mechanisms to relate them to PTSD. We will provide an overview of key genes, as it is outside the scope of this chapter to thoroughly cover all candidate gene studies. The interested reader is directed to more comprehensive reviews of this rapidly changing literature [34–36].

Early studies focused on polymorphisms in the serotonin transporter gene (*5-HTTLPR*), which has been studied in the context of many different psychiatric disorders. There are two meta-analyses that summarize the research on the *5-HTTLPR* polymorphism and PTSD [37, 38]. Both found that there was no association between *5-HTTLPR* and PTSD, although there was some evidence to suggest that the SS genotype may only influence the development of PTSD in a highly trauma-exposed sample [38]. Another neurotransmitter system that has been widely studied in the context of PTSD is the dopaminergic system. There have been analyses of the dopamine transporter gene (*DAT*) and dopamine receptors (*DRD2*, *DRD3*, *DRD4*), with some successes (e.g., [39, 40–43]). The brain-derived neurotrophic factor (*BDNF*) gene has also been analyzed with PTSD in multiple studies. A recent meta-analysis of the Val66Met *BDNF* polymorphism found that overall, there was no association between *BDNF* and PTSD. However, analyses stratified by trauma exposure (some studies used non-trauma-exposed controls, as opposed to fully trauma-exposed samples) indicated that *BDNF* may have an influence when trauma-exposed controls are used as a comparison [44].

Increased focus has been placed on genes involved in the hypothalamic-pituitary-adrenal axis, which plays an important role in the stress response and thus represents a highly plausible physiological mechanism by which variation in these genes may directly affect PTSD. Genes examined include the glucocorticoid receptor (*GR*), corticotrophin-releasing hormone receptor 1 (*CRHR1*), and FK-506 binding protein 5 (*FKBP5*), which are all involved in the glucocorticoid/cortisol pathway of the stress response. *FKBP5* has been examined across many candidate gene studies of PTSD, with multiple significant associations in both traditional candidate gene and GxE analyses (e.g., [45, 46–49]). Studies examining *CRHR1*, using very different samples, have also found significant associations between several SNPs and PTSD [50]. This literature is small but suggests that *CRHR1* may be an important gene in the development of PTSD. There is also some evidence for the involvement of the glucocorticoid receptor (e.g., [51]). Most recently, several studies examining a SNP within the PACAP receptor gene (adenylate cyclase-activating polypeptide 1 receptor type I; *ADCYAP1R1*), rs2267735, have found significant associations with PTSD [52–54]. This gene is also related to the stress response. These findings have been particularly robust for females, which may be related to estrogen-related influence on the PACAP-PAC1 pathway regulation of the cellular stress response [52]. However, not all studies have replicated this finding in independent samples [55, 56].

Genome-Wide Association Studies

Despite the large number of candidate gene studies published, only some have been replicated, and overall findings are mixed. Further, none of the candidate genes studied to date have been significant in GWAS studies. However, it is important to note that genome-wide studies of PTSD are still in their infancy, compared to GWAS of other psychiatric phenotypes such as schizophrenia [57] and even depression [58, 59], and that even across these other phenotypes, candidate genes are not showing up in GWAS. There are currently seven GWAS of PTSD and related phenotypes (see Table 9.1), which will be summarized here. Five of the studies used primarily veteran samples, which were assessed with standard clinical PTSD measures (e.g., Clinician-Administered PTSD Scale [CAPS], Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders [SCID]). The remaining two used epidemiologic samples collected for other studies. The majority focused on PTSD diagnostic status, with only Wolf and colleagues [60] examining a dissociative subtype of PTSD and using symptom severity as an outcome.

Logue and colleagues [61], in the first GWAS of PTSD in veterans, used a relatively small sample of trauma-exposed

Table 9.1 Genome-wide association studies of PTSD

Author (year)	Trauma type	Case ascertainment (setting, method)	Cases (% male)	Controls (% male)	Mean (SD) age	Control exposed?	Ethnicity	Gene identified?	SNP identified?	Summary of findings
Logue et al. (2013) [61]	Combat trauma (most common), various	Setting: VA sample	NHW: 295	NHW: 195 (NR)	51.5 (10.9) in trauma-exposed subsample	Y	US/NHW	*RORA*	rs8042149	NHW: rs8042149 (*RORA*, linked to other psychiatric disorders) associated with PTSD (genome wide)
		Method: CAPS	(65% male in total sample)	AA1: 41 (NR)			US/AA			AA: 2 other *RORA* SNPs nominally significant; only the SNP in veterans survived correction
			AA1: 43 (NR)	AA2: 421 (NR)						
			AA2: 100 (NR)							
Xie et al. (2013) [67]	Various	Setting: university clinics	AA: 444 (45.7)	AA: 2322 (56.9) NHW: 1278 (64.6)	AA: 41.5 (8.7) NHW: 37.7 (9.8)	N (initially; restricted later)	US/NHW	*TLL1*	rs406001	Genome-wide significant: rs406001 (chromosome 7p12)
		Method: SSADDA, DSM-IV	NHW: 300 (39.7)				US/AA		rs6812849	Next best association: *TLL1* gene
									rs7691872	6 *TLL1* SNPs tested in independent replication sample; rs6812849 and rs7691872 were successfully replicated in EAs; none for AAs
										Restricted analyses to TEs only: did not change results
Guffanti et al. (2013) [68]	Various	Setting: DNHS sample; longitudinal cohort study	94 (0)	319 (0)	52.2 (13.5) [cases]; 54.3 (15.9) [controls]	Y	US/AA	lincRNA AC068718.1	rs10170218	Genome-wide significant: rs10170218 (lincRNA AC068718.1 gene)
		Method: structured telephone interview								"Suggestive" evidence for replication in NHSII sample
										Top hits enriched for telomere and immune pathways

Wolf et al. (2014) [60]	Combat, various	Setting: VA clinic	293 (65% male in total sample)	191 (NR)	52 (R = 21–75)	Y	US/NHW	*ADCY8*	rs263232	No significant associations
		Method: CAPS						*PBB6*	rs71534169	rs263232 (*ADCY8*; involved in memory/ LTP) most significant SNP
										rs71534169 (*PBB6*; involved in synaptic processes) also suggestive
Nievergelt et al. (2015) [64]	Combat	Setting: veteran sample	940 [100]	2554 [100]	23.1 (3.4)	Y	US/multiethnic	*PRTFDC1*	rs6482463	*PRTFDC1* (rs6482463) was genome-wide significant via meta-analysis and replicated in an independent sample
		Method: CAPS								25 loci had suggestive associations
										PTSD associated with BPD risk score in PRS analysis

(continued)

Table 9.1 (continued)

Author (year)	Trauma type	Case ascertainment (setting, method)	Cases (% male)	Controls (% male)	Mean (SD) age	Control exposed?	Ethnicity	Gene identified?	SNP identified?	Summary of findings
Ashley-Koch et al. (2015) [65]	Combat	Setting: VA and university clinic	AA: 949 total (69.7% total)	–	AA: 39.06 (9.73)	Y	US/NHW	AA: *UNC13C*	See next column	No SNPs with genome-wide significance
		Method: SCID, CAPS			NHW: 36.28 (10.44)		US/AA			Best SNPS in AAs: rs10768747, rs17504106, rs73419609, rs2862383, rs834811
			NHW: 759 total (84.9% total)					*DSCAM*		Best SNPs in NHW: rs7866350, rs1116255, rs2437772, rs61793204
								NHW: *TBC1D2*		Best SNPs in meta-analysis (NHW and AA combined): rs12232346, rs10762479, rs10002308
								SDC2		Pathway analysis: alternative splicing
								PCDH7		
								Combined: *PRKG1*		
								DDX60L		

Stein et al. (2016) [66]	Various	Setting: army cohorts (NSS and PPDS)	NSS: 3167 (78.4)	NSS: 4507 (82.3)	20.9 [33] in NSS; 26.5 (6.0) in PPDS	Y (both)	US/EA	AA (NSS): *ANKRD55*	rs159572	In the NSS sample, both rs159572 (*ANKRD55*) in AAs and rs11085374 (*ZNF626*) in EAs reached genome-wide significance. These loci were not replicated in the PPDS sample, in other ancestries, or when combined
		Method: CIDI screening scales and PCL	PPDS: 947 (92.5)	PPDS: 4969 (94.7)			US/AA	EA (NSS):	rs11085374	SNP-based heritability from GCTA was not significant
							US/Latino American	*ZNF626*		There were no significant genetic correlations between PTSD and other disorders; however there was pleiotropy between PTSD and rheumatoid arthritis/ psoriasis

AA African-American, *CAPS* Clinician-Administered Post-traumatic Stress Disorder Scale, *Ca* cases, *CIDI* Composite International Diagnostic Interview, *Co* controls, *DNHS* Detroit Nurses' Health Study, *EA* European American, *LTP* long-term potentiation, *NHW* non-Hispanic White, *NR* not reported, *NSS* New Soldier Study, *PCL* PTSD Checklist, *PPDS* Pre/Post Deployment Study, *PRS* polygenic risk score, *PTSD* post-traumatic stress disorder, *SCID* Structured Clinical Interview for DSM Disorders, *SD* standard deviation, *SNP* single nucleotide polymorphism, *SSADDA* semi-structured assessment for drug dependence and alcoholism, *TE* trauma exposed, *VA* Veterans Affairs

veterans and their partners and found that rs8042149, a SNP in the retinoid-related orphan receptor alpha (RORA) gene, was significantly associated with PTSD. Other SNPs in *RORA* were found to be nominally significant in replication samples tested within this paper. Support for the association between rs8042149 and PTSD has also been shown in other samples, such as an epidemiologic cohort with hurricane exposure [62]. However, other studies have failed to replicate the association [63]. Nievergelt and colleagues also used a veteran sample, the Marine Resiliency Study, for their primary analysis [64]. With all ancestry groups combined, there was one locus that reached genome-wide significance, phosphoribosyl transferase domain containing 1 gene (*PRTFDC1*; rs6482463), and was replicated in an additional military sample. There were also 25 loci with suggested associations. The authors further examined the genetic architecture of PTSD by analyzing polygenic risk scores across bipolar disorder, MDD, and schizophrenia. PTSD was associated with bipolar risk scores only [64]. Wolf and colleagues, in their analysis of veterans with PTSD and dissociative symptoms, did not find any loci that reached genome-wide significance for the dissociative PTSD phenotype, although ten loci were suggestive [60].

In a more recent GWAS of veterans, there were no significant associations with PTSD (even when combining samples across races to increase power), but several genes reached nominal significance. The top genes had biologically plausible mechanisms for potential involvement in PTSD (e.g., related to autism and other neurologic disorders) and may be involved in alternative splicing or immune pathways [65]. Further, the newest genetic study of PTSD, published by Stein and colleagues [66], reports GWAS results from two army samples (the New Soldier Study [NSS] and Pre/Post Deployment Study (PDDS), in addition to other advanced molecular genetic analyses. Results showed that rs159572 (in *ANKRD55*) was significant for an African-American [AA] subset of the NSS and rs11085374 (in/near *ZNF626)* was significant for the European American [EA] subset of the NSS. However, neither of these loci were significant in the PDDS sample or in further analyses. SNP-based heritability and cross-disorder correlations were also examined but not significant. However, there was evidence for pleiotropy with PTSD and rheumatoid arthritis and psoriasis, providing support for the role of the immune system in PTSD.

There are two nonveteran GWAS of PTSD. Xie et al. [67] found that rs406001 (on chromosome 7p12) reached genome-wide significance in a EA sample, with two other SNPs in the intron of the Tolloid-like 1 gene (*TLL1*) also of interest (although they did not reach genome-wide significance). The two *TLL1* SNPs replicated in independent samples (EA and combined EA/AA, although not in AA only). This study used a population sample instead of a veteran sample and did not initially restrict analyses to only trauma-exposed individuals (although results were similar when this restriction was placed). The other nonveteran GWAS focused on only AA women [68]. Guffanti and colleagues found that rs10170218, a SNP located in lincRNA AC068718.1, was significantly associated with PTSD in this population and partially replicated in another. Further, the authors also conducted pathway analyses and found that genetic variation relating to telomeres and immune function may be particularly relevant to PTSD [68]. This aligns with other analyses of gene networks within PTSD, which implicate the immune system [69]. Recently, a mitochondrial GWAS identified two mitochondrial variants that may be associated with PTSD risk [70], representing a novel approach to identifying PTSD-related genes.

Given that independent GWAS have not converged on the same SNPs and that there are so few studies to date, the field is clearly in need of more advanced genome-wide studies of PTSD with sufficient sample sizes to identify genetic loci. The Psychiatric Genetics Consortium for PTSD (PGC-PTSD) is a large collaboration created with the goal of advancing PTSD genetic research [71]. The PGC model has been successful for other psychiatric phenotypes, such as schizophrenia [57]. Top PTSD investigators across the world have contributed data to the PGC-PTSD, with the total sample size expected to reach approximately 50,000 individuals, half of who will be PTSD cases. While the large sample size will be an advantage in the search for genetic loci, there are also unique challenges inherent to the PTSD phenotype and the samples available. There is more racial diversity in the PGC-PTSD, with many samples from AA individuals, when compared to other PGC data, which is primarily EA. Although the genetic diversity is a strength of the PGC-PTSD, it also affords analytic challenges, including limits on statistical power, as racial/ethnic subgroups need to be analyzed separately due to potential population stratification issues. Further, trauma exposure is a requirement for the development of PTSD and thus must be considered. Despite these challenges, the PGC-PTSD represents the largest collaborative effort to date and has the potential to greatly inform our knowledge of the genetic architecture of this complex psychiatric phenotype.

Epigenetic Studies

Epigenetic modifications (e.g., DNA methylation changes) are of special interest to studying PTSD due to the "environment" inherent in the disorder (i.e., the traumatic event). Thus, epigenetic and gene expression approaches have become more frequent in the study of PTSD. Often the genes of interest are candidate genes, such as *FKBP5* [49]. Similar to the candidate gene literature, the literature has expanded rapidly, and there are too many methylation and expression

studies to provide a thorough review, and the interested reader should refer to recent reviews for a comprehensive summary of the role of epigenetics in PTSD [26, 35, 72–74]. Notably, the PGC-PTSD also has a workgroup focused on epigenetics, where studies including genome-wide methylation data are being processed through an analytic pipeline to allow for meta-analysis.

Genetics of Sleep Phenotypes

A shared challenge for all genetic studies, behavioral or molecular, is definition of the phenotype. Sleep, and sleep difficulties, is no exception. Within the genetics of problematic sleep literature, phenotypes studied include nightmares, sleep onset latency (SOL), sleep length, sleep quality, subjective trouble falling asleep, subjective report of difficulty staying asleep, night waking, etc. Most genetic studies of insomnia, particularly those that are genome wide, have focused on insomnia symptoms, as opposed to clinical diagnoses [75]. Another challenge in this literature is that sleep is affected by a large number of variables (e.g., medications, caffeine intake) that may provide noise when trying to examine its genetic basis. In the following section, a brief review of the behavioral and molecular genetics of relevant sleep phenotypes is provided, and the interested reader is referred to several recent reviews of the genetics of insomnia and/or other sleep disorders [75–78], as well as circadian rhythms [79].

Twin Studies

There is a large twin literature for insomnia and other sleep phenotypes, with studies ranging across the lifespan from young child to adult samples (see [21, 77] for review). The estimated heritability of sleep phenotypes varies widely, with estimates of insomnia in adults ranging from 0.20 (overall insomnia factor; [80]) to 0.64 (insomnia; [81]). More recently, the longitudinal stability of insomnia heritability in adults has been demonstrated, with findings suggesting that the majority of the genetic influence on insomnia symptoms comes from latent genetic effects as opposed to time-specific sources [82]. There are several twin studies of high relevance to this chapter. First, McCarren and colleagues [83] conducted the only twin study of sleep in veterans, utilizing data on four sleep-related phenotypes and a composite score from 2825 male twin pairs in the VET Registry. Heritability estimates were 0.28 (trouble falling asleep $a^2 = 0.28$), 0.26 (waking up several times per night $a^2 = 0.26$), 0.42 (trouble staying asleep), 0.21 (feeling tired after usual amount of sleep $a^2 = 0.21$), and 0.28 (composite ordinal score). Combined analyses also incorporated combat exposure severity, in addition to additive genetic effects, but this did not alter the genetic contributions to sleep variables. Combat exposure was weakly related to all sleep variables; however, PTSD was not examined in this study and requires future investigation.

Second, there is a subset of the literature that explores genetic overlap between sleep and common psychopathology. There is some evidence for overlap between sleep and internalizing disorders (depression, anxiety), with many studies using child and adolescent samples [84–87]. Estimates of genetic overlap with internalizing psychopathology range from partial (genetic correlations less than 1; [86]) to complete (i.e., the genetic contribution overlapped completely; [87]). None of these studies included externalizing disorders, and the literature on this overlap is limited. However, results from our group, in the first study to examine overlap between sleep and diagnoses of both types of psychopathology in an adult sample, show substantial (greater than 50%) genetic overlap between insomnia and depression, complete genetic overlap between insomnia and anxiety, and partial genetic overlap between insomnia and externalizing disorders (alcohol abuse and dependence, antisocial personality disorder) [88]. Twin studies show that the genetic influences on PTSD, like those on insomnia, overlap significantly with internalizing disorders, with some research showing complete genetic overlap between MDD and PTSD [89–92]. Additionally, PTSD shows modest genetic overlap with externalizing psychopathology [92]. Given this, it is reasonable to expect that there is significant genetic overlap between sleep and PTSD, although no studies to date have specifically examined this relationship.

Finally, as nightmares are a common symptom of PTSD, it is important to discuss their heritability. However, note that twin studies of nightmares do not examine them in the context of PTSD or in trauma-exposed samples. In a sample of Finnish twins, Hublin and colleagues [93] examined the heritability of childhood and adult nightmares (retrospectively reported). Results suggested a moderate heritable component for childhood nightmares ($a^2 \sim 0.35$–0.52) in both sexes, and in adulthood a sex difference was found in that the heritability estimate was higher in women than men (combined sexes: $a^2 \sim 0.27$–45). Another study of children and adolescents estimates nightmare heritability around 50% and shows that it does not overlap with anxiety symptoms [94].

Molecular Genetic Studies

Numerous thorough reviews have been dedicated to the molecular genetics of sleep and circadian rhythms [75–79]. Circadian rhythms govern fundamental physiological functions in almost all organisms, from prokaryotes to humans.

The circadian clocks are intrinsic time-tracking systems with which organisms can anticipate environmental changes and adapt to the appropriate time of day. In mammals, circadian rhythms are generated in pacemaker neurons within the suprachiasmatic nuclei (SCN) and are entrained by light. Disruption of the circadian rhythms can cause depression, insomnia, jet lag, coronary heart disease, and a variety of neurodegenerative disorders (e.g., [95]). Interestingly, peripheral tissues have also been shown to contain independent clocks, the function of which is orchestrated by the SCN [96]. The circadian clocks operate through transcriptional feedback autoregulatory loops that involve the products of circadian clock genes, and following, these genes have been the focus of molecular studies.

The candidate gene literature for sleep phenotypes has focused on fewer genes than that of PTSD; however, there are several candidate genes that have been examined across both phenotypes, representing possible genetic links. Additionally, there are some genes that, despite not being specifically examined in the context of both disorders, have biologically plausible connections to both sleep and PTSD. Candidate genes examined in association with insomnia include circadian genes (e.g., *PER3*, *CLOCK*, *TIMELESS)* and the serotonin transporter *(5-HTTLPR*), among others, with some success, although few replications [75, 77]. In the following section, we will review the candidate genes with potential relevance to both disorders, and then we discuss the GWAS studies of sleep phenotypes.

In discussing sleep candidate gene research, the first set of genes to consider are the circadian clock genes, given their role in establishing the body's circadian rhythm. There are mixed results for the *CLOCK* variant *T3111C* and sleep disturbances, often studied in the context of mental disorders such as depression. Some results indicate that this polymorphism is associated with decreased sleep, while others do not demonstrate any associations with sleep in depressed individuals [97, 98]. There is also some evidence that the *CLOCK* gene may be involved in sleep following antidepressant treatment [99]. Although there have not been candidate gene studies explicitly looking at *CLOCK* in PTSD, the circadian system does influence components of the stress response, particularly glucocorticoid levels, which have their own circadian rhythms (e.g., cortisol typically peaks in the morning) [100]. Landgraf and colleagues [101], in a review of the role of the circadian system in psychopathology, hypothesize that some of the genetic contributions to PTSD vulnerability may result from alterations in *CLOCK* genes, which disrupt glucocorticoid signaling and in turn affect specific brain regions and alter the stress response. Other genes involved with glucocorticoid signaling, such as *FKBP5*, may also be involved through this mechanism [102]. Further, both *ADCYAP1R1* and *RORA*, two other genes examined more thoroughly in the PTSD literature, are related mechanistically to the circadian clock [101]. *ADCYAP1R1* is released by the suprachiasmatic nucleus, which entrains the body to light [103], while *RORA* is released on a circadian rhythm, like glucocorticoids, and also modulates levels of *BMAL*, another important circadian gene [101].

Widely studied across many phenotypes within psychiatric genetics, the serotonin transporter gene, *5-HTTLPR*, has also been implicated in sleep. With regard to sleep problems, carriers of the S allele who were treated with fluoxetine for depression had a higher likelihood of developing insomnia during treatment compared to L allele homozygotes [104]. In a gene-environment interaction approach in a study of caregivers of patients with dementia and non-caregiver controls, Brummett and colleagues [105] found no main effect of *5-HTTLPR* genotype on sleep quality but found that caregivers who were S allele carriers were more likely than their L allele caregiver counterparts to report poor sleep. Further, there is evidence that sleep quality and *5-HTTLPR* genotype interact to affect temperament in children, which supports an early role of sleep in the development of emotions [106]. There are also several studies examining sleep, depression, and serotonin. Less activity in a *MAO-A* (an enzyme that degrades serotonin) VNTR has been associated with sleep quality, as well as depression [107]. The *5-HTTLPR* genotype has also been shown to influence sleep latency in the elderly, including in the context of depression symptoms [108]. In another study of college students, the triallelic S'S' genotype was more common in individuals with both shorter sleep and more depressed mood [109]. The serotonin transporter gene may be related to PTSD under high trauma conditions [38], so there is some evidence for its involvement in both sleep and PTSD phenotypes.

Serotonin is also related to *BDNF* (particularly in psychiatric disorders; [110]), another gene with evidence to suggest that it may be involved in both the development of PTSD and disturbed sleep. As discussed earlier, various studies have examined the Val88Met polymorphism in PTSD, with some showing significance [44]. The *BDNF* gene may also play a role in disturbed sleep: several studies have demonstrated that individuals with insomnia or fatigue have lower serum BDNF levels, when compared to controls, and that this may even differ by insomnia severity (e.g., [111]). Further, the Val88Met polymorphism itself has been shown to regulate sleep intensity and EEG patterns [112, 113]. A recent review of the BDNF and sleep summarizes the literature by hypothesizing that loss of sleep may cause a decrease in BDNF levels, which in turn alters the ability to respond to stressors, eventually leading to the development of stress-related psychopathology [114].

Another common neurotransmitter examined in the PTSD literature is dopamine. PTSD candidate gene studies suggest that the 9′ allele of the *DAT1* polymorphism is related to increased likelihood of PTSD [41, 42, 115], and one study in

particular reported that the 9′ allele carriers were at risk primarily driven by the relation to DSM-5 Criterion E symptoms [42], which includes a sleep symptom. There is also support for dopamine receptor genes in PTSD (e.g., DRD2; [116]). Although prior studies of dopamine genes and sleep have mostly utilized animal sleep models (e.g., [117, 118]), current research is highlighting the emerging role of dopamine genes in the context of human sleep phenotypes. *DAT1* polymorphisms were associated with higher sleepiness in a young adult sample [119], and dopamine transporter polymorphisms in humans have been linked to the response of the reward system following sleep deprivation [120]. Further, a large, collaborative study of the genetics of sleep duration, which examined 50,000 SNPs from 2000 candidate genes, found evidence for the involvement of the dopamine D2 receptor gene (*DRD2*) in sleep duration (see [121] for a more thorough review of the results and replication steps).

Other neurotransmitter systems implicated in the genetics of insomnia include gamma-aminobutyric acid (GABA) and orexin/hypocretin [75]. *GABRA* variants have been shown to interact with lifetime trauma history to predict PTSD [122], and human studies have shown decreased GABA-A receptor binding in certain brain regions of individuals with PTSD [123]. Further, low levels of both serum and cerebrospinal fluid orexin have been shown to be related to combat-related PTSD severity [124]. The comparisons outlined here, although speculative, suggest that based on candidate gene studies, a wide range of neurotransmitter systems may play a role in the genetic overlap between sleep and PTSD and thus warrant future empirical study. A summary can be found in Table 9.2. However, it is important to note that this list is not exhaustive and that many findings have not been replicated.

Genome-Wide Association Studies

Similar to PTSD, genome-wide studies of insomnia and sleep-related phenotypes such as sleep quality and sleep duration do exist, although the sleep literature lags behind other psychiatric phenotypes. While there have been eight sleep GWAS to date (excluding sleep disorders other than insomnia, caffeine, and chronotype), there are only two that examine insomnia-related outcomes [125, 126] and one that used actigraphy data [127] and will be discussed in detail here (see Table 9.3). The remaining five focus on sleep duration [128–132], which may be less relevant to PTSD phenotypes: the sleep and PTSD literature indicates that sleep quality is the most relevant sleep outcomes for veterans [133]. Ban and colleagues [125] conducted the first GWAS of an insomnia phenotype using a large Korean sample. There were no loci that passed genome-wide significance, but the most significant SNPs included rs11208305 (*ROR1*, previously implicated in bipolar disorder) and rs718712 (*PLCB1*, shown to have associations with schizophrenia). SNPs in *CACNA1A*, *GNAS*, *NOS3*, and *ADCY8* were also of interest. Later, Byrne and colleagues [126] conducted a GWAS examining multiple sleep phenotypes (sleep latency, sleep quality, sleep depth, sleep time, sleep duration, insomnia factor score) in an Australian sample. There were no genome-wide significant loci for the insomnia factor score (or other sleep phenotypes), but rs11174478 (in *SLC2A13*) had the most significant association with the insomnia factor score. The most interesting results were for *CACNA1C* (a gene previously implicated in bipolar disorder), which had some evidence for an association with both sleep quality and sleep latency in this sample but was not significant in their replication sample. There were no significant results from pathway analysis. However, note that the *CACNA1C* and sleep quality finding was later replicated by Parsons and colleagues in a British sample [134]. A recent sleep GWAS used a set of objective sleep phenotypes from actigraphy data (as opposed to self-report) [127]. Results, although not corrected for analysis of multiple phenotypes, revealed several genes potentially implicated in regulating sleep efficiency on weekdays (*ULF1*, which is a circadian gene) and sleep latency (*DMRT1*). This GWAS is novel in its approach to sleep phenotypes and represents a useful next direction for phenotypes used in genome-wide studies of sleep.

Overall, the insomnia genetic literature suffers from inconsistent phenotypes and small sample sizes [75, 78], which will need to be addressed in future studies. There are few GWAS of insomnia, even compared to PTSD. Results show no genome-wide significant hits for this insomnia or related phenotypes like sleep quality (only GWAS of sleep duration have generated hits). This is in contrast to PTSD, where multiple significant loci have been documented (although not consistently across studies). Thus, it is unsurprising that there have been no common genes identified through GWAS.

Epigenetics

Epigenetic modifications are important for the regulation and function of genes related to sleep, as the circadian system is constantly interacting with and receiving feedback from the environment. DNA methylation, histone acetylation and deacetylation, and RNA modification, among other epigenetic process, have all been described in relation to circadian gene expression [135, 136]. There is a small literature on epigenetic changes in disturbed sleep and related disorders [135]. Further, epigenetic regulation of clock genes may influence their role in psychiatric disorders [135]. The reader is directed to several current reviews for more details about sleep and circadian epigenetics [135, 136].

Table 9.2 Hypothesized candidate genes related to both sleep and PTSD

Gene or neurotransmitter system	Studied as a candidate for PTSD?	Studied as a candidate for sleep?	PTSD literature	Sleep literature
CLOCK	N	Y	*CLOCK* genes may disrupt glucocorticoid signaling and alter the stress response [101]	Many studies, mixed results; see [75] for review
FKBP5	Y	N	Many studies show associations with *FKBP5* and PTSD (e.g., [45, 46–49])	May be related through involvement in the circadian regulation of glucocorticoid receptors [102]
ADCYAP1R1	Y	N	Multiple studies, some showing significant associations with PTSD (e.g., [52, 53])	Considered a clock gene; affects SCN, phase reset [103]
RORA	Y	N	Significant in PTSD GWAS [61] and some follow-up candidate gene studies (e.g., [62])	Considered a clock gene; regulates BMAL (circadian) and expressed in a circadian fashion [101]
Serotonin	Y	Y	Meta-analysis shows that *5-HTLLPR* (SS genotype) may be associated with PTSD in highly TE individuals [38]	S′ allele related to poor sleep in several samples [104, 105, 108, 109]; genotype interacts with sleep to predict temperament [106], *MAO-A* activity associated with sleep quality [107]
Dopamine	Y	Y	Multiple studies: *DAT1* [41, 42, 115] polymorphism and *DRD* [116] associated with PTSD	*DAT1* associated with higher sleepiness [119]; *DAT* polymorphisms involved in reward following sleep deprivation [120]; DRD2 receptor involved in sleep duration [121]
BDNF	Y	Y	Val88Met meta-analyzed in PTSD may be associated with PTSD when using trauma-exposed controls [44]	Val88Met polymorphism regulates sleep intensity and EEG patterns [112, 113]; individuals with insomnia have lower BDNF levels (e.g., [111])
GABA	Y	Y	*GABRA* associated with PTSD [122]; decreased GABA-A receptor binding in PTSD [123]	Sleep meds (benzodiazepines) act on GABA, patient with mutation in GABA-A receptor [155]
Orexin/hypocretin	N	Y	Low serum/CSF orexin related to combat PTSD severity [124]	Insomnia phenotype in zebrafish with overexpression [156]

5-HTTLPR serotonin transporter-linked polymorphic region, *ADCYAP1R1* adenylate cyclase-activating polypeptide 1 receptor type I, *BDNF* brain-derived neurotrophic factor, *BMAL* brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein, *CSF* cerebrospinal fluid, *DAT* dopamine transporter, *DR* dopamine receptor, *EEG* electroencephalogram, *FKBP5* FK506 binding protein 5, *GABA* gamma-aminobutyric acid, *GWAS* genome-wide association study, *MAO-A* monoamine oxidase A, *RORA* RAR-related orphan receptor A, *PTSD* post-traumatic stress disorder, *SCN* suprachiasmatic nucleus, *TE* trauma exposed

Conclusions

Although the candidate gene literature for PTSD has grown exponentially in recent years, and GWAS of both sleep and PTSD have emerged, there still remains much to learn about the genetic architecture of these traits individually, and even more with regard to their overlap, in trauma-exposed populations. There are many limitations to the candidate gene approach, with inconsistencies in genetic associations across both phenotypes discussed, likely due to differences in phenotypes, ascertainment, and other methodology. The extant GWAS, although successful in identifying some polymorphisms (particularly for PTSD, but less so for sleep), still suffer from small sample sizes and lack of replication across other samples and racial/ethnic populations. Additionally, GWAS investigations as a whole for psychiatric genetics

Table 9.3 Genome-wide association studies of insomnia-related phenotypes

Author year	Sample type/setting	Sample size	Mean (SD) age	Sleep measure	Sleep prevalence	Country/ethnicity	Gene identified?	SNP identified?	Summary of key findings
Ban et al. (2011) [125]	Korean epidemiological study	8179 (7280 controls, 1429 cases)	Range: 40–69	Self-report; categories of overall, onset, middle, and late insomnia	16.5% insomnia	As/Korean	*ROR1 PCLB1*	rs11208305	A total of 3354 SNPs had $p < 0.005$
								rs718712	Most significantly associated with insomnia
									PCLB1 (previously associated with schizophrenia)
									ROR1 (previously associated with bipolar)
Byrne et al. (2013) [126]	Twin registry	2323	31.4 (11.0)	Self-report; insomnia factor score, duration, depth quality, latency, sleep time	NR	Australia/NR	*CACNA1C*	rs7316184	No significant SNPs within GWAS for insomnia factor score or any other phenotypes
								rs7304986	
								rs7301906 rs16929275	
								rs16929276	
								rs16929278	
								rs2051990	Top sleep latency SNPs found in third intron of *CACNA1C* (previously associated with bipolar disorder and schizophrenia); did not replicate in Chronogen Consortium sample
									Other top SNPs for sleep latency: rs7316184, rs7304986, rs7301906, rs16929275, rs16929276, rs16929278, and rs2051990
									Top SNP for sleep quality: rs2302729

(continued)

Table 9.3 (continued)

Author year	Sample type/setting	Sample size	Mean (SD) age	Sleep measure	Sleep prevalence	Country/ethnicity	Gene identified?	SNP identified?	Summary of key findings
Spada et al. (2016) [127]	LIFE adult study, epidemiologic	956	61.5 (10.3)	14 actigraphy parameters (but only reporting on sleep, not daytime results here)	NR	Germany/NR	*UFL1*	rs75842709	*UFL1* – sleep efficiency on weekdays (significant; circadian rhythm gene)
							DMRT1	chr9:865201D	*DMRT1* – sleep latency (significant)
							SMYD1	rs2919869	*SMYD1* – sleep offset (significant)
							CSNK2A1	rs74448913	*CSNK2A1* – sleep latency (nominally significant)
							ZMYM4	rs12069385	*ZMYM4* – sleep latency (nominally significant)
									However, correction was not done for the analysis of multiple phenotypes

As Asian, *NR* not reported, *SD* standard deviation, *SNP* single nucleotide polymorphism

have yet to account for the total variance demonstrated in twin studies. Collaborative approaches, such as the PGC-PTSD, will be essential to collect large enough sample sizes to identify additional loci via GWAS studies and begin to address challenges such as incorporating ancestry appropriately and tackling heterogeneity across phenotypes (which is particularly important for genetic studies of insomnia [75]). The post-GWAS era work will also be critical to taking the knowledge from these studies and understanding the downstream molecular effects of genes of interest from GWAS designs.

Further, new molecular genetic approaches will also provide the opportunity to better understand the genetic architecture of these complex phenotypes. Genome-wide complex trait analysis (GCTA) is a recent technique that estimates the heritability of a trait based on the additive effect of SNPs (and allows for bivariate analyses) [137]. A related statistical analysis, LD (linkage disequilibrium) score regression, estimates heritability from summary statistics [138]. Both approaches should be implemented in PTSD and sleep-related phenotypes. Examination of rare variation may also be beneficial as sample sizes and quality/quantity of sequencing increase. Furthermore, future research utilizing global "omics" platforms (e.g., investigation of the transcriptome and methylome) provides promise for unraveling the complex ways in which genes and environment interact.

Using cross-disorder approaches will be especially useful for understanding potential shared genetic overlap between sleep and PTSD. These have proven useful for disorders such as MDD, bipolar, and schizophrenia, where overlap and significant genetic correlations were found [139, 140]. Polygenic analyses have also provided evidence for overlap between PTSD and bipolar disorder [141]. A common methodology used to examine overlap is the polygenic risk score (PRS) method, where an aggregate genetic risk score is created for a phenotype (e.g., from GWAS summary statistics) and then used to predict another phenotype, resulting in an estimate of overlap in genetic variance [142]. In this context, a PRS for PTSD could be used to predict sleep. As discussed earlier, biometric overlap from twin studies indicates that there are likely shared genetic contributions between sleep and PTSD, and using molecular approaches to address overlap will enable more detailed investigation into how these two common trauma sequelae are related.

There are unique challenges to approaching the relationship between sleep and PTSD, given its bidirectional nature. As disturbed sleep/insomnia is both its own process and a symptom of PTSD, it will be essential to disentangle these relationships when examining the overlap across disorders. One approach is to investigate the heritability of genes that contribute to the sleep symptom of the disorder, as has been done with depression (e.g., [143, 144–146]). Then, the genetic contributions to the sleep symptoms can be compared to those of the other symptoms. An alternate approach would involve examining the overlap between specific sleep phenotypes (e.g., insomnia) and PTSD itself. Ideally, genetically informed prospective and longitudinal data measuring both sleep and PTSD phenotypes would provide the best information, particularly given recent studies identifying sleep as a predictor of future PTSD symptoms (e.g., [11]).

The statistical genetic methodology is constantly changing, so new methods should be incorporated as they arise. There are continuing developments in bioinformatics approaches to gene and pathway analyses, which have been used to examine SNPs and genes of interest from GWAS. Identifying groups of genes and pathways that are enriched within a disorder can inform our knowledge of the disorder's etiology and provide more detail on specific processes that may be involved at the cellular level. A recent gene-based analysis of PTSD has suggested that neuroligin 1, a gene previously associated with autism and other neurological processes, may be important in PTSD [147]. This approach may also help further identify areas of overlap between sleep and PTSD phenotypes. For example, the immune system and stress response systems represent potential areas of focus. Genetic studies of PTSD implicate possible immune mechanisms [69], and there is evidence that insomnia/lack of sleep can produce immunological changes [148]. New research using military populations shows that changes in sleep (i.e., better sleep) result in alterations in expression of genes involved in inflammation, in addition to improving symptoms of depression [149, 150]. This may also be true for PTSD [151]. Further, we know that the stress response system is important in PTSD physiology [152], as well as regulation of sleep [153]. There is evidence that sleep deprivation may alter stress reactivity (e.g., [154]), supporting a focus on the identification of genes that link these two processes (which may relate back to the immune response). Research like this will be essential to not only understand areas where overlap may occur but also apply this in a clinically relevant context, which is the ultimate goal.

References

1. Dedert EA, Green KT, Calhoun PS, Yoash-Gantz R, Taber KH, Mumford MM, Tupler LA, Morey RA, Marx CE, Weiner RD, Beckham JC. Association of trauma exposure with psychiatric morbidity in military veterans who have served since September 11, 2001. J Psychiatr Res. 2009;43(9):830–6.
2. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351(1):13–22. doi:10.1056/NEJMoa040603. PubMed PMID: 15229303.
3. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. Trauma and the Vietnam war generation: report of findings from the National Vietnam Veterans Readjustment study. New York: Bruner/Mazel; 1990.

4. Weiss DS, Marmar CR, Schlenger WE, Fairbank JA, Jordan BK, Hough RL, Kulka RA. The prevalence of lifetime and partial posttraumatic stress disorder in Vietnam theater veterans. J Trauma Stress. 1992;5(3):365–76.
5. Fulton JJ, Calhoun PS, Wagner HR, Schry AR, Hair LP, Feeling N, Elbogen E, Beckham JC. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: a meta-analysis. J Anxiety Disord. 2015;31(1873–7897 (Electronic)):98–107. doi:10.1016/j.janxdis.2015.02.003. PubMed PMID: 25768399.
6. Holowka DW, Marx BP, Kaloupek DG, Keane TM. PTSD symptoms among male Vietnam veterans: prevalence and associations with diagnostic status. Psychol Trauma: Theory Res Pract Policy. 2012;4(3):285–92. doi:10.1037/a0023267.
7. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of posttraumatic stress disorder in U.S. service members returning from military deployments. Mil Med. 2010;175(10):759–62. PubMed PMID: 20968266.
8. Fu J, Li P, Ouyang X, Gu C, Song Z, Gao J, Han L, Feng S, Tian S, Hu B. Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. Neuroscience. 2007;144(4):1186–92. doi:10.1016/j.neuroscience.2006.10.050. Epub 2006/12/13. PubMed PMID: 17157993.
9. Spoormaker VI, Schroter MS, Andrade KC, Dresler M, Kiem SA, Goya-Maldonado R, Wetter TC, Holsboer F, Samann PG, Czisch M. Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. Hum Brain Mapp. 2012;33(10):2362–76. doi:10.1002/hbm.21369. PubMed PMID: 21826762.
10. Spoormaker VI, Sturm KC, Andrade KC, Schroter MS, Goya-Maldonado R, Holsboer F, Wetter TC, Samann PG, Czisch M. The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. J Psychiatr Res. 2010;44(16):1121–8.
11. Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75(6):546–50. doi:10.1016/j.jpsychores.2013.09.004. PubMed PMID: 24290044.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
13. Neylan TC, Marmar CR, Mertzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbance in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
14. Ohayon MM, Shapiro CM. Sleep disturbances and comorbid psychiatric disorders associated with posttraumatic stress disorder in the general population. Compr Psychiatry. 2000;41(6):469–78.
15. Leskin GA, Woodward SH, Young HE, Sheikh JI. Effects of comorbid diagnoses on sleep disturbance in PTSD. J Psychiatr Res. 2002;36(6):449–52. PubMed PMID: 12393315.
16. Schreuder BJ, Kleijn WC, Rooijmans HG. Nocturnal re-experiencing more than forty years after war trauma. J Trauma Stress. 2000;13(3):453–63.
17. Phelps AJ, Forbes D, Hopwood M, Creamer M. Trauma-related dreams of Australian veterans with PTSD: content, affect and phenomenology. Aust N Z J Psychiatry. 2011;45(10):853–60. doi:10.3109/00048674.2011.599314. PubMed PMID: 21859279.
18. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry. 2003;54(10):1092–8. PubMed PMID: 14625152.
19. Woodward SH, Arsenault NJ, Murray C, Bliwise DL. Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry. 2000;48(11):1081–7. PubMed PMID: 11094141.
20. Neale BM, Ferreira MAR, Medland SE, Posthuma D. Statistical genetics: gene mapping through linkage and association. London: Taylor & Francis; 2007.
21. Barclay NL, Gregory AM. Quantitative genetic research on sleep: a review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties. Sleep Med Rev. 2013;17(1):29–40. doi:10.1016/j.smrv.2012.01.008. PubMed PMID: 22560641.
22. Rutter M. Gene-environment interplay. Depress Anxiety. 2010;27(1):1–4. doi:10.1002/da.20641. PubMed PMID: 20043325.
23. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev. 2009;23(7):781–3. doi:10.1101/gad.1787609. PubMed PMID: 19339683; PMCID: PMC3959995.
24. Probst AV, Dunleavy E, Almouzni G. Epigenetic inheritance during the cell cycle. Nat Rev Mol Cell Biol. 2009;10(3):192–206. doi:10.1038/nrm2640. PubMed PMID: 19234478.
25. Waddington CH. Organisers and genes. Cambridge: Cambridge University Press; 1940.
26. Schmidt U, Holsboer F, Rein T. Epigenetic aspects of posttraumatic stress disorder. Dis Markers. 2011;30(2–3):77–87. doi:10.3233/DMA-2011-0749. PubMed PMID: 21508512; PMCID: PMC3825244.
27. Koenen KC. Genetics of posttraumatic stress disorder: review and recommendations for future studies. J Trauma Stress. 2007;20(5):737–50. doi:10.1002/jts.20205. PubMed PMID: 17955543.
28. Afifi TO, Asmundson GJ, Taylor S, Jang KL. The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: a review of twin studies. Clin Psychol Rev. 2010;30(1):101–12. doi:10.1016/j.cpr.2009.10.002. PubMed PMID: 19892451.
29. Kendler KS, Baker JH. Genetic influences on measures of the environment: a systematic review. Psychol Med. 2007;37(5):615–26.
30. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am J Psychiatry. 2002;159(10):1675–81. doi:10.1176/appi.ajp.159.10.1675. PubMed PMID: 12359672.
31. True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch Gen Psychiatry. 1993;50(4):257–64. PubMed PMID: 8466386.
32. Sartor CE, VV MC, Pommer NE, Nelson EC, Grant JD, Duncan AE, Waldron M, Bucholz KK, PAF M, Heath AC. Common genetic and environmental contributions to posttraumatic stress disorder and alcohol dependence in young women. Psychol Med. 2011;41(7):1497–505.
33. Wolf EJ, Mitchell KS, Koenen KC, Miller MW. Combat exposure severity as a moderator of genetic and environmental liability to post-traumatic stress disorder. Psychol Med. 2014;44(7):1499–509. doi:10.1017/S0033291713002286. Epub 2013/09/05. PubMed PMID: 24001428; PMCID: PMC3972364.
34. Almli LM, Fani N, Smith AK, Ressler KJ. Genetic approaches to understanding post-traumatic stress disorder. Int J Neuropsychopharmacol. 2014;17(2):355–70. doi:10.1017/S1461145713001090. PubMed PMID: 24103155; PMCID: PMC4293029.
35. Voisey J, Young RM, Lawford BR, Morris CP. Progress towards understanding the genetics of posttraumatic stress disorder. J Anxiety Disord. 2014;28(8):873–83. doi:10.1016/j.janxdis.2014.09.014. Epub 2014/12/03. PubMed PMID: 25445077.
36. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology. 2016;41(1):297–319. doi:10.1038/npp.2015.266. Epub 2015/09/01. PubMed PMID: 26321314; PMCID: PMC4677147.

37. Navarro-Mateu F, Escamez T, Koenen KC, Alonso J, Sanchez-Meca J. Meta-analyses of the 5-HTTLPR polymorphisms and post-traumatic stress disorder. PLoS One. 2013;8(6):e66227. doi:10.1371/journal.pone.0066227. Epub 2013/07/05. PubMed PMID: 23825531; PMCID: PMC3692498.
38. Gressier F, Calati R, Balestri M, Marsano A, Alberti S, Antypa N, Serretti A. The 5-HTTLPR polymorphism and posttraumatic stress disorder: a meta-analysis. J Trauma Stress. 2013;26(6):645–53. doi:10.1002/jts.21855. Epub 2013/11/14. PubMed PMID: 24222274.
39. Voisey J, Swagell CD, Hughes IP, Morris CP, van Daal A, Noble EP, Kann B, Heslop KA, Young RM, Lawford BR. The DRD2 gene 957C>T polymorphism is associated with posttraumatic stress disorder in war veterans. Depress Anxiety. 2009;26(1):28–33. doi:10.1002/da.20517. PubMed PMID: 18833581.
40. Wolf EJ, Mitchell KS, Logue MW, Baldwin CT, Reardon AF, Aiello A, Galea S, Koenen KC, Uddin M, Wildman D, Miller MW. The dopamine D3 receptor gene and posttraumatic stress disorder. J Trauma Stress. 2014;27(4):379–87. doi:10.1002/jts.21937. PubMed PMID: 25158632; PMCID: PMC4147673.
41. Segman RH, Cooper-Kazaz R, Macciardi F, Goltser T, Halfon Y, Dobroborski T, Shalev AY. Association between the dopamine transporter gene and posttraumatic stress disorder. Mol Psychiatry. 2002;7(8):903–7. doi:10.1038/sj.mp.4001085. PubMed PMID: 12232785.
42. Drury SS, Theall KP, Keats BJ, Scheeringa M. The role of the dopamine transporter (DAT) in the development of PTSD in preschool children. J Trauma Stress. 2009;22(6):534–9. doi:10.1002/jts.20475. PubMed PMID: 19960520; PMCID: PMC4352554.
43. Dragan WL, Oniszczenko W. The association between dopamine D4 receptor exon III polymorphism and intensity of PTSD symptoms among flood survivors. Anxiety Stress Coping. 2009;22(5):483–95. doi:10.1080/10615800802419407. PubMed PMID: 19330578.
44. Wang T. Does BDNF Val66Met polymorphism confer risk for post-traumatic stress disorder? Neuropsychobiology. 2015;71(3):149–53. doi:10.1159/000381352. Epub 2015/05/01. PubMed PMID: 25925851.
45. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299(11):1291–305. doi:10.1001/jama.299.11.1291. PubMed PMID: 18349090; PMCID: PMC2441757.
46. Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Farrer LA, Gelernter J. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. Neuropsychopharmacology. 2010;35(8):1684–92. doi:10.1038/npp.2010.37. PubMed PMID: 20393453; PMCID: PMC2946626.
47. Sarapas C, Cai G, Bierer LM, Golier JA, Galea S, Ising M, Rein T, Schmeidler J, Müller-Myhsok B, Uhr M, Holsboer F, Buxbaum JD, Yehuda R. Genetic markers for PTSD risk and resilience among survivors of the World Trade Center attacks. Dis Markers. 2011;30(2):101–10.
48. Boscarino JA, Erlich PM, Hoffman SN, Rukstalis M, Stewart WF. Association of FKBP5, COMT and CHRNA5 polymorphisms with PTSD among outpatients at risk for PTSD. Psychiatry Res. 2011;188(1):173–4. doi:10.1016/j.psychres.2011.03.002. PubMed PMID: 21440309; PMCID: 3415886.
49. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, Ressler KJ, Rein T, Binder EB. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013;16(1):33–41. doi:10.1038/nn.3275. Epub 2012/12/04. PubMed PMID: 23201972; PMCID: PMC4136922.
50. Lind MJ, Sawyers C, Sheerin C, Amstadter AB. Corticotropin-releasing hormone receptor 1 (CRHR1) polymorphisms and post-traumatic stress disorder. In: Martin CR, Preedy VR, Patel VB, editors. Comprehensive guide to post-traumatic stress disorder. Cham: Springer International Publishing; 2015. p. 1–19.
51. Hauer D, Weis F, Papassotiropoulos A, Schmoeckel M, Beiras-Fernandez A, Lieke J, Kaufmann I, Kirchhoff F, Vogeser M, Roozendaal B, Briegel J, de Quervain D, Schelling G. Relationship of a common polymorphism of the glucocorticoid receptor gene to traumatic memories and posttraumatic stress disorder in patients after intensive care therapy. Crit Care Med. 2011;39(4):643–50. doi:10.1097/CCM.0b013e318206bae6. PubMed PMID: 21169818.
52. Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, Norrholm SD, Kilaru V, Smith AK, Myers AJ, Ramirez M, Engel A, Hammack SE, Toufexis D, Braas KM, Binder EB, May V. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011;470(7335):492–7. doi:10.1038/nature09856. PubMed PMID: 21350482; PMCID: PMC3046811.
53. Rothbaum BO, Kearns MC, Reiser E, Davis JS, Kerley KA, Rothbaum AO, Mercer KB, Price M, Houry D, Ressler KJ. Early intervention following trauma may mitigate genetic risk for PTSD in civilians: a pilot prospective emergency department study. J Clin Psychiatry. 2014;75(12):1380–7. doi:10.4088/JCP.13m08715. Epub 2014/09/05. PubMed PMID: 25188543; PMCID: PMC4293026.
54. Almli LM, Mercer KB, Kerley K, Feng H, Bradley B, Conneely KN, Ressler KJ. ADCYAP1R1 genotype associates with post-traumatic stress symptoms in highly traumatized African-American females. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(3):262–72. doi:10.1002/ajmg.b.32145. PubMed PMID: 23505260; PMCID: PMC3738001.
55. Chang S-C, Xie P, Anton RF, De Vivo I, Farrer LA, Kranzler HR, Oslin D, Purcell SM, Roberts AL, Smoller JW, Uddin M, Gelernter J, Koenen KC. No association between ADCYAP1R1 and posttraumatic stress disorder in two independent samples. Mol Psychiatry. 2011;470:492–7.
56. Uddin M, Chang SC, Zhang C, Ressler K, Mercer KB, Galea S, Keyes KM, McLaughlin KA, Wildman DE, Aiello AE, Koenen KC. Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depress Anxiety. 2013;30(3):251–8. doi:10.1002/da.22037. PubMed PMID: 23280952; PMCID: PMC4081452.
57. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–7. doi:10.1038/nature13595. PubMed PMID: 25056061; PMCID: PMC4112379.
58. CONVERGE consortium. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Accepted, Nature. 2015.
59. Major Depressive Disorder Working Group of the Psychiatric GC, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Muller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W,

Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Volzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2013;18(4):497–511. doi:10.1038/mp.2012.21. PubMed PMID: 22472876; PMCID: PMC3837431.

60. Wolf EJ, Rasmusson AM, Mitchell KS, Logue MW, Baldwin CT, Miller MW. A genome-wide association study of clinical symptoms of dissociation in a trauma-exposed sample. Depress Anxiety. 2014;31(4):352–60. doi:10.1002/da.22260. PubMed PMID: 24677629; PMCID: PMC3984628.
61. Logue MW, Baldwin C, Guffanti G, Melista E, Wolf EJ, Reardon AF, Uddin M, Wildman D, Galea S, Koenen KC, Miller MW. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Mol Psychiatry. 2013;18(8):937–42. doi:10.1038/mp.2012.113. PubMed PMID: 22869035; PMCID: PMC3494788.
62. Amstadter AB, Sumner JA, Acierno R, Ruggiero KJ, Koenen KC, Kilpatrick DG, Galea S, Gelernter J. Support for association of RORA variant and post traumatic stress symptoms in a population-based study of hurricane exposed adults. Mol Psychiatry. 2013;18(11):1148–9. doi:10.1038/mp.2012.189. PubMed PMID: 23319003; PMCID: PMC3977702.
63. Guffanti G, Ashley-Koch AE, Roberts AL, Garrett ME, Solovieff N, Ratanatharathorn A, De Vivo I, Dennis M, Ranu H, Smoller JW, Liu Y, Purcell SM, Veterans Affairs Mid-Atlantic Mental Illness Research E, Clinical Center W, Beckham J, Hauser MA, Koenen KC. No association between RORA polymorphisms and PTSD in two independent samples. Mol Psychiatry. 2014;19(10):1056–7. doi:10.1038/mp.2014.19. PubMed PMID: 25048002.
64. Nievergelt CM, Maihofer AX, Mustapic M, Yurgil KA, Schork NJ, Miller MW, Logue MW, Geyer MA, Risbrough VB, O'Connor DT, Baker DG. Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: a genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. Psychoneuroendocrinology. 2015;51:459–71. doi:10.1016/j.psyneuen.2014.10.017. PubMed PMID: 25456346.
65. Ashley-Koch AE, Garrett ME, Gibson J, Liu Y, Dennis MF, Kimbrel NA, Veterans Affairs Mid-Atlantic Mental Illness Research E, Clinical Center W, Beckham JC, Hauser MA. Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq-Afghanistan era veterans. J Affect Disord. 2015;184:225–34. doi:10.1016/j.jad.2015.03.049. Epub 2015/06/27. PubMed PMID: 26114229; PMCID: PMC4697755.
66. Stein MB, Chen CY, Ursano RJ, Cai T, Gelernter J, Heeringa SG, Jain S, Jensen KP, Maihofer AX, Mitchell C, Nievergelt CM, Nock MK, Neale BM, Polimanti R, Ripke S, Sun X, Thomas ML, Wang Q, Ware EB, Borja S, Kessler RC, Smoller JW, Army Study to Assess R, Resilience in Servicemembers C. Genome-wide association studies of posttraumatic stress disorder in 2 cohorts of US Army soldiers. JAMA Psychiat. 2016; doi:10.1001/jamapsychiatry.2016.0350. Epub 2016/05/12. PubMed PMID: 27167565.
67. Xie P, Kranzler HR, Yang C, Zhao H, Farrer LA, Gelernter J, et al. Biol Psychiatry. 2013;74(9):656–63. doi:10.1016/j.biopsych.2013.04.013. PubMed PMID: 23726511; PMCID: PMC3810148.
68. Guffanti G, Galea S, Yan L, Roberts AL, Solovieff N, Aiello AE, Smoller JW, De Vivo I, Ranu H, Uddin M, Wildman DE, Purcell S, Koenen KC. Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women. Psychoneuroendocrinology. 2013;38(12):3029–38. doi:10.1016/j.psyneuen.2013.08.014. PubMed PMID: 24080187; PMCID: PMC3844079.
69. Breen MS, Maihofer AX, Glatt SJ, Tylee DS, Chandler SD, Tsuang MT, Risbrough VB, Baker DG, O'Connor DT, Nievergelt CM, Woelk CH. Gene networks specific for innate immunity define post-traumatic stress disorder. Mol Psychiatry. 2015;20(12):1538–45. doi:10.1038/mp.2015.9. Epub 2015/03/11. PubMed PMID: 25754082; PMCID: PMC4565790.
70. Flaquer A, Baumbach C, Ladwig KH, Kriebel J, Waldenberger M, Grallert H, Baumert J, Meitinger T, Kruse J, Peters A, Emeny R, Strauch K. Mitochondrial genetic variants identified to be associated with posttraumatic stress disorder. Transl Psychiatry. 2015;5:e524. doi:10.1038/tp.2015.18. Epub 2015/03/11. PubMed PMID: 25756807; PMCID: PMC4354348.
71. Logue MW, Amstadter AB, Baker DG, Duncan L, Koenen KC, Liberzon I, Miller MW, Morey RA, Nievergelt CM, Ressler KJ, Smith AK, Smoller JW, Stein MB, Sumner JA, Uddin M. The psychiatric genomics consortium posttraumatic stress disorder workgroup: posttraumatic stress disorder enters the age of large-scale genomic collaboration. Neuropsychopharmacology. 2015;40(10):2287–97. doi:10.1038/npp.2015.118. Epub 2015/04/24. PubMed PMID: 25904361; PMCID: PMC4538342.
72. Rampp C, Binder EB, Provencal N. Epigenetics in posttraumatic stress disorder. Prog Mol Biol Transl Sci. 2014;128:29–50. doi:10.1016/B978-0-12-800977-2.00002-4. Epub 2014/11/21. PubMed PMID: 25410540.
73. Klengel T, Pape J, Binder EB, Mehta D. The role of DNA methylation in stress-related psychiatric disorders. Neuropharmacology. 2014;80:115–32. doi:10.1016/j.neuropharm.2014.01.013. Epub 2014/01/24. PubMed PMID: 24452011.
74. Malan-Muller S, Seedat S, Hemmings SM. Understanding post-traumatic stress disorder: insights from the methylome. Genes Brain Behav. 2014;13(1):52–68. doi:10.1111/gbb.12102. Epub 2013/11/30. PubMed PMID: 24286388.
75. Gehrman PR, Pfeiffenberger C, Byrne E. The role of genes in the insomnia phenotype. Sleep Med Clin. 2013;8(3):323–31. doi:10.1016/j.jsmc.2013.04.005. PubMed PMID: 24072990; PMCID: PMC3780427.
76. Gehrman PR, Keenan BT, Byrne EM, Pack AI. Genetics of sleep disorders. Psychiatr Clin North Am. 2015;38(4):667–81. doi:10.1016/j.psc.2015.07.004. PubMed PMID: 26600102.
77. Gehrman PR, Byrne E, Gillespie N, Martin NG. Genetics of insomnia. Sleep Med Clin. 2011;6(2):191–202. doi:10.1016/j.jsmc.2011.03.003.
78. Parsons M. On the genetics of sleep disorders: genome-wide association studies and beyond. Adv Genom Genet. 2015;2015(5):293–303.
79. Andreani TS, Itoh TQ, Yildirim E, Hwangbo DS, Allada R. Genetics of circadian rhythms. Sleep Med Clin. 2015;10(4):413–21. doi:10.1016/j.jsmc.2015.08.007. Epub 2015/11/17. PubMed PMID: 26568119; PMCID: PMC4758938.
80. Boomsma DI, van Someren EJ, Beem AL, de Geus EJ, Willemsen G. Sleep during a regular week night: a twin-sibling study. Twin Res Hum Genet. 2008;11(5):538–45. doi:10.1375/twin.11.5.538. PubMed PMID: 18828737.
81. Watson NF, Goldberg J, Arguelles L, Buchwald D. Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. Sleep. 2006;29(5):645–9. PubMed PMID: 16774154.
82. Lind MJ, Aggen SH, Kirkpatrick RM, Kendler KS, Amstadter AB. A longitudinal twin study of insomnia symptoms in adults. Sleep. 2015;38(9):1423–30. doi:10.5665/sleep.4982. PubMed PMID: 26132482; PMCID: PMC4531410.

83. McCarren M, Goldberg J, Ramakrishnan V, Fabsitz R. Insomnia in Vietnam era veteran twins: influence of genes and combat experience. Sleep. 1994;17(5):456–61. PubMed PMID: 7991958.
84. Gregory AM, Rijsdijk F, Dahl RE, McGuffin P, Eley TC. Associations between sleep problems, anxiety, and depression in twins at 8 years of age. Pediatrics. 2006;(1098–4275 (Electronic)) doi:10.1542/peds2005-3118.
85. Gregory AM, Rijsdijk FV, Lau JY, Dahl RE, Eley TC. The direction of longitudinal associations between sleep problems and depression symptoms: a study of twins aged 8 and 10 years. J Sleep Res. 2008;17(0161–8105 (Print)):140–1. D - NLM: PMC2635583 EDAT- 2009/02/26 09:00 MHDA- 2009/03/31 09:00 CRDT- 2009/02/26 09:00 PST - ppublish. PubMed PMID: WOS:000262850300375.
86. Gregory AM, Buysse DJ, Willis TA, Rijsdijk FV, Maughan B, Rowe R, Cartwright S, Barclay NL, Eley TC. Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. J Psychosom Res. 2011;71(4):250–5. doi:10.1016/j.jpsychores.2011.03.011. PubMed PMID: 21911103.
87. Gehrman PR, Meltzer LJ, Moore M, Pack AI, Perlis ML, Eaves LJ, Silberg JL. Heritability of insomnia symptoms in youth and their relationship to depression and anxiety. Sleep. 2011;34(12):1641–6. doi:10.5665/sleep.1424. PubMed PMID: 22131600; PMCID: PMC3208840.
88. Lind MJ, Hawn S, Sheerin C, Aggen SH, Kirkpartrick RM, Kendler KS, Amstadter AB. An examination of the etiologic overlap between the genetic and environmental influences on insomnia and common psychopathology 2016;under review.
89. Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, Bucholz KK, Madden PA, Heath AC, Martin NG, Nelson EC. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Arch Gen Psychiatry. 2012;69(3):293–9. doi:10.1001/archgenpsychiatry.2011.1385. PubMed PMID: 22393221; PMCID: PMC3594801.
90. Fu Q, Koenen KC, Miller MW, Heath AC, Bucholz KK, Lyons MJ, Eisen SA, True WR, Goldberg J, Tsuang MT. Differential etiology of posttraumatic stress disorder with conduct disorder and major depression in male veterans. Biol Psychiatry. 2007;62(10):1088–94. doi:10.1016/j.biopsych.2007.04.036. PubMed PMID: 17617384; PMCID: 2128773.
91. Koenen KC, Fu QJ, Ertel K, Lyons MJ, Eisen SA, True WR, Goldberg J, Tsuang MT. Common genetic liability to major depression and posttraumatic stress disorder in men. J Affect Disord. 2008;105(1–3):109–15. doi:10.1016/j.jad.2007.04.021. PubMed PMID: 17540456; PMCID: PMC2254223.
92. Wolf EJ, Miller MW, Krueger RF, Lyons MJ, Tsuang MT, Koenen KC. Posttraumatic stress disorder and the genetic structure of comorbidity. J Abnorm Psychol. 2010;119(2):320–30. doi:10.1037/a0019035. Epub 2010/05/12. PubMed PMID: 20455605; PMCID: PMC3097423.
93. Hublin C, Kaprio J, Partinen M, Koskenvuo M. Nightmares: familial aggregation and association with psychiatric disorders in a nationwide twin cohort. Am J Med Genet. 1999;88(4):329–36. PubMed PMID: 10402498.
94. Coolidge FL, Segal DL, Coolidge CM, Spinath FM, Gottschling J. Do nightmares and generalized anxiety disorder in childhood and adolescence have a common genetic origin? Behav Genet. 2010;40(3):349–56. doi:10.1007/s10519-009-9310-z. Epub 2009/11/11. PubMed PMID: 19902346.
95. Crocker A, Sehgal A. Genetic analysis of sleep. Genes Dev. 2010;24(12):1220–35. doi:10.1101/gad.1913110. PubMed PMID: 20551171; PMCID: PMC2885658.
96. Hastings M. The brain, circadian rhythms, and clock genes. BMJ. 1998;317(7174):1704–7. PubMed PMID: 9857134; PMCID: PMC1114487.
97. Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, Smeraldi E. Genetic dissection of psychopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. Am J Med Genet B Neuropsychiatr Genet. 2003;121B(1):35–8. doi:10.1002/ajmg.b.20053. PubMed PMID: 12898572.
98. Serretti A, Gaspar-Barba E, Calati R, Cruz-Fuentes CS, Gomez-Sanchez A, Perez-Molina A, De Ronchi D. 3111T/C clock gene polymorphism is not associated with sleep disturbances in untreated depressed patients. Chronobiol Int. 2010;27(2):265–77. doi:10.3109/07420521003663785. Epub 2010/04/08. PubMed PMID: 20370469.
99. Serretti A, Cusin C, Benedetti F, Mandelli L, Pirovano A, Zanardi R, Colombo C, Smeraldi E. Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. Am J Med Genet B Neuropsychiatr Genet. 2005;137B(1):36–9. doi:10.1002/ajmg.b.30130. Epub 2005/06/14. PubMed PMID: 15952199.
100. Chung S, Son GH, Kim K. Circadian rhythm of adrenal glucocorticoid: its regulation and clinical implications. Biochim Biophys Acta. 2011;1812(5):581–91. doi:10.1016/j.bbadis.2011.02.003. Epub 2011/02/16. PubMed PMID: 21320597.
101. Landgraf D, Shostak A, Oster H. Clock genes and sleep. Pflugers Arch. 2012;463(1):3–14. doi:10.1007/s00424-011-1003-9. Epub 2011/08/13. PubMed PMID: 21833490.
102. Yan J, Wang H, Liu Y, Shao C. Analysis of gene regulatory networks in the mammalian circadian rhythm. PLoS Comput Biol. 2008;4(10):e1000193. doi:10.1371/journal.pcbi.1000193. Epub 2008/10/11. PubMed PMID: 18846204; PMCID: PMC2543109.
103. Colwell CS, Michel S, Itri J, Rodriguez W, Tam J, Lelievre V, Hu Z, Waschek JA. Selective deficits in the circadian light response in mice lacking PACAP. Am J Physiol Regul Integr Comp Physiol. 2004;287(5):R1194–201. doi:10.1152/ajpregu.00268.2004. Epub 2004/06/26. PubMed PMID: 15217792.
104. Perlis RH, Mischoulon D, Smoller JW, Wan YJ, Lamon-Fava S, Lin KM, Rosenbaum JF, Fava M. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biol Psychiatry. 2003;54(9):879–83. PubMed PMID: 14573314.
105. Brummett BH, Krystal AD, Ashley-Koch A, Kuhn CM, Zuchner S, Siegler IC, Barefoot JC, Ballard EL, Gwyther LP, Williams RB. Sleep quality varies as a function of 5-HTTLPR genotype and stress. Psychosom Med. 2007;69(7):621–4.
106. Bouvette-Turcot AA, Pluess M, Bernier A, Pennestri MH, Levitan R, Sokolowski MB, Kennedy JL, Minde K, Steiner M, Pokhvisneva I, Meaney MJ, Gaudreau H, Team MR. Effects of genotype and sleep on temperament. Pediatrics. 2015;136(4):e914–21. doi:10.1542/peds.2015-0080. Epub 2015/09/16. PubMed PMID: 26371199.
107. Brummett BH, Krystal AD, Siegler IC, Kuhn C, Surwit RS, Zuchner S, Ashley-Koch A, Barefoot JC, Williams RB. Associations of a regulatory polymorphism of monoamine oxidase-A gene promoter (MAOA-uVNTR) with symptoms of depression and sleep quality. Psychosom Med. 2007;69(5):396–401. doi:10.1097/PSY.0b013e31806d040b. Epub 2007/06/23. PubMed PMID: 17585061; PMCID: PMC2777888.
108. Polito L, Davin A, Vaccaro R, Abbondanza S, Govoni S, Racchi M, Guaita A. Serotonin transporter polymorphism modifies the association between depressive symptoms and sleep onset latency complaint in elderly people: results from the 'InveCe.Ab' study. J Sleep Res. 2015;24(2):215–22. doi:10.1111/jsr.12248. Epub 2014/10/10. PubMed PMID: 25297871.
109. Carskadon MA, Sharkey KM, Knopik VS, McGeary JE. Short sleep as an environmental exposure: a preliminary study associating 5-HTTLPR genotype to self-reported sleep duration and depressed mood in first-year university students. Sleep. 2012;35(6):791–6. doi:10.5665/sleep.1876. Epub 2012/06/02. PubMed PMID: 22654198; PMCID: PMC3353054.

110. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology. 2008;33(1):73–83. doi:10.1038/sj.npp.1301571. Epub 2007/09/21. PubMed PMID: 17882234.
111. Giese M, Unternahrer E, Huttig H, Beck J, Brand S, Calabrese P, Holsboer-Trachsler E, Eckert A. BDNF: an indicator of insomnia? Mol Psychiatry. 2014;19(2):151–2. doi:10.1038/mp.2013.10. Epub 2013/02/13. PubMed PMID: 23399916; PMCID: PMC3903111.
112. Guindalini C, Mazzotti DR, Castro LS, D'Aurea CV, Andersen ML, Poyares D, Bittencourt LR, Tufik S. Brain-derived neurotrophic factor gene polymorphism predicts interindividual variation in the sleep electroencephalogram. J Neurosci Res. 2014;92(8):1018–23. doi:10.1002/jnr.23380. Epub 2014/04/05. PubMed PMID: 24700661.
113. Bachmann V, Klein C, Bodenmann S, Schafer N, Berger W, Brugger P, Landolt HP, The BDNF. Val66Met polymorphism modulates sleep intensity: EEG frequency- and state-specificity. Sleep. 2012;35(3):335–44. doi:10.5665/sleep.1690. Epub 2012/03/02. PubMed PMID: 22379239; PMCID: PMC3274334.
114. Schmitt K, Holsboer-Trachsler E, Eckert A. BDNF in sleep, insomnia, and sleep deprivation. Ann Med. 2016;48(1–2):42–51. doi:10.3109/07853890.2015.1131327. Epub 2016/01/14. PubMed PMID: 26758201.
115. Valente NL, Vallada H, Cordeiro Q, Miguita K, Bressan RA, Andreoli SB, Mari JJ, Mello MF. Candidate-gene approach in posttraumatic stress disorder after urban violence: association analysis of the genes encoding serotonin transporter, dopamine transporter, and BDNF. J Mol Neurosci. 2011;44(1):59–67. doi:10.1007/s12031-011-9513-7. PubMed PMID: 21491204.
116. Duan Z, He M, Zhang J, Chen K, Li B, Wang J. Assessment of functional tag single nucleotide polymorphisms within the DRD2 gene as risk factors for post-traumatic stress disorder in the Han Chinese population. J Affect Disord. 2015;188:210–7. doi:10.1016/j.jad.2015.08.066. Epub 2015/09/14. PubMed PMID: 26363619.
117. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci. 2001;21(5):1787–94. PubMed PMID: 11222668.
118. Craig D, Hart DJ, Passmore AP. Genetically increased risk of sleep disruption in Alzheimer's disease. Sleep. 2006;29(8):1003–7. PubMed PMID: 16944667.
119. Valomon A, Holst SC, Bachmann V, Viola AU, Schmidt C, Zurcher J, Berger W, Cajochen C, Landolt HP. Genetic polymorphisms of DAT1 and COMT differentially associate with actigraphy-derived sleep-wake cycles in young adults. Chronobiol Int. 2014;31(5):705–14. doi:10.3109/07420528.2014.896376. Epub 2014/03/15. PubMed PMID: 24625311.
120. Greer SM, Goldstein AN, Knutson B, Walker MP. A genetic polymorphism of the human dopamine transporter determines the impact of sleep deprivation on brain responses to rewards and punishments. J Cogn Neurosci. 2016;28(6):803–10. doi:10.1162/jocn_a_00939. Epub 2016/02/27. PubMed PMID: 26918589.
121. Cade BE, Gottlieb DJ, Lauderdale DS, Bennett DA, Buchman AS, Buxbaum SG, De Jager PL, Evans DS, Fulop T, Gharib SA, Johnson WC, Kim H, Larkin EK, Lee SK, Lim AS, Punjabi NM, Shin C, Stone KL, Tranah GJ, Weng J, Yaffe K, Zee PC, Patel SR, Zhu X, Redline S, Saxena R. Common variants in DRD2 are associated with sleep duration: the CARe consortium. Hum Mol Genet. 2016;25(1):167–79. doi:10.1093/hmg/ddv434. Epub 2015/10/16. PubMed PMID: 26464489; PMCID: PMC4690488.
122. Nelson EC, Agrawal A, Pergadia ML, Lynskey MT, Todorov AA, Wang JC, Todd RD, Martin NG, Heath AC, Goate AM, Montgomery GW, Madden PA. Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults. Mol Psychiatry. 2009;14(3):234–5. doi:10.1038/mp.2008.81. PubMed PMID: 19229201; PMCID: PMC3291097.
123. Geuze E, van Berckel BN, Lammertsma AA, Boellaard R, de Kloet CS, Vermetten E, Westenberg HG. Reduced GABAA benzodiazepine receptor binding in veterans with post-traumatic stress disorder. Mol Psychiatry. 2008;13(1):74–83. doi:10.1038/sj.mp.4002054. 3. Epub 2007/08/02. PubMed PMID: 17667960.
124. Strawn JR, Pyne-Geithman GJ, Ekhator NN, Horn PS, Uhde TW, Shutter LA, Baker DG, Geracioti TD Jr. Low cerebrospinal fluid and plasma orexin-A (hypocretin-1) concentrations in combat-related posttraumatic stress disorder. Psychoneuroendocrinology. 2010;35(7):1001–7. doi:10.1016/j.psyneuen.2010.01.001. PubMed PMID: 20116928.
125. Ban HJ, Kim SC, Seo J, Kang HB, Choi JK, et al. PLoS One. 2011;6(4):e18455. doi:10.1371/journal.pone.0018455. PubMed PMID: 21494683; PMCID: PMC3071826.
126. Byrne EM, Gehrman PR, Medland SE, Nyholt DR, Heath AC, Madden PA, Hickie IB, Van Duijn CM, Henders AK, Montgomery GW, Martin NG, Wray NR, Chronogen C. A genome-wide association study of sleep habits and insomnia. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(5):439–51. doi:10.1002/ajmg.b.32168. PubMed PMID: 23728906; PMCID: PMC4083458.
127. Spada J, Scholz M, Kirsten H, Hensch T, Horn K, Jawinski P, Ulke C, Burkhardt R, Wirkner K, Loeffler M, Hegerl U, Sander C. Genome-wide association analysis of actigraphic sleep phenotypes in the LIFE Adult Study. J Sleep Res. 2016; doi:10.1111/jsr.12421. Epub 2016/04/30. PubMed PMID: 27126917.
128. Allebrandt KV, Amin N, Muller-Myhsok B, Esko T, Teder-Laving M, Azevedo RV, Hayward C, van Mill J, Vogelzangs N, Green EW, Melville SA, Lichtner P, Wichmann HE, Oostra BA, Janssens AC, Campbell H, Wilson JF, Hicks AA, Pramstaller PP, Dogas Z, Rudan I, Merrow M, Penninx B, Kyriacou CP, Metspalu A, van Duijn CM, Meitinger T, Roenneberg T. A K(ATP) channel gene effect on sleep duration: from genome-wide association studies to function in Drosophila. Mol Psychiatry. 2013;18(1):122–32. doi:10.1038/mp.2011.142. PubMed PMID: 22105623.
129. Gottlieb DJ, Hek K, Chen TH, Watson NF, Eiriksdottir G, Byrne EM, Cornelis M, Warby SC, Bandinelli S, Cherkas L, Evans DS, Grabe HJ, Lahti J, Li M, Lehtimaki T, Lumley T, Marciante KD, Perusse L, Psaty BM, Robbins J, Tranah GJ, Vink JM, Wilk JB, Stafford JM, Bellis C, Biffar R, Bouchard C, Cade B, Curhan GC, Eriksson JG, Ewert R, Ferrucci L, Fulop T, Gehrman PR, Goodloe R, Harris TB, Heath AC, Hernandez D, Hofman A, Hottenga JJ, Hunter DJ, Jensen MK, Johnson AD, Kahonen M, Kao L, Kraft P, Larkin EK, Lauderdale DS, Luik AI, Medici M, Montgomery GW, Palotie A, Patel SR, Pistis G, Porcu E, Quaye L, Raitakari O, Redline S, Rimm EB, Rotter JI, Smith AV, Spector TD, Teumer A, Uitterlinden AG, Vohl MC, Widen E, Willemsen G, Young T, Zhang X, Liu Y, Blangero J, Boomsma DI, Gudnason V, Hu F, Mangino M, Martin NG, O'Connor GT, Stone KL, Tanaka T, Viikari J, Gharib SA, Punjabi NM, Raikkonen K, Volzke H, Mignot E, Tiemeier H. Novel loci associated with usual sleep duration: the CHARGE Consortium Genome-Wide Association Study. Mol Psychiatry. 2015;20(10):1232–9. doi:10.1038/mp.2014.133. Epub 2014/12/04. PubMed PMID: 25469926; PMCID: PMC4430294.
130. Gottlieb DJ, O'Connor GT, Wilk JB. Genome-wide association of sleep and circadian phenotypes. BMC Med Genet. 2007;8(Suppl 1):S9. doi:10.1186/1471-2350-8-S1-S9. PubMed PMID: 17903308; PMCID: PMC1995620.
131. Ollila HM, Kettunen J, Pietilainen O, Aho V, Silander K, Kronholm E, Perola M, Lahti J, Raikkonen K, Widen E, Palotie A, Eriksson JG, Partonen T, Kaprio J, Salomaa V, Raitakari O, Lehtimaki T, Sallinen M, Harma M, Porkka-Heiskanen T, Paunio T. Genome-wide association study of sleep duration in the Finnish population.

J Sleep Res. 2014;23(6):609–18. doi:10.1111/jsr.12175. PubMed PMID: 25109461.
132. Scheinfeldt LB, Gharani N, Kasper RS, Schmidlen TJ, Gordon ES, Jarvis JP, Delaney S, Kronenthal CJ, Gerry NP, Christman MF. Using the Coriell Personalized Medicine Collaborative Data to conduct a genome-wide association study of sleep duration. Am J Med Genet B Neuropsychiatr Genet. 2015;168(8):697–705. doi:10.1002/ajmg.b.32362. Epub 2015/09/04. PubMed PMID: 26333835.
133. Babson KA, Blonigen DM, Boden MT, Drescher KD, Bonn-Miller MO. Sleep quality among U.S. military veterans with PTSD: a factor analysis and structural model of symptoms. J Trauma Stress. 2012;25(6):665–74. doi:10.1002/jts.21757. PubMed PMID: 23225033.
134. Parsons MJ, Lester KJ, Barclay NL, Nolan PM, Eley TC, Gregory AM. Replication of Genome-Wide Association Studies (GWAS) loci for sleep in the British G1219 cohort. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(5):431–8. doi:10.1002/ajmg.b.32106. PubMed PMID: 23780892.
135. Liu C, Chung M. Genetics and epigenetics of circadian rhythms and their potential roles in neuropsychiatric disorders. Neurosci Bull. 2015;31(1):141–59. doi:10.1007/s12264-014-1495-3. Epub 2015/02/06. PubMed PMID: 25652815; PMCID: PMC4821655.
136. Qureshi IA, Mehler MF. Epigenetics of sleep and chronobiology. Curr Neurol Neurosci Rep. 2014;14(3):432. doi:10.1007/s11910-013-0432-6. Epub 2014/01/31. PubMed PMID: 24477387; PMCID: PMC3957188.
137. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet. 2011;88(1):76–82. doi:10.1016/j.ajhg.2010.11.011. PubMed PMID: 21167468; PMCID: PMC3014363.
138. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, Anttila V, Xu H, Zang C, Farh K, Ripke S, Day FR, ReproGen C, Schizophrenia Working Group of the Psychiatric Genomics C, Consortium R, Purcell S, Stahl E, Lindstrom S, Perry JR, Okada Y, Raychaudhuri S, Daly MJ, Patterson N, Neale BM, Price AL. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47(11):1228–35. doi:10.1038/ng.3404. Epub 2015/09/29. PubMed PMID: 26414678; PMCID: PMC4626285.
139. Cross-Disorder Group of the Psychiatric Genomics C. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013;381(9875):1371–9. doi:10.1016/S0140-6736(12)62129-1. Epub 2013/03/05. PubMed PMID: 23453885; PMCID: PMC3714010.
140. Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayes M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisen L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kahler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landen M, Langstrom N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, DJ MI, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Muhleisen TW, Muir WJ, Muller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nothen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnstrom K, Reif A, Ribases M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zollner S, Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR, International Inflammatory Bowel Disease Genetics C. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013;45(9):984–94. doi:10.1038/ng.2711. Epub 2013/08/13. PubMed PMID: 23933821; PMCID: PMC3800159.
141. Solovieff N, Roberts AL, Ratanatharathorn A, Haloosim M, De Vivo I, King AP, Liberzon I, Aiello A, Uddin M, Wildman DE, Galea S, Smoller JW, Purcell SM, Koenen KC. Genetic association analysis of 300 genes identifies a risk haplotype in SLC18A2 for post-traumatic stress disorder in two independent samples. Neuropsychopharmacology. 2014;39(8):1872–9. doi:10.1038/npp.2014.34. PubMed PMID: 24525708; PMCID: PMC4059895.
142. International Schizophrenia C, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460(7256):748–52. doi:10.1038/

nature08185. Epub 2009/07/03. PubMed PMID: 19571811; PMCID: PMC3912837.
143. Lai YC, Huang MC, Chen HC, Lu MK, Chiu YH, Shen WW, Lu RB, Kuo PH. Familiality and clinical outcomes of sleep disturbances in major depressive and bipolar disorders. J Psychosom Res. 2014;76(1):61–7. doi:10.1016/j.jpsychores.2013.10.020. Epub 2013/12/24. PubMed PMID: 24360143.
144. Gass N, Ollila HM, Utge S, Partonen T, Kronholm E, Pirkola S, Suhonen J, Silander K, Porkka-Heiskanen T, Paunio T. Contribution of adenosine related genes to the risk of depression with disturbed sleep. J Affect Disord. 2010;126(1–2):134–9. doi:10.1016/j.jad.2010.03.009. PubMed PMID: 20392501.
145. Saus E, Soria V, Escaramis G, Vivarelli F, Crespo JM, Kagerbauer B, Menchon JM, Urretavizcaya M, Gratacos M, Estivill X. Genetic variants and abnormal processing of pre-miR-182, a circadian clock modulator, in major depression patients with late insomnia. Hum Mol Genet. 2010;19(20):4017–25. doi:10.1093/hmg/ddq316. PubMed PMID: 20656788.
146. Utge SJ, Soronen P, Loukola A, Kronholm E, Ollila HM, Pirkola S, Porkka-Heiskanen T, Partonen T, Paunio T. Systematic analysis of circadian genes in a population-based sample reveals association of TIMELESS with depression and sleep disturbance. PLoS One. 2010;5(2):e9259. doi:10.1371/journal.pone.0009259. PubMed PMID: 20174623; PMCID: PMC2823770.
147. Kilaru V, Iyer SV, Almli LM, Stevens JS, Lori A, Jovanovic T, Ely TD, Bradley B, Binder EB, Koen N, Stein DJ, Conneely KN, Wingo AP, Smith AK, Ressler KJ. Genome-wide gene-based analysis suggests an association between Neuroligin 1 (NLGN1) and post-traumatic stress disorder. Transl Psychiatry. 2016;6:e820. doi:10.1038/tp.2016.69. Epub 2016/05/25. PubMed PMID: 27219346.
148. Savard J, Laroche L, Simard S, Ivers H, Morin CM. Chronic insomnia and immune functioning. Psychosom Med. 2003;65(2):211–21. PubMed PMID: 12651988.
149. Livingston WS, Rusch HL, Nersesian PV, Baxter T, Mysliwiec V, Gill JM. Improved sleep in military personnel is associated with changes in the expression of inflammatory genes and improvement in depression symptoms. Front Psych. 2015;6:59. doi:10.3389/fpsyt.2015.00059. Epub 2015/05/20. PubMed PMID: 25983695; PMCID: PMC4415307.
150. Heinzelmann M, Lee H, Rak H, Livingston W, Barr T, Baxter T, Scattergood-Keepper L, Mysliwiec V, Gill J. Sleep restoration is associated with reduced plasma C-reactive protein and depression symptoms in military personnel with sleep disturbance after deployment. Sleep Med. 2014;15(12):1565–70. doi:10.1016/j.sleep.2014.08.004. Epub 2014/10/15. PubMed PMID: 25311836.
151. Rusch HL, Guardado P, Baxter T, Mysliwiec V, Gill JM. Improved sleep quality is associated with reductions in depression and PTSD arousal symptoms and increases in IGF-1 concentrations. J Clin Sleep Med. 2015;11(6):615–23. doi:10.5664/jcsm.4770. Epub 2015/03/15. PubMed PMID: 25766717; PMCID: PMC4442222.
152. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012;35(1):24–35. doi:10.1016/j.tins.2011.06.007. PubMed PMID: 21798604; PMCID: PMC3206195.
153. Han KS, Kim L, Shim I. Stress and sleep disorder. Exp Neurobiol. 2012;21(4):141–50. doi:10.5607/en.2012.21.4.141. PubMed PMID: 23319874; PMCID: PMC3538178.
154. Minkel J, Moreta M, Muto J, Htaik O, Jones C, Basner M, Dinges D. Sleep deprivation potentiates HPA axis stress reactivity in healthy adults. Health Psychol. 2014;33(11):1430–4. doi:10.1037/a0034219. Epub 2014/05/14. PubMed PMID: 24818608.
155. Buhr A, Bianchi MT, Baur R, Courtet P, Pignay V, Boulenger JP, Gallati S, Hinkle DJ, Macdonald RL, Sigel E. Functional characterization of the new human GABA(A) receptor mutation beta3(R192H). Hum Genet. 2002;111(2):154–60. doi:10.1007/s00439-002-0766-7. Epub 2002/08/22. PubMed PMID: 12189488.
156. Prober DA, Rihel J, Onah AA, Sung RJ, Schier AF. Hypocretin/orexin overexpression induces an insomnia-like phenotype in zebrafish. J Neurosci. 2006;26(51):13400–10. doi:10.1523/JNEUROSCI.4332-06.2006. Epub 2006/12/22. PubMed PMID: 17182791.

The Neurocircuitry of Fear and PTSD

10

Michael B. VanElzakker, Lindsay K. Staples-Bradley, and Lisa M. Shin

Introduction

Since the late 1990s, a neurocircuitry model of post-traumatic stress disorder (PTSD) has emerged, implicating brain structures involved in fear and memory. According to this model, the amygdala is hyperresponsive in PTSD, accompanying an exaggerated fear response. Conversely, structures in the ventral medial prefrontal cortex (vmPFC, which includes rostral anterior cingulate cortex [rACC] and medial frontal gyrus) that normally inhibit the amygdala are hyporesponsive, underlying insufficient fear extinction. Abnormal hippocampal functioning may be related to deficiencies in identifying safe contexts and general declarative memory deficits. Newer evidence suggests that the dorsal anterior cingulate cortex (dACC) is hyperresponsive in PTSD, and several reports implicate the insula (or insular cortex) as functionally abnormal in PTSD and other anxiety disorders. In this chapter, we will briefly explain how fear conditioning and extinction are related to PTSD and then describe the methods and paradigms used in functional neuroimaging studies of PTSD. We will then review functional neuroimaging findings in the amygdala, medial prefrontal cortex (mPFC, including both vmPFC and dACC), hippocampus, and insula in PTSD.

Fear Conditioning and Extinction

An anxiety-related disorder precipitated by a traumatic experience, PTSD involves learned fear. Many researchers view Pavlovian fear conditioning and extinction as a partial model of PTSD, with persistence of PTSD characterized as a failure of normal fear extinction learning and recall [1–6]. At its most basic level, Pavlovian fear *conditioning acquisition* involves the repeated predictive pairing of an aversive unconditioned stimulus (US) (e.g., a shock) with a previously neutral conditioned stimulus (CS) (e.g., a colored light). After repeated presentations of this pairing, presentation of the CS alone elicits a conditioned fear response (CR). In fear *extinction* learning, the CS is repeatedly presented in the absence of the US. Because the CS no longer predicts the aversive US, fear responses to the CS decline across presentations. After fear conditioning and extinction, researchers may measure fear extinction *recall* or the memory that the CS is now "safe" and no longer predicts the US. If extinction learning is properly recalled, the CS should not elicit a fear response. Neuroimaging can measure human brain activation during all phases of a conditioning and extinction paradigm.

The basic neurocircuitry underlying fear conditioning is preserved across mammalian species [1]. Rodent models of fear conditioning are particularly well characterized [7, 8] (discussed in more detail in Chap. 12), implicating the amygdala and its subnuclei as central to both the behavioral expression of fear and to fear conditioning [7–9]. Rodent studies implicate mPFC structures such as prelimbic cortex and infralimbic cortex in fear conditioning, extinction, and extinction recall [10, 11]. Specifically, recruitment of prelimbic cortex (analogous to human dACC) is associated with fear expression, and recruitment of infralimbic cortex (analogous to human vmPFC) is associated with extinction learning and recall [5, 11–13]. Lesion, stimulation, and drug studies have provided evidence that prelimbic cortex projects to the basal nucleus of the amygdala (involved in fear responses) and the infralimbic cortex projects to inhibitory regions of the amygdala such as the lateral central nucleus and intercalated neurons [5, 13].

Human studies replicate these general neurocircuitry findings [1]. Although in vivo functional neuroimaging methods cannot achieve the subnuclei-level spatial resolution of invasive rodent studies, many imaging studies have shown involvement of the amygdala in fear conditioning [14–25]. Healthy humans show amygdala activation to a

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simple US such as shock [26], to a complex US such as aversive videos or pictures [27, 28], or when the CS is presented below conscious awareness [29, 30]. Activation in mPFC regions such as the rACC and dACC has also been associated with fear conditioning in healthy humans [14, 16, 17, 20–23, 28, 31–33]. Human fear conditioning studies have associated activation in both the amygdala and the dACC with CR as measured by skin conductance response [32]. Finally, several studies have found increased insula [14, 16, 17, 19, 23, 28, 30, 31, 33] and hippocampus [14, 16, 20, 30, 31] activation during fear conditioning in healthy humans. Human studies have also shown vmPFC activation both during extinction learning [15, 19, 22, 34] and extinction recall [22, 33]. Findings of amygdala [19, 21–33] and insula [19, 33] involvement in fear extinction have also been reported.

Context plays a crucial role in extinction learning; if conditioning takes place in one room (or country, for combat veterans) and extinction takes place in another, the physical environment serves as a reliable cue that predicts when the CS is "unsafe" and when it is "safe." Studies in both animals and humans suggest that the hippocampus plays an important role in the contextual modulation of fear extinction. In rodents, the use of contextual cues in extinction learning is dependent on connections between the dorsal hippocampus and the lateral nucleus of the amygdala [35]. During extinction recall in humans, hippocampal activation to the CS occurs in the extinction context but not the conditioning context and is correlated with vmPFC activation [34]. This relationship between context and fear extinction appears to be highly relevant to PTSD. According to fear conditioning models of PTSD, whereas combat veterans without the disorder are able to extinguish their conditioned fear from their traumatic experiences after returning home to a "safe" context, veterans with PTSD fail to extinguish their conditioned fear despite the "safe" context (reviewed in [3]).

Fear conditioning and extinction models of PTSD are simplistic in that they do not adequately explain all aspects of the disorder, such as elevated baseline anxiety (even without presentation of an explicit CS/reminder of trauma), emotional responses other than fear, neuroendocrine dysfunction, and more complex cognitive deficits. Fear conditioning paradigms are nonetheless useful for the study of the neurocircuitry of the disorder. If some PTSD symptoms are related to fear conditioning, one would expect to see abnormal recruitment of the amygdala and vmPFC in PTSD during conditioning, extinction learning, and extinction recall, reflecting a failure of vmPFC inhibition of amygdala responsivity. Such findings have indeed been reported [4]. See Fig. 10.1 for anatomical regions of interest in the neurocircuitry of PTSD and fear conditioning. Researchers have several neuroimaging methods and experimental paradigms at their disposal to examine the neurocircuitry of this psychiatric disorder.

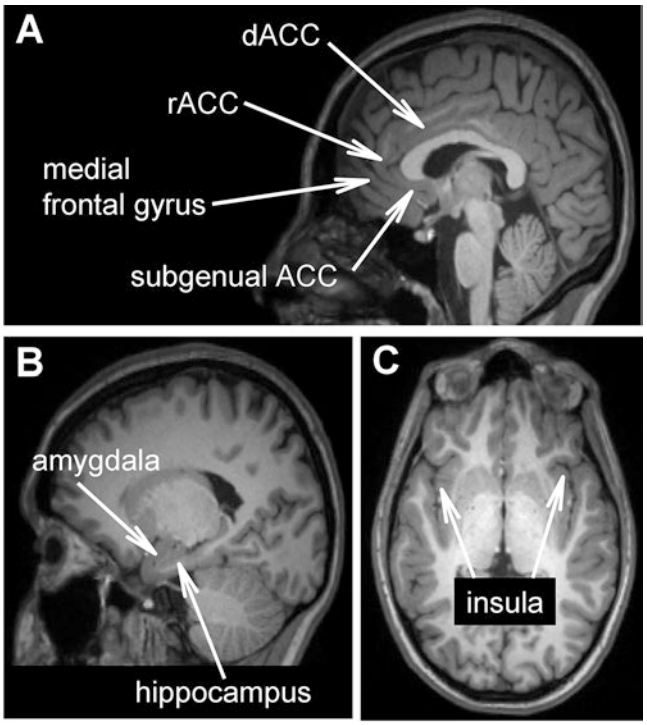

Fig. 10.1 Structural magnetic resonance images (MRIs) showing the structures of interest in this chapter: (**a**) a sagittal MRI slice showing the dorsal anterior cingulate gyrus (*dACC*) and structures comprising the ventral medial prefrontal cortex (*vmPFC*) including the rostral anterior cingulate cortex (*rACC*), medial frontal gyrus, and subgenual ACC; (**b**) a sagittal slice showing the amygdala and hippocampus; and (**c**) a horizontal slice showing bilateral insula (also called the insular cortex)

Imaging Methods

The studies presented in this chapter utilize a variety of neuroimaging techniques, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). All three can be equipped to present participants with experimental stimuli such as pictures, sounds, or finger shocks while recording three-dimensional images of brain function. PET can provide measures of cerebral metabolic rate for glucose, regional cerebral blood flow, or receptor occupancy, whereas fMRI measures blood-oxygen-level-dependent (BOLD) signal. Due to its good spatial and temporal resolution, and its ability to gather both functional and structural images in the same session, fMRI has been the most commonly used imaging technique in recent neuroimaging studies of PTSD.

A typical functional image such as Fig. 10.2 shows areas where the amount of brain activity in one experimental condition compared to another condition differs between PTSD and control groups (see Fig. 10.2 caption for more details). For example, this figure shows that amygdala activation in response to fearful versus happy faces is greater in individuals

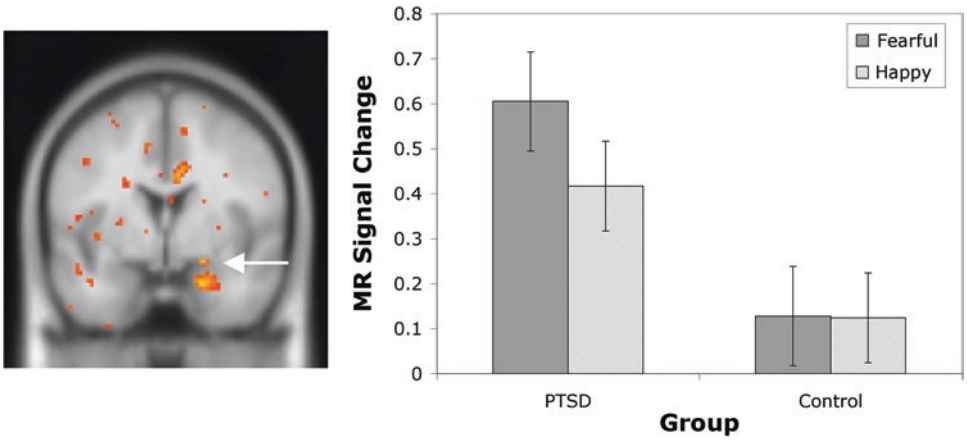

Fig. 10.2 A typical functional image such as Fig. 10.2 illustrates a "difference in differences." The *arrow* indicates activation in the right amygdala, where the amount of brain activity in one experimental condition compared to another condition differs between PTSD and control groups. The data analysis steps that yield such an image are as follows: First, within each subject, we statistically compare brain responses in one condition to those of another condition (e.g., amygdala responses to fearful versus happy faces). This comparison yields a statistical image that shows the brain areas that are "activated" significantly more (or less) in one condition versus another. Second, these "difference" images per subject in the PTSD group are statistically compared to difference images of a control group. The result is an image like Fig. 10.2 that can show brain regions that are significantly more (or less) activated in one group than another. The functional magnetic resonance image (fMRI) in Fig. 10.2 displays activation to fearful versus happy facial expressions in the right amygdala ($z = 3.14$; Montreal Neurological Institute [MNI] coordinates, +22, +2, −14 [*arrow*]; and $z = 3.03$; MNI coordinates, +22, 0, −26) that were greater in the PTSD group versus trauma-exposed control group. The *bar graph* shows signal change in the amygdala in each condition (relative to fixation baseline) for each group. *Error bars* represent standard error of the mean (Reprinted with permission from [36])

with PTSD compared to trauma-exposed individuals without PTSD. Given the fear conditioning model of PTSD, exaggerated amygdala responsivity is to be expected and indeed has been reported [36]. Interestingly, the general neurocircuitry findings predicted by the fear conditioning model of PTSD have been replicated using a wide variety of experimental paradigms, not limited to fear conditioning per se.

Paradigms

Functional neuroimaging studies of PTSD commonly include fear conditioning paradigms, symptom provocation tasks, or other emotional and nonemotional tasks. Fear conditioning studies often use mild finger shocks as the aversive US and can record brain activity during acquisition, extinction, and extinction recall phases. Symptom provocation paradigms detect brain activation differences between symptomatic and neutral states in PTSD. One such paradigm is script-driven imagery, in which participants are presented with audio-recorded narratives ("scripts") of their traumatic and neutral experiences. Other symptom provocation tasks involve exposing participants to trauma-related sounds, odors, or pictures. Trauma-unrelated emotional stimuli include positively and negatively valenced pictures, as well as photographs of faces with varying emotional expressions. Finally, some paradigms implement emotionally neutral cognitive tasks or stimuli or take functional images while participants are at rest. In the following sections, we will describe findings in several brain regions of interest from PTSD studies that have used these paradigms.

Amygdala

The amygdala, a structure involved in fear expression and fear conditioning, is hyperresponsive in individuals with PTSD relative to comparison groups. This general finding has been reported in studies utilizing disparate neuroimaging paradigms including fear conditioning and extinction, symptom provocation, general emotional and neutral stimuli, and resting state.

Evidence of increased amygdala recruitment in PTSD has been found during both the acquisition and the extinction learning phases of fear conditioning paradigms, as well as during extinction learning recall. Bremner et al. reported greater left amygdala activation in a PTSD group relative to a control group in a contrast between a fear acquisition condition (in which a shock was paired with a picture of a blue square) and a control condition (in which participants received random shocks in the absence of a CS) [2]. Milad and colleagues used a different fear conditioning paradigm that included an acquisition phase in which two different colored lights (CS+s) were paired with shock and a third color was not (CS−), followed by an extinction phase in which only one of the two CS+s was extinguished [4, 37]. Relative to trauma-exposed healthy control participants, individuals with PTSD showed increased amygdala responsivity to the

shock [37]. Furthermore, during late extinction learning, the PTSD group had greater amygdala activation in the contrast between the extinguished CS+ versus the CS−, suggesting impaired late extinction learning [4]. Using the same paradigm, Garfinkel and colleagues found that during next-day recall in a never-conditioned (safety) context, individuals with combat-related PTSD showed increased amygdala activation to the extinguished CS+ versus the CS−, while combat controls without PTSD did not [38]. However, when the extinguished CS+ was then represented in the previously conditioned (danger) context, combat controls showed increased amygdala activation to the CS+ versus the CS−, relative to the PTSD group. In a newer study from Brunetti and colleagues, recently robbed bank clerks underwent single-trial conditioning between a startling noise (US) and pleasant or unpleasant emotional pictures, with increased bilateral amygdala activation to conditioned negative pictures in the PTSD group relative to the non-PTSD group [39].

Some symptom provocation studies have replicated the basic finding of relatively increased amygdala activation in PTSD. In an early PET study, Rauch and colleagues reported increased amygdala regional cerebral blood flow in a PTSD group during traumatic versus neutral script-driven imagery [40]. However, that study did not include a non-PTSD comparison group, and subsequent studies were needed to draw more firm conclusions. Shin et al. found increased amygdala activation in the traumatic versus neutral script contrast in male combat veterans with PTSD compared to male combat veterans without PTSD [41]. In a task using auditory cue words, St. Jacques and colleagues found increased amygdala activation during retrieval of negative versus positive autobiographical memories in participants with PTSD versus trauma-unexposed control participants [42].

Amygdala hyperresponsivity in PTSD also has been observed in response to other trauma-related stimuli, such as combat-related sounds, odors, and photographs. Liberzon et al. used SPECT to show increased left amygdala activation to combat noise relative to white noise in combat veterans with PTSD, but not in combat veterans without PTSD or in combat-unexposed control participants [43]. In a similar design but utilizing PET and lacking a non-PTSD control group, Pissiota and colleagues replicated the finding of increased amygdala regional cerebral blood flow in PTSD participants during exposure to combat noises, relative to neutral noise [44]. Vermetten et al. found greater amygdala activation in response to the odor of diesel fuel (a potent reminder of combat for many military veterans) in combat veterans with PTSD, relative to those without PTSD [45]. Morey and colleagues found that participants with PTSD had greater amygdala activation to trauma-related distractor photographs than trauma-exposed healthy control participants [46]. Driessen et al. found greater amygdala responsivity during traumatic versus neutral event recollection in women with borderline personality disorder with comorbid PTSD compared to those without PTSD [47]. Protopopescu et al. found increased amygdala activation in response to viewing trauma-related versus trauma-unrelated words in a PTSD group relative to a trauma-unexposed control group [48]. Brashers-Krug and Jorge showed noncombat and combat-related film clips to combat veterans in an fMRI environment and unexpectedly found that amygdala activation positively predicted PTSD severity during the noncombat film but negatively predicted PTSD severity during the combat film [49]. However, neither subjective ratings of the films nor categorical PTSD diagnoses were reported.

In PTSD, the amygdala is also hyperactivated in response to trauma-unrelated emotional stimuli such as fearful facial expressions. Fearful expressions are essentially predictors of potential threat, and the amygdala is highly responsive to them, even in healthy individuals. Findings of exaggerated amygdala activation to fearful facial expressions in PTSD suggest that functional abnormalities in the amygdala are not specific to trauma-related reminders. For example, Shin et al. found increased amygdala responses to fearful versus happy facial expressions in PTSD relative to trauma-exposed control participants [36] (see Fig. 10.2). Williams and colleagues used a similar paradigm and found that participants with PTSD had greater amygdala activation than a non-traumatized control group in a fearful versus neutral facial expression contrast [50]. Kemp et al. reported greater right amygdala activation to fearful versus neutral faces in a PTSD group, compared to healthy controls or a group with PTSD and comorbid major depressive disorder [51]. In an fMRI study, Garrett and colleagues found that the left amygdala/hippocampus activated more to emotional faces versus scrambled pictures in traumatized youth with and without current PTSD, relative to non-traumatized control youth [52].

In an affective priming task using emotional face stimuli, earthquake survivors with PTSD showed increased left amygdala activation compared to controls [53]. Dickie et al. showed photographs of expressive faces to individuals with PTSD in an fMRI environment and found a positive correlation between PTSD symptom severity and left amygdala activation to successfully-remembered fearful faces [54]. El Khoury-Malhame and colleagues found that attentional bias toward threatening words and faces was positively correlated with amygdala activation in a PTSD group but not in a healthy control group [55]. Finally, Brohawn and colleagues found greater amygdala activation in response to photographs of aversive versus neutral scenes in participants with PTSD compared to trauma-exposed control participants [56].

Interestingly, increased amygdala activation in PTSD can be observed even when emotional visual stimuli are presented below perceptual thresholds, such as in masking paradigms. This has been reported in studies using both trauma-related

and trauma-unrelated images. For example, combat veterans with and without PTSD were shown combat-related and combat-unrelated images above, near, and below recognition threshold using backward masking [57]. In that study, the veterans with PTSD had greater amygdala activation than control participants regardless of the content and recognition threshold. In a contrast between backwardly masked fearful and masked happy faces, Rauch et al. found that participants with PTSD had greater amygdala activation compared to trauma-exposed non-PTSD participants [58]. Similarly, Bryant and colleagues found that individuals with PTSD showed greater amygdala activation to masked fearful versus neutral expressions than did healthy trauma-unexposed control participants [59]. Felmingham et al. reported increased amygdala activation in response to masked fearful faces in a PTSD group relative to trauma-exposed and trauma-unexposed controls [60]. Killgore and colleagues used a masked faces paradigm with fMRI to compare healthy controls to an anxiety disorders group including PTSD, panic disorder, and specific phobia. Relative to the control group, participants with anxiety disorders exhibited increased left amygdala activation to both masked fear versus neutral faces and to masked happy versus neutral faces [61].

Some studies suggest that the amygdala is more active in PTSD versus control groups even during emotionally neutral tasks or at rest. For example, in a SPECT study, Chung et al. reported greater blood flow in the amygdala at rest in participants with PTSD relative to healthy control participants [62] (but see [63]). Lanius et al. studied a sample of participants 6–12 weeks after experiencing a psychologically traumatic event and found that the strength of resting-state functional connectivity between the right amygdala and posterior cingulate cortex predicted future PTSD symptom severity [64]. This relationship remained statistically significant after controlling for comorbid depression. Using a neutral auditory oddball task in an fMRI environment, Bryant and colleagues found greater amygdala responses in participants with PTSD relative to a non-traumatized control group [65]. Furthermore, in a study that recruited bank robbery survivors with and without PTSD, all participants showed increased amygdala activation to negative pictures, but only the PTSD group also showed increased amygdala activation to neutral pictures [66]. In a recognition memory task using emotionally neutral images, Whalley et al. found greater left dorsal amygdala activation in the old versus new contrast in PTSD relative to trauma-exposed participants and participants with depression [67].

Many studies have reported a positive correlation between level of amygdala activation and PTSD symptom severity [39, 41, 44, 48, 54–56, 58, 65, 66, 68, 69]. In addition, PTSD treatment studies [70] have shown that higher pretreatment amygdala activation predicts less improvement with cognitive behavioral therapy (CBT) [71] and a positive CBT response is associated with decreased amygdala activation [72, 73].

It should be noted that not all studies report increased amygdala activation in PTSD [74–80]. Amygdala responses habituate rapidly, and averaging amygdala signal over time in PET and SPECT analyses or across fMRI blocks can dilute the initial activation signal. This could lead to inconsistencies across studies. Another caveat to consider is that amygdala hyperreactivity is not specific to PTSD and has also been observed in other anxiety disorders (e.g., specific phobia, social anxiety disorder) [81]. While amygdala hyperreactivity is common across anxiety disorders, PTSD is unique in that this hyperreactivity may reflect a failure of vmPFC inhibition over fear responses and may also be related to increased dACC activation.

Medial Prefrontal Cortex

mPFC structures are involved in fear expression, fear conditioning and extinction, and emotion regulation. mPFC function in PTSD has been examined with fear conditioning, symptom provocation, and emotional and neutral paradigms. In keeping with the well-characterized relationship between amygdala and vmPFC in rodent fear conditioning studies, some PTSD studies have found a negative correlation between amygdala activation and vmPFC activation [36, 41] (but see [49, 50, 82]). Ventral mPFC function in PTSD has been explicitly examined in fear conditioning studies. Several fear conditioning and extinction studies have reported reduced activation or even deactivation within vmPFC structures (such as rostral anterior cingulate cortex [rACC]) in PTSD groups, relative to control groups. Interestingly, in contrast to the hypoactivity of ventral regions of mPFC, more dorsal regions, such as the dorsal anterior cingulate cortex (dACC), are frequently hyperactive in PTSD. This dissociation has been reported in fear conditioning studies. For example, Bremner and colleagues used PET to demonstrate that, during fear conditioning, women with PTSD had greater dACC activation than trauma-unexposed controls; during extinction, the PTSD group had relatively less subgenual cortex and rACC activation [2]. Brunetti and colleagues found that recently robbed bank clerks with PTSD, relative to those without PTSD, showed increased activation in dorsal mPFC to single-episode conditioning of emotionally negative pictures to an aversive noise [39].

In addition, Milad and colleagues used fMRI and a 2-day fear conditioning and extinction paradigm to study individuals with PTSD and trauma-exposed healthy control participants [4, 83]. During late conditioning and early extinction, when the CS still signaled danger, the PTSD group showed increased dACC activation, relative to the control group. During late extinction, when the CS should have no longer signaled danger, the PTSD group showed decreased vmPFC activation, relative to the control group. During early

extinction recall, the PTSD group showed vmPFC hypoactivation and dACC hyperactivation. This implies decreased inhibitory influence on fear responses from the vmPFC and increased excitatory influence on fear responses from dACC. See Fig. 10.3 for a functional image of early extinction recall. Using the same paradigm, Garfinkel and colleagues found that during both next-day recall in a never-conditioned (safety) context and during next-day renewal in the conditioned (danger) context, combat controls without PTSD showed increased vmPFC activation to the extinguished CS+ versus the CS−, relative to individuals with PTSD [38]. Conducting a resting-state PET scan several days before utilizing that same 2-day fMRI conditioning and extinction paradigm, Marin and colleagues found that resting metabolism for glucose in the dACC positively correlated with PTSD symptoms, and also positively predicted dACC activation and negatively predicted vmPFC and hippocampal activation during extinction recall in PTSD [84]. Another recent study also reported increased dACC activation during extinction recall in PTSD compared to controls [85].

Findings of relatively diminished activation in the vmPFC have been reported in imaging studies involving the presentation of trauma-related material, such as script-driven imagery and trauma-related photos and words. In a symptom provocation study, Whalley and colleagues presented individualized trauma words versus either general trauma words or individualized non-trauma memory words to participants with PTSD as well as depressed and healthy controls. They found that when members of the PTSD group were presented with individualized trauma words, they exhibited increased BOLD response in dorsal mPFC regions including dACC [86]. Bremner and colleagues reported that, compared to female sexual abuse survivors without PTSD, the rACC of female sexual abuse survivors with PTSD failed to activate in response to traumatic versus neutral audio scripts [74]. Using a similar design, Shin and colleagues reported relatively reduced rACC activation in response to traumatic versus neutral scripts in PTSD [79]. Lanius et al. found decreased medial frontal gyrus and rACC activation in participants with PTSD compared to trauma-exposed participants without PTSD in a traumatic versus baseline imagery condition [77]. Using PET, Shin et al. found less activation in medial frontal gyrus during script-driven imagery in male and female Vietnam veterans with PTSD relative to those without PTSD [41]. In a SPECT study, Lindauer et al. found less activation in the medial frontal gyrus in response to traumatic versus neutral scripts in trauma-exposed police officers with PTSD compared to those without PTSD [87]. Using PET

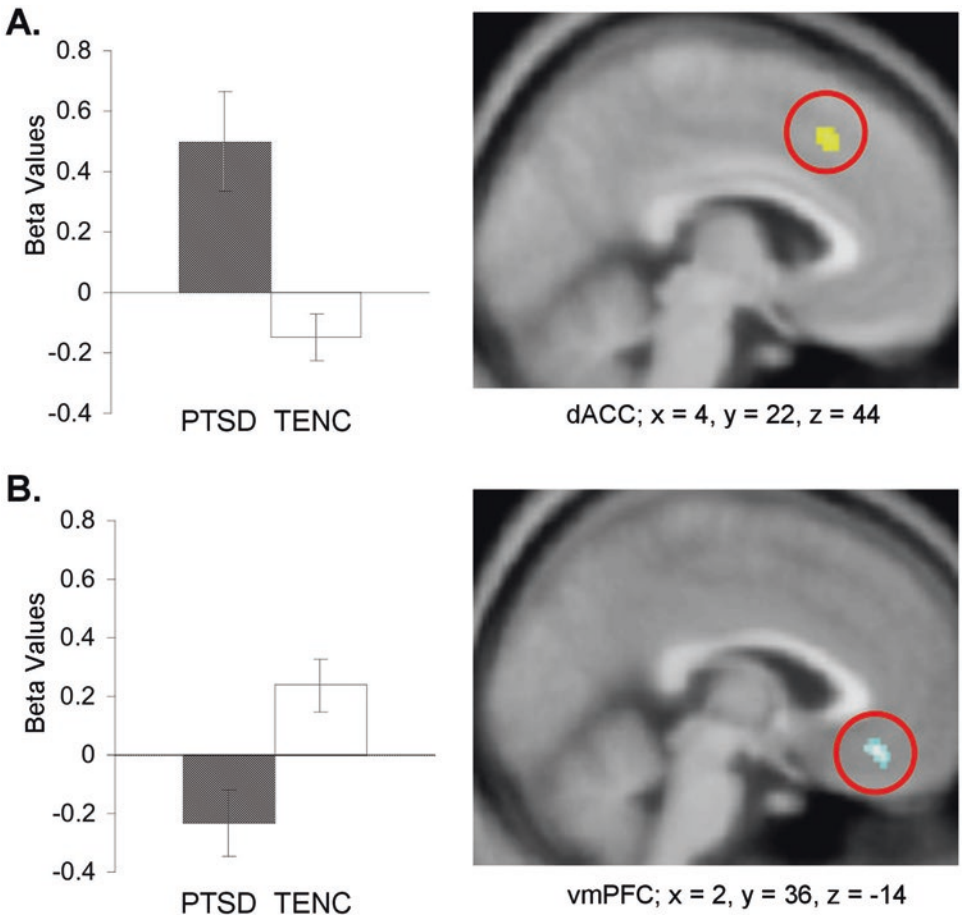

Fig. 10.3 These functional magnetic resonance images (fMRI) show brain activations during early fear extinction recall, compared to baseline: (**a**) dorsal anterior cingulate cortex (*dACC*) activation (*yellow*) and (**b**) ventral medial prefrontal cortex (*vmPFC*) deactivation (*light blue*). *Graphs* show brain activity in these two regions during early extinction recall relative to baseline activity of the two groups (*error bars* indicate standard error of the mean). Numbers following *x*, *y*, and *z* refer to Montreal Neurological Institute (MNI) coordinates. *TENC* trauma-exposed non-PTSD controls (Reprinted with permission from [83])

during traumatic/stressful scripts, Britton and colleagues found more deactivation in the rACC in combat veterans with PTSD compared with combat veterans without PTSD and combat-unexposed controls without PTSD [76]. Lanius et al. found that participants with PTSD, relative to trauma-exposed participants without PTSD, had decreased ACC activation in response to personalized scripts of trauma-unrelated sad and anxiety-provoking events [88]. In another fMRI study, Lanius and colleagues reported less rACC activation in response to trauma scripts versus baseline in individuals with PTSD compared to those with PTSD and comorbid major depression [89]. In an early PET study, Shin and colleagues found lower regional cerebral blood flow in the rACC of combat veterans with PTSD compared to combat veterans without PTSD during combat versus neutral visual imagery [90]. Bremner and colleagues found lower blood flow in vmPFC in response to combat-related versus neutral audio-visual stimuli in combat veterans with PTSD relative to combat veterans without PTSD [75]. In an fMRI study, Yang and colleagues found relatively reduced rACC activation in a trauma-related versus neutral picture contrast in adolescents with PTSD, relative to trauma-exposed controls [91]. Hou and colleagues showed neutral and trauma-related pictures to survivors of a mining accident with and without PTSD. They found relatively diminished rACC activation in the PTSD versus control group [92]. In the combat-related word versus generally negative word contrast of an fMRI emotional Stroop task, Shin et al. found a lack of rACC activation and increased dACC activation in combat veterans with PTSD, relative to combat veterans without PTSD [93].

Studies using pictures of facial expressions frequently have shown relatively diminished vmPFC activation in individuals with PTSD. In an fMRI study, Shin et al. showed pictures of fearful and happy facial expressions to participants with PTSD and trauma-exposed control participants [36]. In the fearful versus happy facial expression contrast, the PTSD group showed relatively reduced activations in the rACC, vmPFC, and also dorsal mPFC (see Fig. 10.4). Using an emotional faces interference paradigm, Offringa et al. found that individuals with PTSD showed less rACC activation than trauma-exposed controls [94]. In an fMRI study comparing a PTSD group to healthy trauma-unexposed control group, Williams and colleagues found less activation in the mPFC in the fearful versus neutral expression contrast in the PTSD group [50]. In a fearful versus neutral facial expression contrast, Kemp et al. found that participants with PTSD and comorbid depression had less activation in the mPFC than participants with PTSD only [51]. In an fMRI study, Fonzo et al. presented a face-matching task to women with PTSD as well as trauma-unexposed women. They found increased dACC activation in response to male versus female faces in the PTSD group, and this dACC activation was positively correlated with hyperarousal symptoms [95]. Crozier and colleagues studied maltreated youth with and without PTSD as well as non-maltreated youth controls and found some gender-specific effects. They found that, while looking at fearful versus calm faces, maltreated girls showed deactivation of rostral mPFC relative to control girls, maltreated boys, and control boys [96]. In an fMRI study of subway fire survivors with PTSD, participants underwent a simple same-different judgment task in which task-irrelevant emotional and neutral facial expressions served as distractors [97]. In the fearful versus neutral face contrast, participants with PTSD showed significantly decreased rACC activation compared to healthy, trauma-unexposed control participants. Dickie et al. found a negative correlation between vmPFC activation to forgotten faces and PTSD symptom severity in a subsequent memory paradigm [54]. In a follow-up to that

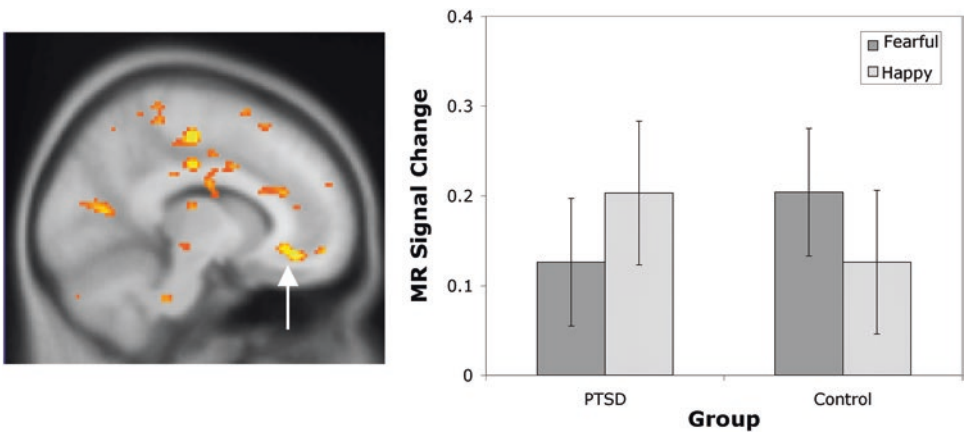

Fig. 10.4 The functional magnetic resonance image shows fearful versus happy activation in the rostral anterior cingulate (*arrow*) ($z = 3.61$; Montreal Neurological Institute [MNI] coordinates, −10, +38, −12) that was greater in the control group than in the PTSD group during the same study as Fig. 10.2. The *bar graph* shows fMRI activation in the rostral anterior cingulate (MNI coordinates, −10, +38, −12) in each condition (relative to fixation baseline) for each group. *Error bars* represent standard error of the mean (Reprinted with permission from [36])

study 6–9 months later, 65% of those participants no longer met the criteria for PTSD diagnosis, and the emotional memory-related increase in subgenual ACC activation was correlated with symptom improvement [69]. In an fMRI study of fearful versus neutral faces, Cisler and colleagues found that PTSD symptom severity in adolescent girls with histories of assault was associated with weakened functional connectivity between perigenual ACC and left amygdala [98].

Studies using trauma-unrelated emotional stimuli other than facial expressions have revealed similar results. Using PET, Bremner et al. studied the retrieval of deeply encoded negative versus neutral valence words in PTSD participants, relative to trauma-unexposed healthy control participants [99]. The PTSD group showed relatively decreased regional cerebral blood flow in the subgenual anterior cingulate cortex and rACC. In another PET study, the same group administered an emotional Stroop task to women with and without PTSD and found that those with PTSD had reduced regional cerebral blood flow in the rACC relative to those without PTSD [100]. Diener et al. used a trauma-unrelated cognitive stressor (mental arithmetic during white noise) and found that the stress-related pain threshold increases in PTSD participants correlated with increased activation in rACC [101]. In a PET study of blood flow responses to aversive versus neutral pictures, Phan et al. found reduced regional cerebral blood flow in the vmPFC in combat veterans with PTSD, relative to trauma-unexposed controls but not relative to combat veterans without PTSD [78]. Hayes and colleagues reported relatively increased dACC activation in combat veterans with severe PTSD symptoms compared to low-symptom veterans during trauma-unrelated emotional distraction [102].

Some studies utilizing neutral stimuli or resting-state imaging have found reduced vmPFC activation or increased dACC activation in PTSD. For example, Semple et al. used PET to compare regional cerebral blood flow in individuals with PTSD and a history of substance abuse to trauma-unexposed healthy control participants. They found that during a neutral valence auditory continuous performance task, the PTSD/substance abuse group had lower regional cerebral blood flow in medial frontal gyrus/ACC [103]. Jovanovic and colleagues used a nonemotional go/no-go task to demonstrate decreased BOLD response in the vmPFC of traumatized women with PTSD relative to traumatized women without PTSD; this decrease was also associated with fear-potentiated startle in a separate fear conditioning task [104]. In another fMRI study, Moores et al. found reduced ACC activation in PTSD participants relative to trauma-unexposed healthy control participants during a neutral-word verbal working memory updating task [105]. Bryant et al. found increased dACC activation in a PTSD group compared to a trauma-unexposed control group during a neutral valence auditory oddball paradigm [65]. Shin et al. reported increased dACC activation during a neutral valence interference task in PTSD participants, relative to trauma-exposed participants without PTSD [106]. In a PET study, Shin et al. found increased resting metabolic rate for glucose in the dACC of combat veterans with PTSD as well as in their combat-unexposed monozygotic twins. In addition, dACC activation in the combat-unexposed twins was positively correlated with the combat-exposed co-twin's PTSD symptom severity [63]. These findings suggest that increased resting dACC activation could be a familial risk factor for PTSD. Osuch et al. used PET to acquire functional brain images of recent car accident survivors, most of whom did not go on to develop PTSD. They found that, during rest, the car accident survivors had greater regional cerebral blood flow in rACC than trauma-unexposed controls, suggesting a possible protective effect of rACC activation against the development of PTSD [107].

Not all studies have reported reduced vmPFC activation in PTSD, however [43, 52, 59, 65, 108, 109]. One potential reason for inconsistent findings is that the normally reduced vmPFC activation seen in PTSD may be limited to conscious processing of stimuli [71, 110].

Several studies have reported that activation in vmPFC regions negatively correlates with symptom severity in PTSD [36, 41, 50, 54, 76, 94, 97, 111] (but see [52, 112, 113]). Several treatment studies have reported a relationship between increased vmPFC activation and PTSD symptom improvement [69, 72, 73, 114, 115] (but see [71]).

Hippocampus

The hippocampus plays a critical role in normal declarative, contextual, episodic, emotional, and spatial memory [116–119]. Abnormal hippocampal function in PTSD may be associated with deficits in any or all of these processes [56, 74, 99, 120–122]. Deficits in declarative memory may be an important link between hippocampal abnormalities and symptoms of PTSD, such as inability to recall important aspects of the traumatic event [123].

PTSD researchers have studied hippocampal function using experimental fear conditioning paradigms, trauma-related stimuli, emotional but trauma-unrelated stimuli, and nonemotional tasks. Across these paradigms, hippocampal findings have been mixed. Evidence from experimental fear conditioning paradigms suggests that individuals with PTSD may have an impaired ability to use both internal and external contextual cues to identify safe contexts and respond appropriately [124]. For example, Milad and colleagues found that individuals with PTSD fail to extinguish fear responses in novel contexts and showed decreased hip-

pocampal activation during extinction recall [4]. Using the same conditioning and extinction paradigm, Garfinkel and colleagues found that during next-day fear renewal in the conditioned (danger) context, combat controls without PTSD showed increased left hippocampus activation to the CS− versus the extinguished CS+, relative to individuals with PTSD [38]. In a separate study, Marin and colleagues found that in a resting-state PET scan conducted 4 days before conditioning and extinction, metabolic rate for glucose in dACC negatively predicted hippocampal activation during extinction recall in PTSD [84].

Studies involving trauma-related stimuli have shown evidence of relatively decreased hippocampal activation in PTSD. An early PET study by Bremner et al. found that, compared to trauma-exposed controls, women who were diagnosed with childhood sexual abuse-related PTSD showed greater deactivation in right hippocampus while listening to trauma-related scripts versus neutral scripts [74]. In a later fMRI study, veterans of the wars in Iraq and Afghanistan showed decreased hippocampal activation while encoding trauma-related images compared to veterans without PTSD [121]. Bremner and colleagues found evidence of relatively decreased hippocampal blood flow during the retrieval of trauma-related and trauma-unrelated emotionally valenced words in a PTSD group compared to a trauma-exposed control group [99]. Improvement of PTSD symptoms has been associated with increases in hippocampal activity during script-driven imagery [73]. However, one study using trauma reminders did not find decreased hippocampus activation in PTSD. Specifically, St. Jacques and colleagues showed increased hippocampal recruitment during cued retrieval of negative versus positive autobiographical memories in a PTSD group compared to a trauma-unexposed control group [42].

Some studies using trauma-unrelated emotional stimuli have found evidence of increased hippocampal activation in PTSD. Whalley and colleagues examined changes in brain activation during the recognition of neutral target images in emotional versus neutral contexts [67]. They found that the PTSD group showed greater hippocampal recruitment for emotional versus neutral contexts than the control group. An fMRI study comparing maltreated youth with and without PTSD to non-maltreated youth controls found that while looking at fearful versus scrambled faces (matched with face stimuli for spatial frequency and luminance but with no recognizable content), maltreated boys showed activation of left hippocampus relative to control boys, maltreated girls, and control girls [96]. In an emotional memory task, Brohawn and colleagues found that, compared to trauma-exposed controls, participants with PTSD showed an exaggerated hippocampal response to negative pictures that were subsequently remembered versus forgotten. They also found that the encoding of negative pictures was associated with greater hippocampal activation than the encoding of neutral pictures in PTSD participants [56].

Hippocampal function in PTSD has also been examined during nonemotional tasks and while participants are at rest. Bremner and colleagues found that the left hippocampus failed to activate in participants with PTSD, compared to trauma-exposed controls, during the encoding of neutral verbal passages [125]. These differences were independent of differences in hippocampal volume. Another study found a lack of hippocampus recruitment in participants with PTSD versus trauma-unexposed controls during a working memory updating task [105]. Molina and colleagues found diminished hippocampal glucose metabolism at rest in PTSD participants compared to trauma-exposed controls, indicating a possible differential pattern of baseline activation in this region [126]. Astur and colleagues found a negative correlation between hippocampus activation and PTSD symptom severity during a virtual spatial navigation task [120]. On the other hand, increased activation of the left hippocampus has been reported in PTSD participants completing a declarative memory task [127, 128]. Individuals with PTSD have also exhibited increased hippocampal blood flow during the resting state [129]. A few functional neuroimaging studies have shown evidence for both increased and decreased hippocampal activation in PTSD. In a PET study by Shin and colleagues, individuals with PTSD showed diminished regional cerebral blood flow in the hippocampus during word-stem completions for deeply versus shallowly encoded words. However, after collapsing across deeply and shallowly encoded conditions, the PTSD group showed greater regional cerebral blood flow in the hippocampus compared to controls [130]. In addition, Werner and colleagues found that, during a face-occupation pairing task, participants with PTSD showed increased hippocampal activation during encoding but decreased parahippocampal activation during retrieval, as compared to trauma-unexposed controls [131].

There is some evidence that activation of the hippocampus relates to symptom severity. Osuch et al. found that in participants with chronic PTSD, hippocampal activation was positively correlated with symptom severity during a script-driven imagery task [132]. Shin et al. reported that hippocampal activation collapsed across conditions was positively correlated with symptom severity in the PTSD group [130]. In contrast, Dickie et al. found that improvement of PTSD symptoms was positively correlated with increases in hippocampal activity while viewing fearful versus neutral faces [69]. In a functional connectivity analysis using fearful versus neutral faces, Cisler and colleagues found connectivity strength between left parahippocampus and vmPFC positively associated with severity of assault exposure in adolescent girls and connectivity strength between right parahippocampal gyrus and left middle frontal gyrus positively associated with PTSD symptom severity [98].

Although the direction of hippocampal functional abnormalities in PTSD varies across studies, it has been well established that hippocampal abnormalities are present in PTSD. Seemingly conflicting findings may reflect the changing role of the hippocampus across various cognitive tasks or different statistical approaches utilized by researchers [133]. Future research will help clarify the nature of the relationship between hippocampal abnormalities and PTSD symptoms.

Insula

In healthy humans, the insula is activated during cognitively demanding emotional tasks [134] and during the anticipation of painful [135, 136] or otherwise negative stimuli [137, 138]. Several functional neuroimaging studies have found evidence of increased activation in the insula in PTSD [81]. According to Etkin and Wager, it is possible that the insula is part of an overactive fear network common to several anxiety disorders [81]. Some groups have speculated that increased insula activation during anticipation of negative stimuli may be associated with some of the hyperarousal symptoms or emotional numbing symptoms that are characteristic of PTSD [108, 139]. It has been suggested that, in patients with PTSD, impaired declarative traumatic memories may be reorganized into somatic memories and that the insula plays a role in this reorganization [140]. Given that the insular cortex is an important brain region in the affective component of pain processing [141], its hyperactivation in PTSD may be related to the common comorbidity of chronic pain with PTSD [142].

A few studies have examined insula responses to pain in PTSD. Geuze and colleagues found that combat veterans with PTSD showed less sensitivity to painful heat stimulation and greater insula activation compared to veterans without PTSD [141]. Strigo and colleagues also reported increased insula activation to painful stimuli in PTSD participants relative to trauma-unexposed participants; however, after repeated exposure to the painful stimulus, the PTSD group showed relatively decreased insula activation compared to the control group [80]. They speculated that increases in insula activation during initial pain stimulation may be associated with altered pain processing, whereas decreases during repeated exposure to pain stimulation may be associated with avoidance symptoms of PTSD.

Studies involving trauma-related stimuli have revealed insula hyperactivation in PTSD. In a SPECT study comparing police officers with PTSD to trauma-exposed police officers without PTSD, Lindauer and colleagues found greater activation to trauma script-driven imagery in the left ventral insula [87]. A later PET study by the same group found increased regional cerebral blood flow in the right insula in a PTSD group compared to a trauma-exposed control group [143]. In another study using script-driven imagery, Lanius and colleagues compared insula activation in groups with PTSD with or without comorbid major depression [89]. After controlling for PTSD symptom severity, the PTSD-only group showed greater left insula activation in response to trauma-related scripts than the group with comorbid depression. This suggests that comorbid depression may be responsible for a portion of the variability in findings across studies. In another symptom provocation study using autobiographical trauma scripts, Nardo and colleagues found evidence of increased insula activation in PTSD [140]. Vermetten and colleagues found increased regional cerebral blood flow in the insula in PTSD during exposure to a trauma-related odor [45].

Increased insula activation in PTSD also has been found in response to trauma-unrelated emotional stimuli. Garrett et al. found increased right insular cortex activation to emotional faces versus scrambled pictures in traumatized youth with and without current PTSD, relative to non-traumatized control youth [52]. Compared to controls, earthquake survivors with PTSD showed an increased right insula BOLD response to an affective priming task that used emotional faces [53]. Fonzo and colleagues found that women with PTSD related to intimate partner violence showed greater insula activation to fearful or angry versus happy faces compared to trauma-unexposed controls [95]. In another study of survivors of intimate partner violence with PTSD, the anticipation of negative versus positive images was associated with increased insula activation [139]. Increased insula activation in PTSD has also been found during an emotional counting Stroop task [93]. In a study involving negative word retrieval, women with childhood abuse-related PTSD showed greater regional cerebral blood flow in insula than trauma-unexposed controls [99]. Retrieval of neutral items encoded in emotional versus neutral contexts has been associated with increased insula activity in PTSD compared to trauma-exposed and depressed controls [67]. Findings of increased insula responsivity in PTSD have also been reported during encoding of face-occupation pairings [131]. In contrast to the above reports of increased insula activation to emotional stimuli, one study found relatively decreased insula activity during an emotional Stroop task in females with abuse-related PTSD, compared to abused females without PTSD [100].

Two studies have found decreased resting-state insula activity in PTSD. Yin and colleagues found decreased insula activation in PTSD compared to trauma-exposed controls [144]. In addition, Molina and colleagues provided evidence of reduced resting glucose metabolism in the insula of a chronic PTSD group [126].

Finally, some studies have found positive correlations between PTSD symptom severity and insula activation [108, 111, 112, 132, 140, 145] (however, see the negative correlation between state dissociation symptoms and insula activation in [111]).

Conclusion

Functional neuroimaging has played a key role in elucidating the neurobiology of PTSD. The literature has provided evidence for hyperresponsivity of the amygdala, dACC, and insula, as well as decreased responsivity of vmPFC. These functional abnormalities have been reported in imaging studies using a wide range of stimuli and tasks. Of particular interest to readers of this volume is the fact that many of the brain regions implicated in the neurocircuitry model of PTSD are also involved in insomnia, sleep, and arousal [146–148], and sleep promotes generalization of fear conditioning extinction in healthy humans [149] (topics to be revisited in Chap. 37). Thus, neuroimaging research leads us to the intriguing hypothesis that the sleep disturbances and fear extinction deficits in PTSD patients may be linked [149–153].

Despite advances in the knowledge of PTSD neurocircuitry, many important issues remain unresolved. For example, functional abnormalities may be acquired sequelae of PTSD or may be pre-existing vulnerability factors that increase the risk for PTSD after trauma exposure. Twin and/or longitudinal studies will be needed to address this question. Understanding the neurobiology of PTSD and the relationships between functional abnormalities and clinical symptoms may lead to improved and personalized treatment and prevention strategies.

References

1. VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM. From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiol Learn Mem. 2014;113:3–18.
2. Bremner JD, Vermetten E, Schmahl C, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. Psychol Med. 2005;35(6):791–806.
3. Jovanovic T, Kazama A, Bachevalier J, Davis M. Impaired safety signal learning may be a biomarker of PTSD. Neuropharmacology. 2011;62(2):695–704.
4. Milad MR, Pitman RK, Ellis CB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66(12):1075–82.
5. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012;63(1):129–51.
6. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol Psychiatry. 2006;60(4):376–82.
7. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84.
8. Paré D, Quirk GJ, LeDoux JE. New vistas on amygdala networks in conditioned fear. J Neurophysiol. 2004;92(1):1–9.
9. Davis M. Neurobiology of fear responses: the role of the amygdala. J Neuropsychiatr Clin Neurosci. 1997;9(3):382–402.
10. Likhtik E, Pelletier JG, Paz R, Paré D. Prefrontal control of the amygdala. J Neurosci. 2005;25(32):7429–37.
11. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature. 2002;420(6911):70–4.
12. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett. 1993;163(1):109–13.
13. Quirk GJ, Garcia R, González-Lima F. Prefrontal mechanisms in extinction of conditioned fear. Biol Psychiatry. 2006;60(4):337–43.
14. Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C. Contextual fear conditioning in humans: cortical-hippocampal and amygdala contributions. J Neurosci. 2008;28(24):6211–9.
15. Barrett J, Armony JL. Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. Psychol Med. 2008;39(02):255.
16. Buchel C, Dolan RJ, Armony JL, Friston KJ. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. J Neurosci. 1999;19(24):10869–76.
17. Buchel C, Morris J, Dolan RJ, Friston KJ. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron. 1998;20(5):947–57.
18. Cheng DT, Knight DC, Smith CN, Helmstetter FJ. Human amygdala activity during the expression of fear responses. Behav Neurosci. 2006;120(6):1187–95.
19. Gottfried JA, Dolan RJ. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nat Neurosci. 2004;7(10):1144–52.
20. Lang S, Kroll A, Lipinski SJ, et al. Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. Eur J Neurosci. 2009;29(4):823–32.
21. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron. 1998;20(5):937–45.
22. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry. 2007;62(5):446–54.
23. Morris JS, Dolan RJ. Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. NeuroImage. 2004;22(1):372–80.
24. Pine DS, Fyer A, Grun J, et al. Methods for developmental studies of fear conditioning circuitry. Biol Psychiatry. 2001;50(3):225–8.
25. Tabbert K, Stark R, Kirsch P, Vaitl D. Dissociation of neural responses and skin conductance reactions during fear conditioning with and without awareness of stimulus contingencies. NeuroImage. 2006;32(2):761–70.
26. Linnman C, Rougemont-Bücking A, Beucke JC, Zeffiro TA, Milad MR. Unconditioned responses and functional fear networks in human classical conditioning. Behav Brain Res. 2011;221(1):237–45.
27. Doronbekov TK, Tokunaga H, Ikejiri Y, et al. Neural basis of fear conditioning induced by video clip: positron emission tomography study. Psychiatry Clin Neurosci. 2005;59(2):155–62.

28. Klucken T, Kagerer S, Schweckendiek J, Tabbert K, Vaitl D, Stark R. Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture–picture conditioning paradigm. Neuroscience. 2009;158(2):721–31.
29. Critchley HD, Mathias CJ, Dolan RJ. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron. 2002;33(4):653–63.
30. Knight DC, Waters NS, Bandettini PA. Neural substrates of explicit and implicit fear memory. NeuroImage. 2009;45(1):208–14.
31. Marschner A, Kalisch R, Vervliet B, Vansteenwegen D, Buchel C. Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning. J Neurosci. 2008;28(36):9030–6.
32. Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL. A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry. 2007;62(10):1191–4.
33. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans. Neuron. 2004;43(6):897–905.
34. Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J Neurosci. 2006;26(37):9503–11.
35. Bouton ME, Westbrook RF, Corcoran KA, Maren S. Contextual and temporal modulation of extinction: behavioral and biological mechanisms. Biol Psychiatry. 2006;60(4):352–60.
36. Shin LM, Wright CI, Cannistraro PA, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry. 2005;62(3):273–81.
37. Linnman C, Zeffiro TA, Pitman RK, Milad MR. An fMRI study of unconditioned responses in post-traumatic stress disorder. Biol Mood Anxiety Disord. 2011;1(1):8.
38. Garfinkel SN, Abelson JL, King AP, et al. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. J Neurosci. 2014;34(40):13435–43.
39. Brunetti M, Sepede G, Ferretti A, Mingoia G, Romani GL, Babiloni C. Response inhibition failure to visual stimuli paired with a 'single-type' stressor in PTSD patients: an fMRI pilot study. Brain Res Bull. 2015;114:20–30.
40. Rauch SL, van der Kolk BA, Fisler RE, et al. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry. 1996;53(5):380–7.
41. Shin LM, Orr SP, Carson MA, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry. 2004;61(2):168–76.
42. St Jacques PL, Botzung A, Miles A, Rubin DC. Functional neuroimaging of emotionally intense autobiographical memories in post-traumatic stress disorder. J Psychiatr Res. 2011;45(5):630–7.
43. Liberzon I, Taylor SF, Amdur R, et al. Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry. 1999;45(7):817–26.
44. Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M. Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. Eur Arch Psychiatry Clin Neurosci. 2002;252(2):68–75.
45. Vermetten E, Schmahl C, Southwick SM, Bremner JD. Positron tomographic emission study of olfactory induced emotional recall in veterans with and without combat-related posttraumatic stress disorder. Psychopharmacol Bull. 2007;40(1):8–30.
46. Morey RA, Dolcos F, Petty CM, et al. The role of trauma-related distractors on neural systems for working memory and emotion processing in posttraumatic stress disorder. J Psychiatr Res. 2009;43(8):809–17.
47. Driessen M, Beblo T, Mertens M, et al. Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. Biol Psychiatry. 2004;55(6):603–11.
48. Protopopescu X, Pan H, Tuescher O, et al. Differential time courses and specificity of amygdala activity in posttraumatic stress disorder subjects and normal control subjects. Biol Psychiatry. 2005;57(5):464–73.
49. Brashers-Krug T, Jorge R. Bi-directional tuning of amygdala sensitivity in combat veterans investigated with fMRI. PLoS One. 2015;10(6):e0130246.
50. Williams LM, Kemp AH, Felmingham K, et al. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. NeuroImage. 2006;29(2):347–57.
51. Kemp AH, Felmingham K, Das P, et al. Influence of comorbid depression on fear in posttraumatic stress disorder: an fMRI study. Psychiatry Res Neuroimaging. 2007;155(3):265–9.
52. Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A. Brain activation to facial expressions in youth with PTSD symptoms. Depress Anxiety. 2012;29(5):449–59.
53. Mazza M, Catalucci A, Mariano M, et al. Neural correlates of automatic perceptual sensitivity to facial affect in posttraumatic stress disorder subjects who survived L'Aquila earthquake of April 6, 2009. Brain Imaging Behav. 2012;6:374–86.
54. Dickie EW, Brunet A, Akerib V, Armony JL. An fMRI investigation of memory encoding in PTSD: influence of symptom severity. Neuropsychologia. 2008;46(5):1522–31.
55. El Khoury-Malhame M, Reynaud E, Soriano A, et al. Amygdala activity correlates with attentional bias in PTSD. Neuropsychologia. 2011;49(7):1969–73.
56. Brohawn KH, Offringa R, Pfaff DL, Hughes KC, Shin LM. The neural correlates of emotional memory in posttraumatic stress disorder. Biol Psychiatry. 2010;68:1023–30.
57. Hendler T, Rotshtein P, Yeshurun Y, et al. Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. NeuroImage. 2003;19(3):587–600.
58. Rauch SL, Whalen PJ, Shin LM, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry. 2000;47(9):769–76.
59. Bryant RA, Kemp AH, Felmingham KL, et al. Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. Hum Brain Mapp. 2008;29(5):517–23.
60. Felmingham K, Williams LM, Kemp AH, et al. Neural responses to masked fear faces: sex differences and trauma exposure in posttraumatic stress disorder. J Abnorm Psychol. 2010;119(1):241–7.
61. WDS K, Britton JC, Schwab ZJ, et al. Cortico-limbic responses to masked affective faces across PTSD, panic disorder, and specific phobia. Depress Anxiety. 2014;31(2):150–9.
62. Chung YA, Kim SH, Chung SK, et al. Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli. Clin Neurophysiol. 2006;117(3):637–42.
63. Shin LM, Lasko NB, Macklin ML, et al. Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry. 2009;66(10):1099–107.
64. Lanius RA, Bluhm RL, Coupland NJ, et al. Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. Acta Psychiatr Scand. 2010;121(1):33–40.
65. Bryant RA, Felmingham KL, Kemp AH, et al. Neural networks of information processing in posttraumatic stress disorder: a functional magnetic resonance imaging study. Biol Psychiatry. 2005;58(2):111–8.

66. Brunetti M, Sepede G, Mingoia G, et al. Elevated response of human amygdala to neutral stimuli in mild post traumatic stress disorder: neural correlates of generalized emotional response. Neuroscience. 2010;168(3):670–9.
67. Whalley MG, Rugg MD, Smith APR, Dolan RJ, Brewin CR. Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. Brain Cogn. 2009;69(1):98–107.
68. Armony JL, Corbo V, Clément M-H, Brunet A. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. Am J Psychiatry. 2005;162(10):1961–3.
69. Dickie EW, Brunet A, Akerib V, Armony JL. Neural correlates of recovery from post-traumatic stress disorder: a longitudinal fMRI investigation of memory encoding. Neuropsychologia. 2011;49(7):1771–8. http://doi.org/10.1016/j.neuropsychologia.2011.02.055
70. Shin LM, Davis FC, VanElzakker MB, Dahlgren MK, Dubois SJ. Neuroimaging predictors of treatment response in anxiety disorders. Biol Mood Anxiety Disord. 2013;3(1):15.
71. Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med. 2008;38(4):555–61.
72. Felmingham K, Kemp A, Williams L, et al. Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. Psychol Sci. 2007;18(2):127–9.
73. Peres JFP, Newberg AB, Mercante JP, et al. Cerebral blood flow changes during retrieval of traumatic memories before and after psychotherapy: a SPECT study. Psychol Med. 2007;37(10):1481–91.
74. Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry. 1999;156(11):1787–95.
75. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry. 1999;45(7):806–16.
76. Britton JC, Phan KL, Taylor SF, Fig LM, Liberzon I. Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. Biol Psychiatry. 2005;57(8):832–40.
77. Lanius RA, Williamson PC, Densmore M, et al. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. Am J Psychiatry. 2001;158(11):1920–2.
78. Phan KL, Britton JC, Taylor SF, Fig LM, Liberzon I. Corticolimbic blood flow during nontraumatic emotional processing in posttraumatic stress disorder. Arch Gen Psychiatry. 2006;63(2):184–92.
79. Shin LM, McNally RJ, Kosslyn SM, et al. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. Am J Psychiatry. 1999;156(4):575–84.
80. Strigo IA, Simmons AN, Matthews SC, et al. Neural correlates of altered pain response in women with posttraumatic stress disorder from intimate partner violence. Biol Psychiatry. 2010;68(5):442–50.
81. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164(10):1476–88.
82. Gilboa A, Shalev AY, Laor L, et al. Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. Biol Psychiatry. 2004;55(3):263–72.
83. Rougemont-Bücking A, Linnman C, Zeffiro TA, et al. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. CNS Neurosci Ther. 2011;17(4):227–36.
84. Marin M-F, Song H, VanElzakker MB, Staples-Bradley LK, Linnman C, Pace-Schott EF, et al. Association of resting metabolism in the fear neural network with extinction recall activations and clinical measures in trauma-exposed individuals. Am J Psychiatry. 2016;173(9):930–8. http://doi.org/10.1176/appi.ajp.2015.14111460
85. Shvil E, Sullivan GM, Schafer S, et al. Sex differences in extinction recall in posttraumatic stress disorder: a pilot fMRI study. Neurobiol Learn Mem. 2014;113(C):101–8.
86. Whalley MG, Kroes MCW, Huntley Z, Rugg MD, Davis SW, Brewin CR. An fMRI investigation of posttraumatic flashbacks. Brain Cogn. 2013;81(1):151–9.
87. Lindauer RJL, Booij J, Habraken JBA, et al. Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. Biol Psychiatry. 2004;56(11):853–61.
88. Lanius RA, Williamson PC, Hopper J, et al. Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. Biol Psychiatry. 2003;53(3):204–10.
89. Lanius RA, Frewen PA, Girotti M, Neufeld RWJ, Stevens TK, Densmore M. Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: a functional MRI investigation. Psychiatry Res Neuroimaging. 2007;155(1):45–56.
90. Shin LM, McNally RJ, Kosslyn SM, et al. A positron emission tomographic study of symptom provocation in PTSD. Ann N Y Acad Sci. 1997;821:521–3.
91. Yang P, Wu M-T, Hsu C-C, Ker J-H. Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. Neurosci Lett. 2004;370(1):13–8.
92. Hou C, Liu J, Wang K, et al. Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. Brain Res. 2007;1144:165–74.
93. Shin LM, Whalen PJ, Pitman RK, et al. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biol Psychiatry. 2001;50(12):932–42.
94. Offringa R, Handwerger Brohawn K, Staples LK, et al. Diminished rostral anterior cingulate cortex activation during trauma-unrelated emotional interference in PTSD. Biol Mood Anxiety Disord. 2013;3(1):10.
95. Fonzo GA, Simmons AN, Thorp SR, Norman SB, Paulus MP, Stein MB. Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. Biol Psychiatry. 2010;68(5):433–41.
96. Crozier JC, Wang L, Huettel SA, De Bellis MD. Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: does gender matter? Dev Psychopathol. 2014;26(2):491–513.
97. Kim MJ, Chey J, Chung A, et al. Diminished rostral anterior cingulate activity in response to threat-related events in posttraumatic stress disorder. J Psychiatr Res. 2008;42(4):268–77.
98. Cisler JM, Scott Steele J, Smitherman S, Lenow JK, Kilts CD. Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: a network-level analysis among adolescent girls. Psychiatry Res. 2013;214:238–46.
99. Bremner JD, Vythilingam M, Vermetten E, et al. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biol Psychiatry. 2003;53(10):879–89.
100. Bremner JD, Vermetten E, Vythilingam M, et al. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. Biol Psychiatry. 2004;55(6):612–20.
101. Diener SJ, Wessa M, Ridder S, Lang S, Diers M, Steil R, Flor H. Enhanced stress analgesia to a cognitively demanding task

in patients with posttraumatic stress disorder. J Affect Disord. 2012;136(3):1247–51. http://doi.org/10.1016/j.jad.2011.06.013
102. Hayes JP, Labar KS, Petty CM, Mccarthy G, Morey RA. Alterations in the neural circuitry for emotion and attention associated with posttraumatic stress symptomatology. Psychiatry Res. 2009;172(1):7–15.
103. Semple WE, Goyer PF, McCormick R, et al. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. Psychiatry. 2000;63(1):65–74.
104. Jovanovic T, Ely T, Fani N, et al. Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample. Cortex. 2013;49(7):1884–91.
105. Moores KA, Clark CR, McFarlane AC, Brown GC, Puce A, Taylor DJ. Abnormal recruitment of working memory updating networks during maintenance of trauma-neutral information in posttraumatic stress disorder. Psychiatry Res. 2008;163(2):156–70.
106. Shin LM, Bush G, Whalen PJ, et al. Dorsal anterior cingulate function in posttraumatic stress disorder. J Trauma Stress. 2007;20(5):701–12.
107. Osuch EA, Willis MW, Bluhm R, Group CNS, Ursano RJ, Drevets WC. Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. Biol Psychiatry. 2008;64(4):327–35.
108. Carrion VG, Garrett A, Menon V, Weems CF, Reiss AL. Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. Depress Anxiety. 2008;25(6):514–26.
109. Zubieta JK, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I. Medial frontal cortex involvement in PTSD symptoms: a SPECT study. J Psychiatr Res. 1999;33(3):259–64.
110. Lanius RA, Williamson PC, Boksman K, et al. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. Biol Psychiatry. 2002;52(4):305–11.
111. Hopper JW, Frewen PA, van der Kolk BA, Lanius RA. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. J Trauma Stress. 2007;20(5):713–25.
112. Herringa RJ, Phillips ML, Fournier JC, Kronhaus DM, Germain A. Childhood and adult trauma both correlate with dorsal anterior cingulate activation to threat in combat veterans. Psychol Med. 2013;43(7):1533–42.
113. Morey RA, Petty CM, Cooper DA, Labar KS, Mccarthy G. Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq War veterans. Psychiatry Res Neuroimaging. 2008;162(1):59–72.
114. Lansing K, Amen DG, Hanks C, Rudy L. High-resolution brain SPECT imaging and eye movement desensitization and reprocessing in police officers with PTSD. J Neuropsychiatr Clin Neurosci. 2005;17(4):526–32.
115. Seedat S, Warwick J, van Heerden B, et al. Single photon emission computed tomography in posttraumatic stress disorder before and after treatment with a selective serotonin reuptake inhibitor. J Affect Disord. 2004;80(1):45–53.
116. Labar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nat Rev Neurosci. 2006;7(1):54–64.
117. Rudy JW, Huff NC, Matus-Amat P. Understanding contextual fear conditioning: insights from a two-process model. Neurosci Biobehav Rev. 2004;28(7):675–85.
118. Rudy JW. Context representations, context functions, and the parahippocampal-hippocampal system. Learn Mem. 2009;16(10):573–85.
119. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science. 1991;253(5026):1380–6.
120. Astur RS, St Germain SA, Tolin D, Ford J, Russell D, Stevens M. Hippocampus function predicts severity of post-traumatic stress disorder. Cyberpsychol Behav. 2006;9(2):234–40.
121. Hayes JP, Labar KS, Mccarthy G, et al. Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. J Psychiatr Res. 2011;45(5):660–9.
122. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 2010;35(1):169–91.
123. Acheson DT, Gresack JE, Risbrough VB. Hippocampal dysfunction effects on context memory: possible etiology for posttraumatic stress disorder. Neuropharmacology. 2012;62(2):674–85. http://doi.org/10.1016/j.neuropharm.2011.04.029
124. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. Prog Brain Res. 2008;167:151–69.
125. Bremner JD, Vythilingam M, Vermetten E, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003;160(5):924–32.
126. Molina ME, Isoardi R, Prado MN, Bentolila S. Basal cerebral glucose distribution in long-term post-traumatic stress disorder. World J Biol Psychiatry. 2010;11(2_2):493–501.
127. Thomaes K, Dorrepaal E, Draijer NPJ, et al. Increased activation of the left hippocampus region in complex PTSD during encoding and recognition of emotional words: a pilot study. Psychiatry Res Neuroimaging. 2009;171(1):44–53.
128. Thomaes K, Dorrepaal E, Draijer N, De Ruiter MB, Van Balkom AJ, Smit JH, Veltman DJ. Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. J Clin Psychiat. 2010;71(12):1636–44. http://doi.org/10.4088/JCP.08m04754blu
129. Sachinvala N, Kling A, Suffin S, Lake R, Cohen M. Increased regional cerebral perfusion by 99mTc hexamethyl propylene amine oxime single photon emission computed tomography in post-traumatic stress disorder. Mil Med. 2000;165(6):473–9.
130. Shin LM, Shin PS, Heckers S, et al. Hippocampal function in posttraumatic stress disorder. Hippocampus. 2004;14(3):292–300.
131. Werner NS, Meindl T, Engel RR, et al. Hippocampal function during associative learning in patients with posttraumatic stress disorder. J Psychiatr Res. 2009;43(3):309–18.
132. Osuch EA, Benson B, Geraci M, et al. Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. Biol Psychiatry. 2001;50(4):246–53.
133. Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother. 2011;11(2):275–85.
134. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage. 2002;16(2):331–48.
135. Chua P, Krams M, Toni I, Passingham R, Dolan R. A functional anatomy of anticipatory anxiety. NeuroImage. 1999;9(6 Pt 1):563–71.
136. Porro CA, Baraldi P, Pagnoni G, et al. Does anticipation of pain affect cortical nociceptive systems? J Neurosci. 2002;22(8):3206–14.
137. Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ. Functional neuroanatomy of aversion and its anticipation. NeuroImage. 2006;29(1):106–16.
138. Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. Neuroreport. 2004;15(14):2261–5.
139. Simmons AN, Paulus MP, Thorp SR, Matthews SC, Norman SB, Stein MB. Functional activation and neural networks in women

with posttraumatic stress disorder related to intimate partner violence. Biol Psychiatry. 2008;64(8):681–90.
140. Nardo D, Högberg G, Flumeri F, et al. Self-rating scales assessing subjective well-being and distress correlate with rCBF in PTSD-sensitive regions. Psychol Med. 2011;41(12):2549–61.
141. Geuze E, Westenberg HGM, Jochims A, et al. Altered pain processing in veterans with posttraumatic stress disorder. Arch Gen Psychiatry. 2007;64(1):76–85.
142. Moeller-Bertram T, Keltner J, Strigo IA. Pain and post traumatic stress disorder review of clinical and experimental evidence. Neuropharmacology. 2012;62(2):586–97. http://doi.org/10.1016/j.neuropharm.2011.04.028
143. Lindauer RJL, Booij J, Habraken JBA, et al. Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial. Psychol Med. 2008;38(4):543–54.
144. Yin Y, Li L, Jin C, Hu X, Duan L, Eyler LT, et al. Abnormal baseline brain activity in posttraumatic stress disorder: a resting-state functional magnetic resonance imaging study. Neurosci Lett. 2011;498(3):185–9. http://doi.org/10.1016/j.neulet.2011.02.069
145. Mickleborough MJS, Daniels JK, Coupland NJ, et al. Effects of trauma-related cues on pain processing in posttraumatic stress disorder: an fMRI investigation. J Psychiatry Neurosci JPN. 2011;36(1):6–14.
146. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.
147. Nofzinger EA. Functional neuroimaging of sleep. Semin Neurol. 2005;25(1):9–18.
148. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry. 2004;161(11):2126–8.
149. Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R, Pitman RK. Sleep promotes generalization of extinction of conditioned fear. Sleep. 2009;32(1):19–26.
150. Pace-Schott EF, Tracy LE, Rubin Z, et al. Interactions of time of day and sleep with between-session habituation and extinction memory in young adult males. Exp Brain Res. 2014;232(5):1443–58.
151. Woodruff ER, Greenwood BN, Chun LE, Fardi S, Hinds LR, Spencer RL. Adrenal-dependent diurnal modulation of conditioned fear extinction learning. Behav Brain Res. 2015;286:249–55.
152. Menz MM, Rihm JS, Salari N, et al. The role of sleep and sleep deprivation in consolidating fear memories. NeuroImage. 2013;75:87–96.
153. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170(4):372–82.

Brain Pathways of Traumatic Memory: Evidence from an Animal Model of PTSD

11

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Introduction

The formation of a memory of a stressful or threatening experience is adaptive and is essential for an organism's survival. Memory of such experiences enables individuals to anticipate harm and organize appropriate defensive behaviors in response to threat. Overall, individuals tend to forget, and even emotion-laden events, which usually are remembered vividly, weaken with the passage of time [1]. Details fade away, and the emotional charge an event once had is quenched. As time goes by, a concerted effort or a strong trigger is needed to recall the event to mind. Finally, it may disappear altogether and no longer be retrievable [1].

However in patients with posttraumatic stress disorder (PTSD), memories of traumatic events remain vivid, chronically active, and disruptive over long periods of time, in terms of the facts and of their emotional and somatic concomitants. The memories of a traumatic event, together with the emotions at the time of the event, shape symptoms such as intrusive thoughts, physiological hyperarousal, and avoidance of traumatic reminders. It has been suggested that the development of PTSD may involve overconsolidation and over-retrievability of certain components of traumatizing events, in conjunction with paradoxical patches of amnesia, as a consequence of faulty encoding and/or consolidation and/or retrieval [1]. Neurobiologically, it has been proposed that the adrenocortical hormones released in response to threatening events might act, via emotional enhancement, to "overconsolidate" the trauma memory at the time of initial encoding, leading to extremely vivid memories, which are more persistent (i.e., long lasting) and stronger (i.e., resistant to disruption) and, therefore, highly resistant to the expected fading over time [2]. The fact that in many cases a single traumatic experience leads to the formation of memories so highly resistant to extinction is not understood yet emphasizes the importance of the search for possible interventions designed to disrupt traumatic memories. There is now considerable evidence that traumatic memories can be changed quantitatively or qualitatively. Pharmacological disruption of the activity of molecules critical for memory consolidation, reconsolidation, and maintenance has been shown to produce enduring fear loss [3–6].

This chapter describes the behavioral findings of a series of animal studies, which focused on aspects related to memory and examined the effects of various interventions administered at certain key points in time, using an animal model for PTSD in a standardized study design and an approach to data analysis that pivots on the post-factum classification of subjects according to three levels of severity of disruption in behavioral responses, whose extremes are well-defined (extreme versus minimal behavioral response groups) [7–10].

Pharmacological Interventions and Memory Trace

It is well established that following initial encoding, memory remains temporarily unstable and vulnerable to disruption [11] until it is consolidated. "Consolidation" of memory refers to a hypothetical storage process whereby a newly formed, fragile, easily disrupted memory undergoes a transformation process, becoming stronger, enduring, and more resilient over time [11–13]. On the cellular level, consolidation requires a sequence of specific molecular processes in the hippocampus and associated structures that involve gene transcription and de novo protein synthesis and culminate in long-term changes in synaptic plasticity [11, 14–18]. In addition, a vast majority of memory consolidation processes take place during sleep [19]. Hence, the resting period that

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follows a traumatic event is critical to consolidation of the newly acquired traumatic memory [20].

Studies demonstrate that upon retrieval, a previously consolidated memory trace becomes labile anew and undergoes a second round of protein synthesis to be restored, a phenomenon known as reconsolidation [21]. In other words, reconsolidation is a temporarily altered state of the memory trace following memory reactivation [22]. Memory reconsolidation after retrieval may be used to update or integrate new information into long-term memories (LTMs) [13, 23]. As mentioned above, there are two discrete periods during which memories may be updated, changed, or erased: during consolidation and reconsolidation processes.

Experimental pharmacological interventions are most likely to be able to affect the structural and functional integrity of memory traces at those stages at which their biological stability is lowest. The most obvious "windows of opportunity" are during the initial consolidation and again during phases of memory retrieval prior to reconsolidation. The series of studies presented in this chapter involved pharmacological and behavioral interventions during these phases, which targeted infrastructural processes such as protein synthesis and synaptic plasticity, and manipulations of the actions of the HPA axis exogenously or endogenously via sleep deprivation, which has been clearly implicated in neuromodulation related to memory.

Interfering with Consolidation Processes

The first group of studies attempted to affect the consolidation process during the initial hours after stress exposure. Employing our validated animal model of PTSD [7, 9, 10, 24], we assessed the effects on behaviors dependent on traumatic memories of a protein synthesis inhibitor (anisomycin), an inhibitor of protein kinase M zeta – ZIP (myristoylated ζ-pseudosubstrate inhibitory peptide), an inhibitor of the regulation of protein synthesis (mammalian target of rapamycin (mTOR)) (rapamycin), the neuromodulator stress hormone (corticosterone), and the beta-blocker propranolol and the effects of postexposure sleep deprivation.

Intervention with Anisomycin, a Protein Synthesis Inhibitor

The effect of protein synthesis inhibition has, to date, not been examined in an animal model of PTSD. The effect of protein synthesis inhibition has been examined widely in behavioral paradigms such as Pavlovian conditioning [25–28] and hippocampal-dependent spatial memory tasks [29, 30]. The majority of findings indicate that the critical time for protein synthesis is during or immediately after training. Employing our validated animal model of PTSD [7, 9, 10, 24], we assessed the long-term behavioral effects of a single intraventricular microinjection of either anisomycin (100 μg/μl in artificial cerebrospinal fluid (ACSF)) or vehicle to rats 1 h before or 1 h after exposing them for 15 min to PSS or to sham-PSS (viz., to used or unused cat litter, respectively). Seven days later, we quantified the behavior of these rats in two well-established, stress-related paradigms – the elevated plus maze (EPM) and the acoustic startle response (ASR). These paradigms measure anxiety-like, fearful, avoidant, and hypervigilant/hyperalert behaviors, which parallel the different aspects of traumatic stress-induced behaviors in humans [31]. Exploratory behavior in the EPM served as our main framework for assessing the overall stress-related behavior of the rats, whereas the magnitude of response and the habituation to the acoustic stimulus in the ASR paradigm were used to quantify specifically hyperalertness [32]. Finally, we used the results of these paradigms in a statistically validated cutoff behavioral criteria model [7, 10, 32, 33] to functionally classify rats according to their overall stress-related behavior. Our findings demonstrated that both before and after exposure to PSS, anisomycin reduced anxiety-like and avoidant behavior in the EPM paradigm, reduced the mean startle amplitude, and reversed the stress-induced habituation deficit as compared to controls [34]. When anisomycin was microinjected before PPS exposure, no animals with extreme behavioral responses (EBR or PTSD-like phenotype) were found among the exposed rats, as compared to control rats injected with ACFS, where 50% fulfilled criteria for PTSD-like phenotype (EBR rats). Administration of anisomycin after stress exposure reduced the prevalence of EBR animals to 10% as compared to 57.5% in the ACFS control group, suggesting that anisomycin was effective in preventing PTSD-like responses in this model (Fig. 11.1).

The results imply that persistent anxiety-like behavior after PSS is associated with a protein synthesis-dependent process related to memory consolidation and therefore that early post-stress interventions which disrupt consolidation may be a useful approach for mitigating PTSD symptoms [34].

Early Post-stressor Microinjection of Rapamycin

The mammalian target of rapamycin (mTOR) is a phosphoinositide kinase family serine-threonine protein kinase that modulates cell growth, proliferation, and synaptic plasticity via the regulation of protein synthesis [35, 36]. Several reports indicate that components of the mTOR pathway are engaged following learning [35, 37–39], and rapamycin, a selective inhibitor of mTOR activity, when administered around training, blocks LTM formation in a number of behavioral paradigms [35, 37, 40–43]. It is activated by a number of growth factors including brain-derived neurotrophic factor (BDNF) and regulates protein synthesis mainly through the phosphorylation of two downstream targets,

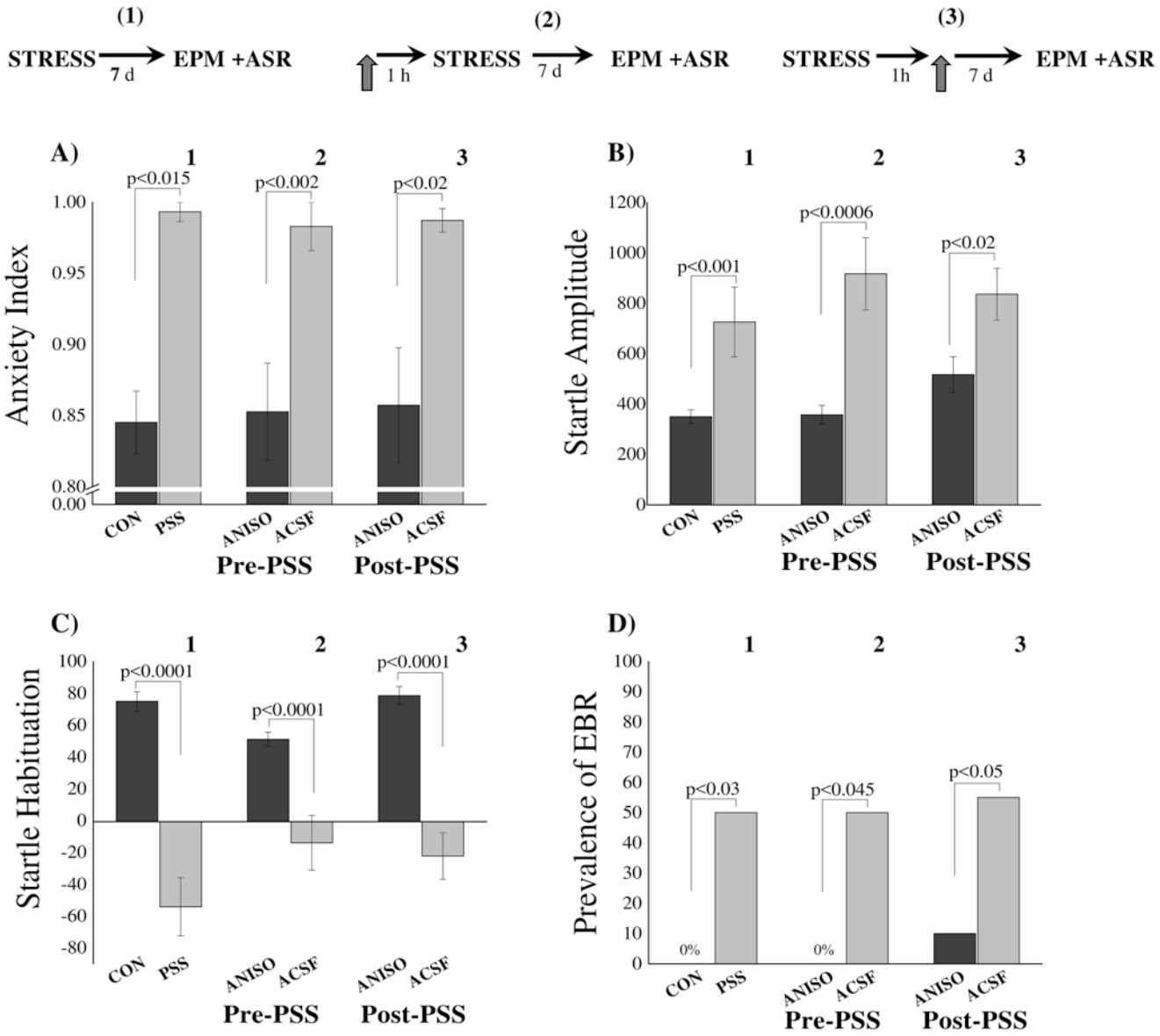

Fig. 11.1 Effect of microinjection of anisomycin 1 h before or after a single exposure to a predator scent stress: (*1*) The behavioral procedure used for the naïve and stress-exposed rats, (*2*) the behavioral procedure used for the pre-exposure microinfusion, and (*3*) the behavioral procedure used for the postexposure microinfusion. *Vertical open arrows* represent microinfusion (anisomycin or ACFS). (**a**) Anxiety Index. (**b**) The mean startle amplitude of rats in response to the 30 startle pulses. (**c**) Percent habituation of startle response. (**d**) Prevalence of extreme behavioral response (EBR). A single 10-min exposure to a predator scent significantly increased Anxiety Index ($F(5,44) = 6.4$, $p < 0.0002$) and mean startle amplitude ($F(1,15) = 9.7$, $p < 0.01$) and caused a significant deficit in the habituation of ASR ($F(5,44) = 23.5$, $p < 0.0001$) in exposed rats as compared to controls. Intraventricular microinjection of anisomycin 1 h before or after PSS significantly decreased anxiety-like behavior and completely reversed the stress-induced habituation deficit and lowered the mean startle amplitude in anisomycin-treated animals as compared to ACSF-treated rats (startle habituation, injected before $F(1,11) = 15.5$, $p < 0.003$, and injected after $F(1,15) = 53.0$, $p < 0.0001$; startle response, injected before $F(1,13) = 20.4$, $p < 0.0006$, and injected after $F(1,16) = 6.9$, $p < 0.002$). There were significant differences in the prevalence of EBR (PTSD-like response) among groups (Pearson $\chi 2 = 16.4$, df = 5, $p < 0.006$). The prevalence of EBR in predator-exposed rats was 50.0%. Intraventricular microinjection of anisomycin 1 h before or immediately after the stressogenic event significantly diminished extreme behavioral response, as compared to ACFS-injected control animals. The data represent group mean ± S.E.M or percentage

p70S6K and eukaryotic initiation factor 4E-binding proteins, which are critically involved in initiation, the rate-limiting step of translation [35, 36]. The behavioral effects of intrahippocampal and amygdalar microinjections of rapamycin (600 nM in ACSF) 1 h after PSS exposure were assessed. Behavior was assessed 7 days later in the EPM and ASR tests and freezing response to a trauma reminder on day 8. Rapamycin postexposure was ineffective in preventing

PTSD-like behavioral responses. Neither prevalence rates of individuals with extreme behavioral response patterns nor subsequent freezing responses to a trauma cue differed between the treatment group and controls.

Early Post-stressor Microinjection of ZIP, an Inhibitor of Protein Kinase M Zeta

Protein kinase M zeta (PKMζ) is an atypical protein kinase C isoform that has been implicated in the protein synthesis-dependent maintenance of long-term potentiation (LTP) and memory storage in the brain [44, 45]. PKMζ can maintain LTP because the kinase is autonomously active in neural tissue [45] and, thus, able to persistently enhance synaptic strength [46]. It has been shown that long-term memory can be "erased" by infusion of ZIP into the insular cortex (IC) [47]. The authors reported that in the IC, the activity of PKMζ is specifically involved in the storage of memories but not in their acquisition. Therefore, one may speculate that inhibiting PKMζ activity after traumatic experience may interfere with the process through which fearful memories become pathological and may lead to PTSD. We therefore assessed the long-term effects of ZIP, a specific, membrane-permeant peptide that mimics the autoregulatory domain of PKMζ and thus acts as an inhibitor, microinjected 1 h after stress exposure, into four brain structures widely implicated in the neurobiology of memory processes as well as in anxiety states: the dorsal hippocampus (DH), basolateral amygdala (BLA), lateral ventricle (LV), and insular cortex (IC) (Fig. 11.2). Stress-induced behavioral responses were assessed in the EPM and the ASR tests on day 7 and trauma cue-triggered freezing response on day 8.

The results showed that inactivation of PKMζ with ZIP injected to the LV or DH within 1 h of exposure to stress effectively reduced PTSD-like behavioral disruption and trauma cue response 8 days later, resulting in statistically significant reductions (37.5% and 44.4%, respectively) in the prevalence rates of EBR (PTSD-like) individuals at 7 days, with concomitant increases in the prevalence of MBR individuals of 12.5% and 11.1%, respectively, as compared to scrambled (Scr)-ZIP controls, indicating a significant shift toward less extreme stress-induced behavioral disruption. The DH/LV ZIP-treated individuals demonstrated markedly less extreme trauma cue freezing responses (27.7% and 23.9% of time freezing, respectively) than the Scr-ZIP control groups (49.3% and 57% of time freezing). In contrast, immediate post-stressor ZIP microinfusion to the amygdala and IC was ineffective in attenuating stress-induced behavioral disruptions. We hypothesize that ZIP microinjected to the hippocampus and lateral ventricle disrupted traumatic memory consolidation processes.

Early Post-stressor Intervention with Corticosterone

After the initial demonstration that suppressing protein synthesis during consolidation interfered with the formation of the traumatic memory, we were particularly interested to examine if the effects of manipulation of the native stress-related neuromodulators associated with encoding and consolidation processes would also participate in processes.

The key processes of the primary consolidation of the initial trauma memory into long-term traces and trauma cue-triggered reactivation take place at times during which the stress response cascade is activated, i.e., the fast-acting autonomic (sympathetic) nervous system (ANS) and the slow hypothalamic-pituitary-adrenocortical [HPA] axis. Sympathetic nervous system responses include the release of the catecholamines, epinephrine, and norepinephrine from the adrenal medulla. Activation of the HPA axis leads, via intermediate steps, to the release of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex [48]. Glucocorticoids can enter the brain and exert their actions principally via intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These key memory-related processes are thus likely to be affected by components, mediators, and end products of these physiologic systems, directly or indirectly [49]. The complex interactions among the various stress-related hormones in the emotionally aroused state experienced during trauma exposure presumably impact on the formation of the characteristically durable traumatic memories in PTSD.

Animals were treated once with corticosterone at doses of 0.1, 3.0, 5.0, 15.0, or 25.0 mg/kg 1 h after stress exposure and compared with vehicle-treated and unexposed controls [50] (Fig. 11.3). Behavior was assessed at day 30 and freezing response to the trauma reminder on day 31 [50]. The results clearly showed that a single 25 mg/kg dose of corticosterone administered 1 h after stress exposure resulted in a statistically significant reduction of 22.0% in the prevalence rates of EBR (PTSD-like) individuals at 30 days, with a concomitant increase of 14.3% in the prevalence of MBR individuals, as compared to saline controls – i.e., a significant shift toward less extreme behavioral disruption ensuing from traumatic stress. Individuals in the high-dose corticosterone group responded markedly less to the trauma cue (24% of time freezing) than the saline-control group (80% of time freezing). This pattern of response suggests that the single high-dose corticosterone treatment conferred some degree of resilience to subsequent trauma-related stress exposure. Paradoxically, lower doses of corticosterone (0.1–5.0 mg/kg) were not only ineffective in attenuating stress-induced behavioral disruptions but in fact significantly increased the

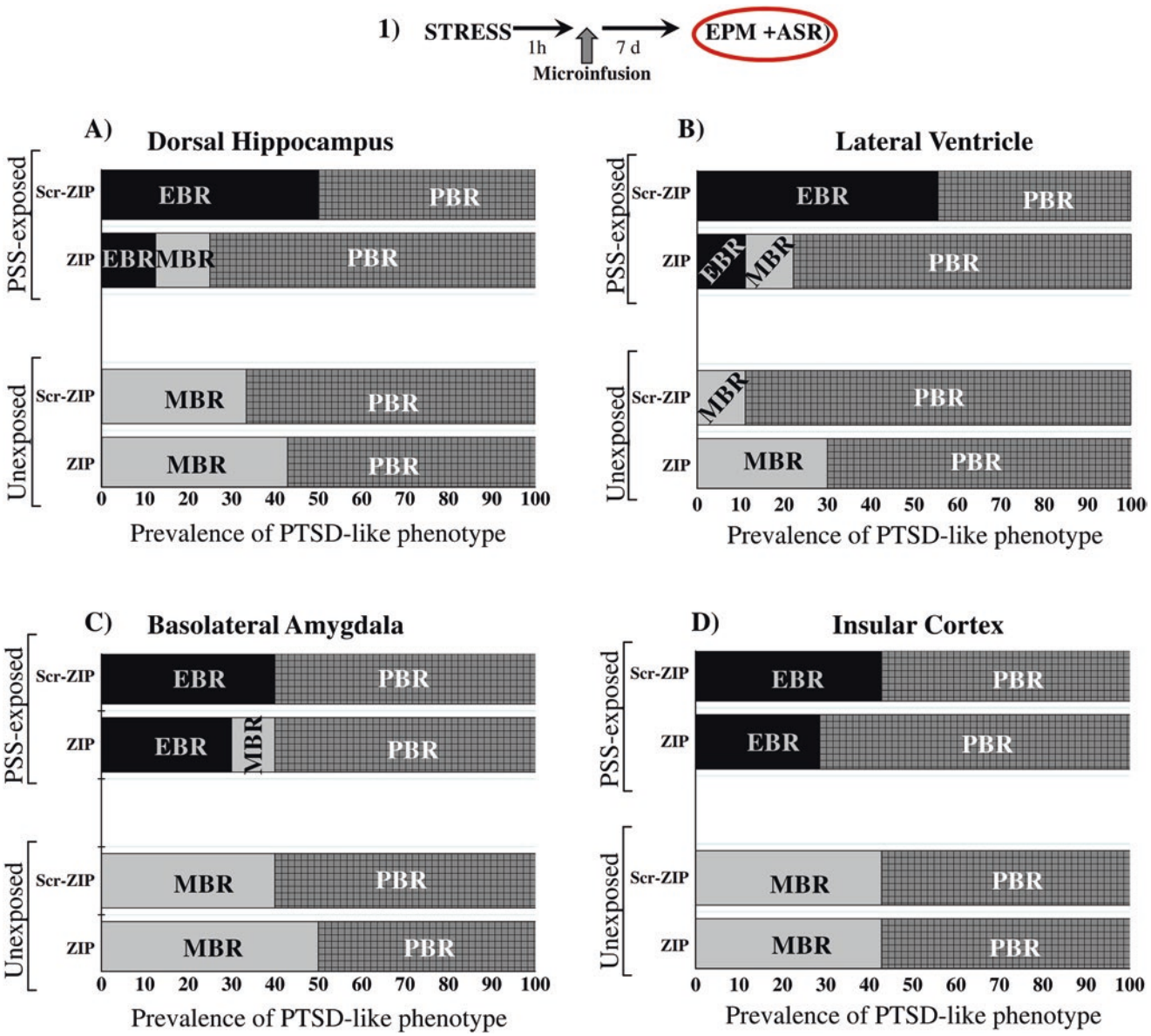

Fig. 11.2 Effect of administration of ZIP/Scr-ZIP 1 h after a single exposure to a predator scent stress: (1) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents microinjection (ZIP or Scr-ZIP). (**a**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the dorsal hippocampus. (**b**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the lateral ventricle. (**c**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the basolateral amygdala. (**d**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the insular cortex. When microinjected to the DH and LV, but not to the BLA or IC, ZIP significantly decreased the prevalence rate of individuals displaying EBR as compared to Scr-ZIP-microinjected rats, reflecting decreased anxiety-like behavior and traumatic fear and memory in ZIP-treated animals. Data represent prevalence of affected rats

propensity of individuals to show extreme behavioral responses at day 30 and significantly increased freezing response to the trauma cue as compared to vehicle. The dose-response curve for corticosterone thus conformed to the inverted U-shaped curve previously reported [51]. The neurobiological mechanisms underlying the dose-dependent effects of corticosterone appear to be the result of differential activation of the mineralocorticoid and glucocorticoid receptor systems in different brain areas through a complex system of time-dependent modulators and/or modulation of gene expression through transcription or via transrepression [52–56].

The possibility that the high-dose corticosterone regimen affected behaviors via memory processes was subsequently borne out by a follow-up study employing a nonspatial object recognition memory task. Similar dose dependence was displayed. Low-dose corticosterone enhanced performance of the task, whereas high dose impaired it, presumably by

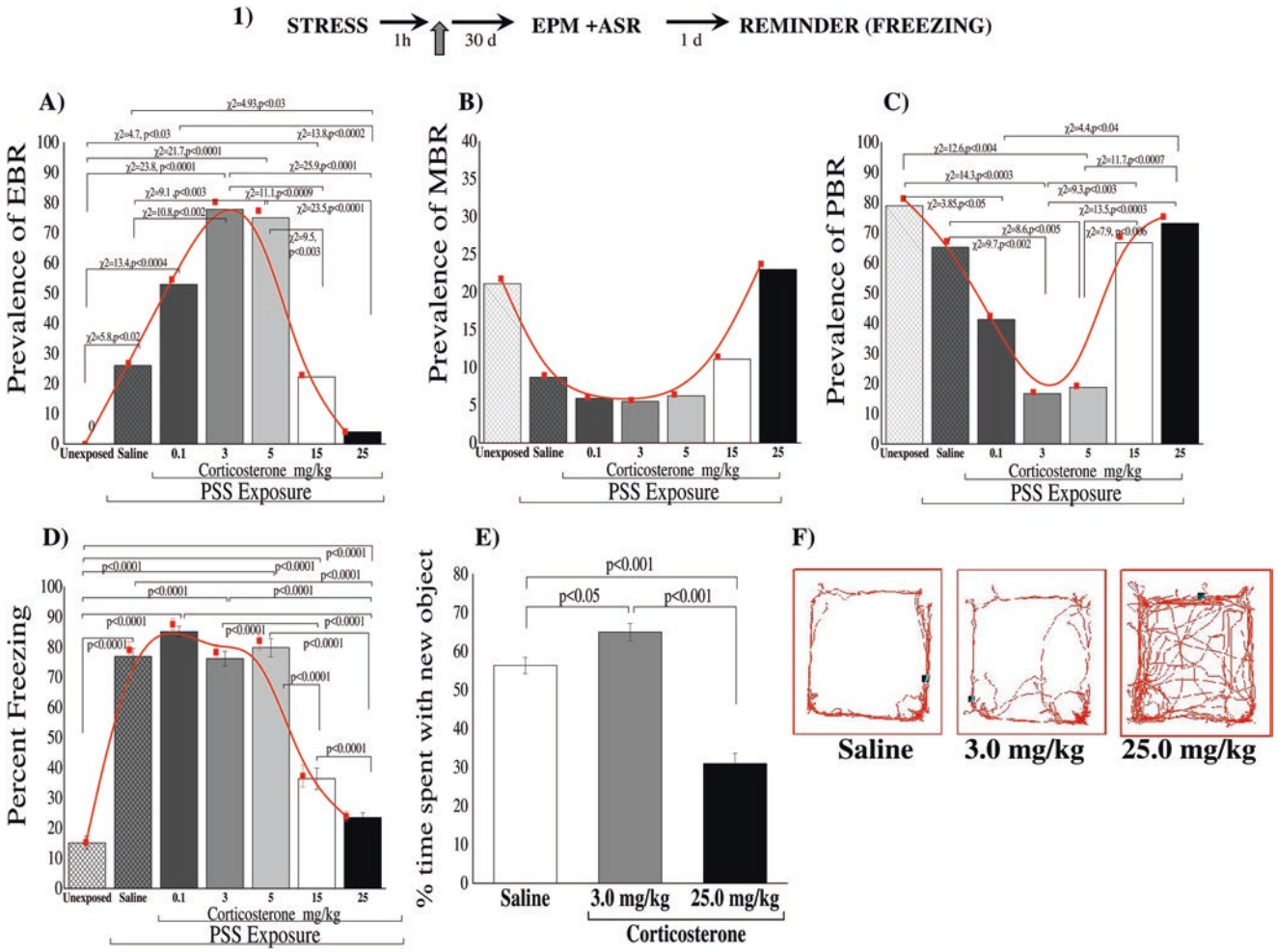

Fig. 11.3 Effect of administration of corticosterone 1 h after a single exposure to a predator scent stress: (*1*) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents intraperitoneal injection (corticosterone or vehicle). (**a**) Prevalence of EBR rats. (**b**) Prevalence of MBR rats. (**c**) Prevalence of PBR rats. (**d**) Percent freezing (immobility time, in sec). (**e**) The test phase of a 24-h object recognition memory consolidation test. (**f**) Average exploring path length. Early treatment with high-dose corticosterone reduced the prevalence of PTSD-like behavioral responses (EBR) relative to saline-control treatment and to low-dose treatment. The exposed rats treated with vehicle or low-dose corticosterone displayed significantly more immobility than unexposed controls. Exposed animals treated with high-dose corticosterone (15.0 or 25.0 mg/kg) displayed significantly less immobility than saline controls or the low-dose corticosterone group. A single injection of high-dose corticosterone resulted in significantly lower exploration activity for the novel object compared to the saline-control group and to low-dose corticosterone indicating that low-dose corticosterone enhanced performance of the task, whereas high dose impaired it, presumably by interfering with memory consolidation

interfering with memory consolidation, suggesting that one possible mechanism underlying the overall effect involved the disruption of consolidation of traumatic (fearful) memories [50].

Early Post-stressor Intervention with Propranolol

A large body of evidence from animal studies indicates that adrenergic stress hormones released peripherally during emotionally arousing experiences modulate the storage of memory for the experience [57]. The ability of β-adrenoceptor blockade to reduce anxiety and fear has been quite firmly established by studies in human subjects and animals, although this is not true for every experimental paradigm involving anxiety and fear. In the clinical arena, Vaiva et al. [58] gave propranolol (40 mg) to 11 people admitted to the hospital following a motor vehicle accident or physical assault without any serious physical injuries. They were compared with eight patients who refused propranolol but agreed to participate in the study. Two months later, the propranolol group had fewer symptoms of PTSD (1/11) than controls (3/8). A pilot study by Pitman and colleagues [59] found similar results. The effect of two different doses of propranolol (10.0 and 15.0 mg/kg) administered immediately after PSS exposure was assessed at days 30 (EPM and ASR) and 31 (reminder response). Propranolol proved to be ineffective in attenuating stress-induced behavioral

disruption. The propensity of treated individuals to develop extreme behavioral responses (PTSD-like) and the degree of vulnerability to a trauma cue 31 days after the index stress exposure were indistinguishable from exposed controls [60]. The physiological efficacy of the doses of propranolol was verified by collecting cardiovascular data telemetrically, and the results showed that the same treatment regimen effectively reduced post-stressor heart rate responses. Thus, propranolol effectively attenuated physiological functions, but failed to have behavioral effects in preventing posttraumatic responses, suggesting that propranolol was ineffective in preventing the development of posttraumatic responses in this animal model for PTSD [60]. In keeping with these results, a number of clinical studies published since then have reported similarly disappointing outcomes. In a double-blind, randomized, controlled trial of 14 days of propranolol administered within 48 h of injury to patients admitted to a surgical trauma center, no benefit over placebo on depressive or posttraumatic stress symptoms was found [61]. Sharp et al. [62] reported that propranolol does not reduce risk for acute stress disorder in pediatric burn patients. In a retrospective study performed on military burn soldiers injured in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF), propranolol did not decrease PTSD development. The prevalence of PTSD in patients receiving propranolol was the same as those not receiving propranolol [63].

Post-stressor Intervention with Sleep Deprivation

Convergent evidence has accumulated that sleep serves as an off-line period in which newly encoded hippocampus-dependent memories are gradually adapted to preexisting knowledge networks [64–67]. Sleep following learning is known to enhance the consolidation of newly acquired memory traces [68–71] through an active reorganization of representations, whereas acute sleep deprivation (SD) may disrupt this process and impair retrieval functions [72]. Wagner et al. [71] reported that brief periods of sleep immediately following learning cause preservation of emotional memories over 4 years. We therefore hypothesized that interfering with memory consolidation processes by SD immediately after traumatic experience will reduce posttraumatic stress symptoms and incidence. Rats were deprived of sleep for 6 h throughout the first resting phase after predator scent stress exposure. Behaviors in the elevated plus maze and acoustic startle response tests were assessed 7 days later and served for classification into behavioral response groups. Freezing response to a trauma reminder was assessed on day 8. We found that 6 h of SD after PSS exposure resulted in a significant moderation of behavior patterns representing stress-induced anxiety, avoidance, and hyperarousal responses on the EPM and ASR tests. A resounding overall shift in the prevalence rates of animals fulfilling criteria for EBR, which were effectively reduced to nil, was mirrored by a concomitant increase in minimal behavioral responders (Fig. 11.4a). Freezing responses to the late (day 8) neutral trauma cue were markedly attenuated (16.4% of time freezing in the treatment group as compared with 75.8% for untreated controls) (Fig. 11.4b). As memory is required to bridge the time interval between stress exposure and trauma cue, and because the SD procedure intentionally spanned the time frame within which memory consolidation processes take place at the cellular level McGaugh [11], the reduction in freezing responses suggests that memory-related processes were affected. In other words, postexposure SD may affect traumatic memory consolidation and thereby effectively ameliorate long-term, stress-induced, PTSD-like behavioral disruptions.

In addition to the behavioral tests, we launched a study to examine factors affecting neural/dendritic synaptic connectivity in response to interventions with sleep deprivation. We demonstrate that early post-stressor intervention with SD, which attenuates posttraumatic stress response, was associated with a dramatic increase in the number of dendrites of dentate granule cells, total dendritic length, and dendritic spine density, as compared to vehicle controls (Fig. 11.4 (C+D)). Although the precise molecular mechanisms underlying the factors that regulate the orientation, morphology, and elaboration of dendritic processes are largely unknown, there is now compelling evidence that outgrowth and morphogenesis of the dendritic arbor depends on the coordinated action of brain-derived neurotrophic factor (BDNF). Therefore, we also evaluated the BDNF expression. Hippocampal expression of BDNF demonstrated that post-exposure SD also corrected the clear-cut stress-induced downregulation of hippocampal BDNF expression [73] displayed by exposed-untreated rats. In light of the involvement of neurotrophins, and particularly of BDNF, in neuronal plasticity [74, 75], axonal and dendritic branching and remodeling [76–79], and proliferation of pyramidal neurons and their proximal dendrite growth [80], such an upregulation would enhance synaptic plasticity and stabilization of synaptic connectivity, enabling adaptive behavioral responses, i.e., increased resilience. Overall, the results of this study suggest that prevention of sleep in the early aftermath of stress exposure may be beneficial in attenuating traumatic, stress-related sequelae. Postexposure SD impairs hippocampus-dependent traumatic memory formation and consolidation, a mechanism possibly pertinent to the development of PTSD.

To summarize, interference with consolidation processes appears to represent a valid avenue for attenuating subsequent PTSD symptoms by affecting the durability of long-term trauma memories. The findings that single high-dose corticosteroids might be effective in attenuating the neuromodulatory

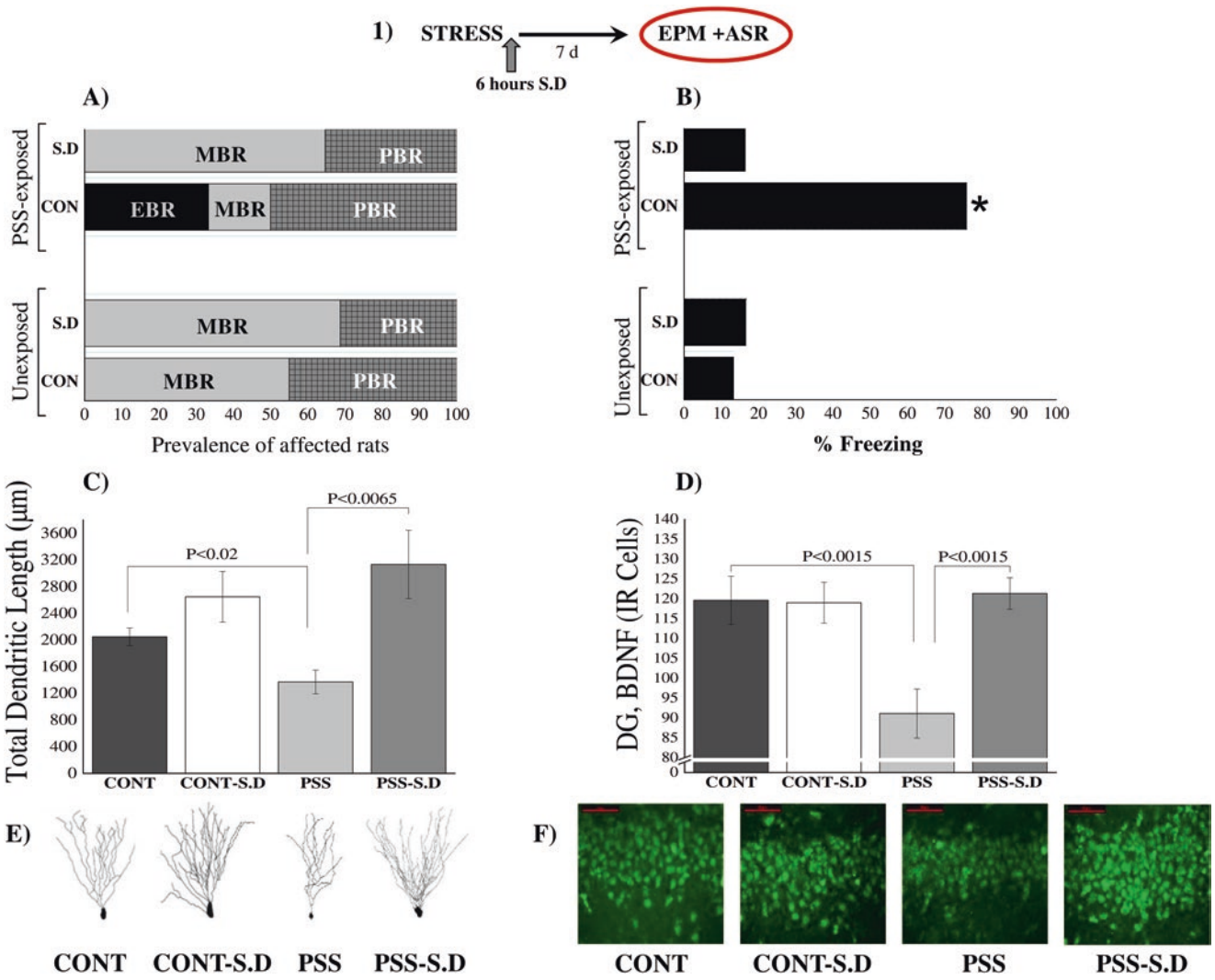

Fig. 11.4 Effect of postexposure sleep deprivation on behavioral stress responses: (*1*) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents sleep deprivation. (**a**) Effect of postexposure sleep deprivation on relative prevalence rates according to CBC classification. Postexposure sleep deprivation reduced the prevalence of PTSD-like behavioral responses (EBR) relative to the exposed-untreated group and concomitantly increased the prevalence of minimal behavioral responders. No differences were observed in the prevalence of partial behavioral responses. (**b**) Percent freezing (immobility time, in sec). Postexposure sleep deprivation decreased the immobility time in response to trauma cue as compared to exposed-untreated animals. (**c**) Effect of postexposure sleep deprivation on dendritic morphology in the dentate gyrus granule cells. Quantitative analysis of total dendritic length (µm) of dentate gyrus granule cells from the suprapyramidal blade. (**d**) Effect of postexposure sleep deprivation on BDNF immunoreactivity in the hippocampus: The quantitative analysis of BDNF immunostaining in the dentate gyrus of unexposed-untreated rats, unexposed rats treated with sleep deprivation, exposed-untreated rats and exposed rats treated with sleep deprivation. (**e**) Computer-generated plots of reconstructions and photomicrographs of the dendritic tree from granule cells. Exposed animals treated with sleep deprivation exhibited significantly greater total dendritic length as compared to exposed-untreated animals. (**f**) Representative photographs of BDNF immunoreactivity in the dentate gyrus of unexposed-untreated rats, unexposed rats treated with sleep deprivation, exposed-untreated rats, and exposed rats treated with sleep deprivation. Photographs were acquired at 40× magnification (Scale bar, 50 µm). The cells in green were BDNF positive. The data represent group mean ± S.E.M or percentage

effects of the stress response and the lack of efficacy of β-blockade are of particular clinical relevance. In addition, intentional prevention of sleep in the early aftermath of stress exposure may well be beneficial in attenuating traumatic stress-related sequelae. These evidence shed light on the importance of posttraumatic "off-line" processing and consolidation, in a specific timing (i.e., natural sleep time), to long-term adaptive recovery from the traumatic event. Postexposure SD impairs hippocampus-dependent traumatic memory formation and consolidation and therefore may be a simple, yet effective, intervention for the secondary prevention of stress-induced psychopathologies.

Interfering with Reconsolidation Processes

Given that it is often not possible to administer a consolidation-blocking agent, the possibility of later affecting the traumatic memory by pharmacologically blocking reconsolidation is particularly clinically relevant [81]. The temporarily destabilized state of memories between their reactivation, often in response to triggering by trauma reminder or cues, and their subsequent reconsolidation presents an equally important target for study. The clinical impact of potential interventions at later stages hardly requires explanation. The benefit for patient populations could be significant, considering that the window of opportunity for preventive interventions, i.e. during consolidation, is quite narrow and that there are quite significant issues which arise from the lack of reliable predictive factors in the acute phase.

The next series of studies employed the same interventions as the consolidation studies and the same approach to data analysis. The reactivating stimulus was unused cat litter and was administered either 7, 10, or 14 days after the initial PSS exposure. The results show that the exposed groups displayed significant behavioral responses to the reminder cue comparable to the responses to the original traumatic event. Behavioral responses were assessed at days 30–31 in a manner identical to the consolidation study protocols.

Post-reminder Administration of Anisomycin

Microinjection of anisomycin (at two different doses) 1 h after the reminder/cue did not attenuate the behavioral responses evaluated 3 days later. Thus, exposure to the situational cue followed by microinjection of anisomycin does not eliminate the subsequent anxiety-like behavioral changes. The results thus suggest that persistent anxiety-like behavior after predator stress does not appear to become sensitive to protein synthesis inhibitors after reactivation and reconsolidation.

Post-reminder Microinjection of Rapamycin

We assessed the effect of intra-hippocampal and amygdalar microinjections of rapamycin (600 nM in ACSF) on trauma cue responsiveness and on prevalence rates of individuals displaying extreme, partial, and minimal behavioral responses to PSS. In the longer term, rapamycin did not attenuate the onset of PTSD-like behaviors or the prevalence rates of severely affected individuals and actually had no effects on the behaviors of the rats. These findings are in contrast with previous studies that show that systemic rapamycin disrupts contextual fear memory consolidation when the drug is given around the time of learning [40] or disrupts reconsolidation when given after retrieval [40, 82]. Moreover, microinjection of rapamycin into the amygdala [37] or into the DH [83] after fear memory retrieval disrupted performance. In line with our data, Glover et al. [82] reported differential vulnerabilities of cued and context fear memories to systemic rapamycin treatment. The authors reported that systemic rapamycin disrupts both the consolidation and reconsolidation of context fear memory as measured by fear-potentiated startle, but had no effect on the consolidation or the reconsolidation of cued fear memory. It is not clear why the consolidation and reconsolidation of traumatic fear memory is impervious to rapamycin treatment. It is possible that trauma/fear memories work very differently from other memories.

Post-reminder Administration of Corticosterone

Animals were treated once with corticosterone at doses of 3.0, 15.0, or 25.0 mg/kg 1 h after trauma reminder. The results clearly showed that all doses of corticosterone administered immediately after memory reactivation 14 days following PSS exposure were without effects and did not attenuate the onset of PTSD-like behaviors or the prevalence rates of severely affected individuals (Fig. 11.5). Rats given either low-dose or high-dose corticosterone single-dose regimen were indistinguishable from vehicle controls on the EPM or ASR tests after 30 days. Taken together, in contrast to our previous data demonstrating that (high-dose) corticosterone disrupted traumatic memory consolidation, these results indicate that corticosterone was ineffective in disrupting reconsolidation.

To summarize, the finding that the reactivation and reconsolidation phase was not sensitive to pharmacological manipulations by anisomycin, corticosterone, or rapamycin, unlike the findings from non-trauma memories, suggests that the dynamics of traumatic memory processing after reactivation are more complex than previously thought.

The lack of observable efficacy of the interventions during reactivation-reconsolidation of traumatic memory may stem from a number of reasons:

(a) *Dosage*: The memories that have been formed under stressful conditions are stronger and less labile when reactivated [84]. It is possible that higher doses are required in order to disrupt reconsolidation than consolidation.
(b) *Reactivating stimulus*: Although the stimulus we employed sufficed to cause reactivation of behavioral disruptions at levels similar to the original stress exposure, the destabilization of the memory was not sufficient to render it vulnerable to the interventions. Possibly a more potent stimulus might achieve this.
(c) *Qualities of traumatic memories*: It is possible that there are far greater distinctions between traumatic memories and other forms of memory than are presently known. Their biomolecular and/or physiological and/or morphologic characteristics or even their brain circuits may be

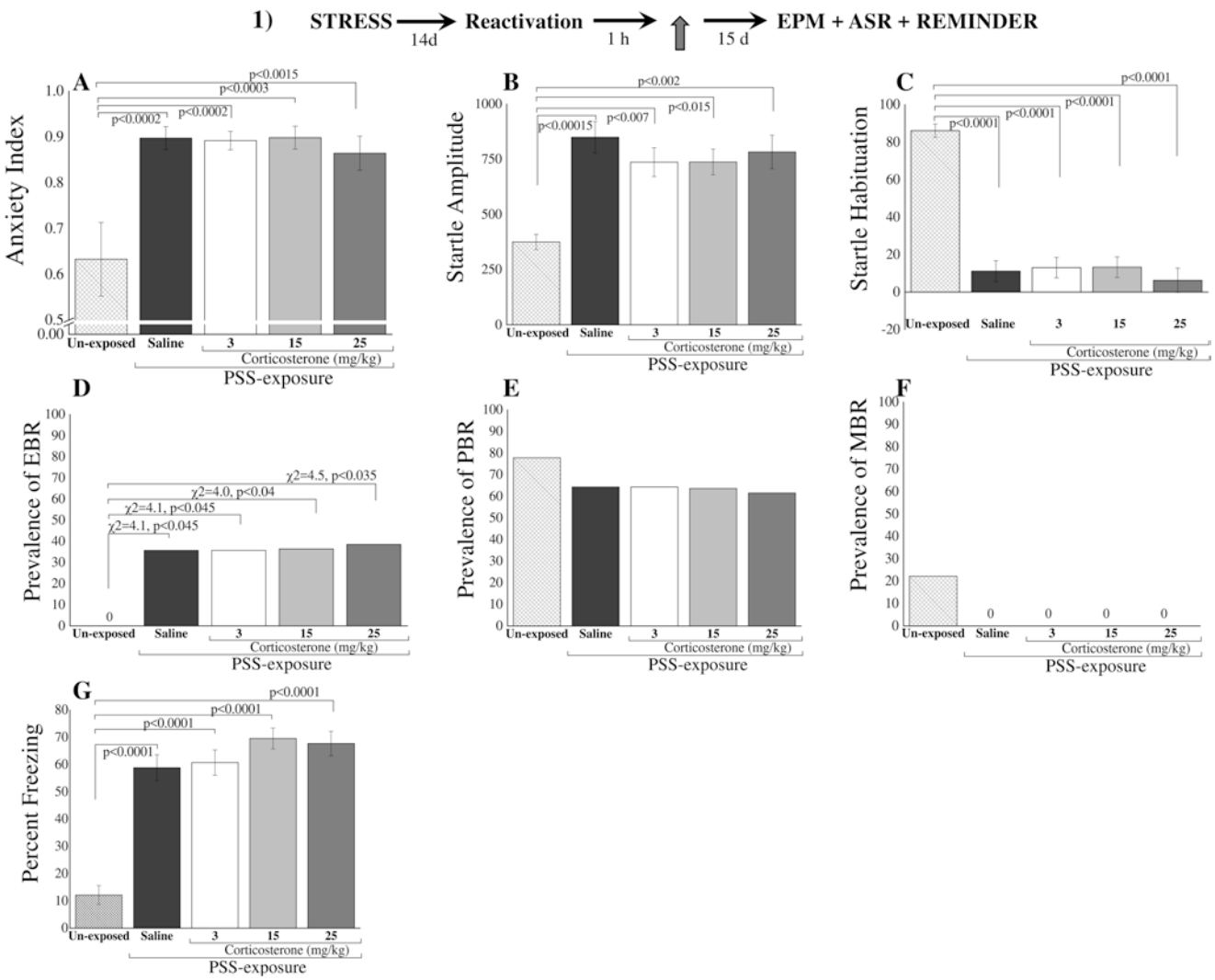

Fig. 11.5 The effects of early post-reminder administration of corticosterone: (*1*) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents intraperitoneal injection (corticosterone or vehicle). (**a**) Anxiety Index. (**b**) The mean startle amplitude of rats in response to the 30 startle pulses. (**c**) Percent habituation of startle response. (**d**) Prevalence of EBR rats. (**e**) Prevalence of MBR rats. (**f**) Prevalence of PBR rats. (**g**) Freezing (immobility time, in sec) There were significant differences between the groups in terms of Anxiety Index ($F(3,43) = 5.9$, $p < 0.002$), mean startle response ($F(3,43) = 8.5$, $p < 0.00015$), and startle habituation ($F(3,43) = 36.8$, $p < 0.0001$). Bonferroni test confirms that PSS exposure significantly increased Anxiety Index and mean startle amplitude and caused a significant deficit in the habituation of ASR in exposed rats injected with vehicle or corticosterone, as compared to unexposed controls. No differences were observed between the exposed groups treated with vehicle or corticosterone. The prevalence of EBR rats in the exposed group given vehicle or varying doses of corticosterone was 35.7, 35.7, 36.4, and 38.5% of the total population and differed significantly from the unexposed group (χ^2=4.1, $p < 0.044$, χ^2=4.1, $p < 0.044$, χ^2=4.0, $p < 0.04$, χ^2=4.5, $p < 0.035$), in which there were no EBR individuals. There were no significant differences in the prevalence of individuals displaying PBR and MBR among groups. Post hoc Bonferroni confirms that exposed rats treated with vehicle or corticosterone displayed significantly more immobility than unexposed controls ($p < 0.0001$ for all groups). The data represent group mean ± S.E.M or percentage

such that the interventions could not affect them. On the clinical and psychological levels, they certainly manifest very distinctive characteristics, compared to other forms of memory, and this might stem from equally distinctive characteristics at the biomolecular level.

(d) *Single-dose regimens*: Possibly multiple doses coupled with recurrent reactivation-reconsolidation would be more effective than single doses.

Long-Term Repeated Intervention in Reconsolidation

A regimen of repeated corticosterone treatment paired with reactivating the traumatic memory over 15 consecutive days, with the same range of doses of corticosterone (3.0, 15.0, and 25.0 mg/kg) injected 1 h after memory reactivation, was next assessed (Fig. 11.5), beginning on day 14 postexposure.

Behavioral responses were assessed in the EPM and the ASR tests at day 30. Exposure- and trauma cue-triggered freezing response was assessed 1 day later.

Low-dose corticosterone (3.0 mg/kg) resulted in a statistically significant reduction of 40.0% in the prevalence rates of EBR individuals at 30 days, with a concomitant increase of 16.7% in the prevalence of MBR individuals, as compared to saline controls. Moreover, these animals responded markedly less to the trauma cue (17.7% of time freezing) than the saline-control group (44.7% of time freezing). One plausible explanation for our data is that corticosterone may facilitate the extinction of a traumatic memory trace. Based on the finding that glucocorticoids impair the retrieval of emotional information, we thus suggest that by inhibiting memory retrieval, corticosterone may weaken the traumatic memory trace and thus reduce behavioral symptoms. We propose that repeated low-dose corticosterone administered following the reactivation of a traumatic memory could therefore potentially represent a novel treatment for PTSD. The results suggest that repeated paired low-dose corticosterone and trauma memory reactivation may be worthy of study in the clinical arena.

"Erasing" the Trace

One theoretically efficient way to eliminate unwanted and traumatic fear would be to "erase" the fear memory itself, although in humans this is ethically questionable. One approach to "erasing" memory is to target the molecules within neurons that maintain long-term memories. Although there are several candidate molecules involved in memory maintenance [85, 86], PKMζ in particular has received considerable attention as a substrate for long-term memory. This study assessed the long-term effects of ZIP, microinjected 10 days after stress exposure directly into four brain structures: the DH, BLA, LV, and IC (Fig. 11.6). Behavioral responses were assessed in the EPM and the ASR tests 7 days after treatment and cue-triggered freezing response on day 8.

Administration to the amygdala, hippocampus, or LV did not affect anxiety-like behaviors, prevalence of EBR, or trauma reminder responses, whereas administration to the insula was highly effective. Together with the data from the consolidation study on ZIP, this indicates that memory consolidation had been completed within this period and had become independent of the hippocampus. This effect was most obvious in the prevalence rates of EBR among treatment groups; 30–40% fulfilled the criteria for EBR in the amygdala/hippocampus/LV groups, whereas in the IC-ZIP-treated group, none of the animals fulfilled the criteria. The specific effect of PKMζ inactivation in the IC (at a time when the traumatic memory was completely consolidated into fixed and stable memory) indicates that the memories somehow remained amenable to alteration in a manner effectively (phenomenologically) equivalent to their erasure.

This implies that PSS and fear-related memories are initially rapidly processed in hippocampal (complex)-dependent processes. The traumatic memories follow a pathway over time, becoming encoded in cortical structures, independent of the hippocampus. One such pathway appears to involve the insular cortex, which brings the insular cortex to the forefront as a potential region of significance in processes related to traumatic stress-induced disorders. The IC is highly interconnected with the amygdala, hypothalamus, and periaqueductal gray matter and is involved in the processing of a range of sensory and motor modalities (visceral sensory, visceral motor, vestibular, gustatory, olfactory, visual, auditory, tactile, and motor function) and more complex modalities such as pain, emotion, and attention [87]. It may well represent a crucial junction in processes involved in anxiety states.

Translating Rodent Studies of "Cortisol-Impaired Consolidation Processes" to Humans

Information on the effect of cortisol injection on recovery from trauma is limited, although a series of naturalistic studies have demonstrated that administration of cortisone following septic shock reduces the incidence of PTSD [88–90]. Several studies have reported that exogenously administered cortisol reduces PTSD symptoms in patients with chronic PTSD [91–93].

In a pilot study based on the findings of the animal study above, 25 participants who had experienced a traumatic event accompanied by acute symptoms were recruited from the emergency room and randomized to receive double-blind hydrocortisone (100–140 mg based on body weight) or placebo, beginning approximately 5.5 h after the trauma [94]. Fifteen hydrocortisone participants and ten placebo participants who completed the study were assessed for PTSD symptoms 2 weeks, 1 month, and 3 months after the intervention. The findings demonstrated attenuating effects of hydrocortisone on subsequent acute stress reaction and acute PTSD. Follow-up assessments at 1 and 3 months after the trauma revealed statistically significant reduced scores on total clinician-administered PTSD scale (CAPS), VAS anxiety, and VAS depression in the steroid-treated participants as compared to placebo-treated controls. Although the statistical significance of prevalence rates of PTSD and/or acute stress response is severely curbed by the small size of the population sample, the attenuating effect on the severity of PTSD core symptoms was clearly demonstrated. Since a single administration of intravenous hydrocortisone is safe

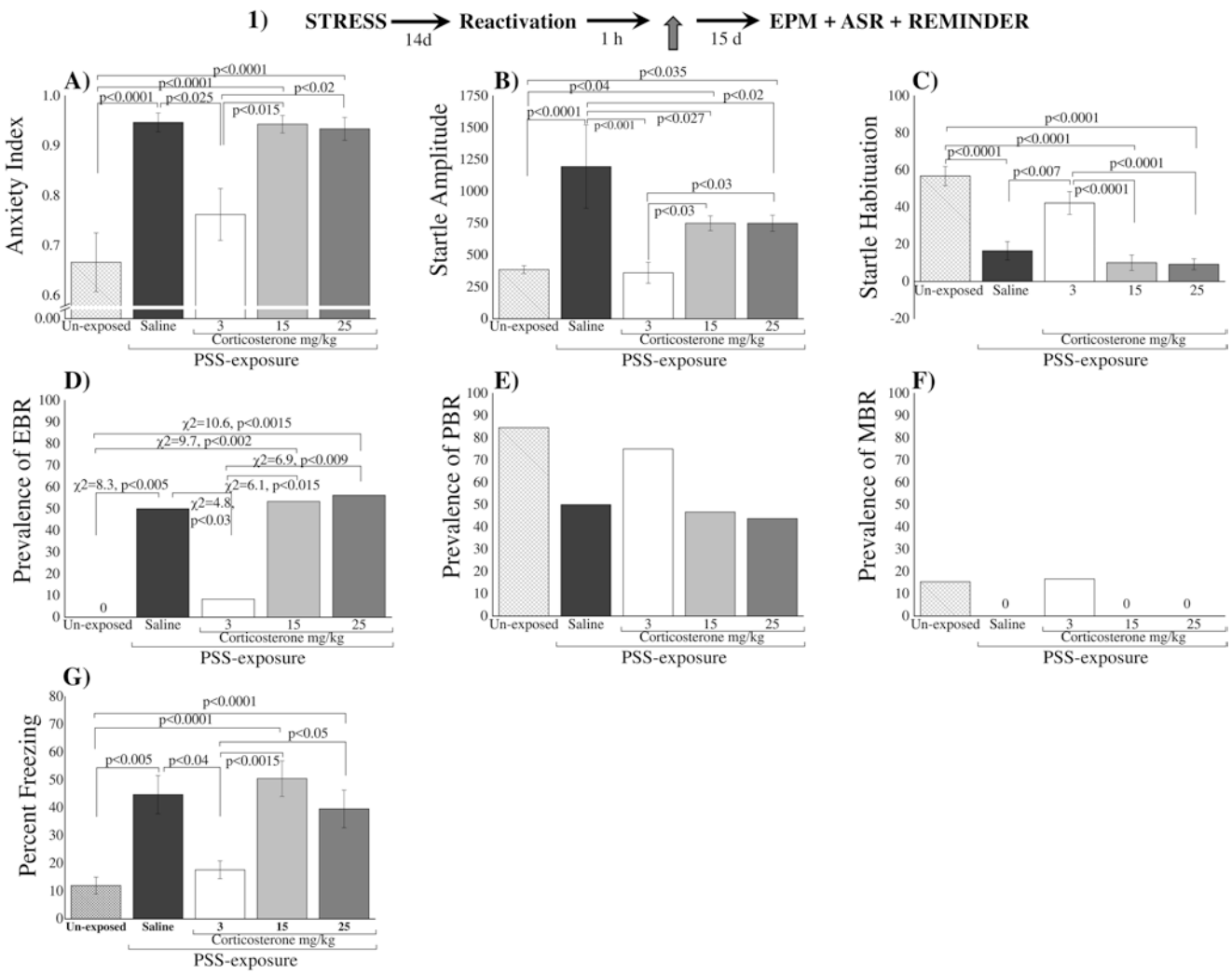

Fig. 11.6 The effects of repeated post-reminder administration of corticosterone: (*1*) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents intraperitoneal injection (corticosterone or vehicle). (**a**) Anxiety Index. (**b**) The mean startle amplitude of rats in response to the 30 startle pulses. (**c**) Percent habituation of startle response. (**d**) Prevalence of EBR rats. (**e**) Prevalence of MBR rats. (**f**) Prevalence of PBR rats. (**g**) Freezing (immobility time, in sec). There were significant differences between the groups in terms of Anxiety Index ($F(4,61) = 11.8$, $p < 0.0001$), mean startle response ($F(4,61) = 6.4$, $p < 0.0003$), and startle habituation ($F(4, 61) = 22.0$, $p < 0.0001$). Bonferroni test confirms that PSS exposure significantly increased Anxiety Index and mean startle amplitude and caused a significant deficit in the habituation of ASR in exposed rats treated with vehicle or corticosterone at doses of 15.0 and 25 mg/kg, as compared to unexposed controls. Animals exposed and treated with low-dose corticosterone displayed significantly lower Anxiety Index and mean startle response and higher startle habituation as compared to vehicle or high-dose corticosterone. Repeated treatment with low-dose corticosterone reduced the prevalence of PTSD-like behavioral responses (EBR) relative to vehicle-control treatment and to high-dose treatment (Pearson $\chi^2=17.2$, df = 4, $p < 0.002$). There were no significant differences in the prevalence of individuals displaying PBR and MBR among groups. Exposed rats treated with low-dose corticosterone displayed significantly less immobility than unexposed controls or then animals treated with high-dose corticosterone ($p < 0.0001$ for all groups). The data represent group mean ± S.E.M or percentage

and well tolerated – causing no serious complications – it provides a viable option for secondary prevention. This study provides supportive evidence that the use of high-dose hydrocortisone in trauma care may be protective against the subsequent development of PTSD after traumatic experience [94]. A single, high dose of hydrocortisone immediately after a traumatic experience seems to assist in "recalibrating" the HPA axis, thereby facilitating those processes required for a return to homeostasis and hence for post-stress recovery. Additionally, the exogenous hydrocortisone may act indirectly to prevent PTSD by reducing the norepinephrine requirement [95, 96]. The possible therapeutic benefits implied by the results of this prospective pilot study warrant further investigation on a larger scale and may call for reconsideration of the currently accepted clinical indications for steroid treatment in trauma patients.

Translating Rodent Studies of "Sleep Deprivation-Impaired Consolidation Processes" to Humans

As for sleep deprivation intervention following a traumatic event, we designed a pilot clinical study under the hypothesis that preventing sleep on the first night after exposure to a traumatic event will reduce the risk for developing PTSD. Twelve emergency room patients who underwent a traumatic event were instructed to either sleep [sleep-encouraged group (SE)] or stay awake (SD group) during the first night following the traumatic event. PTSD-related symptoms were evaluated 1 and 3 months following the traumatic event. None of the subjects in the SD group met the criteria for PTSD, either 1 or 3 months following the traumatic event. In contrast, at the 4-week follow-up assessment, two participants (33.3%) in the SE group met the criteria for PTSD, and one participant (16.7%) met these criteria 3 months following the traumatic event. Although the statistical significance of these results is severely curbed by the small sample size of the study, the results are very encouraging, especially in light of the results of the animal model study. Previous studies have demonstrated the beneficial effects of SD on aversive memory consolidation in healthy volunteers [71, 97, 98]. For instance, Kuriyama and colleagues [97] used movie clips of motor vehicle accidents as stimuli for aversive episodic memory encoding and reported that SD reduced the fear responses to the aversive material [97]. Porcheret et al. [98] reported that a period of SD on the first night after viewing experimental trauma (trauma film paradigm) decreased the psychological impact of the trauma and the number of intrusive memories of the event. Taken together, our pilot clinical study provides supportive evidence that SD during the first natural resting phase following a potentially traumatic event may protect against subsequent development of PTSD.

Summary

The results of this series of interventions potentially affecting the persistently disruptive effects of traumatic memories revealed a number of interesting characteristics that are apparently quite distinct from other forms of memory. Several interventions succeeded in weakening the traumatic memory when administered once during initial memory consolidation yet were ineffective during the processes involved in the reactivation and reconsolidation phase. These included direct microinjection of anisomycin (LV) or ZIP (hippocampus, ICV) and systemic administration of high-dose corticosterone. None of these interventions affected the reactivation and reconsolidation phase. Interventions using rapamycin and lower doses of corticosterone were ineffective during both phases, as was propranolol. In addition, the long-term anxiolytic effects of SD appear to stem from a diurnal cycle-dependent mechanism, such that preventing sleep during the first natural resting phase following the traumatic exposure is beneficial in preventing the traumatic sequelae. Postexposure SD may disrupt the consolidation of aversive or fearful memories by facilitating correctly timed interactions between glucocorticoid and adrenergic systems.

A treatment regimen based on repeated reactivation and administration of corticosterone over 15 consecutive days with low-dose corticosterone was highly beneficial in attenuating reconsolidation and facilitated extinction, whereas all other doses were ineffective (Fig. 11.7). The physical location of traumatic memories was shown to change over time, with a shift from the hippocampus to the insular cortex, which brings the insular cortex to the forefront as a potential region of significance in processes related to traumatic stress-induced disorders (Fig. 11.8).

Corticosteroid treatment is a feasible avenue for clinical interventions, and in fact the findings of the single high-dose corticosterone animal study have already been applied in a clinical pilot study with encouraging results. A repeated low-dose regimen during reactivation and reconsolidation is under consideration, again based on these studies.

We provide initial evidence that the first natural resting phase after exposure to a traumatic event is the critical time for SD to be effective in attenuating the traumatic, stress-related sequelae. Further studies, both in animal models and in humans, are required to determine if, indeed, "don't sleep on it" is the best advice to give a patient following exposure to a traumatic event.

Conclusions

Trauma memories appear to work very differently from other memories. Many studies have demonstrated that non-traumatic memories are vulnerable to anisomycin, rapamycin, or propranolol during reactivation and reconsolidation, whereas trauma memories proved immune to the same interventions. This demonstrates that much research remains to be done in order to find the difference. Predator scent stress and fear-related memories are initially rapidly processed in hippocampal (complex)-dependent processes. The traumatic memories are seen to follow a physical pathway over time, becoming encoded in cortical structures, independent of the hippocampus complex. One such pathway appears to involve the insular cortex, which brings the insular cortex to the forefront as a potential region of significance in processes related to traumatic stress-induced disorders. On the biological level, anisomycin (LV), high-dose corticosterone, or ZIP (hippocampus, LV) disrupts traumatic memory consolidation and hence was beneficial in reducing PTSD-like behavioral responses. ZIP administered in the insula was effective in altering stable memories, and

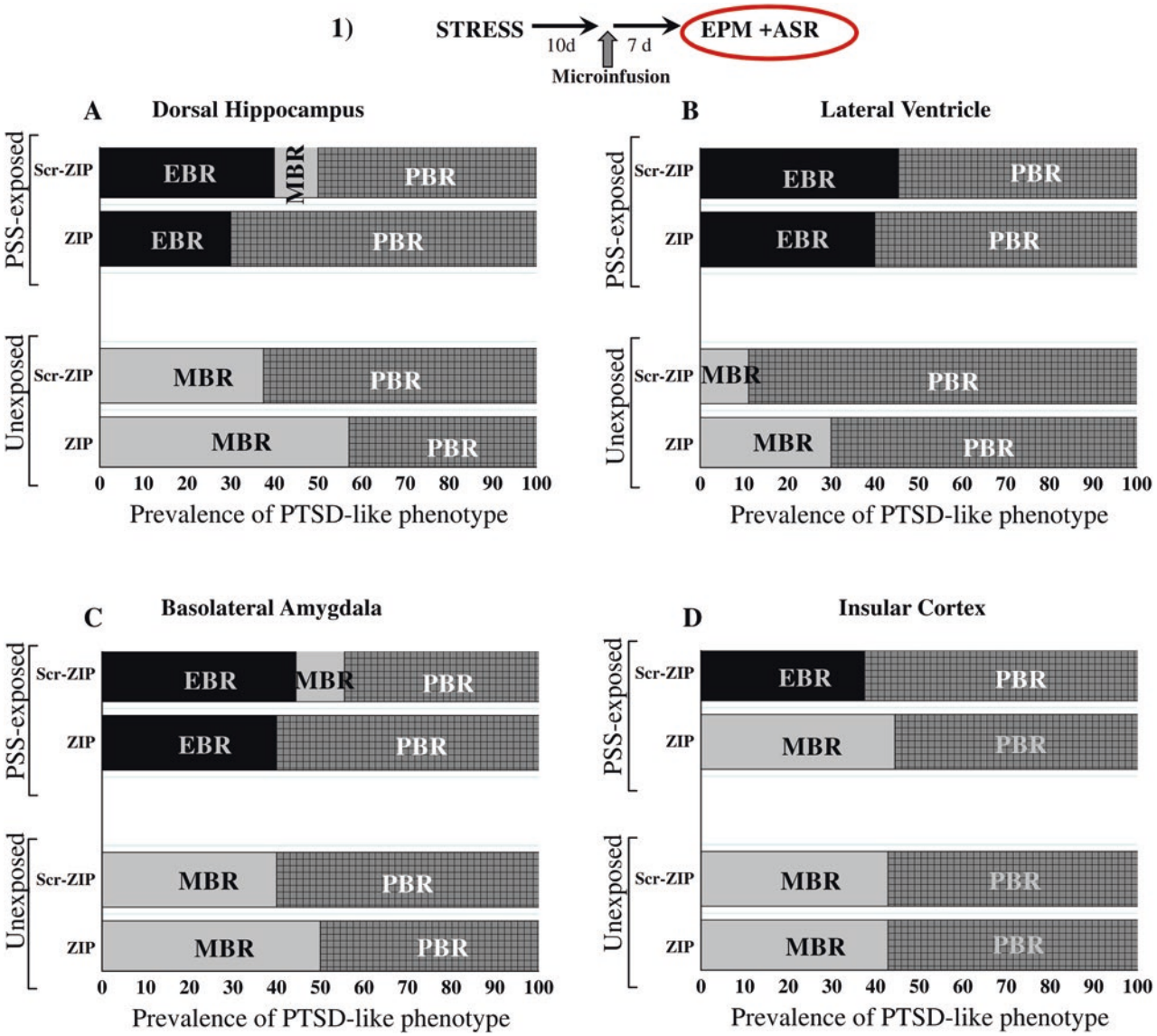

Fig. 11.7 Effect of administration of ZIP/Scr-ZIP 10 days after a single exposure to a predator scent stress: (*1*) The behavioral procedure used for the unexposed and PSS-exposed rats. *Vertical open arrow* represents microinjection (ZIP or Scr-ZIP). (**a**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the dorsal hippocampus. (**b**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the lateral ventricle. (**c**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the basolateral amygdala. (**d**) The effects of early post-stressor microinjection of ZIP/Scr-ZIP to the insular cortex. When microinjected to the IC, but not to the BLA, DH, or LV, ZIP significantly decreased the prevalence rate of individuals displaying EBR as compared to Scr-ZIP-microinjected rats, reflecting decreased anxiety-like behavior and traumatic fear and memory in ZIP-treated animals. Data represent prevalence of affected rats

repeated low-dose corticosterone was effective in interfering with reactivation and reconsolidation during extinction.

Based on the results of the animal studies discussed above, there are two optimal time windows for intervention with corticosterone subsequent to exposure to a highly stressful event:

1. During the initial time window after the traumatic experience, when the traumatic memory is in a labile state, using a single high dose of corticosterone.
2. In the long term, during the time window between reactivation, reconsolidation, and extinction, repeated low-dose corticosterone may be effective in disrupting the trauma memories.

The importance of these studies for clinical interventions in PTSD patients was emphasized by the clinical pilot study on hydrocortisone. The other substances are not readily applicable clinically, but the search for clinically feasible interventions is well worth the effort.

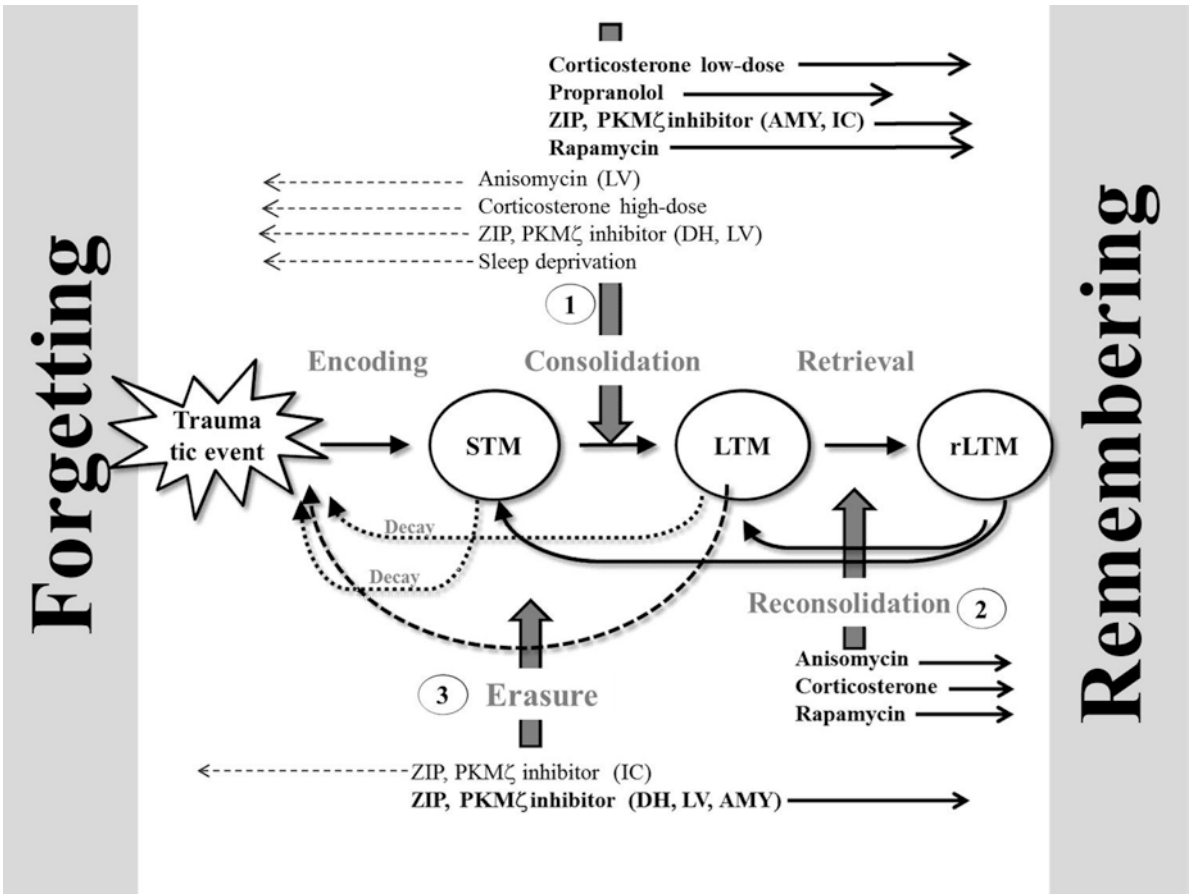

Fig. 11.8 Encoding, consolidation, and reconsolidation of memory: (*1*) Memory formation is associated with initial encoding to establish a short-term memory followed by a time-dependent consolidation phase to establish a stable long-term memory. Once a memory is a long-term memory, it remains fixed or permanent [12, 99]. A typical demonstration of a consolidation blockade: applying anisomycin, high-dose corticosterone, or ZIP (into hippocampus or lateral ventricle) or manipulation of sleep deprivation, 1 h after predator scent stress, results in impaired long-term memory (LTM), a pattern that defines consolidation impairment. (*2*) Reactivation of long-term memory and reconsolidation render the memory labile once more. A typical demonstration of a reconsolidation blockade of fear memory: applying anisomycin, corticosterone, or rapamycin 1 h after reactivation does not affect traumatic memory reconsolidation. (*3*) In the absence of retrieval, long-term memory may be actively erased by a variety of manipulations (such as PKMζ) by interfering with the molecular mechanisms involved in molecular maintenance

References

1. van Praag HM. The cognitive paradox in posttraumatic stress disorder: a hypothesis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28(6):923–35.
2. Pitman RK. Post-traumatic stress disorder, hormones, and memory. Biol Psychiatry. 1989;26(3):221–3.
3. Villain H, Benkahoul A, Drougard A, Lafragette M, Muzotte E, Pech S, et al. Effects of propranolol, a beta-noradrenergic antagonist, on memory consolidation and reconsolidation in mice. Front Behav Neurosci. 2016;10:49.
4. Giustino TF, Fitzgerald PJ, Maren S. Revisiting propranolol and PTSD: memory erasure or extinction enhancement? Neurobiol Learn Mem. 2016;130:26–33.
5. Drexler SM, Merz CJ, Hamacher-Dang TC, Tegenthoff M, Wolf OT. Effects of cortisol on reconsolidation of reactivated fear memories. Neuropsychopharmacology. 2015;40(13):3036–43.
6. Taylor JR, Torregrossa MM. Pharmacological disruption of maladaptive memory. Handb Exp Pharmacol. 2015;228:381–415.
7. Cohen H, Joseph Z, Matar M. The relevance of differential response to trauma in an animal model of post-traumatic stress disorder. Biol Psychiatry. 2003;53(6):463–73.
8. Cohen H, Zohar J. Animal models of post traumatic stress disorder: the use of cut off behavioral criteria. The Annals New-York Academy of Sciences. 2004;1032:167–78.
9. Cohen H, Zohar J, Matar MA, Kaplan Z, Geva AB. Unsupervised fuzzy clustering analysis supports behavioral cutoff criteria in an animal model of posttraumatic stress disorder. Biol Psychiatry. 2005;22:22.
10. Cohen H, Zohar J, Matar MA, Zeev K, Loewenthal U, Richter-Levin G. Setting apart the affected: the use of behavioral criteria in animal models of post traumatic stress disorder. Neuropsychopharmacology. 2004;29(11):1962–70.
11. McGaugh JL. Memory--a century of consolidation. Science. 2000;287(5451):248–51.
12. McGaugh JL. Time-dependent processes in memory storage. Science. 1966;153:1351–8.
13. Nader K, Hardt O. A single standard for memory: the case for reconsolidation. Nat Rev Neurosci. 2009;10(3):224–34.

14. Flexner LB, Flexner JB, De La Haba G, Roberts RB. Loss of memory as related to inhibition of cerebral protein synthesis. J Neurochem. 1965;12(7):535–41.
15. Davis HP, Squire LR. Protein synthesis and memory: a review. Psychol Bull. 1984;96(3):518–59.
16. Dudai Y. Consolidation: fragility on the road to the engram. Neuron. 1996;17(3):367–70.
17. Abel T, Martin KC, Bartsch D, Kandel ER. Memory suppressor genes: inhibitory constraints on the storage of long-term memory. Science. 1998;279(5349):338–41.
18. Abel T, Lattal KM. Molecular mechanisms of memory acquisition, consolidation and retrieval. Curr Opin Neurobiol. 2001;11(2):180–7.
19. Melo I, Ehrlich I. Sleep supports cued fear extinction memory consolidation independent of circadian phase. Neurobiol Learn Mem. 2016;132:9–17.
20. Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem. 2001;8(2):112–9.
21. Quirk GJ, Pare D, Richardson R, Herry C, Monfils MH, Schiller D, et al. Erasing fear memories with extinction training. J Neurosci. 2011;30(45):14993–7.
22. Dudai Y. Reconsolidation: the advantage of being refocused. Curr Opin Neurobiol. 2006;16(2):174–8.
23. Dudai Y. Molecular bases of long-term memories: a question of persistence. Curr Opin Neurobiol. 2002;12(2):211–6.
24. Cohen H, Matar MA, Joseph Z. Animal models of post-traumatic stress disorder. Curr Protoc Neurosci. 2013; doi:10.1002/0471142301.ns0945s64.
25. Berman DE, Dudai Y. Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. Science. 2001;291(5512):2417–9.
26. Lattal KM, Abel T. Different requirements for protein synthesis in acquisition and extinction of spatial preferences and context-evoked fear. J Neurosci. 2001;21(15):5773–80.
27. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 2000;406(6797):722–6.
28. Santini E, Ge H, Ren K, Pena de Ortiz S, Quirk GJ. Consolidation of fear extinction requires protein synthesis in the medial prefrontal cortex. J Neurosci. 2004;24(25):5704–10.
29. Lattal KM, Honarvar S, Abel T. Effects of post-session injections of anisomycin on the extinction of a spatial preference and on the acquisition of a spatial reversal preference. Behav Brain Res. 2004;153(2):327–39.
30. Meiri N, Rosenblum K. Lateral ventricle injection of the protein synthesis inhibitor anisomycin impairs long-term memory in a spatial memory task. Brain Res. 1998;789(1):48–55.
31. Adamec R. Transmitter systems involved in neural plasticity underlying increased anxiety and defense – implications for understanding anxiety following traumatic stress. Neurosci Biobehav Rev. 1997;21(6):755–65.
32. Cohen H, Zohar J, Matar MA, Kaplan Z, Geva AB. Unsupervised fuzzy clustering analysis supports behavioral cutoff criteria in an animal model of posttraumatic stress disorder. Biol Psychiatry. 2005;58(8):640–50.
33. Cohen H, Matar MA, Joseph Z. Animal models of post-traumatic stress disorder. Curr Protoc Neurosci. 2013; Chapter 9: Unit9 45.
34. Cohen H, Kaplan Z, Matar MA, Loewenthal U, Kozlovsky N, Zohar J. Anisomycin, a protein synthesis inhibitor, disrupts traumatic memory consolidation and attenuates posttraumatic stress response in rats. Biol Psychiatry. 2006;60(7):767–76.
35. Bekinschtein P, Katche C, Slipczuk LN, Igaz LM, Cammarota M, Izquierdo I, et al. mTOR signaling in the hippocampus is necessary for memory formation. Neurobiol Learn Mem. 2007;87:303–7.
36. Hay N, Sonenberg N. Upstream and downstream of mTOR. Genes Dev. 2004;18:1926–45.
37. Parsons RP, Gafford GM, Helmstetter FJ. Translational control via the mammalian target of rapamycin (mTOR) pathway is critical for the formation and stability of long term fear memory in amygdala neurons. J Neurosci. 2006;26:12977–83.
38. Slipczuk L, Bekinschtein P, Katche C, Cammarota M, Izquierdo I, Medina JH. BDNF activates mTOR to regulate GluR1 expression required for memory formation. PLoS One. 2009;4:e6007.
39. Qi S, Mizuno M, Yonezawa K, Nawa H, Takei N. Activation of mammalian target of rapamycin signaling in spatial learning. Neurosci Res. 2010;68:88–93.
40. Blundell J, Kouser M, Powell CM. Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. Neurobiol Learn Mem. 2008;90(1):28–35.
41. Helmstetter FJ, Parsons RG, Gafford GM. Macromolecular synthesis, distributed synaptic plasticity, and fear conditioning. Neurobiol Learn Mem. 2008;89(3):324–37.
42. Belelovsky K, Kaphzan H, Elkobi A, Rosenblum K. Biphasic activation of the mTOR pathway in the gustatory cortex is correlated with and necessary for taste learning. J Neurosci. 2009;29(23):7424–31.
43. Gafford GM, Parsons RG, Helmstetter FJ. Consolidation and reconsolidation of contextual fear memory requires mammalian target of rapamycin-dependent translation in the dorsal hippocampus. Neuroscience. 2011;182:98–104.
44. Ling DS, Benardo LS, Serrano PA, Blace N, Kelly MT, Crary JF, et al. Protein kinase Mzeta is necessary and sufficient for LTP maintenance. Nat Neurosci. 2002;5(4):295–6.
45. Sacktor TC, Osten P, Valsamis H, Jiang X, Naik MU, Sublette E. Persistent activation of the zeta isoform of protein kinase C in the maintenance of long-term potentiation. Proc Natl Acad Sci U S A. 1993;90(18):8342–6.
46. Kelly MT, Crary JF, Sacktor TC. Regulation of protein kinase Mzeta synthesis by multiple kinases in long-term potentiation. J Neurosci. 2007;27(13):3439–44.
47. Shema R, Sacktor TC, Dudai Y. Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKM zeta. Science. 2007;317:951–3.
48. Schwabe L, Joels M, Roozendaal B, Wolf OT, Oitzl MS. Stress effects on memory: an update and integration. Neurosci Biobehav Rev. 2012;36(7):1740–9.
49. Gold PE, McGaugh JL. A single-trace, two process view of memory storage processes. In: JDaD D, editor. Short-term memory. New York: Academic Press; 1975. p. 355–78.
50. Cohen H, Matar MA, Buskila D, Kaplan Z, Zohar J. Early post-stressor intervention with high-dose corticosterone attenuates post-traumatic stress response in an animal model of posttraumatic stress disorder. Biol Psychiatry. 2008;64(8):708–17.
51. Sapolsky RM. Why stress is bad for your brain. Science. 1996;273(5276):749–50.
52. Conrad CD, Lupien SJ, McEwen BS. Support for a bimodal role for type II adrenal steroid receptors in spatial memory. Neurobiol Learn Mem. 1999;72(1):39–46.
53. Joels M. Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci. 2006;27(5):244–50.
54. Kohda K, Harada K, Kato K, Hoshino A, Motohashi J, Yamaji T, et al. Glucocorticoid receptor activation is involved in producing abnormal phenotypes of single-prolonged stress rats: a putative post-traumatic stress disorder model. Neuroscience. 2007;148(1):22–33.
55. Roozendaal B. 1999 Curt P. Richter award. Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology. 2000;25(3):213–38.
56. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21(1):55–89.
57. Cahill L, McGaugh JL. Modulation of memory storage. Curr Opin Neurobiol. 1996;6(2):237–42.

58. Louvart H, Maccari S, Vaiva G, Darnaudery M. Prenatal stress exacerbates the impact of an aversive procedure on the corticosterone response to stress in female rats. Psychoneuroendocrinology. 2009;34(5):786–90.
59. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry. 2002;51(2):189–92.
60. Cohen H, Kaplan Z, Koresh O, Matar MA, Geva AB, Zohar J. Early post-stressor intervention with propranolol is ineffective in preventing posttraumatic stress responses in an animal model for PTSD. Eur Neuropsychopharmacol. 2011;21(3):230–40.
61. Stein MB, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: results from a randomized controlled proof-of-concept trial in physically injured patients. J Trauma Stress. 2007;20(6):923–32.
62. Sharp S, Thomas C, Rosenberg L, Rosenberg M, Meyer W 3rd. Propranolol does not reduce risk for acute stress disorder in pediatric burn trauma. J Trauma. 2010;68(1):193–7.
63. McGhee LL, Maani CV, Garza TH, Desocio PA, Gaylord KM, Black IH. The effect of propranolol on posttraumatic stress disorder in burned service members. J Burn Care Res. 2009;30(1):92–7.
64. Born J, Rasch B, Gais S. Sleep to remember. Neuroscientist. 2006;12:410–24.
65. Maquet P. The role of sleep in learning and memory. Science. 2001;294:1048–52.
66. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005;437:1272–8.
67. Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol. 2006;57:139–66.
68. Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem. 2004;11:679–85.
69. Maquet P. Sleep on it! Nat Neurosci. 2000;3(12):1235–6.
70. Peigneux P, Laureys S, Delbeuck X, Maquet P. Sleeping brain, learning brain. The role of sleep for memory systems. Neuroreport. 2001;12(18):A111–24.
71. Wagner U, Hallschmid M, Rasch B, Born J. Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry. 2006;60(7):788–90.
72. Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P. A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. Sleep. 2010;33(10):1315–22.
73. Kozlovsky N, Matar MA, Kaplan Z, Kotler M, Zohar J, Cohen H. Long-term down-regulation of BDNF mRNA in rat hippocampal CA1 subregion correlates with PTSD-like behavioural stress response. Int J Neuropsychopharmacol. 2007;10(6):741–58.
74. Shieh PB, Ghosh A. Molecular mechanisms underlying activity-dependent regulation of BDNF expression. J Neurobiol. 1999;41(1):127–34.
75. Thoenen H. Neurotrophins and activity-dependent plasticity. Prog Brain Res. 2000;128:183–91.
76. Lom B, Cohen-Cory S. Brain-derived neurotrophic factor differentially regulates retinal ganglion cell dendritic and axonal arborization in vivo. J Neurosci. 1999;19(22):9928–38.
77. McAllister AK. Subplate neurons: a missing link among neurotrophins, activity, and ocular dominance plasticity? Proc Natl Acad Sci U S A. 1999;96(24):13600–2.
78. Shimada A, Mason CA, Morrison ME. TrkB signaling modulates spine density and morphology independent of dendrite structure in cultured neonatal Purkinje cells. J Neurosci. 1998;18(21):8559–70.
79. Yacoubian TA, Lo DC. Truncated and full-length TrkB receptors regulate distinct modes of dendritic growth. Nat Neurosci. 2000;3(4):342–9.
80. Segal R, Pomeroy S, Stiles C. Axonal growth and fasciculation linked to differential expression of BDNF and NT3 receptors in developing cerebellar granule cells. J Neurosci. 1995;15:4970–81.
81. Tronson NC, Taylor JR. Molecular mechanisms of memory reconsolidation. Nat Rev Neurosci. 2007;8(4):262–75.
82. Glover EM, Ressler KJ, Davis M. Differing effects of systemically administered rapamycin on consolidation and reconsolidation of context vs. cued fear memories. Learn Mem. 2011;17(11):577–81.
83. Myskiw JC, Rossato JI, Bevilaqua LR, Medina JH, Izquierdo I, Cammarota M. On the participation of mTOR in recognition memory. Neurobiol Learn Mem. 2008;89(3):338–51.
84. Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci. 2004;24(20):4787–95.
85. Kandel ER. The biology of memory: a forty-year perspective. J Neurosci. 2009;29(41):12748–56.
86. Maren S. Seeking a spotless mind: extinction, deconsolidation, and erasure of fear memory. Neuron. 2011;70(5):830–45.
87. Nagai M, Kishi K, Kato S. Insular cortex and neuropsychiatric disorders: a review of recent literature. Eur Psychiatry. 2007; 22(6):387–94.
88. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry. 2001;50(12):978–85.
89. Schelling G, Richter M, Roozendaal B, Rothenhausler HB, Krauseneck T, Stoll C, et al. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit Care Med. 2003;31(7):1971–80.
90. Schelling G, Stoll C, Kapfhammer HP, Rothenhausler HB, Krauseneck T, Durst K, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. Crit Care Med. 1999;27(12):2678–83.
91. Aerni A, Traber R, Hock C, Roozendaal B, Schelling G, Papassotiropoulos A, et al. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiatry. 2004;161(8):1488–90.
92. Miller MW, McKinney AE, Kanter FS, Korte KJ, Lovallo WR. Hydrocortisone suppression of the fear-potentiated startle response and posttraumatic stress disorder. Psychoneuroendocrinology. 2011;36:970–80.
93. Suris A, North C, Adinoff B, Powell CM, Greene R. Effects of exogenous glucocorticoid on combat-related PTSD symptoms. Ann Clin Psychiatry. 2010;22(4):274–9.
94. Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, et al. High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. Eur Neuropsychopharmacol. 2011;21(11):796–809.
95. McReynolds JR, Donowho K, Abdi A, McGaugh JL, Roozendaal B, McIntyre CK. Memory-enhancing corticosterone treatment increases amygdala norepinephrine and Arc protein expression in hippocampal synaptic fractions. Neurobiol Learn Mem. 2010;93(3):312–21.
96. Sun Z, Fan Y, Zha Q, Zhu MY. Corticosterone up-regulates expression and function of norepinephrine transporter in SK-N-BE(2)C cells. J Neurochem. 2010;113(1):105–16.
97. Kuriyama K, Soshi T, Kim Y. Sleep deprivation facilitates extinction of implicit fear generalization and physiological response to fear. Biol Psychiatry. 2010;68(11):991–8.
98. Porcheret K, Holmes EA, Goodwin GM, Foster RG, Wulff K. Psychological effect of an analogue traumatic event reduced by sleep deprivation. Sleep. 2015;38(7):1017–25.
99. Glickman S. Perseverative neural processes and consolidation of the memory trace. Psychol Bull. 1961;58:218–33.

Brain Structural Abnormalities in Posttraumatic Stress Disorder and Relations with Sleeping Problems

12

Israel Liberzon, Xin Wang, and Hong Xie

Introduction

Posttraumatic stress disorder (PTSD) has been increasingly recognized as a major public health problem that leads to substantial suffering, health-care costs, and lost productivity [16, 64, 108]. Many PTSD patients complain about sleep problems including insomnia, frequent nocturnal awakenings, nightmares, and difficulty initiating sleep [68–71, 93, 136]. Trauma-related nightmares and sleep disturbances are included in the intrusive and hyperarousal symptom clusters in the PTSD definition in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [60]. Over the past decades, mounting studies examined brain structures of PTSD patients in search for the neurobiological mechanisms underlying PTSD symptoms. In this chapter, we summarize the finding of structural brain abnormalities reported in PTSD and review the evidence linking between brain structural properties and sleep problems in the studies of PTSD.

Brain Structural Abnormalities in PTSD

Except a few early computerized axial tomography (CAT) studies in PTSD patients [110], the majority of neuroimaging studies on brain structure of PTSD patients utilize magnetic resonance imaging (MRI) approaches. These MRI studies examined brain structural properties including volume, cortical thickness, and voxel-based morphometry (VBM, a measure of signal density of gray matter on MRI images). Recent studies also utilized diffusion tensor imaging (DTI) technique that measures the diffusion of water molecules in the axon in the white matter neural fibers, to calculate mean, radial, or axial diffusivity (MD, RD, or AD) and fractional anisotropy (FA) of white matter tracks. These DTI measures have been used as indexes of fiber integrity in the white matter. The majority of structural studies used diagnostic criteria for PTSD as described in DSM version III or IV for inclusion. Structural differences were usually defined as differences between PTSD patients and control individuals without PTSD. Generally, control subjects had either experienced the same or similar trauma to PTSD patients, but did not meet diagnostic criteria for PTSD, and in some studies control subjects had never experienced any significant trauma. Below, we review findings grouping them by specific brain regions and summarize them in Tables 12.1 and 12.2, for adult and pediatric patients, respectively.

Hippocampus

Hippocampus is a temporal lobe structure implicated in learning and memory processing as well as in emotion processing, contextual processing, stress regulation, and more [11, 42, 119, 147]. PTSD symptoms had been also associated with deficits in memory function and negative emotion processing [11], implicating hippocampus in PTSD-related pathophysiology. Accordingly, abnormal activation of the hippocampus had been suggested by functional MRI studies of PTSD patients, as compared to trauma-exposed and healthy control subjects (reviewed by [80, 112]). Multiple structural MRI studies thus examined the hippocampal volume and VBM in diverse cohorts of adult PTSD patients including survivors of combat, physical/sexual abuse, disasters, and childhood mal-

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Table 12.1 Summary of structural MRI studies on adult PTSD

Literature (author; year)	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus (HC)	Amygdala	Prefrontal and cingulate cortices	Other brain regions
Abe et al. (2006)	Attack; mixed; 9	Trauma exposed; mixed; 16	DTI			FA increase in the left ACC	
Baldacara et al. (2011)	Violence; mixed; 42	Trauma exposed; mixed; 42	Volume				Smaller left cerebellum and vermis
Bing et al. (2013)	MVA, mixed, 20	Healthy; mixed; 20	Thickness			Thinner in left mPFC, inferior frontal, ACC	Thinner in right superior temporal cortex
Bonne et al. (2001)	Unclear; mixed; 10	Trauma exposed; mixed; 27	Volume	No group difference and over time change	No group and overtime change		
Bremner et al. (1995)	Combat; mixed; 26	Trauma-free; mixed; 22	Volume	Smaller right HC			
Bremner et al. (1997)	Childhood abuse; mixed; 17	Trauma-free; mixed; 17	Volume	Smaller left HC	No difference		No difference in temporal lobe
Bremner et al. (2003)	Childhood abuse; F; 10	Childhood abuse; F; 12	Volume	Smaller right and left HC in PTSD vs two control groups			
		Trauma-free; F; 11					
Cardenas et al. (2011)	Veteran; M; 25	Trauma exposed; M; 22	Volume (DBM)			PTSD: non-PTSD: no difference	PTSD: non-PTSD: no difference
						worsen PTSD: non-PTSD: decrease in dlPFC, ACC	worsen PTSD: non-PTSD: decrease in insula, anterior temporal lobe
Chao et al. (2012)	Combat; M; 21	Combat; M; 20	VBM				Lower density in left precentral, occipital, and right angular cortices
Chao et al. (2013)	Combat; mixed; current PTSD; 39, remitted PTSD; 34	Combat; mixed; 43, nonexposed; mixed; 75;	Volume	Smaller HC in current PTSD	No difference	Smaller caudal ACC in current PTSD	Smaller insula, corpus callosum, total brain volume in current PTSD
Chen et al. (2009)	Disaster; mixed; 12	Trauma exposed; mixed; 12	VBM			Lower density in left medial frontal gyrus	Lower density in bilateral insula
Chen et al. (2012)	Disaster; M; 10	Trauma exposed; M; 10	VBM			Lower density in left ACC in PTSD *vs* trauma-free control	
		Trauma-free; M; 20;					
Corbo et al. (2005)	Mixed trauma; mixed; 14	Trauma-free; mixed; 14	VBM			Lower density in right cingulate gyrus	Lower density in left insula
Depue et al. (2014)	Combat with PTSD+TBI; mixed; 16	Combat; mixed; 21	VBM		Decreased density and volume		
			Volume				

Eckart et al. (2011)	Mixed civilian traumas; M; 20	Trauma exposed; M; 19	Volume			Smaller volume in left rostral middle frontal in PTSD and isthmus cingulate cortices in PTSD and trauma-exposed control	Smaller right volume in right inferior parietal cortex in PTSD and trauma-exposed control
		Trauma-free; M; 13	VBM			Lower density in bilateral ACC, left isthmus cingulate cortices in PTSD and trauma-exposed control	Lower density in right inferior parietal cortex in PTSD and trauma-exposed control
Emdad et al. (2006)	Mixed; M; 23	Trauma-free; M; 17	VBM	Smaller bilateral HC			
			Volume	Lower density in right HC			
Fani et al. (2012)	Interpersonal trauma; F; 25	Trauma exposed; F; 26	DTI			Lower FA in bilateral posterior cingulum	Lower FA in left superior longitudinal fasciculus, high FA in right lateral occipital cortex, uncorrected
Felmingham et al. (2009)	Civilian trauma; mixed; 21	Trauma exposed; mixed; 17	VBM	Lower density in bilateral HC		Lower density in bilateral rostral ACC, bilateral superior medial frontal cortex, left orbitofrontal gyrus	Lower density in left middle temporal gyrus and left supramarginal gyrus
Fennema-Notestine et al. (2002)	Intimate partner violence; F; 11	Trauma exposed; F; 11	Volume	No difference	No difference		
		Trauma-free; F; 17					
Geuze et al. (2008)	Veteran; M; 25	Trauma exposed; M; 25	Cortical thickness			Thinner in bilateral superior, middle frontal, and left inferior frontal gyri	Thinner in left superior temporal gyrus
Gilbertson et al. (2002)	Combat; monozygotic twins; M; 17	Trauma exposed; monozygotic twins; M; 23	Volume	Smaller HC in PTSD twin pairs than control twin pairs	No difference		
Golier et al. (2005)	Holocaust; mixed; 14	Trauma-free; mixed; 20	Volume	No difference			Larger left lateral temporal lobe and bilateral superior temporal gyrus in two holocaust groups
		Trauma-exposed; mixed; 13					

(continued)

Table 12.1 (continued)

Literature (author; year)	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus (HC)	Amygdala	Prefrontal and cingulate cortices	Other brain regions
Gurvits et al. (1996)	Combat; M; 7	Trauma exposed; M; 7	Volume	Smaller in bilateral HC in PTSD	No difference		CSF volume increased in PTSD and trauma-exposed groups
		Trauma-free; M; 8					
Hakamata et al. (2007)	Cancer; F; 14	Cancer; F; 100	VBM			Smaller gray matter density in right orbitofrontal cortex	
		Healthy; F; 70					
Hara et al. (2008)	Cancer; F; 15	Cancer; F; 15	Volume	No difference	No difference		
		Healthy; F; 15					
Hedges et al. (2007)	Combat; M; 6	Trauma exposed; M; 5	Volume	No difference			Smaller right superior, middle, inferior temporal volume, fusiform and parahippocampus volume
Herringa et al. (2012)	Combat; mixed; 13;	Combat; mixed; 15;	VBM			Lower density in subgenual ACC and right middle frontal gyrus	Lower density in caudate, hypothalamus, left insula, middle temporal gyrus
Irle et al. (2009)	Childhood abuse; F; 10	Trauma-free; F; 25	Volume	Smaller bilateral HC	Smaller bilateral amygdala		
Jatzko et al. (2006)	Disaster; mixed; 15	Trauma-free; mixed; 15	Volume	No difference			No difference in total brain volume, gray and white matter volume, and density
			VBM				
Kasai et al. (2008)	Combat; monozygotic twins; M; 18	Trauma exposed; monozygotic twins; M; 23	VBM	Lower density in right HC in PTSD		Lower density in pregenual ACC in PTSD	Lower density in bilateral insula in PTSD
Kim et al. (2006)	Disaster; mixed; 21	Trauma-free; mixed; 21	DTI			Lower FA in the left rostral, subgenual, dorsal ACC	
Kitayama et al. (2006)	Abuse; mixed; 8	Trauma-free; mixed; 13	Volume			Smaller volume in right ACC	
Kitayama et al. (2007)	Abuse; F; 9	Trauma-free; F; 9	Volume				Smaller posterior mid-body/total CC area ratio
Kuo et al. (2012)	Combat; mixed; 42	Trauma exposed; mixed; 45	Volume		Larger volume		
Bossini et al. (2008)	Mixed trauma; mixed; 34	Trauma-free; mixed; 34	Volume	Smaller bilateral HC			Smaller brain gray matter volume, larger brain white matter volume, no difference in brain volume and CSF volume
Levitt et al. (2006)	Combat; monozygotic twins; M; 20	Trauma exposed; monozygotic twins; M; 23	Volume				No differences in vermis volume

Levy-Gigi et al. (2013)	Mixed trauma; mixed; 39	Trauma exposed; mixed; 31	Volume	Smaller bilateral HC; increased after CBT	No difference	Smaller volume in medial orbitofrontal cortex	No difference in total brain volume
Li et al. (2006)	Fire disaster; mixed; 12	Trauma exposed; mixed; 12	VBM	Lower density in left HC			
Lindauer et al. (2005)	Mixed trauma; mixed; 18	Trauma exposed; mixed; 14	Volume	Smaller HC, no change after treatment	No difference		Larger total and left parahippocampal gyrus
Lindauer et al. (2004)	Traumatized police officers; mixed; 14	Trauma exposed; mixed; 14	Volume	Smaller HC	No difference		No difference in parahippocampal gyrus, gray matter, white matter and CSF
Lindauer et al. (2006)	Traumatized police officers; mixed; 12	Trauma exposed; mixed; 12	Volume	Smaller bilateral HC			
Lindemer et al. (2013)	Combat; mixed; 65	Combat; mixed; 39	Cortical thickness				Vertex based: thinner in bilateral postcentral and middle temporal; left fusiform; right precuneus, and inferior temporal
							ROI based: thinner in right postcentral and left insula
Liu et al. (2012)	Disaster; M; 10	Trauma exposed; M; 10	Cortical thickness			Thinner in right inferior frontal cortex	Thinner in left precuneus and right parahippocampus
Lyoo et al. (2011)	Disaster; mixed; 30	Trauma-free; mixed; 36	Cortical thickness			Thicker in right dlPFC, left superior and inferior frontal cortices 1 year later	
						No difference 5 years later	
May et al. (2004)	Combat; monozygotic twins; M; 20	Trauma exposed; monozygotic twins; M; 23	Volume				Greater cavum septum pellucidum in PTSD twins
Morey et al. (2012)	Military; mixed; 99	Trauma exposed; mixed; 101	Volume	Smaller left HC	Smaller bilateral amygdala		

(continued)

Table 12.1 (continued)

Literature (author; year)	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus (HC)	Amygdala	Prefrontal and cingulate cortices	Other brain regions
Nardo et al. (2010)	Occupational trauma; mixed; 21,	Trauma exposed; mixed; 22	VBM		Lower density in no treatment response PTSD (5 NR) than response PTSD (10 R)	Lower density in left PCC in PTSD than non-PTSD	Lower density in left precuneus, lingual, and posterior parahippocampal gyrus in PTSD than non-PTSD
						Lower density in bilateral PCC and left middle and medial frontal gyri in NR than R	Lower density in left precentral, right anterior insula, and anterior parahippocampal gyrus in NR than R
Nardo et al. (2013)	Accident/assault mixed; 15	Trauma exposed; mixed; 17	VBM			Low density in right PFC, including superior, middle, and inferior frontal and rACC	
Niedtfeld et al. (2013)	Abuse; F; 21	Trauma-free; F; 31	VBM	No difference	No difference	Greater density in dlPFC in borderline with PTSD	Greater density in left superior temporal gyrus in borderline with PTSD
Pavic et al. (2007)	Combat; mixed; 15	Trauma-free; mixed; 15	Volume	Smaller right HC in PTSD than control, smaller right HC than left HC in PTSD			
Pitman et al. (2006)	Combat; monozygotic twins; M; 20	Trauma exposed; monozygotic twins; M; 24		Smaller HC in PTSD twin pairs			
Rauch et al. (2003)	Combat; F; 9	Trauma exposed; F; 9	Volume			Smaller pregenual ACC, subcallosal cortex	
Rocha-Rego et al. (2012)	Assault; mixed; 16	Trauma exposed; mixed; 16	VBM	No difference	No difference	Low density in pregenual ACC, premotor cortex	
Rogers et al. (2009)	Attack; mixed; 9	Trauma exposed; mixed; 16	Volume	No difference	Smaller bilateral amygdala		
			VBM				
Saar-Ashkenazy et al. (2014)	Civilian trauma; mixed; 20	Trauma-free; mixed; 17	Volume				Smaller corpus callosum, no difference in white matter and gray matter volume
Schuff et al. (2011)	Veterans; M; 17	Trauma exposed; M; 15	ASL			Lower FA in PFC, ACC and PCC	Higher rCBF in right parietal, superior temporal gyri
			DTI				

Starcevic et al. (2014)	Unclear; M; 49	Trauma exposed; M; 30	Volume	No difference	Smaller volume	No difference in PFC	
Stein et al. (1997)	Childhood abuse; F; 21	Trauma-free; F; 21	Volume	Smaller left HC			
Sui et al. (2010)	Sexual assault; F; 11	Trauma-free; F; 12	VBM	Lower density in right HC	Lower density in right amygdala	Higher density in right PCC	Higher density in left insula, cerebellum, including pyramis, uvula, declive, and nodule
Sui et al. (2010)	Sexual assault; F; 11	Trauma exposed; F; 8	VBM			Lower density in bilateral medial frontal and left middle frontal cortices, higher density in right PCC in PTSD	Lower density in left middle temporal and fusiform cortices in PTSD;
		Trauma-free; F; 12					Higher density in right postcentral, bilateral precentral, and inferior parietal cortices in PTSD
Tan et al. (2013)	Mine disaster; M; 12	Symptom improved; M; 7	VBM				Lower gray matter density in right lingual gyrus in chronic PTSD *vs* symptom-improved group
		Trauma exposed; M; 14					Right superior frontal and left superior parietal lobe in PTSD *vs* trauma control
Tavanti et al. (2012)	Mixed trauma; mixed; 25	Trauma-free; mixed; 25	Volume			Smaller bilateral frontal lobes	Smaller bilateral occipital lobes
			VBM			Lower density in left frontal lobe	Lower density in right inferior temporal gyrus
Villarreal et al. (2002)	Mixed trauma; mixed; 12	Trauma-free; mixed; 10	Volume	Smaller bilateral HC			Volume reduction in white matter
Villarreal et al. (2004)	Mixed trauma; mixed; 12	Trauma-free; mixed; 10	Volume				Smaller corpus callosum total volume, and genu, mid-body, and isthmus subregional volume
Vythilingam et al. (2005)	Combat; mixed; 14	Trauma exposed; mixed; 23	Volume	Smaller bilateral head of HC in PTSD than civilians, smaller right HC in trauma-exposed veterans than civilians			
		Trauma-free; mixed; 22					
		Trauma-free civilians; mixed; 29					

(continued)

Table 12.1 (continued)

Literature (author; year)	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus (HC)	Amygdala	Prefrontal and cingulate cortices	Other brain regions
Wang et al. (2010)	Combat; M; 17	Trauma exposed; M; 19	Volume	Smaller HC and CA3/dentate gyrus subfield volumes			
Weniger et al. (2008)	Childhood abuse; F; 10	Trauma-free; F; 25	Volume	Smaller HC in PTSD	Smaller amygdala in PTSD		
		Trauma exposed; F; 13					
Wignall et al. (2004)	Accident; mixed; 15	Trauma-free; mixed; 11	Volume	Smaller right HC	No difference		Smaller brain volume
Woodward et al. (2009)	Combat; mixed; 50	Trauma exposed; mixed; 47	Volume			Smaller volume in lateral OFC and pars orbitalis	Smaller volume in parahippocampus, superior temporal region
			Cortical thickness			Thinner thickness in rostral and caudal ACC	Thinner thickness in superior temporal cortex
Woodward et al. (2006)	Combat; mixed; 51	Trauma exposed; mixed; 48	Volume			Smaller ACC volume	
Woodward et al. (2007)	Combat; mixed; 51	Trauma exposed; mixed; 48	Volume				Smaller cranial and CSF volume
Yamasue et al. (2003)	Attack; mixed; 9	Trauma exposed; mixed; 16	VBM			Lower density in the left ACC	
Yehuda et al. (2007)	Combat; M; 17	Trauma exposed; M; 16	Volume	No difference			
Zhang et al. (2011)	Disaster; M; 17	Trauma-free; M; 28;	DTI			Increased FA in left superior frontal gyrus in PTSD *vs* trauma-free controls	
		Generalized anxiety disorder (GAD); M; 20				Decreased FA in ACC in PTSD *vs* GAD	
Zhang et al. (2011)	Disaster; M; 10	Trauma exposed; M; 10	Volume	Smaller volume and lower density in left HC			Smaller volume and lower density in bilateral calcarine and left parahippocampus
			VBM				
Zandieh et al. (2016)	Torture; mixed; 9	Violent-free; mixed; 10	Volume	Smaller volume in left HC			
Fani et al. (2016)	Mixed trauma; F: 13	Trauma exposed; F; 41	DTI			Decreased FA in ACC in PTSD	
Luo et al. (2016)	Bereavement; mixed; 57	Trauma- exposed; mixed; 11	Volume	Left HC atrophy in PTSD and trauma-exposed group	No difference		
		trauma-free; mixed; 39					

Li et al. (2016)	Earthquake; mixed; 67	Trauma exposed; mixed; 78	Cortical thickness Volume				Greater thickness in the right superior temporal gyrus, inferior parietal lobule, and left precuneus; reduced volume in the posterior corpus callosum
Helpman et al. (2016)	Mixed trauma; mixed; 25 (11 remitters; 14 non-remitters)	Trauma exposed; mixed; 25	Cortical thickness Volume			Left rACC thinning and reduced volume from pre- to posttreatment in remitters	
Mueller et al. (2015)	Combat; M; 40	Trauma exposed; M; 45	Cortical thickness Volume			Cortical thinning in rACC	Cortical thinning in insula
Sun et al. (2015)	Traffic accidents; mixed; 15	Trauma exposed; mixed; 14	DTI				Decreased FA in commissural tracts connecting bilateral superior/middle frontal gyrus
Bierer et al. (2015)	Combat; M; 12	Trauma exposed; M; 8	DTI			Lower MD in the right cingulum bundle	
Chalavi et al. (2015)	Interpersonal trauma; F; 33	Trauma exposed; F; 28	Volume	Smaller bilateral HC, especially bilateral subfield CA2-3, right CA4-DG, and left presubiculum			

Table 12.2 Summary of structural MRI studies on pediatric PTSD

Literature	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus	Amygdala	Prefrontal and cingulate cortices	Other brain regions
Carrion et al. (2001)	Mixed trauma; mixed; 24	Trauma-free; mixed; 24	Volume	No difference	No differences		Smaller total brain and cerebral gray matter volumes
Carrion et al. (2009)	Interpersonal trauma; mixed; 24;	Trauma-free; mixed; 24	Volume			Larger volume in bilateral superior and inferior PFC	Smaller volume in the pons
			VBM			Greater density in bilateral ventral PFC	
De Bellis et al. (1999)	Maltreatment; mixed; 44	Trauma-free; mixed; 61	Volume	No difference	No difference	No difference	Smaller volume in cerebral, intracranial, and corpus callosum, larger volume in bilateral lateral ventricles and CSF
De Bellis et al. (2001)	Maltreatment; mixed; 9	Trauma-free; mixed; 9	Volume	No difference	No difference		No difference in temporal lobe
De Bellis et al. (2002)	Maltreatment; mixed; 28;	Trauma-free; mixed; 66;	Volume	No difference	No difference	Smaller total and white matter volume in PFC	Smaller cerebral and intracranial volume; right temporal, and corpus callosum volume; larger frontal lobe CSF and lateral ventricular volume
De Bellis et al. (2002)	Maltreatment; mixed; 43;	Trauma-free; mixed; 61	Volume				Larger cerebral volume and unadjusted gray matter volume in superior temporal gyrus (STG), smaller STG white matter volume

(continued)

Table 12.2 (continued)

Literature	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus	Amygdala	Prefrontal and cingulate cortices	Other brain regions
De Bellis et al. (2003)	Maltreatment; mixed; 61;	Trauma-free; mixed; 122	Volume				Larger prefrontal CSF volumes and smaller midsagittal corpus callosum in both boys and girls with PTSD; smaller cerebral, rostrum, and isthmus corpus callosum volumes; and greater lateral ventricular volume in boys with PTSD
De Bellis et al. (2006)	Maltreatment; mixed; 58	Trauma exposed with GAD; mixed; 13	Volume				Smaller brain stem volume and bilateral cerebellum volume in PTSD, larger cerebellar volume in PTSD boys
		Trauma-free; mixed; 98					
De Bellis et al. (2010)	Maltreatment; mixed; 49	Maltreatment; mixed; 49	Volume	No difference			
		Trauma-free; mixed; 118					
Jackowski et al. (2008)	Maltreatment; mixed; 17	Trauma-free; mixed; 15	DTI				Lower FA in anterior and posterior mid-body corpus callosum regions
Richert et al. (2006)	Mixed trauma; mixed; 23	Trauma-free; mixed; 24	Volume			Larger gray matter volume in the middle and inferior ventral PFC	
Tupler et al. (2006)	Maltreatment; mixed; 61	Trauma-free; mixed; 122	Volume	Larger bilateral HC			
Ahmed et al. (2012)	Mixed trauma; mixed; 21	Trauma exposed; mixed; 32	VBM			Low density in right ACC	Low density in left insula, right precuneus
			Thickness				Thinner thickness in insula

(continued)

Table 12.2 (continued)

Literature	PTSD (trauma; gender; N)	Control (trauma; gender; N)	Measure	Brain structures			
				Hippocampus	Amygdala	Prefrontal and cingulate cortices	Other brain regions
De Bellis et al. (2015)	Maltreatment; mixed; 38	Trauma exposed; mixed; 35	Volume				smaller cerebral and cerebellar total volume and gray matter volumes, smaller superior posterior brain regional gray matter volumes, larger white matter and CSF volumes in bilateral superior frontal-parietal region
		Trauma-free; mixed; 59	DTI				lower AF in occipital region to corpus callosum
Morey et al. (2016)	Maltreatment; mixed; 32	Trauma exposed; mixed; 31	Volume	Large right HC in non-PTSD group vs PTSD and non-trauma control groups	Large left amygdala in non-PTSD group vs PTSD and non-trauma control groups	Smaller right vmPFC in PTSD group	
		Trauma-free; mixed; 57					
Keding et al. (2015)	Mixed trauma; mixed; 27	Trauma-free; mixed; 27	VBM	No difference		Smaller gray matter volume in right anterior vmPFC	Reduced gray matter volume in bilateral fusiform gyrus and left occipital cortex

treatment. The majority of volumetric studies reported smaller left, right, or bilateral hippocampal volumes in PTSD patients [7–10, 15, 17, 36, 47, 50, 57, 76, 82–84, 88, 109, 111, 120, 127, 139, 140, 144, 146, 149, 157]. In contrast, a smaller but meaningful number of studies failed to find difference in hippocampal volume in PTSD [6, 40, 48, 52, 53, 59, 117, 126, 156]. The meta-analyses published to date in general confirm smaller hippocampal volume in PTSD patients [61, 78, 107, 125], and the most recent largest meta-analysis examining neuroimaging and clinical data from 1868 subjects across 16 cohorts confirmed the presence of smaller hippocampus in PTSD [87]. Studies of the size of the subdivisions of hippocampus suggest that the dentate gyrus and adjacent anterior hippocampus specifically might be smaller in PTSD patients [140, 143]. Furthermore, some studies had found that hippocampal volume is smaller in veterans with current PTSD as compared to veterans with remitted PTSD, potentially suggesting that the hippocampal volume may be associated with the presence of active PTSD symptoms [17]. In concert, VBM-based studies also reported decreased gray matter density in hippocampal regions in PTSD patients [36, 39, 62, 77, 129, 130].

These structural findings were met with substantial interest because the convergence of functional and structural MRI findings suggests that the hippocampus may play a role in PTSD development. With respect to the functional significance of the volumetric findings, several studies reported relationships between hippocampal volume and the severity of PTSD symptoms, especially reexperiencing or dissociative symptoms [8, 39, 47, 82, 83, 127, 134, 139, 140, 144]. Furthermore, it has been also reported that in PTSD veterans, a smaller right hippocampal volume was positively correlated with deficits in short-term verbal memory, suggesting that alterations of hippocampal structure may be related to the memory functions of PTSD patients [8]. Interestingly, more recent data suggested that these findings might be at least to some degree reversible, as some interventions may be able to alter the hippocampal volume of PTSD patients.

For example, a SSRI treatment that increases hippocampal volume of PTSD patients also reduces PTSD symptoms and significantly improved verbal memory [137]. Similarly, cognitive behavioral therapy (CBT), which had been demonstrated as effective treatment for PTSD, also increased hippocampal and medial orbital frontal volume associated with the clinical symptom improvement in PTSD patient [76]. However, these relationships between reduction of hippocampal volume and memory function or PTSD symptoms have not been detected in other studies [40, 117, 143, 150]. Thus, existing findings linking the abnormalities of hippocampal structure to symptom levels in PTSD patients are yet to be firmly established, and additional work clarifying these relationships is needed. Further examination of these relationships carries promise to further advance current understanding of PTSD pathophysiology.

The structural characteristics of hippocampus have been studied in pediatric PTSD as well, and the findings have not been as consistent as those in adult subjects. Several studies reported no significant differences in hippocampal volumes in children with PTSD or in young adults with maltreatment history, as compared to maltreated children without PTSD or healthy children without maltreatment history [13, 23, 25, 27]. For example, Morey and colleagues reported smaller hippocampus volume in PTSD children [98]; however, a different study reported that pediatric PTSD patients with a maltreatment history had larger hippocampus than control subjects who did not have a maltreatment history [135]. In this study, this was contributed by hippocampal white matter, but not gray matter volume. Furthermore, hippocampal volume was positively related to severity of PTSD symptoms and the age of trauma exposure in this study [135]. In a recent study, although no group difference in hippocampus gray matter volume between PTSD youth and health youth was found, there was group-by-age interaction in the right anterior hippocampus, such that age was negatively associated with hippocampal gray matter volume in PTSD youth, but positively predicted hippocampal gray matter volume in healthy youth [63]. This suggested that dynamic developmental changes in hippocampal volume might lead to differential outcomes in PTSD and healthy youth. Studies of adult patients with PTSD secondary to childhood abuse also reported smaller hippocampi as compared to control subjects with no childhood abuse histories [9].

In summary, the preponderance of structural MRI studies finds smaller hippocampus in adult PTSD patients as compared to non-PTSD subjects. Initial evidence suggests that the reduction of hippocampal volume in PTSD patients might be associated with memory deficits and the severity of PTSD symptoms. However, pediatric PTSD patients may show a normal or even larger-sized hippocampus in childhood and smaller hippocampus in adulthood. Further studies are needed to continue examining the link between the hippocampus and brain development and hippocampal function in PTSD.

Amygdala

The amygdala has received much attention in PTSD research because it plays important roles in fear learning and the generation of emotional responses. Functional neuroimaging studies have demonstrated that the amygdala of PTSD patients is hyperresponsive during exposure to trauma-related cues as compared to subjects without PTSD [43, 145]. The structural properties of amygdala have also been examined in structural MRI studies, but the results of these studies have not been consistent.

A substantial number of cross-sectional studies found no differences in amygdala volume between PTSD patients and control subjects [6, 9, 40, 47, 50, 52, 76, 83, 88, 116, 146]. The amygdala volume of pediatric PTSD patients was also reported as not different from amygdala volumes in age-matched controls [13, 23, 28, 29]. Similarly, longitudinal study in adult PTSD patients and trauma-exposed controls reported that amygdala size did not differ at 1 week and 6 months after trauma [6, 23]. In concert, longitudinal study in pediatric PTSD patients reported a similar negative finding [23]. Finally, while earlier meta-analysis, including 11 studies from 1996 to 2004, reported smaller left amygdala in PTSD patients [61], a more recent meta-analysis of nine studies suggested that amygdala volumes did not differ between PTSD subjects, trauma-exposed non-PTSD subjects, and trauma-free control groups [154]. The differences in imaging data processing and statistical analysis used, like manual tracing in early MRI studies vs automated assessment by specialized software, may explain some of the differences found. One pediatric PTSD meta-analysis also reported no difference in amygdala in PTSD children compared to non-PTSD controls from four pediatric PTSD studies, totaling 85 PTSD and 123 controls [95].

On the other hand, various structural abnormalities of amygdala in PTSD patients had been reported in some studies. Several studies reported reduced amygdala volume or gray matter density in PTSD subjects as compared to trauma-exposed controls [31, 57, 97, 117, 126], and Rogers and colleague found that specifically left amygdala volume was negatively correlated with the severity of PTSD symptoms [117]. In agreement, cancer-related intrusive recollections or reexperiencing symptoms had been associated with smaller left amygdala volume [91]. Amygdala size reduction and cognition impairment were found in female PTSD patients with a history of childhood abuse displayed [144], and lower amygdala gray matter density was lower in female rape survivors [129], suggesting that these findings might be more likely to show in women, especially following rape or child-

hood abuse. Smaller amygdalae volume was also negatively associated with PTSD symptoms in maltreated pediatric PTSD patients [98]. In contrast, another study found larger amygdala in PTSD veterans than in non-PTSD veterans [73]. In addition, asymmetry between the right and left amygdala of PTSD patients has also been reported [6]; treatment study involving eye movement desensitization and reprocessing suggested that the size of the right amygdala may predict responsiveness to this treatment [102].

In summary, the findings to date have not been consistent with respect to structural abnormalities in amygdala of PTSD patients. The volume of amygdala might be no different, or potentially smaller, in some PTSD patients, and similarly the gray matter intensity of amygdala might also be lower in some but not all PTSD patients. Because of potential amygdala role in some pathological mechanism of PTSD development, further examination of the amygdala complex structural feature in PTSD patients is necessary.

Cingulate Cortex

Among other key regions implicated in PTSD is anterior cingulate cortex (ACC). The cingulate gyrus is divided into the anterior cingulate cortex and the posterior cingulate cortex (PCC). ACC is further divided into rostral and caudal subdivisions (rACC and cACC). The PCC also includes the isthmus of the cingulate gyrus.

ACC has intensive connections with adjacent medial PFC and other regions including amygdala, insular cortex, hippocampus, and PCC. ACC has been implicated both in important emotional and cognitive functions [44]. In PTSD patients, greater ACC activations as compared to controls without PTSD were reported during fear conditioning and recall of extinction learning. The hyperactivity of ACC may relate to increased fear expression in PTSD patients [49, 112]. Accumulating structural studies have also examined the ACC structural properties in PTSD patients. Volumetric studies reported smaller volumes of ACC, including both rACC and cACC in PTSD patients as compared to controls without PTSD [17, 39, 67, 114, 152]. VBM studies also reported reduced gray matter density in ACC regions [21, 22, 39, 55, 62, 72, 101, 116, 155]. Studies of cortical thickness reported thinner ACC in PTSD patients as well [99, 113]. The meta-analyses confirm smaller ACC and decrease in ACC volume and gray matter density in the PTSD groups comparing PTSD with trauma-free controls [61, 94]. Therefore, reduction of gray matter structure in ACC is consistently reported in adult PTSD patients.

Limited studies explored the factors that may affect ACC gray matter structure in PTSD patients. In a twin study of PTSD veterans, PTSD patients have decreased gray matter density in rACC in contrast to non-PTSD veterans [62]. In contrast, no differences were found in their homozygous twin, suggesting that the low gray matter density in rACC is acquired rather than a predisposing risk factor. Another civilian PTSD study did not find rACC structural difference, either in cortical thickness or in volume, between PTSD and healthy control, but thinning in the left rACC, and volume reduction was found following treatment in remitted PTSD patients, suggesting rACC change may respond to psychotherapy [54]. Further studies are clearly needed to examine the mechanisms of ACC gray matter reduction in PTSD. Finally, DTI studies on white matter integrity of ACC in PTSD patients did not report consistent findings. Both increase [1] and decrease [38, 65, 121, 159] in FA, as well as no difference [34], have been reported in the ACC of PTSD individuals as compared to controls. The lower mean diffusivity was reported in right cingulum bundle in Gulf War veterans with PTSD, which is negatively associated with CAPS score [4]. The differences in the DTI measures might suggest that white matter connectivity in ACC regions may be altered in PTSD patients, but confirmation of these differences is needed.

PCC has also been examined in PTSD, and smaller volumes of bilateral isthmus cingulate cortices have been found in traumatized refugees with or without PTSD, as compared to trauma-free controls [35]. Localized subregions within the left isthmus cingulate cortices of these refugees had also lower gray matter density. The volumes of isthmus cingulate cortex of each side were negatively correlated with the intensity of traumatic experiences, suggesting that trauma exposure itself may be a factor [35]. Similarly, lower gray matter density in the left PCC has been reported for public transportation workers with PTSD when compared to trauma-exposed workers without PTSD [102]. In addition, the PTSD patients in this study who did not respond to eye movement desensitization and reprocessing therapy had lower gray matter density in the PCC than the PTSD patients who were helped by this therapy, suggesting that PCC structural properties may also predict the treatment outcome in PTSD patients. In contrast, a different study of rape victims with or without PTSD and healthy controls found that gray matter density significantly increased in the right PCC of PTSD victims as compared to healthy controls [129]. The DTI studies found that FA in PCC is significantly lower in PTSD veterans as compared with veterans without PTSD [37]. In summary, the limited studies of PCC mainly reported reduction of gray matter density in PCC regions.

Prefrontal Cortex (PFC)

The PFC is a large cortical area that consists of frontal lobe regions anterior to the premotor areas. It is divided into the medial/lateral (m/l) subdivisions, each in turn subdivided

into the ventral/dorsal (v/d) subdivisions, and a rostral (r) division referring to regions around Brodmann area 10. Functional neuroimaging studies have reported alterations in activation in the PFC, especially mPFC, in PTSD patients as compared to non-PTSD controls. Abnormalities in various subregions of PFC could represent different functional aspects of PTSD clinical picture, for example, hypoactivation in dmPFC may represent to failure of emotion reappraisal, altered activity in rmPFC to a heightened salience of emotional- and error-related stimuli, and diminished activity in vmPFC to a failure to maintain extinction of conditioned fear [81]. Functions of the PFC depend on extensive structural connections between PFC and other brain regions. For example, reciprocal connections between vmPFC and amygdala are associated with mutual activation changes during emotional challenges, which has led to a hypothesis of deficient top-down inhibition in PTSD pathogenesis [80, 145].

In concert with functional neuroimaging studies, volumetric studies have reported reduced volume of subcallosal regions of vmPFC, left rmPFC, and bilateral lateral orbitofrontal cortex in adult PTSD patients as compared to controls without PTSD [35, 76, 114]. Thinner cortex in bilateral superior, middle frontal, and left inferior frontal cortex has also reported in adult PTSD patients as compared to controls without PTSD [5, 46, 86, 150, 153]. VBM structural studies reported that the gray matter density is lower in PTSD patients in regions in lPFC and mPFC including the pregenual ACC [39, 51, 101, 116]. The gray matter volume reduction in mPFC in PTSD subjects has been confirmed by a meta-analysis of 17 PTSD studies when compared to traumatized and non-traumatized controls [78]. Finally, the DTI studies of white matter connectivity in PTSD patients report increased FA in the left dlPFC of PTSD patients [159]. In summary, the differences in volume, gray matter density, and cortical thickness suggest a reduction of PFC gray matter structure in adult PTSD patients, and limited DTI examinations suggest a possible alteration of white matter connectivity in PFC as well.

Several longitudinal studies have also investigated dynamic changes in PFC structure in the PTSD patients. We have detected changes over time in PFC after traumatic experiences. Left superior prefrontal cortex volume was reduced from initial days to 3 months after trauma in motor vehicle accident survivors who developed PTSD by 3 months after trauma, which differed from no changes observed in trauma-exposed control over the same time period [142]. This suggests possibly progressive reduction of PFC gray matter during PTSD development over initial post-trauma period. Additional longitudinal study also found progressive changes in cortical thickness years after trauma. In this study, an initially thicker right dlPFC, left superior FC, and inferior FC in traumatized survivors with PTSD at 1 year after trauma disappeared when subjects were reexamined after 5 years. Therefore, normalization of thickened dlPFC in chronic PTSD patients may be related to reduction of PTSD symptoms over time [89]. In a different longitudinal study that compared PTSD patients and healthy controls at baseline and 24 months later, the PTSD group did not show structural changes between the two time points [12]. However, PTSD patients with the most severe symptoms showed changes over time in frontal and temporal cortices and the brain stem that was positively correlated with decreased verbal memory and delayed facial recognition [12]. One study of non-PTSD survivors of earthquake reported an association between posttraumatic stress symptoms and gray matter density changes in OFC from pre-trauma to 2–4 months after exposure [122]. In summary, limited longitudinal studies suggest post-trauma dynamic changes in PFC that may be associated with PTSD symptom development and maintenance. However, these findings remain to be replicated.

Finally, the pediatric PTSD studies also showed greater gray matter volume in vPFC in maltreated PTSD children as compared to age- and gender-matched healthy children without a history of maltreatment [14, 115], but opposite results were also reported of smaller PFC volume in maltreatment adolescent victims with PTSD [28, 29, 63, 98]. The PFC structure of pediatric PTSD patients remains less well studied so far.

In summary, structural changes in PFC of PTSD patients have been increasingly reported in recent years. Existing studies suggest abnormalities in the structure of PFC in adult PTSD patients as compared to non-PTSD controls. Longitudinal investigations of progressive alterations in structures of PFC and ACC during the post-trauma period are still in progress, and so far the findings had not been entirely consistent. Furthermore, children with PTSD may experience different types of structural alterations in the PFC than adults.

Other Brain Regions

Existing structural MRI studies also reported structural abnormalities in several brain regions besides hippocampus, amygdala, cingulate cortex, and PFC; however, these findings are sparse and have not been consistently replicated.

Global Volumes

Total brain volume, gray matter volume, cortical gray matter, white matter, ventricles, cerebral spinal fluid (CSF), as well as cavum septum pellucidum and the supratentorial cranial vault have been assessed in different PTSD studies. Many studies did not report differences in brain volumes, gray matter volume, or white matter volume in PTSD subjects and controls [59, 76, 83, 118], but some did find smaller brain volumes or gray matter volumes in adult or pediatric PTSD

patients [7, 13, 24, 27, 133, 139, 146, 153]. The maltreatment youth victims with PTSD also showed negative correlation between PTSD symptoms and brain volume in one study [24]. The supratentorial cranial vault was significantly smaller in interpersonal violence victims with PTSD [40], but a larger cavum septum pellucidum volume is more frequently seen in PTSD patients and their homozygotic co-twins than non-PTSD controls [92, 111]. Volume of the CSF was smaller in PTSD veterans in one study [151], but CSF in the lateral ventricle was not different in PTSD and control adults in other studies [40, 83]. Larger ventricular volumes were reported in children with PTSD [26, 27], but a different study reported smaller lateral ventricles in adult PTSD patients who were suffering from headache relative to PTSD patients who did not have headache [41]. In summary, multiple factors including developmental processes in interaction with type and timing of trauma exposure and PTSD development could contribute to diverging finding appearing in the literature, and large-scale studies are still needed; appropriate control for global volumes is highly advisable for studies examining specific structural properties in PTSD.

Temporal Lobe

Volume, gray matter density, and cortical thickness of the temporal lobe have been examined in PTSD patients in several studies. The total volume of the temporal lobe was not different in PTSD patients as compared to healthy controls [40, 140]. There was also no difference in the volume of temporal lobe between the adult PTSD who has a childhood abuse history and healthy controls [9]. However, a different longitudinal study reported that PTSD veterans with worsened symptoms over 2–3 years had a decrease in the volume of temporal lobe that was significantly greater than the changes in the veterans without PTSD over a similar time period [12], but no changes in the other pediatric PTSD longitudinal study [23]. In contrast, larger temporal lobe was found in holocaust survivors with and without PTSD as compared to trauma-free controls [48].

Individual temporal gyri have also been examined in some studies. The superior, middle, inferior, and transverse temporal gyri were smaller in combat-related PTSD patients [153]. However, the bilateral superior temporal gyri (STG) were reported to be larger in holocaust survivors with and without PTSD as compared to trauma-free controls [48]. However, the STG and transverse temporal gyri were smaller in combat-related PTSD patients [153]. Gray matter density was also greater in the STG of borderline personality disorder (BPD) patients comorbid with PTSD than the BPD patients without PTSD [104]. The cortical thickness studies indicated thinner cortical thickness in STG of PTSD groups [5, 46], and white matter volume in the right STG was also significantly reduced in PTSD patients [53]. Interestingly, it has been suggested that right STG play an important role in auditory sensory gating differences in PTSD, based on the fact that M50 auditory sensory gating in the right hemisphere was impaired in the PTSD group, and the severity of this impairment was positively associated with a thickness decrease in the right STG [56]. In pediatric PTSD, however, anterior and posterior STG gray volumes were reported as larger, but white matter as smaller, compared to controls [28, 29]. Lower gray matter density has been reported in the MTG of PTSD veterans [39, 55] and sexual assault victims with PTSD [129, 130]. Self-reported anxiety and ITG volume were negatively correlated in the PTSD group, but were positively correlated in the major depression group, suggesting that PTSD and major depression might exhibit different types of structural alterations in the same brain region [72].

Parahippocampal Gyri (PHG)

A few studies examined PHG and adjacent regions such as the fusiform gyrus. PHG in both hemispheres were found to be of normal size in traumatized police officers with PTSD [83]. However, the smaller PHG have been reported in PTSD patients who experienced civilian trauma [40, 153]. Lower gray matter density in PHG of PTSD patients has been reported [102, 158]. The thinner cortical thickness was also reported in PHG of PTSD patients [86, 153]. Studies also reported lower white matter volume of PHG and fusiform gyrus in PTSD patients [53].

Frontal Lobe

Supplementing results from the PFC, few other studies reported bilaterally reduced gray matter densities in the precentral cortex of PTSD patients relative to trauma-exposed and trauma-free healthy controls [18, 72, 102], but high gray matter density in the precentral cortex has been reported in PTSD patients after sexual assault [130]. The other study reported that the frontal lobe volume may be smaller in a PTSD group [20, 35, 133]. In a DTI study, the decreased FA value was also seen in bilateral superior/middle frontal gyrus in traffic accident victims with PTSD and FA value negatively correlated with CAPS score [131].

Insular Cortex

Low gray matter density has been reported in VBM studies in the insular cortices of PTSD patients as compared to non-PTSD controls [2, 20, 22, 62, 102]. The insula volume was also lower in PTSD patients as compared to the trauma-exposed and trauma-free controls [17]. However, volumes of insular cortex did not differ in PTSD and non-PTSD groups in a different study [133]. Cortical thickness in the left insula was reported as thinner in veterans with combat PTSD after mild traumatic brain injury [85]. An adolescent PTSD study

reported that the insula thickness was significantly reduced in the PTSD group compared to the non-PTSD group, and the thickness of the left insula was also significantly correlated with cognitive performance and delayed recall [2].

Parietal Lobe

Larger angular gyrus was mentioned in PTSD subjects in one study [114], but a different study did not find differences in parietal lobe volumes [40]. Cortical thinning was reported in the postcentral cortex and precuneus of PTSD patients after mild traumatic brain injury in a recent study [85]. The thinning in postcentral cortex and precuneus was negatively correlated with cumulative trauma exposures over lifetime in PTSD veterans [85]. Patients with recent-onset PTSD were reported to exhibit cortical thinning in the left parietal lobe [86]. But thicker cortical thickness in inferior parietal lobule in PTSD patients was reported in one earthquake study [79]. Reduced gray matter densities in precuneus and other parietal regions in PTSD subjects relative to trauma-exposed and trauma-free controls were also reported in some VBM studies [2, 35, 102, 132], but a higher density in right postcentral and inferior parietal cortices was reported in PTSD following sexual assault [130]. A reduction in white matter FA in posterior angular gyrus has been reported in a DTI study [121].

Occipital Lobe

Previous studies reported traumatized subjects have smaller occipital gray matter volumes than trauma-free controls [40]. The recent studies reported smaller occipital lobe volumes in the PTSD group [133]. The VBM studies also showed lower gray matter density in fusiform gyrus and occipital lobe in adult PTSD and pediatric PTSD [18, 63, 132]. The DTI studies reported high FA in right lateral occipital cortex in adult PTSD [37] and lower mean diffusivity in occipital region connecting to corpus callosum in pediatric PTSD [24].

Corpus Callosum

Few studies reported a smaller corpus callosum volume or lower density, especially in middle and posterior subdivisions, in both adult and child PTSD patients [27, 66, 79, 118, 138]. One structural and functional combined study reported corpus callosum volume reduction in anterior and middle subdivisions in PTSD group that was associated with declines in associative memory [118]. In addition, a DTI study suggested that FA is reduced in the middle body of corpus callosum of PTSD children [58].

Cerebellum and Subcortical Nuclei

Lower density in caudate and hypothalamus in combat PTSD was reported [55], but the caudate and putamen volumes did not differ in children with PTSD [28, 29]. One study reported that the amygdala, thalamus, and globus pallidus volumes were negatively correlated with PTSD reexperiencing symptom in police officers, suggesting that these structures may be linked to some PTSD symptom [123]. The cerebellum findings have also been inconsistent. The smaller cerebellum and lower gray matter densities in the posterior vermis were reported in studies of children with PTSD [14, 24, 30], and volumes of the left cerebellar hemisphere and the vermis were smaller and were negatively correlated with PTSD symptoms and depressive symptoms, in a different study [3]. However, female victims of rape with PTSD have been shown to have increased gray matter density in the left cerebellar hemisphere [129]. By contrast, PTSD and non-PTSD veterans showed no differences in total cerebellar volume, vermis volume, or volumes in three divisions of the midsagittal vermis [40]. No differences in cerebellar volumes were also seen when PTSD veterans were compared to their identical co-twins [75].

In summary, a number of brain regions have been assessed in structural studies of PTSD patients. STG, insula cortex, and corpus callosum abnormalities are reported relatively consistently, but the literature is still limited.

Summary

As reviewed above, a substantial number of studies have examined structural properties of the brains of PTSD patients. Multiple studies have reported consistent differences in the structural properties of a range of brain regions including reduced hippocampal volume, reduced volumes of the PFC and ACC, reduced size and FA of the corpus callosum, and low gray matter density in the insular cortex. However, differences in other regions remain to be replicated, confirmed, and clarified. Additional studies are required in order to confirm these findings. Several studies have tested correlations between structural measures and functional indices like PTSD symptom severity, to further examine the relationship between brain structure and PTSD pathophysiology.

Brain Structural Alteration in PTSD and Sleep

Although mounting evidences suggest brain structural alterations in PTSD patients, very few studies examine the relation of these brain structural alterations and sleep problems in the PTSD patients. Sleep is regulated by activity in several brain regions, including hypothalamus, thalamus, and brain stem nuclei like locus coeruleus and reticular formation [124]; thus structural or functional changes in these regions associated with PTSD or other pathological states can lead to specific sleep abnormalities associated with the disorder. Furthermore, PTSD's critical memory functions like mem-

ory consolidation are highly dependent on sleep physiology and on integrity of brain structures like hippocampus, linking PTSD structural changes, sleep, and PTSD pathophysiology. Finally, neuroimaging studies suggest that specific sleep abnormalities may be associated with functional and structural changes in specific brain regions. For example, the fMRI study found that activation also increases in amygdala and ACC when dreaming [90]. Brain structure studies of insomnia implicate structural alternations in the similar regions as those reported in PTSD studies, i.e., hippocampus, ACC, and PFC [105, 106, 128]. For example, although the hippocampal volume of the primary insomnia (PI) patients does not significantly differ from that of good sleepers, the hippocampal volume of PI patients was negatively associated with duration of insomnia and arousal index [105]. One study reports cortical thinning in ACC and lPFC in PI patients as compared to good sleepers, but no relationship between cortical thickness and sleep quality was found in either groups [128]. However, another study reported a larger rACC volume in PI patients and negative correlation of rACC volume and sleep quality [148].

The common brain regions implicated both in sleep disorders and PTSD raise a possibility that the structural properties of these regions might be associated with sleep problems in PTSD patients. However, very few studies explored the sleep problems and brain structure in trauma-exposed people who do or do not develop PTSD. One PTSD study reported negative relationship between hippocampal size, especially CA3/dentate subfields, and insomnia severity as well as worse sleep quality in veterans with and without PTSD [103]. The insomnia severity was stronger associated with CA3/dentate volume than the overall PTSD severity. A VBM study also reported that the gray matter density of left hippocampus in trauma survivors is inversely associated with insomnia, but not PTSD symptom severity, suggesting that smaller hippocampus might be associated specifically with the sleep deficit [96]. A different study of traumatized subjects reported that insomnia or nightmares were significantly associated with reduced gray matter volume in hippocampus, amygdala, ACC, and insula cortex [100], correlation mainly driven by the PTSD group. In contrast, another study did not find significant relationship between sleep quality and hippocampal volume, but inverse correlations were observed between global cortical volume and orbitofrontal and ACC volume with sleep quality [19]. It has been suggested that successful sleep can restore neuron connectivity, maintain cognitive capability, and regulate emotional processes [33]. As mentioned above, intact sleep is also important for the memory consolidation and integration of new experience at day time into existing knowledge [32]. Recent studies provided evidences that sleep, especially REM sleep, may play an important role in emotion regulation, as it is critical for appropriate fear extinction/safety learning [33, 45, 74, 141]. It is possible, for example, that chronic insomnia may affect structure of these key brain regions even before trauma exposure, which may increase risk for PTSD development. On the other hand, the sleep problems after trauma exposure may also exacerbate the structural changes in PTSD patients. Therefore, brain structural alternations due to sleep problems may both contribute to PTSD development and to maintenance to PTSD symptoms after traumatic events. This raises however the possibility that even targeted sleep intervention addressing sleep problems may more generally affect PTSD pathophysiology.

In summary, these early studies provide limited initial findings on brain structural properties that may relate to the sleep problems in PTSD patients. Furthermore, a lack of longitudinal investigations either pre- to post-trauma or over post-trauma periods makes it unable to address an important question that any brain structural alterations associated with sleep problems of PTSD patients are predisposed risk factors before trauma exposure vs consequences of PTSD.

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References

1. Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Iwanami A, Ohtani T, Masutani Y, Kato N, Ohtomo K. Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. Psychiatry Res Neuroimaging. 2006;146(3):231–42.
2. Ahmed F, Spottiswoode BS, Carey PD, Stein DJ, Seedat S. Relationship between neurocognition and regional brain volumes in traumatized adolescents with and without posttraumatic stress disorder. Neuropsychobiology. 2012;66(3):174–84.
3. Baldacara L, Jackowski AP, Schoedl A, Pupo M, Andreoli SB, Mello MF, Lacerda AL, Mari JJ, Bressan RA. Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample. J Psychiatr Res. 2011;45(12):1627–33.
4. Bierer LM, Ivanov I, Carpenter DM, Wong EW, Golier JA, Tang CY, Yehuda R. White matter abnormalities in Gulf war veterans with posttraumatic stress disorder: a pilot study. Psychoneuroendocrinology. 2015;51:567–76.
5. Bing X, Ming-guo Q, Ye Z, Jing-na Z, Min L, Han C, Yu Z, Jia-jia Z, Jian W, Wei C, Han-jian D, Shao-xiang Z. Alterations in the cortical thickness and the amplitude of low-frequency fluctuation in patients with post-traumatic stress disorder. Brain Res. 2013;1490(0):225–32.
6. Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, Shalev AY. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am J Psychiatry. 2001;158(8):1248–51.
7. Bossini L, Tavanti M, Calossi S, Lombardelli A, Polizzotto NR, Galli R, Vatti G, Pieraccini F, Castrogiovanni P. Magnetic resonance imaging volumes of the hippocampus in drug-naive patients with post-traumatic stress disorder without comorbidity conditions. J Psychiatr Res. 2008;42(9):752–62.

8. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(7):973–81.
9. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. Biol Psychiatry. 1997;41(1):23–32.
10. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003;160(5):924–32.
11. Brewin CR. The nature and significance of memory disturbance in posttraumatic stress disorder. Annu Rev Clin Psychol. 2011;7:203–27.
12. Cardenas VA, Samuelson K, Lenoci M, Studholme C, Neylan TC, Marmar CR, Schuff N, Weiner MW. Changes in brain anatomy during the course of posttraumatic stress disorder. Psychiatry Res Neuroimaging. 2011;193(2):93–100.
13. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry. 2001;50(12):943–51.
14. Carrion VG, Weems CF, Watson C, Eliez S, Menon V, Reiss AL. Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric posttraumatic stress disorder: an MRI study. Psychiatry Res. 2009;172(3):226–34.
15. Chalavi S, Vissia EM, Giesen ME, Nijenhuis ER, Draijer N, Cole JH, Dazzan P, Pariante CM, Madsen SK, Rajagopalan P, Thompson PM, Toga AW, Veltman DJ, Reinders AA. Abnormal hippocampal morphology in dissociative identity disorder and post-traumatic stress disorder correlates with childhood trauma and dissociative symptoms. Hum Brain Mapp. 2015;36(5):1692–704.
16. Chan AO, Medicine M, Air TM, McFarlane AC. Posttraumatic stress disorder and its impact on the economic and health costs of motor vehicle accidents in South Australia. J Clin Psychiatry. 2003;64(2):175–81.
17. Chao L, Weiner M, Neylan T. Regional cerebral volumes in veterans with current versus remitted posttraumatic stress disorder. Psychiatry Res. 2013;213(3):193–201.
18. Chao LL, Lenoci M, Neylan TC. Effects of post-traumatic stress disorder on occipital lobe function and structure. Neuroreport. 2012;23(7):412–9.
19. Chao LL, Mohlenhoff BS, Weiner MW, Neylan TC. Associations between subjective sleep quality and brain volume in Gulf war veterans. Sleep. 2014;37(3):445–52.
20. Chen S, Li L, Xu B, Liu J. Insular cortex involvement in declarative memory deficits in patients with post-traumatic stress disorder. BMC Psychiatry. 2009;9:39.
21. Chen Y, Fu K, Feng C, Tang L, Zhang J, Huan Y, Cui J, Mu Y, Qi S, Xiong L, Ma C, Wang H, Tan Q, Yin H. Different regional gray matter loss in recent onset PTSD and non PTSD after a single prolonged trauma exposure. PLoS One. 2012;7(11):e48298.
22. Corbo V, Clement MH, Armony JL, Pruessner JC, Brunet A. Size versus shape differences: contrasting voxel-based and volumetric analyses of the anterior cingulate cortex in individuals with acute posttraumatic stress disorder. Biol Psychiatry. 2005;58(2):119–24.
23. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry. 2001;50(4):305–9.
24. De Bellis MD, Hooper SR, Chen SD, Provenzale JM, Boyd BD, Glessner CE, MacFall JR, Payne ME, Rybczynski R, Woolley DP. Posterior structural brain volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. Dev Psychopathol. 2015;27(4 Pt 2):1555–76.
25. De Bellis MD, Hooper SR, Woolley DP, Shenk CE. Demographic, maltreatment, and neurobiological correlates of PTSD symptoms in children and adolescents. J Pediatr Psychol. 2010;35(5):570–7.
26. De Bellis MD, Keshavan MS. Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. Neurosci Biobehav Rev. 2003;27(1–2):103–17.
27. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. A.E. Bennett Research Award. Developmental traumatology. Part II: brain development. Biol Psychiatry. 1999;45(10):1271–84.
28. De Bellis MD, Keshavan MS, Frustaci K, Shifflett H, Iyengar S, Beers SR, Hall J. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. Biol Psychiatry. 2002;51(7):544–52.
29. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry. 2002;52(11):1066–78.
30. De Bellis MD, Kuchibhatla M. Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry. 2006;60(7):697–703.
31. Depue BE, Olson-Madden JH, Smolker HR, Rajamani M, Brenner LA, Banich MT. Reduced amygdala volume is associated with deficits in inhibitory control: a voxel- and surface-based morphometric analysis of comorbid PTSD/mild TBI. Biomed Res Int. 2014;2014:691505.
32. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114–26.
33. Dresler M, Spoormaker VI, Beitinger P, Czisch M, Kimura M, Steiger A, Holsboer F. Neuroscience-driven discovery and development of sleep therapeutics. Pharmacol Ther. 2014;141(3):300–34.
34. Durkee CA, Sarlls JE, Hommer DW, Momenan R. White matter microstructure alterations: a study of alcoholics with and without post-traumatic stress disorder. PLoS One. 2013;8(11):e80952.
35. Eckart C, Stoppel C, Kaufmann J, Tempelmann C, Hinrichs H, Elbert T, Heinze HJ, Kolassa IT. Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. J Psychiatry Neurosci. 2011;36(3):176–86.
36. Emdad R, Bonekamp D, Sondergaard HP, Bjorklund T, Agartz I, Ingvar M, Theorell T. Morphometric and psychometric comparisons between non-substance-abusing patients with posttraumatic stress disorder and normal controls. Psychother Psychosom. 2006;75(2):122–32.
37. Fani N, King TZ, Jovanovic T, Glover EM, Bradley B, Choi K, Ely T, Gutman DA, Ressler KJ. White matter integrity in highly traumatized adults with and without post-traumatic stress disorder. Neuropsychopharmacology. 2012;37(12):2740–6.
38. Fani N, King TZ, Shin J, Srivastava A, Brewster RC, Jovanovic T, Bradley B, Ressler KJ. Structural and functional connectivity in posttraumatic stress disorder: associations with FKBP5. Depress Anxiety. 2016;33(4):300–7.
39. Felmingham K, Williams LM, Whitford TJ, Falconer E, Kemp AH, Peduto A, Bryant RA. Duration of posttraumatic stress disorder predicts hippocampal grey matter loss. Neuroreport. 2009;20(16):1402–6.
40. Fennema-Notestine C, Stein MB, Kennedy CM, Archibald SL, Jernigan TL. Brain morphometry in female victims of intimate

partner violence with and without posttraumatic stress disorder. Biol Psychiatry. 2002;52(11):1089–101.
41. Filipovic BR, Djurovic B, Marinkovic S, Stijak L, Aksic M, Nikolic V, Starcevic A, Radonjic V. Volume changes of corpus striatum, thalamus, hippocampus and lateral ventricles in posttraumatic stress disorder (PTSD) patients suffering from headaches and without therapy. Cent Eur Neurosurg. 2011;72(3):133–7.
42. Garfinkel SN, Abelson JL, King AP, Sripada RK, Wang X, Gaines LM, Liberzon I. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. J Neurosci. 2014;34(40):13435–43.
43. Garfinkel SN, Liberzon I. Neurobiology of PTSD: a review of neuroimaging findings. Psychiatric Annals. 2009;39(6):370–81.
44. Gasquoine PG. Localization of function in anterior cingulate cortex: from psychosurgery to functional neuroimaging. Neurosci Biobehav Rev. 2013;37(3):340–8.
45. Germain A. Sleep disturbances as the Hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170(4):372–82.
46. Geuze E, Westenberg HG, Heinecke A, de Kloet CS, Goebel R, Vermetten E. Thinner prefrontal cortex in veterans with posttraumatic stress disorder. NeuroImage. 2008;41(3):675–81.
47. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 2002;5(11):1242–7.
48. Golier JA, Yehuda R, De Santi S, Segal S, Dolan S, de Leon MJ. Absence of hippocampal volume differences in survivors of the Nazi Holocaust with and without posttraumatic stress disorder. Psychiatry Res. 2005;139(1):53–64.
49. Greco JA, Liberzon I. Neuroimaging of fear-associated learning. Neuropsychopharmacology. 2016;41(1):320–34.
50. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry. 1996;40(11):1091–9.
51. Hakamata Y, Matsuoka Y, Inagaki M, Nagamine M, Hara E, Imoto S, Murakami K, Kim Y, Uchitomi Y. Structure of orbitofrontal cortex and its longitudinal course in cancer-related post-traumatic stress disorder. Neurosci Res. 2007;59(4):383–9.
52. Hara E, Matsuoka Y, Hakamata Y, Nagamine M, Inagaki M, Imoto S, Murakami K, Kim Y, Uchitomi Y. Hippocampal and amygdalar volumes in breast cancer survivors with posttraumatic stress disorder. J Neuropsychiatry Clin Neurosci. 2008;20(3):302–8.
53. Hedges DW, Thatcher GW, Bennett PJ, Sood S, Paulson D, Creem-Regehr S, Brown BL, Allen S, Johnson J, Froelich B, Bigler ED. Brain integrity and cerebral atrophy in Vietnam combat veterans with and without posttraumatic stress disorder. Neurocase. 2007;13(5):402–10.
54. Helpman L, Papini S, Chhetry BT, Shvil E, Rubin M, Sullivan GM, Markowitz JC, Mann JJ, Neria Y. PTSD remission after prolonged exposure treatment is associated with anterior cingulate cortex thinning and volume reduction. Depress Anxiety. 2016;33(5):384–91.
55. Herringa R, Phillips M, Almeida J, Insana S, Germain A. Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans. Psychiatry Res. 2012;203(2–3):139–45.
56. Hunter M, Villarreal G, McHaffie GR, Jimenez B, Smith AK, Calais LA, Hanlon F, Thoma RJ, Canive JM. Lateralized abnormalities in auditory M50 sensory gating and cortical thickness of the superior temporal gyrus in post-traumatic stress disorder: preliminary results. Psychiatry Res. 2011;191(2):138–44.
57. Irle E, Lange C, Sachsse U, Weniger G. Further evidence that post-traumatic stress disorder but not dissociative disorders are related to amygdala and hippocampal size reduction in trauma-exposed individuals. Acta Psychiatr Scand. 2009;119(4):330–1.
58. Jackowski AP, Douglas-Palumberi H, Jackowski M, Win L, Schultz RT, Staib LW, Krystal JH, Kaufman J. Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. Psychiatry Res. 2008;162(3):256–61.
59. Jatzko A, Rothenhofer S, Schmitt A, Gaser C, Demirakca T, Weber-Fahr W, Wessa M, Magnotta V, Braus DF. Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods. J Affect Disord. 2006;94(1–3):121–6.
60. Jorge RE. Posttraumatic stress disorder. Continuum Minneap Minn. 2015;21(3 Behavioral Neurology and Neuropsychiatry):789–805.
61. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev. 2006;30(7):1004–31.
62. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry. 2008;63(6):550–6.
63. Keding TJ, Herringa RJ. Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. Neuropsychopharmacology. 2015;40(3):537–45.
64. Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry. 2000;61(Suppl 5):4–12. discussion 13–14
65. Kim SJ, Jeong DU, Sim ME, Bae SC, Chung A, Kim MJ, Chang KH, Ryu J, Renshaw PF, Lyoo IK. Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder. Neuropsychobiology. 2006;54(2):120–5.
66. Kitayama N, Brummer M, Hertz L, Quinn S, Kim Y, Bremner JD. Morphologic alterations in the corpus callosum in abuse-related posttraumatic stress disorder: a preliminary study. J Nerv Ment Dis. 2007;195(12):1027–9.
67. Kitayama N, Quinn S, Bremner JD. Smaller volume of anterior cingulate cortex in abuse-elated posttraumatic stress disorder. J Affect Disord. 2006;90(2–3):171–4.
68. Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. Am J Psychiatry. 2002;159(5):855–7.
69. Krakow B, Germain A, Warner TD, Schrader R, Koss M, Hollifield M, Tandberg D, Melendrez D, Johnston L. The relationship of sleep quality and posttraumatic stress to potential sleep disorders in sexual assault survivors with nightmares, insomnia, and PTSD. J Trauma Stress. 2001a;14(4):647–65.
70. Krakow B, Haynes PL, Warner TD, Santana E, Melendrez D, Johnston L, Hollifield M, Sisley BN, Koss M, Shafer L. Nightmares, insomnia, and sleep-disordered breathing in fire evacuees seeking treatment for posttraumatic sleep disturbance. J Trauma Stress. 2004;17(3):257–68.
71. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, Cheng D, Emmons S, Germain A, Melendrez D, Sandoval D, Prince H. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001b;286(5):537–45.
72. Kroes MC, Rugg MD, Whalley MG, Brewin CR. Structural brain abnormalities common to posttraumatic stress disorder and depression. J Psychiatry Neurosci. 2011;36(4):256–65.
73. Kuo JR, Kaloupek DG, Woodward SH. Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. Arch Gen Psychiatry. 2012;69(10):1080–6.
74. Levin R, Nielsen T. Nightmares, bad dreams, and emotion dysregulation. A review and new neurocognitive model of dreaming. Curr Dir Psychol Sci. 2009;18:84–8.
75. Levitt JJ, Chen QC, May FS, Gilbertson MW, Shenton ME, Pitman RK. Volume of cerebellar vermis in monozygotic twins discordant

for combat exposure: lack of relationship to post-traumatic stress disorder. Psychiatry Res. 2006;148(2–3):143–9.
76. Levy-Gigi E, Szabo C, Kelemen O, Keri S. Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. Biol Psychiatry. 2013;74(11):793–800.
77. Li L, Chen S, Liu J, Zhang J, He Z, Lin X. Magnetic resonance imaging and magnetic resonance spectroscopy study of deficits in hippocampal structure in fire victims with recent-onset posttraumatic stress disorder. Can J Psychiatry. 2006;51(7):431–7.
78. Li L, Wu M, Liao Y, Ouyang L, Du M, Lei D, Chen L, Yao L, Huang X, Gong Q. Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. Neurosci Biobehav Rev. 2014;43:163–72.
79. Li S, Huang X, Li L, Du F, Li J, Bi F, Lui S, Turner JA, Sweeney JA, Gong Q. Posttraumatic stress disorder: structural characterization with 3-T MR imaging. Radiology. 2016;280(2):537–44.
80. Liberzon I, Martis B. Neuroimaging studies of emotional responses in PTSD. Ann N Y Acad Sci. 2006;1071(1):87–109.
81. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. Prog Brain Res. M. S. O. E. Ronald De Kloet and V. Eric, Elsevier. 2007;167:151–69.
82. Lindauer RJ, Olff M, van Meijel EP, Carlier IV, Gersons BP. Cortisol, learning, memory, and attention in relation to smaller hippocampal volume in police officers with posttraumatic stress disorder. Biol Psychiatry. 2006;59(2):171–7.
83. Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, den Heeten GJ, Gersons BP. Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. Biol Psychiatry. 2004;56(5):356–63.
84. Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, Den Heeten GJ, Gersons BP. Effects of psychotherapy on hippocampal volume in out-patients with post-traumatic stress disorder: a MRI investigation. Psychol Med. 2005;35(10):1421–31.
85. Lindemer ER, Salat DH, Leritz EC, McGlinchey RE, Milberg WP. Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF veterans and the impact of comorbid TBI. Neuroimage Clin. 2013;2:601–11.
86. Liu Y, Li YJ, Luo EP, Lu HB, Yin H. Cortical thinning in patients with recent onset post-traumatic stress disorder after a single prolonged trauma exposure. PLoS One. 2012;7(6):e39025.
87. Logue MW, Rooij SJH v, Dennis EL, Davis SL, Haswell CC, Lebois LAM, Kaufman ML, Wolff JD, O'Connor L, Gruber SA, Baker JT, Winternitz SR, Ressler KJ, Lagopoulos J, Geuze E, Stevens JS, Jovanovic T, Olff M, Nawijn L, Zuiden M v, Frijling JL, Koch SB, Bryant RA, Korgaonkar M, Miller MW, Hayes JP, Spielberg JM, Wolf EJ, Salat DH, Milberg WP, McGlinchey RE, McLaughlin KA, Sheridan MA, Peverill M, Liberzon I, King AP, Wang X, Jahanshad N, Thompson PM, Harpaz-Rotem I, Levy I, Abdallah CG, Wrocklage K, Krystal JH, Stein DJ, Ipser J, Koopowitz S, Lanius R, Densmore M, Veltman DJ, Thomaess K, Morey RA. Smaller amygdala and hippocampal volume in posttraumatic stress disorder from multi-site investigation by enigma and PGC consortia. Neuropsychopharmacology. 2016;41(S1):S455–630.
88. Luo Y, Shan H, Liu Y, Wu L, Zhang X, Ma T, Zhu W, Yang Y, Wang J, Cao Z. Decreased left hippocampal volumes in parents with or without posttraumatic stress disorder who lost their only child in China. J Affect Disord. 2016;197:223–30.
89. Lyoo IK, Kim JE, Yoon SJ, Hwang J, Bae S, Kim DJ. The neurobiological role of the Dors lateral prefrontal cortex in recovery from trauma longitudinal brain imaging study among survivors of the south Korean subway disaster. Arch Gen Psychiatry. 2011;68(7):701–13.
90. Maquet P, Peters J, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature. 1996;383(6596):163–6.
91. Matsuoka Y, Yamawaki S, Inagaki M, Akechi T, Uchitomi Y. A volumetric study of amygdala in cancer survivors with intrusive recollections. Biol Psychiatry. 2003;54(7):736–43.
92. May FS, Chen QC, Gilbertson MW, Shenton ME, Pitman RK. Cavum septum pellucidum in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. Biol Psychiatry. 2004;55(6):656–8.
93. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatry. 2002;159(10):1696–701.
94. Meng Y, Qiu C, Zhu H, Lama S, Lui S, Gong Q, Zhang W. Anatomical deficits in adult posttraumatic stress disorder: a meta-analysis of voxel-based morphometry studies. Behav Brain Res. 2014;270:307–15.
95. Milani AC, Hoffmann EV, Fossaluza V, Jackowski AP, Mello MF. Does pediatric post-traumatic stress disorder alter the brain? Systematic review and meta-analysis of structural and functional magnetic resonance imaging studies. Psychiatry Clin Neurosci. 2017;71(3):154–69
96. Mohlenhoff BS, Chao LL, Buckley ST, Weiner MW, Neylan TC. Are hippocampal size differences in posttraumatic stress disorder mediated by sleep pathology? Alzheimer Dement J Alzheimer Assoc. 2014;10(3 0):S146–54.
97. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, Haswell CC, Nasser JD, Wagner HR, McCarthy G. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry. 2012;69(11):1169–78.
98. Morey RA, Haswell CC, Hooper SR, De Bellis MD. Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. Neuropsychopharmacology. 2016;41(3):791–801.
99. Mueller SG, Ng P, Neylan T, Mackin S, Wolkowitz O, Mellon S, Yan X, Flory J, Yehuda R, Marmar CR, Weiner MW. Evidence for disrupted gray matter structural connectivity in posttraumatic stress disorder. Psychiatry Res. 2015;234(2):194–201.
100. Nardo D, Högberg G, Jonsson C, Jacobsson H, Hällström T, Pagani M. Neurobiology of sleep disturbances in PTSD patients and traumatized controls: MRI and SPECT findings. Front Psychiatry. 2015;6:134.
101. Nardo D, Hogberg G, Lanius RA, Jacobsson H, Jonsson C, Hallstrom T, Pagani M. Gray matter volume alterations related to trait dissociation in PTSD and traumatized controls. Acta Psychiatr Scand. 2013;128(3):222–33.
102. Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M. Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J Psychiatr Res. 2010;44(7):477–85.
103. Neylan TC, Mueller SG, Wang Z, Metzler TJ, Lenoci M, Truran D, Marmar CR, Weiner MW, Schuff N. Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. Biol Psychiatry. 2010;68(5):494–6.
104. Niedtfeld I, Schulze L, Krause-Utz A, Demirakca T, Bohus M, Schmahl C. Voxel-based morphometry in women with borderline personality disorder with and without comorbid posttraumatic stress disorder. PLoS One. 2013;8(6):e65824.
105. Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D, Lee GH, Hong SB. The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J Clin Neurol. 2012;8(2):130–8.
106. O'Byrne JN, Berman Rosa M, Gouin JP, Dang-Vu TT. Neuroimaging findings in primary insomnia. Pathol Biol (Paris). 2014;62(5):262–9.

107. O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 2015;232(1):1–33.
108. O'Donnell ML, Creamer M, Elliott P, Atkin C. Health costs following motor vehicle accidents: the role of posttraumatic stress disorder. J Trauma Stress. 2005;18(5):557–61.
109. Pavic L, Gregurek R, Rados M, Brkljacic B, Brajkovic L, Simetin-Pavic I, Ivanac G, Pavlisa G, Kalousek V. Smaller right hippocampus in war veterans with posttraumatic stress disorder. Psychiatry Res. 2007;154(2):191–8.
110. Peters J, van Kammen DP, van Kammen WB, Neylan T. Sleep disturbance and computerized axial tomographic scan findings in former prisoners of war. Compr Psychiatry. 1990;31(6):535–9.
111. Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, Shenton ME, Yehuda R, Orr SP. Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. Ann N Y Acad Sci. 2006;1071:242–54.
112. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I. Biological studies of posttraumatic stress disorder. Nat Rev Neurosci. 2012;13(11):769–87.
113. Qi S, Mu Y, Liu K, Zhang J, Huan Y, Tan Q, Shi M, Wang Q, Chen Y, Wang H, Wang H, Zhang N, Zhang X, Xiong L, Yin H. Cortical inhibition deficits in recent onset PTSD after a single prolonged trauma exposure. Neuroimage Clin. 2013;3:226–33.
114. Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, McMullin K, Whalen PJ, Makris N. Selectively reduced regional cortical volumes in post-traumatic stress disorder. Neuroreport. 2003;14(7):913–6.
115. Richert KA, Carrion VG, Karchemskiy A, Reiss AL. Regional differences of the prefrontal cortex in pediatric PTSD: an MRI study. Depress Anxiety. 2006;23(1):17–25.
116. Rocha-Rego V, Pereira MG, Oliveira L, Mendlowicz MV, Fiszman A, Marques-Portella C, Berger W, Chu C, Joffily M, Moll J, Mari JJ, Figueira I, Volchan E. Decreased premotor cortex volume in victims of urban violence with posttraumatic stress disorder. PLoS One. 2012;7(8):e42560
117. Rogers MA, Yamasue H, Abe O, Yamada H, Ohtani T, Iwanami A, Aoki S, Kato N, Kasai K. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. Psychiatry Res. 2009;174(3):210–6.
118. Saar-Ashkenazy R, Cohen JE, Guez J, Gasho C, Shelef I, Friedman A, Shalev H. Reduced corpus-callosum volume in posttraumatic stress disorder highlights the importance of interhemispheric connectivity for associative memory. J Trauma Stress. 2014;27(1):18–26.
119. Sala M, Perez J, Soloff P, Ucelli di Nemi S, Caverzasi E, Soares JC, Brambilla P. Stress and hippocampal abnormalities in psychiatric disorders. Eur Neuropsychopharmacol. 2004;14(5):393–405.
120. Sarac-Hadzihalilovic A, Dilberovic F. Detection of the hippocampal formation asymmetry in patients with posttraumatic stress disorder. Bosn J Basic Med Sci. 2007;7(2):162–5.
121. Schuff N, Zhang Y, Zhan W, Lenoci M, Ching C, Boreta L, Mueller SG, Wang Z, Marmar CR, Weiner MW, Neylan TC. Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: an MRI study. NeuroImage. 2011;54(Supplement 1):S62–8.
122. Sekiguchi A, Sugiura M, Taki Y, Kotozaki Y, Nouchi R, Takeuchi H, Araki T, Hanawa S, Nakagawa S, Miyauchi CM, Sakuma A, Kawashima R. Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. Mol Psychiatry. 2013;18(5):618–23.
123. Shucard JL, Cox J, Shucard DW, Fetter H, Chung C, Ramasamy D, Violanti J. Symptoms of posttraumatic stress disorder and exposure to traumatic stressors are related to brain structural volumes and behavioral measures of affective stimulus processing in police officers. Psychiatry Res. 2012;204(1):25–31.
124. Siegel JM. The neurobiology of sleep. Semin Neurol. 2009;29(4):277–96.
125. Smith ME. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. Hippocampus. 2005;15(6):798–807.
126. Starcevic A, Postic S, Radojicic Z, Starcevic B, Milovanovic S, Ilankovic A, Dimitrijevic I, Damjanovic A, Aksić M, Radonjic V. Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naive PTSD participants. Biomed Res Int. 2014;2014:6.
127. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med. 1997;27(4):951–9.
128. Suh S, Kim H, Dang-Vu TT, Joo E, Shin C. Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. Sleep. 2016;39(1):161–71.
129. Sui S-G, Zhang Y, Wu M-X, Xu J-M, Duan L, Weng X-C, Shan B-C, Li L-J. Abnormal cerebellum density in victims of rape with post-traumatic stress disorder: voxel-based analysis of magnetic resonance imaging investigation. Asia Pac Psychiatry. 2010;2(3):129–35.
130. Sui SG, Wu MX, King ME, Zhang Y, Ling L, Xu JM, Weng XC, Duan L, Shan BC, Li LJ. Abnormal grey matter in victims of rape with PTSD in Mainland China: a voxel-based morphometry study. Acta Neuropsychiatr. 2010;22(3):118–26.
131. Sun YW, Hu H, Wang Y, Ding WN, Chen X, Wan JQ, Zhou Y, Wang Z, Xu JR. Inter-hemispheric functional and anatomical connectivity abnormalities in traffic accident-induced PTSD: a study combining fMRI and DTI. J Affect Disord. 2015;188:80–8.
132. Tan L, Zhang L, Qi R, Lu G, Li L, Liu J, Li W. Brain structure in post-traumatic stress disorder: a voxel-based morphometry analysis. Neural Regen Res. 2013;8(26):2405–14.
133. Tavanti M, Battaglini M, Borgogni F, Bossini L, Calossi S, Marino D, Vatti G, Pieraccini F, Federico A, Castrogiovanni P, De Stefano N. Evidence of diffuse damage in frontal and occipital cortex in the brain of patients with post-traumatic stress disorder. Neurol Sci. 2012;33(1):59–68.
134. Tischler L, Brand SR, Stavitsky K, Labinsky E, Newmark R, Grossman R, Buchsbaum MS, Yehuda R. The relationship between hippocampal volume and declarative memory in a population of combat veterans with and without PTSD. Ann N Y Acad Sci. 2006;1071:405–9.
135. Tupler LA, De Bellis MD. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. Biol Psychiatry. 2006;59(6):523–9.
136. van Liempt S, van Zuiden M, Westenberg H, Super A, Vermetten E. Impact of impaired sleep on the development of PTSD symptoms in combat veterans: a prospective longitudinal cohort study. Depress Anxiety. 2013;30(5):469–74.
137. Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry. 2003;54(7):693–702.
138. Villarreal G, Hamilton DA, Graham DP, Driscoll I, Qualls C, Petropoulos H, Brooks WM. Reduced area of the corpus callosum in posttraumatic stress disorder. Psychiatry Res. 2004;131(3):227–35.
139. Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA, Kodituwakku PW, Hart BL, Escalona R, Brooks WM. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biol Psychiatry. 2002;52(2):119–25.

140. Vythilingam M, Luckenbaugh DA, Lam T, Morgan CA 3rd, Lipschitz D, Charney DS, Bremner JD, Southwick SM. Smaller head of the hippocampus in Gulf war-related posttraumatic stress disorder. Psychiatry Res. 2005;139(2):89–99.
141. Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem. 2001;8(2):112–9.
142. Wang X, Xie H, Cotton AS, Duval ER, Tamburrino MB, Brickman KR, Elhai JD, Ho SS, McLean SA, Ferguson EJ, Liberzon I. Preliminary study of acute changes in emotion processing in trauma survivors with PTSD symptoms. PLoS One. 2016;11(7):e0159065.
143. Wang Z, Neylan TC, Mueller SG, Lenoci M, Truran D, Marmar CR, Weiner MW, Schuff N. Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Arch Gen Psychiatry. 2010;67(3):296–303.
144. Weniger G, Lange C, Sachsse U, Irle E. Amygdala and hippocampal volumes and cognition in adult survivors of childhood abuse with dissociative disorders. Acta Psychiatr Scand. 2008;118(4):281–90.
145. Weston CSE. Posttraumatic stress disorder: a theoretical model of the hyperarousal subtype. Front Psych. 2014;5:37.
146. Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, Woodruff PW. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. Biol Psychiatry. 2004;56(11):832–6.
147. Wingenfeld K, Wolf OT. Stress, memory, and the hippocampus. Front Neurol Neurosci. 2014;34:109–20.
148. Winkelman JW, Plante DT, Schoerning L, Benson K, Buxton OM, O'Connor SP, Jensen JE, Renshaw PF, Gonenc A. Increased rostral anterior cingulate cortex volume in chronic primary insomnia. Sleep. 2013;36(7):991–8.
149. Winter H, Irle E. Hippocampal volume in adult burn patients with and without posttraumatic stress disorder. Am J Psychiatry. 2004;161(12):2194–200.
150. Woodward SH, Kaloupek DG, Grande LJ, Stegman WK, Kutter CJ, Leskin L, Prestel R, Schaer M, Reiss AL, Eliez S. Hippocampal volume and declarative memory function in combat-related PTSD. J Int Neuropsychol Soc. 2009;15(6):830–9.
151. Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ. Brain, skull, and cerebrospinal fluid volumes in adult posttraumatic stress disorder. J Trauma Stress. 2007;20(5):763–74.
152. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry. 2006;59(7):582–7.
153. Woodward SH, Schaer M, Kaloupek DG, Cediel L, Eliez S. Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 2009;66(12):1373–82.
154. Woon FL, Hedges DW. Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. J Neuropsychiatry Clin Neurosci. 2009;21(1):5–12.
155. Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O, Kuroki N, Fukuda R, Tochigi M, Furukawa S, Sadamatsu M, Sasaki T, Aoki S, Ohtomo K, Asukai N, Kato N. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. Proc Natl Acad Sci U S A. 2003;100(15):9039–43.
156. Yehuda R, Golier JA, Tischler L, Harvey PD, Newmark R, Yang RK, Buchsbaum MS. Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. J Psychiatr Res. 2007;41(5):435–45.
157. Zandieh S, Bernt R, Knoll P, Wenzel T, Hittmair K, Haller J, Hergan K, Mirzaei S. Analysis of the metabolic and structural brain changes in patients with torture-related post-traumatic stress disorder (TR-PTSD) using (1)(8)F-FDG PET and MRI. Medicine (Baltimore). 2016;95(15):e3387.
158. Zhang J, Tan Q, Yin H, Zhang X, Huan Y, Tang L, Wang H, Xu J, Li L. Decreased gray matter volume in the left hippocampus and bilateral calcarine cortex in coal mine flood disaster survivors with recent onset PTSD. Psychiatry Res. 2011;192(2):84–90.
159. Zhang L, Zhang Y, Li L, Li Z, Li W, Ma N, Hou C, Zhang Z, Zhang Z, Wang L, Duan L, Lu G. Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions. J Affect Disord. 2011;133(1–2):294–9.

PET Ligand-Binding-Specific Imaging Proteins in the Brain: The Application in PTSD

13

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Introduction

Positron emission tomography (PET) is a dynamic and integrative research tool that is used to conduct empiric studies of neuronal functioning. In the past, attempts to investigate the neurologic dysfunction that characterizes PTSD have been largely limited by our technological capabilities. The development of novel radioligands that are compatible with PET has opened a new avenue of inquiry that allows us to study neurochemical systems in vivo to identify pathophysiology associated with psychiatric syndromes. With the use of precise ligands, PET can be used to trace or quantify any neurobiological process or molecule as long as the ligand can be labeled with a radioisotope.

In this section, we summarize significant PET findings in several neurobiological systems implicated in PTSD. We hope that this chapter will provide a framework for understanding the state of PTSD research from a neuroimaging perspective, as well as demonstrate the value of PET as a research tool in our field.

Regional Cerebral Blood Flow

PET imaging has been used extensively to localize the structural correlates of PTSD via symptom provocation and cognitive activation paradigms. In both models, regional cerebral blood flow (rCBF) data are used to delineate neural structures or regions that are active during specific emotional processes and, more specifically, understand how these regions function differently in patients with PTSD. In symptom provocation studies, patients are reminded of traumatic events by sounds, scripts, or images. In cognitive activation studies, patients perform emotional tasks that activate specific neural systems without initiating symptoms. Used in conjunction with PET imaging and the radioligand [^{15}O]H_2O, which quantifies cerebral blood flow, these paradigms have allowed us to determine specific brain areas involved in the pathophysiology of PTSD including the cerebellum, insula, putamen, medial prefrontal cortex, and anterior cingulate cortex (e.g., [31, 32, 44, 45]).

While these studies help us explain differences in regional blood flow, they do not explain the molecular dysfunction from which these regional differences arise. To investigate specific neurochemical systems associated with PTSD, we use PET imaging with radioligands designed to bind to specific neural proteins.

Serotonin

Animal models suggest that serotonin dysfunction plays a role in the etiology of PTSD. Recent PET imaging studies in PTSD patients have focused on the hypothesized pathology, from animal experiments, of the serotonin 1A (5-HT_{1A}R) and 1B (5-HT_{1B}R) receptors and the serotonin transporter.

Serotonin 1A Receptor

In 2003, Toth discovered that 5-HT_{1A}R is downregulated in the hippocampus of animals exposed to chronic stress [54], and 5-HT_{1A}R knockout mice are hyperresponsive to stressful stimuli. These findings inspired several translational PET imaging studies in mood and anxiety disorders such as panic and major depressive disorder. These early studies found reductions in 5-HT_{1A}R binding potential (BP_{ND}) in regions within a cortico-limbic-striatal circuit involved in mood

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regulation and emotion [42, 49]. Bonne et al. [4] then performed a keystone study in PTSD 5-HT_{1A}R binding using PET and the radioligand [^{18}F]CFWAY. Specifically, they compared PTSD patients with matched healthy controls under resting state conditions. Despite the reductions found in the aforementioned studies, there was no significant change in 5-HT_{1A}R binding in the PTSD group indicating that receptor expression may not be effected after exposure to a traumatic event that resulted in PTSD [4]. Although neuroimaging studies of 5-HT_{1A}R binding and function have not yet been specifically studied in PTSD-related sleep disturbances, i.e., disrupted sleep or nightmares, this specific association appears to be a worthwhile topic for further study. For example, it was shown that chronic sleep restriction causes a gradual and chronic desensitization of the 5-HT_{1A}R [47] and may therefore indicate a process that represents an integral component in the etiology of PTSD. Exploration of the link between 5-HT_{1A}R and sleep may therefore suggest an avenue for treatment development for PTSD patients. Although not yet explored in the treatment of PTSD, partial 5-HT_{1A}R agonists may be of particular interest given not only their anxiolytic properties but specifically their effects on sleep architecture [38].

Serotonin 1B Receptor

Several contemporary studies have found decreased 5-HT_{1B} receptor function after extreme stress exposure in animals resulting in depressive and anxious phenotypes [9–11, 34, 50]. In humans, PET imaging with the 5-HT_{1B}-selective radiotracer [^{11}C]P943 revealed increased ventral striatal BP_{ND} in individuals with alcohol dependence, a common comorbidity in PTSD patients, indicating that there were likely 1B receptor alterations in PTSD [29]. In response to these findings, Murrough et al. sought to investigate the expression of 5-HT_{1B}R in PTSD, trauma-exposed controls, and healthy non-traumatized individuals. Under resting conditions, participants underwent a PET scan using [^{11}C]P943, the same selective ligand used in the abovementioned alcohol dependence cohort, and regional BP_{ND} was measured in a cortico-limbic-striatal circuit. Significantly decreased BP_{ND} was found in the amygdala, anterior cingulate, and caudate of both trauma-exposed groups, PTSD, and trauma-exposed controls. Furthermore, earlier trauma exposure was associated with more severe reductions in [^{11}C]P943 binding potential. The authors hypothesized that early traumas' marked effect on BP_{ND} indicated that a developmental aspect might exist in the pathophysiology of PTSD. Specifically exposure to a traumatic event reduces serotonin 1B expression, which has downstream effects (see Fig. 13.1) ultimately leading to decreased neurogenesis in brain regions implicated in PTSD such as the amygdala and anterior cingulate [39]. Interestingly, Murrough et al. [40] also investigated 5-HT1BR binding in individuals with major depressive disorder without trauma exposure. In contrast to the widespread alterations found in PTSD, the authors found localized reduced 5-HT1BR signaling in the ventral striatum/ventral pallidum. It thus appears that reduced 5-HT1BR may be a component of several psychiatric disorders, but differential localization of these alterations may underlie the different phenotypes we see in MDD and PTSD. Perhaps these specific changes could 1 day be used as biological markers to aid in psychiatric diagnosis.

Serotonin Transporter

Alterations in serotonin signaling in PTSD are not only seen at the receptor level. A genetic variant of the serotonin transporter (5-HTT) has been shown to be associated with an increased risk of developing PTSD after a traumatic event [13, 25, 30, 46]. Moreover, some pharmacologic therapies for PTSD target 5-HTT and have been shown to exert a specific neural responses after administration. For instance, a recent PET study of PTSD patients demonstrated increased function in the orbitofrontal cortex during exposure to personalized trauma scripts after treatment with paroxetine [17]. This increase in function may be partially responsible for the decrease in PTSD symptomology seen after treatment with an SSRI. Based on this evidence, Murrough et al. [41] examined the 5-HTT receptor BP_{ND}, under resting state conditions, using another selective radioligand [^{11}C]AFM in PTSD patients versus healthy controls. The authors chose the amygdala as their primary region of interest based on the amygdala's key role in fear processing and the robust body of evidence implicating the amygdala in the pathophysiology of PTSD. Significantly reduced [^{11}C]AFM BP_{ND} was found in the amygdala of PTSD patients compared to controls. Additionally, measures of anxiety severity were inversely correlated with BP_{ND}. The authors hypothesized that decreased 5-HTT leads to abnormal functioning in the amygdala, which in turn leads to hyperreactive fear responses and increased anxiety. Though these results indicate that altered 5-HTT signaling in the amygdala contributes to the pathophysiology of PTSD, the authors caution that it is presently unknown whether this reduction represents an antecedent risk factor for developing PTSD or results after a severe traumatic event [41]. Importantly though, the described alterations in 5-HTT binding are line with the therapeutic effects of 5-HTT reuptake inhibitors in PTSD where subjective improvement in sleep quality has been reported to be associated with paroxetine treatment [52].

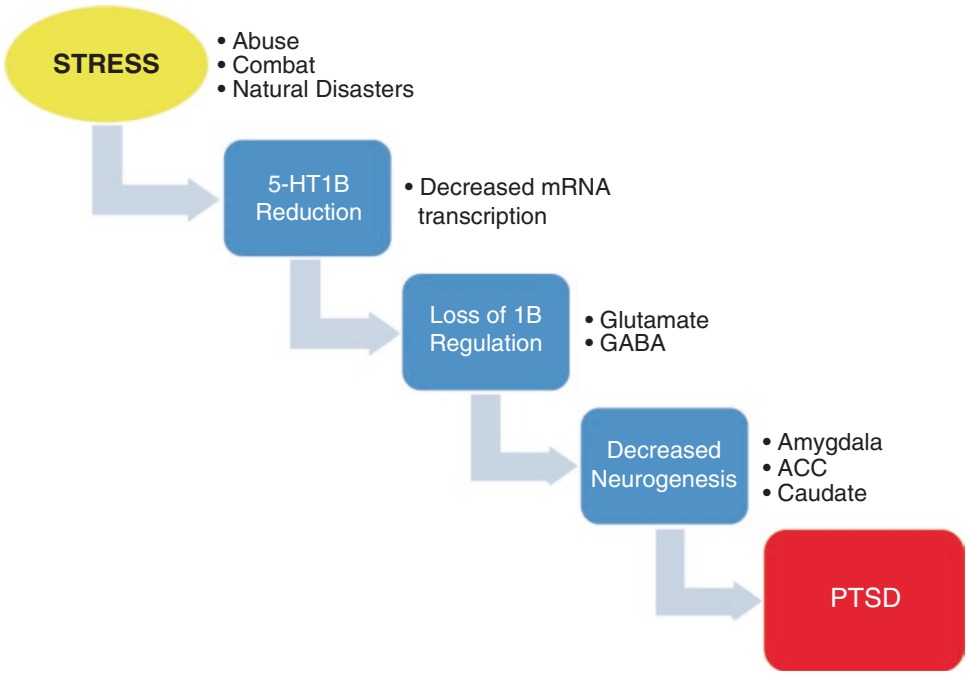

Fig. 13.1 Hypothesized downstream effect of stress on the serotonin 1B receptor ($5\text{-HT}_{1B}R$) [39]

γ-Aminobutyric Acid Receptor

The γ-aminobutyric acid receptor ($GABA_AR$) has been a target of interest ever since the efficacy of benzodiazepines was demonstrated in anxiety disorders [5]. Animal models of chronic stress have shown $GABA_AR$ alterations in cerebral cortices and hippocampus [12, 35, 36, 59]. Human pharmacologic studies also provide evidence that modified $GABA_AR$ signaling can lead to the severe anxiety seen in PTSD [15]. Furthermore, treatment of PTSD with benzodiazepines has been shown to be efficacious, though there are mixed reports of its ability to treat principal symptomology [2, 7]. Specifically, more recently a magnetic resonance spectroscopy study in combat veterans with PTSD reports an association between low brain GABA concentrations and poor sleep quality providing further evidence about the importance of GABAergic mechanisms mediating certain components of the PTSD phenotype, i.e., abnormal sleep behaviors [37]. Based on this existing body of evidence, Bremner et al. sought to examine $GABA_AR$ volume of distribution in Vietnam veterans with combat-related PTSD using SPECT and the selective radioligand [^{123}I]iomazenil. Consistent with the animal literature, they found a decreased volume of distribution of $GABA_AR$ in the prefrontal cortex of PTSD patients compared to healthy controls. The authors offered three explanations for these findings: (1) stress downregulates $GABA_AR$ expression, (2) stress alters receptor or endogenous ligand affinity, or (3) low levels of $GABA_AR$ exist prior to their traumatic event predisposing the individual to developing PTSD. Regardless of the actual pathophysiology, this group concluded that since these alterations were found within the prefrontal cortex, an area implicated in PTSD, this decrease in $GABA_AR$ has a role in PTSD symptomology [5].

A few years later, the same group conducted a follow-up study to assess the generalizability of their initial findings in Vietnam veterans. They once again employed SPECT and [^{123}I]iomazenil; however, their patient population was limited to Gulf War veterans with PTSD. This group was selected to test whether $GABA_AR$ alterations could be seen after a shorter duration of PTSD. Unlike their original report, they did not find differences in $GABA_AR$ in any brain region between the PTSD group and matched healthy controls. Though the authors offered several explanations for this discrepancy, their primary justification was that the Gulf War study group was experiencing a milder form of PTSD as evidenced by fewer severe symptoms and a shorter duration [20]. In 2008, Geuze et al. continued the investigation into $GABA_AR$ using PET and the ligand [^{11}C]flumazenil in veterans with and without PTSD. Consistent with the animal data and [5], they found significantly reduced $GABA_AR$ binding throughout the frontal cortex, amygdala, hippocampus, and caudate nucleus. The authors discussed possible deficits that may result from $GABA_AR$ within a certain region (Table 13.1). Overall, these three studies provide ample evidence to implicate the $GABA_AR$ in PTSD; however, further work will be required to tease out differences in GABAergic function related to duration, symptom severity, and trauma type [22]. In addition, while neuroimaging has been used to elucidate GABAergic mechanisms in sleep regulation and its dysfunction in PTSD, molecular imaging techniques have not yet sufficiently explored this topic.

Table 13.1 Hypothesized functional deficits in brain regions found to have decreased $GABA_AR$ binding [22]

Region	Functional deficit
Frontal cortex	Working memory
Hippocampus	Modulation of emotional behavior
Amygdala	Fear processing
Caudate nucleus	Implicated in other anxiety disorders

Dopamine

Dopamine is associated with mood, emotion, cognitive functioning, and stress response. Furthermore, dopaminergic dysfunction has been implicated in the hyperarousal symptom cluster commonly seen in PTSD patients [8, 57, 58]. For instance, high plasma and urinary dopamine levels have been reported in traumatized individuals with and without PTSD [14, 18, 26]. In addition, several genetic alterations have been linked to dopaminergic dysfunction in PTSD [6, 16, 51].

Of particular interest in recent years has been variation in the dopamine transporter (DAT) gene (SLC6A3), which functions in synaptic dopamine reuptake. The 9-repetition (9R) allele, a specific variant located at this gene, has been shown to increase PTSD susceptibility [55]. Furthermore, healthy individuals with the 9R allele have demonstrated increased DAT levels in particular brain areas (e.g., [56]). With this evidence in mind, Hoexter et al. performed one of the only molecular imaging studies of dopamine using single-photon emission computed tomography (SPECT) and the selective ligand [^{99m}TC]-TRODAT to investigate DAT density in PTSD compared to trauma-exposed controls. They found increased DAT BP_{ND} in the striatum of the patient group compared to trauma controls, indicating dopaminergic hyperactivity leading to amplified and prolonged fear responses in PTSD [27]. The specific implications of these findings are discussed in Fig. 13.2. Although not yet sufficiently explored using molecular neuroimaging techniques, the association between dopamine dysfunction and abnormal sleep in PTSD [21] was supported by reports that periodic leg movements are often found in sleep disorder patients [28], including PTSD [48]. Similar to other monoaminergic mechanisms, neuroimaging methods have not yet been sufficiently used to explore the specific molecular targets that could play a role in mediating abnormal sleep patterns and nightmares in PTSD. With novel treatments that target this system being currently explored, one would hope that this specific link will be studied in the near future.

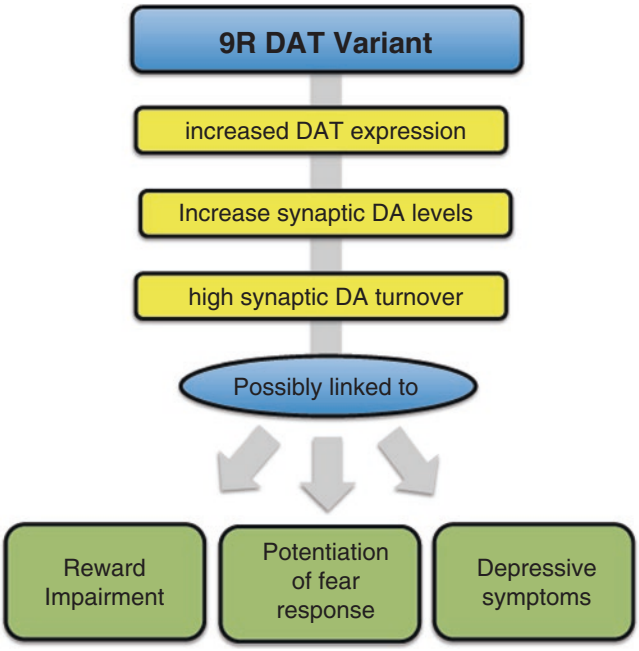

Fig. 13.2 Hypothesized contribution of 9R DAT variant on PTSD characteristics [27]

μ-Opioid Receptor

Preclinical work has suggested that opioidergic mechanisms are implicated in amygdala-regulated processes including feeding behaviors [24], antinociception [53], normal fear responses [60], and conditioned fear [23]. The development of [11C]-carfentanil, a high affinity opiate ligand, made possible the translation of some of these preclinical findings to humans by facilitating the localization of μ-opioid receptors via PET imaging [19].

Abnormal cerebral blood flow in brain areas such as the hippocampus, somatosensory areas, cerebellum, insula, putamen, medial prefrontal cortex, and anterior cingulate cortex is known to be associated with dysfunctional emotional processing [31, 32, 44, 45]. To more clearly understand the mechanisms that underlie these blood flow changes, Liberzon et al. [33] used [^{11}C]-carfentanil and PET in a group of 12 healthy people to examine the functional relationship between blood flow and μ-opioid binding potential, a measure of receptor density. They found that higher baseline binding potential was related to lower blood flow in temporal and basal forebrain regions during exposure to emotionally aversive images. The inverse association between receptor density and regional blood flow implied an inhibitory or anxiolytic role of the endogenous opioid system.

This relationship was further investigated by Zubieta et al. using [^{11}C]-carfentanil and PET in a group of healthy women [61]. They found that during a state of self-induced sadness, μ-opioid receptor density increased in the anterior cingulate, ventral pallidum, amygdala, and inferior temporal cortex, signifying a compensatory response following down-regulation of the endogenous neurotransmitter in these areas. These data further demonstrated a strong link between emotional regulation and μ-opioid neurotransmission.

Liberzon et al. conducted the first study to investigate the role of μ-opioid transmission in PTSD specifically [31, 32]. Rather than using a cognitive activation paradigm like previous related studies, here they investigated baseline μ-opioid binding potential in a group of combat veterans with PTSD, combat-exposed veterans without PTSD, and a healthy control group. Compared to healthy controls, both trauma-exposed groups demonstrated reduced binding potential in the amygdala, nucleus accumbens, dorsal frontal cortex, and insular cortex and increased binding potential in the orbitofrontal cortex. Concerning the PTSD group specifically, data revealed reduced binding potential in the anterior cingulate cortex and increased binding in orbitofrontal cortex. These results validated previous studies concerning the relationship between the μ-opioid system and emotional processing, but, importantly, they revealed a more intricate relationship between this system and PTSD specifically.

Conclusion

The development of novel radioligands has allowed us to explore precise molecular processes that are implicated in the pathophysiology of PTSD via PET imaging. Importantly, molecular quantification of receptors and transporters has enabled us translate hypotheses about neural dysfunction from animal models to the living human brain. However, while there is strong evidence that abnormal sleep and nightmares are key symptoms of PTSD, PET and SPECT imaging techniques have not yet been sufficiently used to describe the neurochemical mechanisms that mediate these symptom domains. Such studies, however, offer the possibility to not only unravel further the etiology of PTSD but have the potential to also support treatment development efforts.

As we continue to explore the pathophysiology of PTSD by using existing radioligands in innovative ways, new radioligands will continue to emerge. Novel targets can be identified through animal experiments and other molecular imaging projects in disorders that are related or comorbid with PTSD. Bailey and Neumeister [1] recently reviewed several animal and human studies of anxiety that implicate altered cannabinoid type 1 (CB1) receptor-mediated signaling in the development of stress-related psychopathology. Furthermore, recent PET imaging with the CB1-selective radioligand [^{11}C]OMAR has demonstrated an upregulation of CB1 receptor density in men with alcohol dependence, a frequent comorbidity with PTSD, when compared to healthy individuals [43]. This work represents one of the many avenues that could be explored in the future with specific ligands and PET imaging. The endocannabinoid system appears of particular interest for better understanding the role of sleep disturbances and its treatment in PTSD given a recent report showing that use of cannabis was particularly high in trauma survivors who aimed to improve their sleep [3].

The data presented in this chapter represent remarkable leaps in our understanding of PTSD, although abnormal sleep which is a core symptom of PTSD has not yet taken advantage of recent developments in this area. However, it is important to recognize the limits of their applications. PTSD is a multiplex disorder whose pathogenesis involves many interconnected neurobiological systems. It is necessary to understand how these individual systems function differently in people with and without PTSD; but to fully understand the pathogenesis of this complex disorder, we must decipher how each of these pieces fits into a larger, more synergetic picture.

References

1. Bailey CR, Neumeister A (2011) Cb1 receptor-mediated signaling emerges as a novel lead to evidencebased treatment development for stress-related psychopathology. Neurosci Lett. 502(1):1–4.
2. Bernardy NC, Lund BC, Alexander B, Friedman MJ. Prescribing trends in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2012;73(3):297–303.
3. Bonn-Miller M, Babson K, Vandrey R. Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend. 2014;136:162–5.
4. Bonne O, Bain E, Neumeister A, Nugent AC, Vythilingam M, Carson RE, Luckenbaugh DA, Eckelman W, Herscovitch P, Drevets WC, Charney DS. No change in serotonin type 1A receptor binding in patients with posttraumatic stress disorder. Am J Psychiatry. 2005;162(2):383–5.
5. Bremner JD, Innis RB, Southwick SM, Staib L, Zoghbi S, Charney DS. Decreased benzodiazepine receptor binding in prefrontal cortex in combat-related posttraumatic stress disorder. Am J Psychiatry. 2000;157(7):1120–6.
6. Broekman BF, Olff M, Boer F. The genetic background to PTSD. Neurosci Biobehav Rev. 2007;31(3):348–62.
7. Capehart BP. Benzodiazepines, posttraumatic stress disorder, and veterans: good news and why we're not done yet. J Clin Psychiatry. 2012;73(3):307–9.
8. Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry. 1993;50(4):295–305.
9. Clark MS, Sexton TJ, McClain M, Root D, Kohen R, Neumaier JF. Overexpression of 5-HT1B receptor in dorsal raphe nucleus using herpes simplex virus gene transfer increases anxiety behavior after inescapable stress. J Neurosci. 2002;22(11):4550–62.
10. Clark MS, Vincow ES, Sexton TJ, Neumaier JF. Increased expression of 5-HT1B receptor in dorsal raphe nucleus decreases fear-potentiated startle in a stress dependent manner. Brain Res. 2004;1007(1–2):86–97.
11. Critchley MA, Handley SL. Effects in the X-maze anxiety model of agents acting at 5-HT1 and 5-HT2 receptors. Psychopharmacology. 1987;93(4):502–6.
12. Cullinan WE, Wolfe TJ. Chronic stress regulates levels of mRNA transcripts encoding beta subunits of the GABA(A) receptor in the rat stress axis. Brain Res. 2000;887(1):118–24.
13. Kilpatrick DG, Koenen KC, Ruggiero KJ, Acierno R, Galea S, Resnick HS, et al. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. Am J Psychiatry. 2007;164:1693–9.
14. De Bellis MD, Baum AS, Birmaher B, Ryan ND. Urinary catecholamine excretion in childhood overanxious and posttraumatic stress disorders. Ann N Y Acad Sci. 1997;821:451–5.

15. Dorow R, Horowski R, Paschelke G, Amin M, Braestrup C. Severe anxiety induced by FG 7142, a β-carboline ligand for benzodiazepine receptors (letter). Lancet. 1983;2:98–9.
16. Drury SS, Theall KP, Keats BJ, Scheeringa M. The role of the dopamine transporter (DAT) in the development of PTSD in preschool children. J Trauma Stress. 2009;22(6):534–9.
17. Fani N, Ashraf A, Afzal N, Jawed F, Kitayama N, Reed L, Bremner JD. Increased neural response to trauma scripts in posttraumatic stress disorder following paroxetine treatment: a pilot study. Neurosci Lett. 2011;491(3):196–201.
18. Friedman MJ, Jalowiec J, McHugo G, Wang S, McDonagh A. Adult sexual abuse is associated with elevated neurohormone levels among women with PTSD due to childhood sexual abuse. J Trauma Stress. 2007;20(4):611–7.
19. Frost JJ, Douglass KH, Mayberg HS, Dannals RF, Links JM, Wilson AA, Ravert HT, Crozier WC, Wagner HN Jr. Multicompartmental analysis of [11C]-carfentanil binding to opiate receptors in humans measured by positron emission tomography. J Cereb Blood Flow Metab. 1989;9(3):398–409.
20. Fujita M, Southwick SM, Denucci CC, Zoghbi SS, Dillon MS, Baldwin RM, Bozkurt A, Kugaya A, Verhoeff NP, Seibyl JP, Innis RB. Central type benzodiazepine receptors in Gulf war veterans with posttraumatic stress disorder. Biol Psychiatry. 2004;56(2):95–100.
21. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry. 2003;54:1092–8.
22. Geuze E, van Berckel BN, Lammertsma AA, Boellaard R, de Kloet CS, Vermetten E, Westenberg HG. Reduced GABAA benzodiazepine receptor binding in veterans with post-traumatic stress disorder. Mol Psychiatry. 2008;13(1):74–83. 3. Epub 2007 Jul 31
23. Good AJ, Westbrook RF. Effects of a microinjection of morphine into the amygdala on the acquisition and expression of conditioned fear and hypoalgesia in rats. Behav Neurosci. 1995;109(4):631–41.
24. Gosnell BA. Involvement of mu opioid receptors in the amygdala in the control of feeding. Neuropharmacology. 1988;27(3):319–26.
25. Lee HJ, Lee MS, Kang RH, Kim H, Kim SD, Kee BS, et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. Depress Anxiety. 2005;21:135–9.
26. Hamner MB, Diamond BI. Elevated plasma dopamine in posttraumatic stress disorder: a preliminary report. Biol Psychiatry. 1993;33(4):304–6.
27. Hoexter MQ, Fadel G, Felício AC, Calzavara MB, Batista IR, Reis MA, Shih MC, Pitman RK, Andreoli SB, Mello MF, Mari JJ, Bressan RA. Higher striatal dopamine transporter density in PTSD: an in vivo SPECT study with [(99m)Tc]TRODAT-1. Psychopharmacology (Berl). 2012;224:337–45.
28. Hornyak M, Feige B, Rieman D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance, and treatment. Sleep Med Rev. 2006;10(3):169–77.
29. Hu J, Henry S, Gallezot JD, Ropchan J, Neumaier JF, Potenza MN, Sinha R, Krystal JH, Huang Y, Ding YS, Carson RE, Neumeister A. Serotonin 1B receptor imaging in alcohol dependence. Biol Psychiatry. 2010;67(9):800–3.
30. Kolassa IT, Ertl V, Eckart C, Glockner F, Kolassa S, Papassotiropoulos A, et al. Association study of trauma load and SLC6A4 promoter polymorphism in posttraumatic stress disorder: evidence from survivors of the Rwandan genocide. J Clin Psychiatry. 2010;71:543–7.
31. Liberzon I, King AP, Britton JC, Phan KL, Abelson JL, Taylor SF. Paralimbic and medial prefrontal cortical involvement in neuroendocrine responses to traumatic stimuli. Am J Psychiatry. 2007;164(8):1250–8.
32. Liberzon I, Taylor SF, Phan KL, Britton JC, Fig LM, Bueller JA, Koeppe RA, Zubieta JK. Altered central micro-opioid receptor binding after psychological trauma. Biol Psychiatry. 2007;61(9):1030–8. Epub 2006 Aug 30
33. Liberzon I, Zubieta JK, Fig LM, Phan KL, Koeppe RA, Taylor SF. Mu-opioid receptors and limbic responses to aversive emotional stimuli. Proc Natl Acad Sci U S A. 2002;99(10):7084–9.
34. Lin D, Parsons LH. Anxiogenic like effect of serotonin1Breceptor stimulation in the rat elevated plusmaze. Pharmacol Biochem Behav. 2002;71(4):581–7.
35. Lin HC, Tseng YC, Mao SC, Chen PS, Gean PW. GABAA receptor endocytosis in the basolateral amygdala is critical to the reinstatement of fear memory measured by fear-potentiated startle. J Neurosci. 2011;31(24):8851–61.
36. Medina JH, Novas ML, Wolfman CNV, De Stein ML, De Robertis E. Benzodiazepine receptors in rat cerebral cortex and hippocampus undergo rapid and reversible changes after acute stress. Neuroscience. 1983;9:331–5.
37. Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. Sleep. 2014;37(5):893–900.
38. Monti JM. Serotonin control of sleep-wake behavior. Sleep Med Rev. 2011;15(4):269–81.
39. Murrough JW, Czermak C, Henry S, Nabulsi N, Gallezot JD, Gueorguieva R, Planeta-Wilson B, Krystal JH, Neumaier JF, Huang Y, Ding YS, Carson RE, Neumeister A. The effect of early trauma exposure on serotonin type 1B receptor expression revealed by reduced selective radioligand binding. Arch Gen Psychiatry. 2011;68(9):892–900.
40. Murrough JW, Henry S, Hu J, Gallezot JD, Planeta-Wilson B, Neumaier JF, Neumeister A. Reduced ventral striatal/ventral pallidal serotonin1B receptor binding potential in major depressive disorder. Psychopharmacology (Berl). 2011;213(2–3):547–53.
41. Murrough JW, Huang Y, Hu J, Henry S, Williams W, Gallezot JD, Bailey CR, Krystal JH, Carson RE, Neumeister A. Reduced amygdala serotonin transporter binding in posttraumatic stress disorder. Biol Psychiatry. 2011;70(11):1033–8.
42. Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, Eckelman W, Herscovitch P, Charney DS, Drevets WC. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci. 2004;24:589–91.
43. Neumeister A, Normandin MD, Murrough JW, Henry S, Bailey CR, Luckenbaugh DA, Tuit K, Zheng MQ, Galatzer-Levy IR, Sinha R, Carson RE, Potenza MN, Huang Y. Positron emission tomography shows elevated cannabinoid CB (1) receptor binding in men with alcohol dependence. Alcohol Clin Exp Res. 2012;36:2104–9. 2
44. Osuch EA, Benson B, Geraci M, Podell D, Herscovitch P, McCann UD, Post RM. Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. Biol Psychiatry. 2001;50(4):246–53.
45. Osuch EA, Willis MW, Bluhm R, CSTS Neuroimaging Study Group, Ursano RJ, Drevets WC. Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. Biol Psychiatry. 2008;64(4):327–35.
46. Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, et al. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry. 2009;66:1201–9.
47. Roman V, Walstra I, Luiten PG, Meerlo P. Too little sleep gradually desensitizes the serotonin 1A receptor system. Sleep. 2005;28(12):1505–10.
48. Ross RJ, Ball WA, Dinges DF, Kribbs NB, Morrison AR, Silver SM, Mulvaney FD. Motor dysfunction during sleep in posttraumatic stress disorder. J Sleep Res Sleep Med. 1994;17(8):723–32.
49. Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]

WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry. 2000;57:174–80.
50. Sari Y. Serotonin 1B receptors: from protein to physiological function and behavior. Neurosci Biobehav Rev. 2004;28(6):565–82.
51. Segman RH, Cooper-Kazaz R, Macciardi F, Goltser T, Halfon Y, Dobroborski T, Shalev AY. Association between the dopamine transporter gene and posttraumatic stress disorder. Mol Psychiatry. 2002;7(8):903–7.
52. Stein DJ, Davidson J, Seedat S, Beebe K. Paroxetine in the treatment of posttraumatic stress disorder: pooled analysis of placebo-controlled studies. Expert Opin Pharmacother. 2003;4(10):1829–38.
53. Tershner SA, Helmstetter FJ. Antinociception produced by mu opioid receptor activation in the amygdala is partly dependent on activation of mu opioid and neurotensin receptors in the ventral periaqueductal gray. Brain Res. 2000;865(1):17–26.
54. Toth M. 5-HT1A receptor knockout mouse as a genetic model of anxiety. Eur J Pharmacol. 2003;463:177–84.
55. Valente NL, Vallada H, Cordeiro Q, Miguita K, Bressan RA, Andreoli SB, Mari JJ, Mello MF. Candidate-gene approach in posttraumatic stress disorder after urban violence: association analysis of the genes encoding serotonin transporter, dopamine transporter, and BDNF. J Mol Neurosci. 2011;44(1):59–67. Epub 2011 Mar 29
56. van de Giessen E, de Win MM, Tanck MW, van den Brink W, Baas F, Booij J. Striatal dopamine transporter availability associated with polymorphisms in the dopamine transporter gene SLC6A3. J Nucl Med. 2009;50(1):45–52.
57. Vermetten E, Bremner JD. Circuits and systems in stress. I. Preclinical studies. Depress Anxiety. 2002;15(3):126–47.
58. Vermetten E, Bremner JD. Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. Depress Anxiety. 2002;16(1):14–38.
59. Weizman R, Weizman A, Kook KA, Vocci F, Deutsch SI, Paul SM. Repeated swim stress alters brain benzodiazepine receptors measured in vivo. J Pharmacol Exp Ther. 1989;249:701–7.
60. Wilson MA, Junor L. The role of amygdala mu-opioid receptors in anxiety-related responses in two rat models. Neuropsychopharmacology. 2008;33(12):2957–68.
61. Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA. Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch Gen Psychiatry. 2003;60(11):1145–53.

Part IV

Assessment of Sleep in Relation to Combat-Related PTSD

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The following ten chapters on sleep assessment in sleep- and combat-related PTSD provide a comprehensive resource of information on what is known clinically regarding sleep aspects of PTSD, approaches to their assessment in clinical and clinical-research settings, and select issues highly relevant to sleep and PTSD from clinical sleep medicine and the basic science of sleep. Highlights include a comprehensive guide to general PTSD assessment including segments that apply directly to sleep (Blevins et al. of Chapter 14) and discussion of the limitations of assessing sleep only through primary PTSD instruments and how they can be enhanced by instruments designed to directly assess sleep. Vasdev and Shapiro discuss sleep disturbances more appropriately being considered core than "secondary" symptoms of PTSD that prominently include insomnia, nightmare awakenings, as well as abrupt awakenings with anxiety absent recall of dreams. Germain et al. reminds us of a broader spectrum of disruptive nocturnal behaviors that are reported with PTSD and the advantages and limitations of various modalities that can be used for their assessment. Khawaja et al. provide a comprehensive review of the use of actigraphy, a modality that has the advantages of providing extended objective assessment in naturalistic environments, along with the limitations of measuring body movement and not direct activity of the brain. The current relevance of this discussion is heightened by the growing popular use of related commercial technology for self-monitoring.

From the aforementioned chapters, the reader can discern the status of the current state of knowledge regarding fundamental issues that the PTSD sleep field has addressed for several decades and has historically seemed to some to represent a conundrum [1]. The content, however, provides relative current consensus around such issues including the near ubiquity of subjective sleep disturbances with PTSD and their modest and variable manifestations with standard physiological assessments. One caveat to such observations is the possible effect of setting where the laboratory anecdotally can provide a feeling of safety and unusually good sleep for the subject with PTSD. In addition, as Germain et al. remind the reader, there are tools that can look beyond the surface electrode or movement sensor, and brain imaging and (less definitively) spectral EEG have indicated alterations of arousal states during sleep with PTSD.

Then there is the matter of rapid eye movement (REM) sleep, long implicated in PTSD due to the association of REM sleep with dreaming and the prominent abnormal dream experiences of many with PTSD. It now seems relatively clear that PTSD is not associated with characteristic abnormalities of the amount or timing of REM sleep (in contrast with major depression).

Positive findings do include fragmented patterns of REM sleep during the early development of PTSD [2] and with PTSD in association with early life trauma [3]. A meta-analysis supported elevated eye movement density during REM sleep with PTSD [4]. The chapter by Woodward et al. provides sorely needed information regarding polysomnographic correlates of nightmare awakenings, an issue that has previously been addressed by limited data and assumptions. In their substantial series, nightmare awakenings are preceded by both REM and non-REM sleep although the association with REM sleep far exceeds the proportion of total sleep represented by REM. In addition, there were associations of more elaborate dream content and trends associating nightmare distress with the amount of preceding REM sleep. While confirming that not all relevant dream mentation in PTSD is REM related, the findings clearly support the need to investigate the REM sleep state to better understand how emotional processing during sleep is altered in PTSD.

Three remaining chapters are noteworthy for addressing emerging issues in the sleep PTSD field. One addresses comorbidity with sleep apnea (Krakow et al. of Chapter 21) for which there are studies not indicating an increased association of sleep apnea and PTSD to studies (of the chapter's authors) where the association is almost ubiquitous. Criticism of one of the studies not finding an increased association as utilizing inadequately sensitive methods raises an alternative consideration of whether the more sensitive methods employed by the authors identify alterations to breathing and arousal that are a consequence of pathological anxiety. The evidence for high rates for sleep breathing disorders in at least some PTSD populations, with independent replication among studies of Veterans, is compelling and, even more so, is the clinically important evidence that treatment of co-occurring sleep apnea will improve PTSD. Analysis of heart rate variability (HRV) as a tool for interrogating autonomic function is discussed in informative detail by van Boxtel et al. While the chapter reviews mixed data regarding daytime autonomic balance, our laboratory has recently found evidence for compromise of the normal shift toward parasympathetic dominance during sleep with PTSD [5]. If replicated, such patterns of nocturnal autonomic function may come to be considered important determinants of daytime function and health risk with PTSD. Finally, two chapters (Spoormaker of Chapter 19; Lipinska et al. of Chapter 23) address sleep and memory and learning. Recent interest in sleep's impact on memory and learning in PTSD has been influenced by a burgeoning cognitive neuroscience literature linking learning, memory, and sleep. These chapters emphasize disruption of learning consolidation during sleep by increased arousal thereby affecting extinction learning and declarative memory. While both of these represent important impairments in PTSD, might there be potential modifications of emotional memory during sleep in addition to consolidation (particularly during REM sleep) that can serve to beneficially alter the perspective and emotional state of a well-rested person? Harnessing such capacities may provide important means for reducing the suffering and improving the lives of people with PTSD.

References

1. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep—what a nightmare! Sleep Med Rev. 2000;4(2):183–200.
2. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatry. 2002;159(10):1696–701.
3. Insana SP, Kolko DJ, Germain A. Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. Biol Psychol. 2012;89(3):570–9.
4. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44(4):660–9.
5. Kobayashi I, Lavela J, Mellman TA. Nocturnal autonomic balance and sleep in posttraumatic stress disorder and resilience. J Traumatic Stress. 2014;27(6):712–6.

Assessment of Posttraumatic Stress Disorder

14

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Assessment of Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a chronic and debilitating mental disorder that represents a pathological outcome following exposure to catastrophic life events such as combat, physical or sexual assault, transportation accidents, and natural disasters. PTSD is a multifaceted syndrome comprising multiple related but distinct symptom clusters (reexperiencing the trauma, avoidance of trauma-related reminders, emotional numbing, hyperarousal) and often co-occurs with other mental disorders such as depression, anxiety disorders, and substance use disorders. PTSD also often co-occurs with sleep disorders such as insomnia and obstructive sleep apnea, which, in addition to arousal-related sleep disturbance included in the symptom criteria for PTSD, highlights the importance of assessing sleep among those with PTSD.

Originally classified as an anxiety disorder when it was introduced as a mental disorder in *DSM-III* in 1980, PTSD is now grouped in the trauma- and stressor-related disorders in *DSM-5*, along with other disorders with a stressful life event as a diagnostic criterion, including reactive attachment disorder, disinhibited social engagement disorder, acute stress disorder, and adjustment disorders. In addition to this reclassification, a number of substantive revisions to the PTSD diagnostic criteria were made for *DSM-5*. These include (a) a more specific explication of Criterion A and removing Criterion A2 requiring an emotional response to the trauma of fear, horror, or helplessness; (b) an increase from 17 to 20 symptom criteria, with three new symptoms and revision of several existing symptoms; (c) an increase from three to four symptom clusters, with the separation of avoidance symptoms from numbing symptoms and a reconceptualization of the numbing symptoms as negative alterations in cognitions and mood; and (d) the addition of a dissociative subtype. Further, diagnostic criteria for children 6 years old or younger are specified separately. Perhaps the most significant change to the PTSD criteria is the separation of avoidance and numbing, a decision made primarily on the basis of factor analytic evidence that these are distinct symptom clusters (e.g., [41]).

The complexity of the typical clinical presentation of PTSD poses significant challenges for psychological assessment. Fortunately, over the last 30 years, substantial progress has been made in the development and validation of a wide range of assessment measures for a variety of research and clinical applications. In this chapter we describe a number of the most widely used measures used in the assessment of PTSD, including interviews, self-report measures, brief screening measures, multiscale inventories, and measures of closely related symptoms such as dissociation, guilt, and sleep disturbance. Due to space limitations, we limit our review to PTSD measures for adults and do not cover assessment of trauma exposure, assessment of PTSD in children, or assessment of acute stress disorder or complex PTSD. Recent reviews on these topics may be found elsewhere (e.g., [8, 32]).

Given that *DSM-5* was only recently released, many descriptions of the measures and the summaries of their supporting psychometric evidence are based on *DSM-IV* or earlier versions of the PTSD diagnostic criteria. Presumably most of the measures discussed will be updated for *DSM-5*, and the psychometric properties of the revised versions will be investigated. For those measures that have been revised for *DSM-5*, including the Clinician-Administered PTSD Scale (CAPS) and PTSD Checklist

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(PCL), we summarize the specific revisions and related psychometric evidence.

Review of Assessment Instruments

In this section we review the most widely used assessment instruments of PTSD symptomatology in traumatized adults. We begin with a review of structured interviews and self-report measures, which are further categorized based on whether or not they correspond directly with *DSM* diagnostic criteria. This is followed by a section on brief screening measures and multiscale inventories that include a PTSD scale. Last, we review assessment instruments for dissociation and posttraumatic guilt.

Although we do not discuss assessment of trauma exposure in detail, it is important to note at the outset the importance of establishing Criterion A in diagnosing PTSD. To meet full diagnostic criteria for PTSD, an individual must not only have all the requisite symptoms, but these symptoms must have developed in response to a stressful life event that satisfies the definition of a trauma as described in Criterion A. Although the definition of Criterion A has evolved since *DSM-III* (see [113], for a full discussion), the essence of a traumatic stressor is exposure to an event involving life threat or serious injury, through directly experiencing the event, witnessing it, or learning about it happening to a loved one. Some of the instruments described below include items assessing trauma exposure. Those that do not may be supplemented by administration of one of many available trauma exposure measures (for a review, see [42, 98, 107]). Some of the most widely used stand-alone trauma exposure measures include the Life Stressor Checklist – Revised (LSC-R; [127]), Trauma History Questionnaire (THQ; [60]), and Traumatic Life Events Questionnaire (TLEQ; [79]). Both the LSC-R and TLEQ include assessment of A2 (e.g., experience of fear, helplessness, or horror at the time of the event), while the THQ assesses only A1 (e.g., experienced an event involving actual or threatened death or serious injury). All three instruments assess for a wide variety of potentially traumatic events including natural disaster, combat, serious accident, life-threatening illness, and sexual and physical assault. Another trauma exposure measure, the Life Events Checklist for *DSM-5* (LEC-5; [118]), was recently updated to reflect changes to Criterion A in *DSM-5*. The LEC was originally developed as the trauma assessment component of the Clinician-Administered PTSD Scale (discussed below). The revised version is available in two formats, standard and extended. The standard version is a checklist that assesses for different levels of exposure (e.g., experienced, witnessed, learned about) to 17 categories of potentially traumatic events. The extended version includes the standard version plus a series of questions designed to identify the worst event and determine whether it meets the definition of a trauma according to *DSM-5* Criterion A.

Structured Interviews

Structured interviews are essential tools in the assessment and diagnosis of psychopathology. Because the prompts are standardized, structured interviews promote systematic and comprehensive coverage of all diagnostic criteria. Further, interviews provide clinicians the opportunity to clarify potentially confusing symptoms and other diagnostic criteria to ensure that respondents know what is being asked. Finally, and most importantly, interviews allow clinicians to use clinical judgment to evaluate the relevance and severity of respondents' symptom reports. For these reasons, structured interviews are considered to be the gold standard for diagnosing mental disorders and are used as the criterion in evaluating the performance of self-report measures. In this section we briefly review five of the most widely used structured interviews for the assessment of PTSD.

Clinician-Administered PTSD Scale

Developed in 1989 at the National Center for PTSD, the Clinician-Administered PTSD Scale (CAPS; [12, 13]) is one of the most widely used and extensively validated structured interviews for PTSD. The CAPS assesses all *DSM-IV* PTSD criteria, including Criterion A, the 17 DSM-IV PTSD symptoms, and degree of functional impairment. In addition, the CAPS assesses associated symptoms of dissociation and guilt, response validity, overall symptom severity, and degree of improvement since a prior assessment. Further, for symptoms that are not inherently linked to the index traumatic event – including the emotional numbing, hyperarousal, and dissociative symptoms – the CAPS assesses the degree of trauma relatedness, using a specific prompt and three-point rating scale (definitely, probably, unlikely). The CAPS may be used to assess PTSD over the past month, the past week, or the worst month lifetime.

The CAPS provides standardized initial and follow-up prompts to assess the frequency and intensity of each symptom, which are rated on separate five-point (0–4) rating scales. Prompts and rating scales reference specific behavioral anchors to increase precision and enhance reliability. Frequency and intensity scores for each item may be summed to create a symptom severity score, and frequency, intensity, and severity scores may be summed across items to create composite scores for each symptom cluster and for the full PTSD syndrome.

A number of scoring rules have been developed and evaluated for converting CAPS symptom ratings into a dichotomous PTSD diagnosis [115]. The most commonly used rule is the F1/I2 rule, which involves considering items with a frequency rating of 1 or higher and an intensity score of 2 or higher as symptom endorsed, then following the *DSM-IV* diagnostic rule (1 reexperiencing symptom, 3 avoidance/numbing symptoms, and 2 hyperarousal symptoms). The CAPS has been extensively evaluated and has been shown to have excellent psychometric properties in a wide range of populations and settings [116].

The CAPS has been revised for *DSM-5*, and the resulting CAPS-5 [117] is currently undergoing psychometric evaluation. The goals for the revision were to (a) achieve concordance with *DSM-5* PTSD criteria by adding items to assess new symptoms and revising existing items to accurately reflect modifications to existing symptoms and (b) streamline administration and scoring while (c) maintaining backward compatibility insofar as possible with the CAPS for *DSM-IV*. The CAPS-5 still provides standard initial and follow-up prompts to evaluate the frequency and intensity of symptoms, but prompts are presented in a more user-friendly format and sequence. Further, although interviewers still make interim ratings of frequency and intensity, they combine this information, using prespecified thresholds, to make a final rating of symptom severity on a single 0–4 scale. This approach, including the symptom-specific threshold values, is based on one of the previously developed rationally derived CAPS scoring rules, the Clinician-Rated 60 (CR60) rule.

PTSD Symptom Scale: Interview Version

The PTSD Symptom Scale – Interview Version (PSS-I; [51]) is a 17-item structured interview with each item corresponding to one of the 17 *DSM-IV* PTSD symptom criteria. Interviewers ask a brief initial prompt for each criterion and then rate severity over the past 2 weeks on a four-point scale (0 = not at all, 1 = once per week or less/a little, 2 = two to four times per week/somewhat, 3 = 5 or more times per week/very much). The original *DSM-III-R* version of the PSS-I included anchors describing only intensity (e.g., 1 = a little), which was later revised to include anchors describing both intensity and frequency, albeit on a single scale. The PSS-I yields symptom severity and diagnostic data. A total symptom severity score is obtained by summing ratings for all 17 items. A PTSD diagnosis is obtained by counting symptoms rated as one or greater as present and applying the *DSM-IV* diagnostic rule.

PSS-I scores have demonstrated strong psychometric properties. Foa et al. [51] found the PSS-I to have good reliability, as indicated by an alpha of 0.85 and mean item-scale total correlation of 0.45. Test-retest reliability for the total severity score also was high (0.80), as was the kappa coefficient for a PTSD diagnosis (0.91). Using the SCID-PTSD module as the criterion, the PSS-I demonstrated excellent diagnostic utility, with sensitivity of 0.94, specificity of 0.96, and efficiency of 0.94. Extending Foa et al.'s [51] initial psychometric study, Foa and Tolin [50] provided further evidence for the reliability, internal consistency, and convergent validity of the PSS-I. Additionally, the PSS-I was found to have greater diagnostic sensitivity when compared to the CAPS. In sum, the PSS-I appears to be a reliable and valid instrument of PTSD with good diagnostic utility. It is easy to administer and yields both symptom severity and diagnostic information. Disadvantages of the PSS-I include relatively limited evidence of discriminant validity and the assessment of symptoms over the past 2 weeks instead of the past month, which is the time frame required to make a PTSD diagnosis.

The PSS-I has been revised for *DSM-5*, and the PSS-I-5 [49] has demonstrated initial psychometric merit. Foa et al. [53] provided initial evidence for the internal consistency (alpha = 0.89), test-retest reliability ($r = 0.87$), interrater reliability (kappa = 0.84), and convergent and discriminant validity of the PSS-I-5 with several other measures of PTSD and related constructs. Although similar to the original PSS-I in structure and format, one notable change is the assessment of symptoms over the past month instead of the past 2 weeks.

Structured Clinical Interview for DSM-IV: PTSD Module

The Structured Clinical Interview for *DSM-IV* (SCID; [46]) is a comprehensive interview assessing all major psychiatric disorders, including PTSD. The PTSD module of the SCID (SCID-PTSD) may be administered as part of the full interview or independently as a stand-alone measure. In the SCID-PTSD, interviewers ask a trauma exposure screening question followed by 17 questions assessing the 17 PTSD symptom criteria. The interview may be discontinued at the point at which symptom criteria are not met. Each symptom is rated on a three-point scale (1 = absent, 2 = subthreshold, and 3 = threshold, with an additional rating of ? = inadequate information), and a PTSD diagnosis is obtained by counting symptoms rated as present and applying the *DSM-IV* diagnostic rule. The SCID-PTSD does not yield a PTSD symptom severity score.

The SCID-PTSD historically has been regarded as the gold standard PTSD assessment instrument against which many other measures are compared. In the National Vietnam Veterans Readjustment Study (NVVRS), the SCID-PTSD demonstrated high interrater reliability with coefficients of 0.94 and 0.87 for lifetime and current diagnoses, respectively

[80]. It also was found to have strong convergent validity with the Mississippi Scale (kappa = 0.53) and the PK scale of the MMPI (kappa = 0.48) and adequate to excellent sensitivity and specificity (0.81 and 0.89, respectively) when compared against a composite PTSD diagnosis [81]. More recently, the strong reliability of the SCID-PTSD has been replicated by Zanarini and Frankenburg [130] and Lobbestael et al. [83]. In addition to the psychometric evidence for the 17 symptom items, the trauma exposure screening question has also demonstrated good sensitivity and specificity [43]. The SCID was recently revised for *DSM-5* (SCID-5, [47]) but information regarding the psychometric properties of the SCID-5 PTSD module is not yet available.

Composite International Diagnostic Interview: PTSD Module

The Composite International Diagnostic Interview (CIDI; [128]) is another comprehensive interview assessing most major psychiatric disorders. The CIDI was intended for use in large epidemiological studies and is based on the Diagnostic Interview Schedule (DIS; [103]). It expands on the DIS, which assesses *DSM* diagnostic criteria, by also assessing diagnostic criteria of the *International Classification of Diseases* (ICD), to allow for cross-national comparative studies. A revised and expanded version of the CIDI was introduced by the World Health Organization in 1998, which included a greatly expanded PTSD module that could be administered in conjunction with or independent of the full interview. The PTSD module (CIDI-PTSD) includes a comprehensive assessment of lifetime trauma exposure, 17 items assessing PTSD symptoms, and 2 items assessing trauma-related guilt. The CIDI-PTSD also includes items assessing clinical distress and functional impairment. Each item is rated using a yes/no format. The latest version of the CIDI (CIDI 3.0; [73]) is similar in format and content to its earlier version and is available in more than 30 languages.

Numerous studies have examined the psychometric properties of the various versions of the CIDI (for reviews, see [4, 76, 124]), but fewer studies have examined the psychometric properties of the CIDI-PTSD. In an examination of initial version of the CIDI-PTSD across five sites, Peters et al. [101] found the CIDI-PTSD to demonstrate good internal consistency, with an alpha of 0.76 and 0.86 for the ICD 10 and *DSM-III-R* diagnostic criteria, respectively. In the same study, the CIDI-PTSD exhibited poor to good concurrent validity with a clinician diagnosis, with kappa of 0.26 and 0.66 for *DSM-III-R* and ICD 10 diagnoses, respectively. Using the latest version of the CIDI (Version 3.0), Haro et al. [62] found adequate agreement between the CIDI-PTSD and SCID-PTSD (kappa = 0.49 for lifetime prevalence). Similarly, Kimerling et al. [75] found adequate agreement between the CIDI-PTSD and CAPS (kappa = 0.56 for lifetime prevalence). In sum, the CIDI-PTSD appears to demonstrate adequate reliability and concurrent validity. Its structured design is suitable for its intended use in large epidemiological studies, but the yes/no format and lack of symptom severity rating make it less useful in a clinical setting.

Structured Interview for PTSD

The Structured Interview for PTSD (SIP; [37]) is a 19-item structured interview with 17 items corresponding to the 17 PTSD symptom criteria and 2 items assessing trauma-related guilt. The interview was originally introduced as the SI-PTSD [35], but was renamed the SIP at the time of its revision from assessing *DSM-III* to *DSM-IV* PTSD criteria. Interviewers ask a series of initial prompts and follow-up questions for each criterion and then rate severity on a five-point scale (0–4). Rating scale anchors are supplemented with descriptors to help clarify the meaning of each rating and reflect a combination of frequency, severity, and functional impairment. The SIP yields current and lifetime symptom severity and diagnostic data. Total symptom severity score is obtained by summing ratings for all 19 items; an alternative symptom severity score corresponding to *DSM-IV* criteria also may be calculated by excluding the two guilt items. A PTSD diagnosis is obtained by counting the symptoms rated as two or greater as present and applying the *DSM-IV* diagnostic rule.

SIP scores have demonstrated strong psychometric properties. The original version of the interview has shown high internal consistency (alpha = 0.94), good test-retest (0.71) and interrater (0.97–0.99) reliability, and high diagnostic agreement with the SCID-PTSD (kappa = 0.79) [35]. Similarly, the revised SIP has shown high internal consistency (alpha = 0.80), test-retest reliability (0.89), and interrater reliability (0.90) [37]). In sum, the SIP appears to demonstrate strong psychometric properties. It has the advantage of offering symptom severity and diagnostic information, as well as information about guilt. The major disadvantage of the SIP is the relatively limited number of studies examining its psychometric properties.

Self-Report Measures

DSM Correspondent

PTSD Checklist

The PTSD Checklist (PCL; [114]) is a 17-item *DSM*-correspondent self-report measure of PTSD. Developed in

1990 at the National Center for PTSD, the PCL was originally based on *DSM-III-R* criteria, was revised in 1994 for *DSM-IV*, and recently was revised again for *DSM-5*. PCL items consist of short phrases reflecting *DSM* symptom criteria. Respondents are instructed to indicate how much they were bothered by each symptom in the past month, using a five-point (1 = not at all to 5 = extremely) rating scale. There are three versions of the PCL (military, civilian, and specific), which differ only in how the stressful event is labeled in the first eight items, i.e., the items that specifically mention an index event. The military version (PCL-M) refers to "a stressful military experience," the civilian version (PCL-C) refers to "a stressful experience from the past," and the specific version (PCL-S) refers to "the stressful experience," which respondents are instructed to identify before completing the symptom items. The PCL may be used as a continuous measure of PTSD symptom severity for symptom clusters or for the entire PTSD syndrome by summing scores over items within a given cluster or by summing all 17 items. The PCL may also be used to derive a dichotomous PTSD diagnosis by considering each item rated as "2 = moderately" or higher as a symptom endorsed, then following the DSM-IV diagnostic rule.

The PCL is one of the most widely used self-report PTSD measures. It has been thoroughly investigated in a wide range of trauma populations and has excellent psychometric properties [122]. The PCL has been used for screening (e.g., [5]), measuring changes in symptom severity in treatment studies (e.g., [54]), estimating PTSD prevalence (e.g., [65]), and predicting PTSD diagnostic status based on a structured interview (e.g., [14]). The PCL has been the basis for much of the extensive confirmatory factory analytic literature that has identified the symptom structure of PTSD [41] and led to the separation of avoidance and numbing into distinct clusters in DSM-5.

The PCL was recently revised for *DSM-5*. Notable changes include (a) an increase from 17 to 20 items, with creation of new items and revision of existing items to achieve correspondence with DSM-5 criteria for PTSD, and (b) a change in the rating scale from 1–5 to 0–4. In addition, instead of military, civilian, and specific versions as for the PCL, the PCL-5, like the specific version of the PCL, requires that an index event be identified before responding to symptom items. There are three versions of the PCL-5, one with a brief Criterion A section that helps respondents identify an index event, one with the extended version of the LEC-5, and one without a Criterion A section, for use when an index event has been identified by some other method. Initial studies examining the psychometric properties of the PCL-5 have provided strong evidence for its internal consistency, test-retest reliability, and convergent and discriminant validity [16, 19, 129].

Posttraumatic Stress Diagnostic Scale

The Posttraumatic Stress Diagnostic Scale (PDS; [48]) is the revised version of the Modified Posttraumatic Stress Scale – Self-Report Version (MPSS – SR; [45]), which is a slightly revised version of the original Posttraumatic Stress Scale – Self-Report Version (PSS – SR; [51]). Modifications across the different versions include slight rewording of items, inclusion of frequency and severity ratings, and change in time frame assessed. The most recently modified PDS is a 49-item self-report instrument assessing all six *DSM-IV* PTSD criteria with 21 items assessing exposure to a traumatic event (Criterion A), 17 items assessing PTSD symptoms (Criterion B–D), 2 items assessing duration (Criterion E), and 9 items assessing functional impairment (Criterion F). Symptoms are assessed over the past month and rated on a four-point scale (0 = not at all or only one time, 1 = once a week or less/once in a while, 2 = two or four times a week/half the time, 3 = five or more times a week/almost always). The PDS yields a continuous symptom severity score and a dichotomous diagnostic score, with items rated as 1 or greater counted as symptoms endorsed.

The PDS has been demonstrated to have strong psychometric properties in several studies. Foa et al. [52] found the PDS to have high internal consistency (alpha = 0.92), good test-retest reliability (0.92), and good diagnostic utility when compared with the SCID-PTSD (sensitivity = 0.89, specificity = 0.75, kappa = 0.65). In the same study, the PDS demonstrated strong convergent validity with another PTSD measure but poor discriminant validity with a depression measure. The reliability, convergent and discriminant validity, and diagnostic utility of PDS scores have more recently been extended to a wide variety of trauma populations [1, 6, 61]. Taken together, the PDS appears to be a well-validated self-report instrument assessing all *DSM* PTSD criteria.

The PDS was recently revised for *DSM-5*, with the resulting PDS-5 including 17 items assessing trauma exposure, 20 items assessing PTSD symptoms, 2 items assessing distress and impairment, and 2 items assessing symptom onset and duration. Symptoms are assessed over the past month and rated on a slightly modified four-point scale (0 = not at all, 1 = once a week or less/once in a while, 2 = two or three times a week/somewhat, 3 = four or five or more times a week/very much, and 4 = six or more times a week/severe). An initial study of the PDS-5 provided evidence for internal consistency (alpha = 0.95), test-retest reliability (r = 0.90), and convergent and discriminant validity [53].

Davidson Trauma Scale

The Davidson Trauma Scale (DTS; [33]) is a self-report measure with 17 items corresponding to the 17 PTSD symptoms. Symptoms are assessed over the past week and are rated on separate scales for frequency (0 = not at all, 1 = once only, 2 = two to three times, 3 = four to six times, 4 = every

day) and severity (0 = not all distressing, 1 = minimally distressing, 2 = moderately distressing, 3 = markedly distressing, 4 = extremely distressing). The DTS was designed to yield a symptom severity score, but its diagnostic utility also has been examined in several studies.

DTS scores have demonstrated high internal consistency (alpha >0.90 for frequency, severity, and total scores), good test-retest reliability (0.86), and moderate convergent validity with other PTSD measures (0.64–0.78) [36]. The reliability, internal consistency, and convergent and discriminant validity of the DTS have been replicated in several studies (e.g., [1, 91]). Although no scoring rules exist for converting frequency and severity items into symptom counts, several DTS total score cutoffs have been suggested and investigated with regard to diagnostic utility. Cutoff scores of 40 and 32 have indicated high sensitivity and specificity in two separate studies [36, 91]; however, Adkins et al. [1] found the diagnostic utility of the DTS using a cutoff score of 43 to be significantly lower than two other self-report PTSD measures. Thus, the DTS has demonstrated stronger psychometric properties as a continuous symptom severity measure than as a dichotomous diagnostic tool.

Detailed Assessment of Posttraumatic Stress

The Detailed Assessment of Posttraumatic Stress (DAPS; [23]) is a comprehensive 104-item self-report instrument assessing *DSM-IV* PTSD diagnostic criteria and other trauma-related phenomena. It includes two validity scales assessing positive and negative response bias; four trauma specification scales assessing trauma exposure, onset, peritraumatic distress, and peritraumatic dissociation; four posttraumatic stress scales assessing PTSD symptoms and impairment; and three associated features scales assessing trauma-specific dissociation, substance abuse, and suicidality. PTSD symptoms are assessed for the past month and rated on a five-point Likert scale (1 = never, 2 = less than once a week, 3 = about once a week, 4 = two or three times a week, 5 = four or more times a week). Raw scale scores are converted to T-scores based on a normative sample of trauma survivors, with T>65 indicating a clinically significant elevation. The DAPS yields symptom severity and diagnostic information. Decision rules for making a probable PTSD diagnosis are included in the DAPS professional manual.

The DAPS has strong psychometric properties. Briere [23] found all of the clinical scales to have relatively high internal consistency with alphas ranging from 0.67 to 0.98 with a mean of 0.88. The PTSD symptom scales were strongly correlated with other PTSD scales including the CAPS, PCL, Civilian Mississippi Scale, and Impact of Event Scale (*r*s = 0.68–0.89) and less strongly correlated with less closely related constructs including measures of depression (0.61–0.78), somatization (0.32–0.47), antisocial personality features (0.23–0.27), and mania (−0.01–0.10). Additionally, the PTSD symptom scales demonstrated strong diagnostic utility when compared with the CAPS (sensitivity = 0.88, specificity = 0.86, kappa = 0.73). Advantages of the DAPS include comprehensive coverage of both core and associated features of PTSD, validity scales, and standardized norms. Disadvantages include its length and the limited number of studies investigating its psychometric properties.

Non-DSM Correspondent

Impact of Event Scale and Impact of Event Scale-Revised

The Impact of Event Scale (IES; [67]) is one of the first self-report measures of posttraumatic responses. It contains 15 items and is based on Horowitz's [66] conceptualization of reactions to extreme stressors and covers two primary symptom domains, intrusion and avoidance. The scale was revised in 1997 with seven additional items: six items assessing hyperarousal and one item assessing dissociative flashbacks (IES – R; [120]). Symptoms are assessed over the past week and rated on a five-point Likert scale for severity (0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, 4 = extremely). The IES – R was designed as a continuous measure of symptom severity and does not yield diagnostic information [119].

The original IES has demonstrated adequate reliability and internal consistency [67, 109]; however, its convergent and discriminant validity have been questioned. In a review of 23 studies using the IES, Sundin and Horowitz [109] reported wide variability in the convergent validity between the intrusion and avoidance scales and other measures of PTSD (0.49–0.79 for intrusion, 0.29–0.80 for avoidance). A similar pattern of psychometric characteristics has been found for the IES – R, with evidence supporting its reliability and internal consistency [1, 9, 120], but questioning its convergent validity (e.g., [9]). Additionally, the IES – R hyperarousal items have demonstrated lower internal consistency and reliability than the intrusion and avoidance items [7, 9]. In reference to the convergent validity of the IES – R, Beck et al. [9] noted that the seemingly low convergent validity of the IES – R with other measures of PTSD may not necessarily reflect poorly on its psychometric properties, but rather reflect differences in content coverage.

Unlike many other measures of PTSD, the IES – R was not designed to correspond directly to the *DSM* PTSD criteria and does not directly assess all 17 PTSD symptom criteria (e.g., sense of foreshortened future, diminished interest). The relatively limited coverage of posttraumatic stress responses provided by IES – R items is its main disadvantage. Advantages include its popularity in clinical research and translation into a number of different languages.

Mississippi Scale for Combat-Related PTSD and Civilian Mississippi Scale

The Mississippi Scale for Combat-Related PTSD [72] is another of the earliest self-report measures of posttraumatic stress and for many years was the most widely used measure of combat-related PTSD. The Mississippi Scale consists of 35 items assessing PTSD symptoms, trauma-related guilt, and suicidality. Items are rated on a five-point Likert scale with verbal anchors indicating either frequency (e.g., 1 = never to 5 = very frequently) or the degree to which a respondent considers the item to be true (e.g., 1 = not at all true to 5 = extremely true). The Mississippi Scale has excellent psychometric properties and was selected as one of the primary measures of combat-related PTSD in the National Vietnam Veterans Readjustment Study (NVVRS; [80]).

To assess PTSD symptoms in civilians in the NVVRS, the Civilian Mississippi Scale (CMS) was developed. Four items were added to the CMS to provide better coverage of *DSM-III-R* criteria for PTSD, and existing items referring to the military were rephrased. In 1996, Norris and Perilla developed a revised version of the scale, the Revised Civilian Mississippi Scale (RCMS), with 30 items, including 28 items from the original CMS and 2 new items assessing intrusion symptoms. Eighteen items are linked to a traumatic event, while the other 12 items are not. Unlike the original CMS which uses different rating scale anchors depending on item content, the RCMS uses a single five-point Likert scale (1 = not at all true, 2 = slightly true, 3 = somewhat true, 4 = very true, 5 = extremely true). Items are summed to create total and subscale (reexperiencing, avoidance, and hyperarousal) symptom severity scores.

CMS scores have shown high internal consistency (alpha = 0.89) and split-half reliability (0.80) [111]. Additionally, the RCMS scores also have exhibited high internal consistency (0.88 and 0.92) in English and Spanish versions [99]. When used as a diagnostic measure (with symptoms endorsed at three or greater counted as present), RCMS had 84% diagnostic agreement with the CIDI-PTSD [100]. Other psychometric studies of the CMS and RCMS have failed to support its psychometric merit. Lauterbach et al. [82] found a stronger association between CMS with measures of general distress than with other measures of PTSD. In addition, Adkins et al. [1] found the CMS to have poorer convergent and discriminant validity than several other measures of PTSD. Furthermore, a few studies have found weaker psychometric properties for the ten CMS items that are reverse scored, suggesting a need for further item-level analyses [18, 68].

In sum, the CMS and RCMS have demonstrated strong reliability but questionable convergent and discriminant validity. This inconsistent psychometric support is the main limitation to using the CMS or RCMS. Strengths include the assessment of clinically relevant associated features (e.g., guilt) and its relatively short scale length.

Trauma Symptom Inventory

Among the self-report measures reviewed in this chapter, the Trauma Symptom Inventory (TSI; [22]) provides the most comprehensive coverage of trauma-related symptomatology and dysfunction. The 100-item TSI includes three validity scales (response level, atypical response, and inconsistent response) and ten clinical scales (anxious arousal, depression, anger/irritability, intrusive experiences, defensive avoidance, dissociation, sexual concerns, dysfunctional sexual behavior, impaired self-references, and tension reduction behavior). Symptom frequency is assessed within the past 6 months on a four-point Likert scale (0 = never to 3 = often) and is not directly linked to a specific traumatic event. Standardized norms and T-scores are available. Briere [26] recently published a revised version of the TSI, the TSI – 2, with 136 items, 3 additional scales (insecure attachment, somatic preoccupations, and suicidality), and 2 additional subscales (hyperarousal and other directedness).

The TSI clinical scales have demonstrated good internal consistency with mean alphas ranging from 0.82 to 0.87 across three studies [22, 27, 104]. In the original psychometric evaluation, Briere [22] also found TSI scores to demonstrate acceptable convergent, predictive, and incremental validity. Seven of the ten TSI clinical scales have been demonstrated to differentiate PTSD and non-PTSD groups, with the strongest diagnostic utility for the anxious arousal and defensive avoidance scales [88]. In addition, TSI clinical scales exhibited good convergent validity with PTSD and other conceptually related symptom measures [6, 89, 106]. Last, several studies have examined the utility of the TSI validity scales in malingering detection (e.g., [6, 39, 40]). Although the original TSI validity scales were generally not found to be effective – the substantially modified atypical response scale in the TSI – two have exhibited significant improvement in its ability to detect malingering [59].

In sum, the TSI has demonstrated strong psychometric properties, and the TSI-2 is a promising new instrument warranting further psychometric investigation. Although the length of the TSI may yield its administration unfeasible in certain settings, its comprehensive coverage of posttraumatic responses provides useful clinical information for treatment planning.

Brief Screening Measures

Unfortunately, traumatic events capable of eliciting PTSD often affect more than one individual at a time. Large-scale traumatic events such as war and natural disasters can overwhelm health and mental health care resources, making swift assessment of needs and vulnerability essential to inform tri-

age decisions. Further, in some settings, such as primary care clinics, there is a need for very brief measures for routine assessment of potential PTSD. Screening instruments such as those described in this section meet this need by allowing rapid preliminary assessment of likely PTSD diagnostic status. Unlike the longer diagnostic measures described above, PTSD screening measures do not assess full diagnostic criteria, focusing instead only on the symptoms, associated features, and correlates best capable of successfully and efficiently predicting PTSD diagnosis [20].

Trauma Screening Questionnaire

The Trauma Screening Questionnaire (TSQ) is an abbreviated version of the PSS-SR intended for screening purposes [21, 51]. The TSQ consists of ten items tapping reexperiencing and hyperarousal symptoms, modified to allow two (yes/no) rather than four response options. The TSQ demonstrated good reliability and diagnostic utility in both the initial validation study and more recently in a large sample of assault victims administered 1–3 weeks posttrauma [112] and a large sample of trauma-exposed individuals with psychotic disorders [38]. Of note, updating it to reflect *DSM-5* criteria would require addition of a single item concerning reckless or destructive behavior [2].

SPAN

The SPAN [34] is an abbreviated version of the DTS adapted for use as a brief screening instrument. The measure is named for the four items startle, physiological arousal, anger, and numbness. According to the limited research available, the SPAN has demonstrated screening performance comparable to that of the full DTS [20, 92]. Of note, however, some have questioned the content validity of the SPAN given that it does not include items referring to cardinal PTSD symptoms of reexperiencing and avoidance [55].

Primary Care PTSD Screen

The Primary Care PTSD Screen (PC-PTSD; [31]) is a four-item screening questionnaire commonly administered in both VA medical centers and community-based outpatient clinics [30]. Each yes/no item corresponds to one of the four symptom groups commonly associated with PTSD (reexperiencing, hyperarousal, avoidance, and emotional numbing). The PC-PTSD has demonstrated good reliability [102] and acceptable diagnostic utility using a cutoff of three according to limited number of published reports [17, 74]. A revised version of the PC-PTSD for DSM-5 is under development [97].

Multiscale Inventories

In addition to stand-alone measures, some multiscale inventories, such as the MMPI-2 and PAI discussed in this section, include PTSD scales. Multiscale inventories are useful in the assessment of PTSD because they assess a wide range of psychopathology, including many disorders commonly comorbid with PTSD such as depression, anxiety, and substance use disorders. They may also include response validity scales to detect random responding and over- or underreporting of symptoms, which are particularly valuable in forensic contexts, when the veracity of self-report might be in question.

MMPI-2

The MMPI-2 is the most widely used psychological test [58] and has been examined extensively in the assessment of PTSD. The earliest studies, conducted with male combat veterans and using the original MMPI, resulted in the identification of a characteristic F-2-8 profile and a specialized PTSD, the PK scale [44, 70]. Subsequent research regarding a characteristic profile has found considerable heterogeneity in individual profiles, although scales F, 2, and 8 are among the most common elevations (e.g., [57, 123]).

The original PK scale comprised 49 MMPI items found to empirically differentiate Vietnam veterans with and without PTSD. When the MMPI was revised, three redundant PK items were dropped, and one item was reworded, resulting in the current 46-item PK scale on the MMPI-2 [84]. Keane et al. [70] found that a raw score cutoff of 30 on the original PK scale had good diagnostic utility with 82% correct classification in two separate samples. The diagnostic utility of the PK scale has generally been supported, although cutoffs and correct classification rates have varied across studies [58]. The PK scale has been used to assess PTSD in civilian trauma samples, although some concern has been raised that it may function more as a measure of nonspecific distress than as a measure of PTSD specifically (e.g., [93, 105, 121]). The PK scale has also been investigated as a stand-alone measure of PTSD and appears to perform as well in this format as it does when embedded in the full MMPI-2 [64, 85].

To date, only one published study has focused on use of the MMPI-2 to assess *DSM-5* PTSD. Specifically, Koffel and colleagues [77] used items from a shorter, restructured form of the MMPI-2 (MMPI-2-RF; [10]) to create scales capable of assessing novel *DSM-5* PTSD criteria. The generated scales showed poor specificity in that they correlated similarly with PTSD, depression, and substance use disorders. In light of Koffel and colleagues' results, Wolf and Miller [125] speculated that the MMPI-2 general distress scale (RCd) might be the strongest predictor of DSM-5 PTSD. Continued investigation of the MMPI-2's utility in assessing DSM-5 PTSD is warranted.

PAI

The Personality Assessment Inventory (PAI; [94]) is a 344-item multiscale inventory that, like the MMPI-2, assesses a wide range of psychopathology as well as various forms of response bias. In contrast to the MMPI-2, the PAI was

developed using a construct-validation approach that enhances both content validity and discriminant validity. Further, the PAI includes a specialized PTSD scale, the Traumatic Stress (ARD-T) subscale of the Anxiety-Related Disorder (ARD) scale. Although ARD-T does not cover all *DSM* criteria for PTSD, it was designed to directly assess PTSD symptoms and associated features and includes five items assessing reexperiencing symptoms and three items assessing guilt, experiential avoidance, and loss of interest.

As with other PAI scales, ARD-T scores are provided as T-scores. Given the discrepancy between the relatively high base rate of trauma exposure and comparatively low incidence of PTSD, a conservative cutoff of 90 T on ARD-T is recommended for use in clinical populations [94]. In a nonclinical sample of trauma-exposed adult women, McDevitt-Murphy et al. [89] found that ARD-T scores of 70 T or higher resulted in acceptable diagnostic efficiency for PTSD. That study and others with similar focus have established the utility of ARD-T in the assessment of PTSD (e.g., [90]). Of note, given that ARD-T was not intended to reflect the entire spectrum of PTSD symptomatology, caution should be exercised before relying on ARD-T scores in isolation in diagnostic decision-making [95]. Morey also developed a series of diagnostic rules included in the accompanying PAI software program intended to facilitate accurate diagnosis which include the PTSD LOGIT function, an actuarial formula designed to identify those with PTSD by pulling information from a variety of scales. While the PTSD LOGIT function has not been extensively studied and validated to date, a recent study by Calhoun et al. [29] supported its utility in assessing PTSD by demonstrating that PTSD LOGIT diagnostic performance was consistent with other well-validated PTSD assessment measures including the CAPS.

Assessment of Other Trauma-Related Symptoms

In addition to the classic symptoms of PTSD, individuals exposed to trauma may experience a number of other trauma-related symptoms. In this section we discuss two of the most common of these, dissociation and guilt. Both of these are particularly relevant to *DSM-5* PTSD diagnostic criteria. DSM-5 now includes a dissociative subtype, characterized by prominent depersonalization and derealization. In addition, *DSM-5* includes three new symptoms potentially related to guilt, including exaggerated negative beliefs about oneself, others, or the world, distorted blame of self or others about the cause or consequences of the trauma, and persistent negative emotional state such as fear, horror, anger, guilt, or shame. In this section, we also discuss trauma-related sleep disturbance, which is one of the most frequent complaints among those with PTSD and important to assess in any PTSD evaluation.

Dissociation

Dissociation is defined as the disintegration of usually integrated processes such as consciousness, memory, identity, or perception of the environment [3]. Numerous studies have indicated a relationship between dissociation and exposure to traumatic stressors, and many researchers consider dissociation to be a common posttraumatic response [25] and precipitating the addition of a dissociative subtype of PTSD in *DSM-5*. At present, the Dissociative Subtype of PTSD Scale (DSPS; [126]) is the only published measure explicitly designed to assess for dissociative PTSD. Initial investigation of the 15-item self-report measure supported its psychometric properties and revealed a three-factor structure (depersonalization/derealization, loss of awareness, and psychogenic amnesia).

Additionally, several of the PTSD instruments described above include dissociation specific items or subscales (e.g., CAPS-5, DAPS, TSI). Those PTSD instruments that do not assess dissociation may be supplemented by the administration of an instrument specifically dedicated to the assessment of dissociative experiences. One such instrument is the Peritraumatic Dissociative Experiences Questionnaire (PDEQ; [86]). The ten-item PDEQ assesses dissociative responses occurring during or immediately after a traumatic event. Symptom severity is rated on a five-point Likert scale (1 = not at all true to 5 = extremely true). The PDEQ is one of the most widely used self-report measures of peritraumatic dissociation and has been demonstrated to have strong psychometric properties (for a review, see [87]).

Another widely used self-report dissociation measure is the Dissociative Experiences Scale (DES; [11]). The 28-item DES assesses general dissociative symptoms that are not linked to a specific traumatic event. Symptom frequency is rated on a scale from 0% to 100% in increments of 10%. Although the DES was created as a general dissociation measure, several factor analytic studies have identified three subscales: amnesia, absorption, and depersonalization (for a review, see [108]). As a general dissociation measure, the psychometric properties of the DES have been supported [11, 110].

The Multiscale Dissociation Inventory (MDI; [24]) is a more recently developed dissociation measure with 30 items assessing six types of dissociation: disengagement, depersonalization, derealization, emotional constriction, memory disturbance, and identity dissociation. Symptom frequency is assessed over the past month on a five-point Likert scale (1 =

never to 5 = very often). One strength of the MDI is the availability of standardized norms to assist in the interpretation of clinically significant endorsement of dissociative symptomatology. Although the number of studies investigating the psychometric properties of the MDI is limited, available studies have consistently supported its psychometric merit [15, 24].

Guilt

The development and experience of guilt subsequent to trauma is a frequent and clinically significant sequela of PTSD, so much so that in *DSM-5* – within the new symptom of persistent experience of negative emotions – guilt was formally added to the diagnostic criteria [28, 63]. Recognizing the important connection between guilt and PTSD, Kubany et al. [78] developed the Trauma-Related Guilt Inventory (TRGI), a 32-item measure designed specifically to assess for event-specific trauma-related guilt. TRGI questions are rated on a five-point scale with variable response options across subscales. The TRGI can be divided into three distinct subscales measuring global (trait) guilt, guilt-related cognitions, and the affective components of guilt. Based on both the initial validation studies performed by Kubany and colleagues and subsequent investigations (see [96] for a review), the TRGI has been shown to possess good psychometric properties across a variety of trauma populations.

Trauma-Related Sleep Disturbance

Nightmares and sleep problems are part of the diagnostic criteria for PTSD, and sleep disturbance has long been recognized as an area of significant distress and impairment to those exposed to trauma. All of the *DSM*-correspondent PTSD measures described above assess nightmares and sleep problems because these are two of the core symptoms of PTSD. However, assessment of sleep disturbance is typically limited to just these two problems, and they are generally assessed with just one item each. Given the strong connection between trauma and sleep disturbance, many clinical and research contexts may require a more detailed assessment using a focal measure. The Pittsburgh Sleep Quality Index – Addendum for PTSD (PSQI-A; [56]) is one of the only self-report measures specifically assessing trauma-related sleep disturbance. It includes seven items assessing the frequency of sleep disturbances common to PTSD rated on a four-point scale ("not during the past month" to "three or more times a week"), as well as three additional items assessing the severity of trauma-related nightmares rated on a four-point scale ("none" to "severe"). Based on the initial validation study by Germain et al. [56] and a more recent validation study by Insana et al. [69], the PSQI-A demonstrated strong internal consistency and convergent validity. It has since been translated in several other languages and shown to possess satisfactory psychometric properties.

Summary and Conclusions

In this chapter we have described a number of the most commonly used measures for assessing PTSD and associated features in adult trauma survivors. Clinicians and investigators now have available a wide range of well-validated assessment instruments for evidence-based assessment of PTSD, including structured interviews, self-report measures, and multiscale inventories. Each type of measure has strengths and limitations. Structured interviews administered by an experienced clinician are considered the gold standard for diagnosis, but are time-consuming and expensive. Self-report measures are easy to administer and score and are particularly useful for large-scale assessments, but are subject to symptom exaggeration or minimization. Brief screening measures require minimal time and effort to administer and score, but do not provide full coverage of the PTSD syndrome. Multiscale inventories provide information about comorbid conditions and response bias, but are time-consuming and do not provide full coverage of PTSD.

A multimethod approach, involving a structured interview, one or more self-report measures, and a multiscale inventory, would be ideal and has long been advocated in PTSD assessment (e.g., [71, 81]). However, in some assessment contexts, this may be too burdensome to implement routinely. In such cases, we recommend administering a structured interview whenever possible. If an interview is not feasible, a well-validated DSM-correspondent self-report measure would be the next best choice, especially if it has been validated against a structured interview specifically in the target population. Brief screening measures are typically followed up by referrals for more intensive evaluations.

If a multimethod approach is feasible, an important consideration is how best to sequence administration of the various measures. There is no one-size-fits-all solution. However, one practical option is to (a) have clients complete any preliminary paperwork and screening measures, such as a trauma exposure checklist; (b) briefly review screening measures and move to a standard intake interview, which typically includes an overview of the client's main problems and chief complaint, a psychosocial history, and a mental status exam; (c) shift to a more detailed focus on trauma and PTSD, using a structured PTSD interview as well as any additional focal interviews for PTSD-related problems such as dissociation, guilt, and sleep disturbance; and (d) finish by having the respondent complete any additional questionnaires, including measures of PTSD and related problems and

multiscale inventories. Within this sequence, sleep disturbance may be assessed at several different points. First, clients may volunteer it as one of their main problems or even their chief complaint. Second, sleep disturbance in general is typically assessed in a mental status exam. Third, sleep disturbance linked specifically to the index traumatic event is assessed in a PTSD interview. Finally, additional details regarding sleep disturbance, including severity ratings, are obtained from PTSD questionnaires, focal sleep questionnaires, and multiscale inventories.

With the publication of *DSM-5*, most of the measures discussed in this chapter will need to be revised to be consistent with the new PTSD diagnostic criteria, and more research will need to be conducted to evaluate not only the psychometric properties of the new versions. Revisions of some measures are already available and undergoing psychometric evaluation, including the CAPS-5 and PCL-5, and can be used in clinical and research applications at least tentatively as the field of traumatic stress transitions to the *DSM-5* criteria and awaits definitive empirical evidence regarding the reliability and validity of *DSM-5*-correspondent measures.

References

1. Adkins JW, Weathers FW, McDevitt-Murphy M, Daniels JB. Psychometric properties of seven self-report measures of posttraumatic stress disorder in college students with mixed civilian trauma exposure. J Anxiety Disord. 2008;22:1393–402.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th text revision ed. Washington, DC: American Psychiatric Association.
4. Andrews G, Peters L. The psychometric properties of the composite international diagnostic interview. Soc Psychiatry Psychiatr Epidemiol. 1998;33:80–8.
5. Andrykowski MA, Cordova MJ, Studts JL, Miller TW. Posttraumatic stress disorder after treatment for breast cancer: prevalence of diagnosis and use of the PTSD checklist—civilian version (PCL-C) as a screening instrument. J Consult Clin Psychol. 1998;66:586–90.
6. Arbisi PA, Erbes CR, Polusny MA, Nelson NW. The concurrent and incremental validity of the trauma symptom inventory in wome n reporting histories of sexual maltreatment. Assessment. 2010;17:406–18.
7. Baumert J, Simon H, Gundel H, Schmitt C, Ladwig K. The impact of event scale – revised: evaluation of the subscales and correlations to psychophysiological startle response patterns in survivors of a life-threatening cardiac event: an analysis of 129 patients with an implanted cardioverter defibrillator. J Affect Disord. 2004;82:29–41.
8. Beck JG, Sloane DM. The Oxford handbook of traumatic stress disorders. New York: Oxford University Press; 2012.
9. Beck JG, Grant DM, Read JP, Clapp JD, Coffey SF, Miller LM, Palyo SA. The Impact of event scale – revised: psychometric properties in a sample of motor vehicle accident survivors. J Anxiety Disord. 2008;22:187–98.
10. Ben-Porath YS, Tellegen A. MMPI-2-RF (Minnesota Multiphasic Personality Inventory-2-Restructured Form): manual for administration and scoring. Minneapolis: University of Minnesota Press; 2008.
11. Bernstein EM, Putnam FW. Development, reliability, and validity of a dissociation scale. J Nerv Ment dis. 1986;174:727–35.
12. Blake D, Weathers F, Nagy L, Kaloupek D, Klauminzer G, Charney D, Keane T. Clinician-Administered PTSD Scale (CAPS). Boston: National Center for Post-traumatic Stress Disorder. Behavioral Science Division; 1990.
13. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8:75–90.
14. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). Behav Res Ther. 1996;34:669–73.
15. Blevins CA, Weathers FW, Mason EA. Construct validity of three depersonalization measures in trauma-exposed college students. J Trauma Dissociation. 2012;13:539–53.
16. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for *DSM-5* (PCL-5): development and initial psychometric evaluation. J Trauma Stress. 2015;28:489–98.
17. Bliese PD, Wright KM, Adler AB, Cabrera O, Castro CA, Hoge CW. Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. J Consult Clin Psychol. 2008;76(2):272.
18. Bourque LB, Shen H. Psychometric characteristics of Spanish and English versions of the civilian Mississippi scale. J Trauma Stress. 2005;18:719–28.
19. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, Keane TM. Psychometric properties of the PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (PCL-5) in veterans. Psychological Assessment. Advance online publication, http://dx.doi.org/10.1037/pas0000254. 2015.
20. Brewin CR. Systematic review of screening instruments for adults at risk of PTSD. J Trauma Stress. 2005;18(1):53–62.
21. Brewin CR, Rose S, Andrews B, Green J, Tata P, McEvedy C, Turner S, Foa EB. Brief screening instrument for post-traumatic stress disorder. Br J Psychiatry. 2002;181(2):158–62.
22. Briere J. Trauma Symptom Inventory (TSI). Odessa: Psychological Assessment Resources; 1995.
23. Briere J. Detailed Assessment of Posttraumatic Stress (DAPS). Odessa: Psychological Assessment Resources; 2001.
24. Briere J. Multiscale Dissociation Inventory (MDI). Odessa: Psychological Assessment Resources; 2002.
25. Briere J. Dissociative symptoms and trauma exposure: specificity, affect dysregulation, and posttraumatic stress. J Nerv Ment Dis. 2006;194:78–82.
26. Briere J. Trauma Symptom Inventory – 2 (TSI – 2). Odessa: Psychological Assessment Resources; 2011.
27. Briere J, Elliott DM, Harris K, Cotman A. Trauma symptom inventory: psychometrics and association with childhood and adult victimization in clinical samples. J Interpers Violence. 1995;10:387–401.
28. Browne KC, Trim RS, Myers US, Norman SB. Trauma-related guilt: conceptual development and relationship with posttraumatic stress and depressive symptoms. J Trauma Stress. 2015;28(2):134–41.
29. Calhoun PS, Boggs CD, Crawford EF, Beckham JC. Diagnostic efficiency of the Personality Assessment Inventory LOGIT function for posttraumatic stress disorder in women. J Pers Assess. 2009;91:409–15.
30. Calhoun PS, McDonald SD, Guerra VS, Eggleston AM, Beckham JC, Straits-Troster K, VA Mid-Atlantic MIRECC OEF/OIF

Registry Workgroup. Clinical utility of the primary care-PTSD screen among US veterans who served since September 11, 2001. Psychiatry Res. 2010;178(2):330–5.
31. Cameron RP, Gusman D. The primary care PTSD screen (PC-PTSD): development and operating characteristics. Prim Care Psychiatr. 2003;9(1):9–14.
32. Courtois CA, Ford JD. Treating complex traumatic stress disorders: an evidence-based guide. New York: Guilford; 2009.
33. Davidson J. Davidson trauma scale (DTS). North Tonawanda: Multi-Health Systems; 1996.
34. Davidson J. SPAN Addendum to DTS manual. New York: Multi-Health Systems; 2002.
35. Davidson JRT, Smith R, Kudler H. Validity and reliability of the *DSM-III* criteria for posttraumatic stress disorder: experience with a structured interview. J Nerv Ment Dis. 1989;177:336–41.
36. Davidson JRT, Book SW, Colket JT, Tupler LA, Roth S, David D, Feldman ME. Assessment of a new self-rating scale for posttraumatic stress disorder. Psychol Med. 1997;27:153–60.
37. Davidson JRT, Malik MA, Travers J. Structured interview for PTSD (SIP): psychometric validation for DSM-IV criteria. Depress Anxiety. 1997;5:127–9.
38. de Bont PA, van den Berg DP, van der Vleugel BM, de Roos C, de Jongh A, van der Gaag M, van Minnen A. Predictive validity of the Trauma Screening Questionnaire in detecting posttraumatic stress disorder in patients with psychotic disorders. Br J Psychiatry. 2015;206(5):408–16.
39. Edens JF, Otto RK, Dwyer TJ. Susceptibility of the trauma symptom inventory to malingering. J Pers Assess. 1998;71:379–92.
40. Efendov AA, Sellbom ML, Bagby RM. The utility and comparative incremental validity of the MMPI-2 and trauma symptom inventory validity scales in the detection of feigned posttraumatic stress disorder. Psychol Assess. 2008;20:317–26.
41. Elhai JD, Palmieri PA. The factor structure of posttraumatic stress disorder: a literature update, critique of methodology, and agenda for future research. J Anxiety Disord. 2011;25:849–54.
42. Elhai JD, Gray MJ, Kashdan TB, Franklin CL. Which instruments are most commonly used to assess traumatic event exposure and posttraumatic effects?: a survey of traumatic stress professionals. J Trauma Stress. 2005;18:541–5.
43. Elhai JD, Franklin LC, Gray MJ. The SCID PTSD module's trauma screen: validity with two samples in detecting trauma history. Depression Anxiety. 2008;25:737–41.
44. Fairbank JA, Keane TM, Malloy PF. Some preliminary data on the psychological characteristics of Vietnam veterans with posttraumatic stress disorders. J Consult Clin Psychol. 1983;51:912–9.
45. Falsetti SA, Resnick HS, Resick PA, Kilpatrick DG. The modified PTSD symptom scale: a brief self-report measure of posttraumatic stress disorder. Behav Ther. 1993;16:161–2.
46. First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for DSM-IV Axis I disorders (SCID-I), clinical version. Washington, DC: American Psychiatric Association; 1996.
47. First MB, Williams JB, Karg RS, Spitzer RL. Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV). Arlington: American Psychiatric Association; 2015.
48. Foa EB. Posttraumatic Stress Diagnostic Scale (PDS). Minneapolis: National Computer Systems; 1995.
49. Foa EB, Capaldi S. Manual for the administration and scoring of the PTSD symptom scale – interview for DSM-5 (PSS-I-5). Retrieved from https://www.div12.org/wp-content/uploads/2014/11/PSSI-5-Manual.pdf. 2013.
50. Foa EB, Tolin DF. Comparison of the PTSD symptom scale-interview version and the clinician-administered PTSD scale. J Trauma Stress. 2000;13:181–91.
51. Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J Trauma Stress. 1993;6:459–73.
52. Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. Psychol Assess. 1997;9:445–51.
53. Foa EB, McLean CP, Zang Y, Zhong J, Powers MB, Kauffman BY, Rauch S, Porter K, Knowles K. Psychometric properties of the posttraumatic diagnostic scale for DSM-5 (PDS-5). Psychol Assess. Advance online publication. 2015. http://dx.doi.org/10.1037/pas0000259.
54. Forbes D, Creamer M, Biddle D. The validity of the PTSD checklist as a measure of symptomatic change in combat-related PTSD. Behav Res Ther. 2001;39:977–86.
55. Ford JD. Posttraumatic stress disorder: scientific and professional dimensions. New York: Academic; 2009.
56. Germain A, Hall M, Krakow B, Shear MK, Buysse DJ. A brief sleep scale for posttraumatic stress disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. J Anxiety Disord. 2005;19:233–44.
57. Glenn DM, Beckham JC, Sampson WS, Feldman ME, Hertzberg MA, Moore SD. MMPI-2 profiles of Gulf and Vietnam combat veterans with chronic posttraumatic stress disorder. J Clin Psychol. 2002;58:371–81.
58. Graham JR. MMPI-2: assessing personality and psychopathology. 5th ed. New York: Oxford University Press; 2012.
59. Gray MJ, Elhai JD, Briere J. Evaluation of the atypical response scale of the trauma symptom inventory – 2 in detecting simulated posttraumatic stress disorder. J Anxiety Disord. 2010;24:447–51.
60. Green B. Trauma history questionnaire. In: Stamm BH, Varra EM, editors. Measurement of stress, trauma, and adaptation. Lutherville: Sidran Press; 1996. p. 366–8.
61. Griffin MG, Uhlmansiek MH, Resick PA, Mechanic MB. Comparison of the posttraumatic stress disorder scale versus the clinician-administered posttraumatic stress disorder scale in domestic violence survivors. J Trauma Stress. 2004;17:497–503.
62. Haro JM, Arbabzadeh-Bouchez S, Brugha TS, De Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. Int J Methods Psychiatr Res. 2006;15:167–80.
63. Hendin H, Haas AP. Suicide and guilt as manifestations of PTSD. Am J Psychiatr. 1991;148(5):586–91.
64. Herman DS, Weathers FW, Litz BT, Keane TM. Psychometric properties of the embedded and stand-alone versions of the MMPI-2 Keane PTSD Scale. Assessment. 1996;3:437–42.
65. Hoge CW, McGurk D, Thomas J, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med. 2008;358:453–63.
66. Horowitz MJ. Stress response syndromes. New York: Jason Aronson; 1976.
67. Horowitz MJ, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med. 1979;41:209–18.
68. Inkelas M, Loux LA, Bourque LB, Widawski M, Nguyen LH. Dimensionality and reliability of the Civilian Mississippi Scale for PTSD in a post-earthquake community. J Trauma Stress. 2000;13:149–67.
69. Insana SP, Hall M, Buysse DJ, Germain A. Validation of the Pittsburgh Sleep Quality Index Addendum for Posttraumatic Stress Disorder (PSQI-A) in US male military veterans. J Trauma Stress. 2013;26:192–200.
70. Keane TM, Malloy PF, Fairbank JA. Empirical development of an MMPI subscale for the assessment of combat-related posttraumatic stress disorder. J Consult Clin Psychol. 1984;52:888–91.

71. Keane TM, Wolfe J, Taylor KL. Post-traumatic stress disorder: evidence for diagnostic validity and methods of psychological assessment. J Clin Psychol. 1987;43:32–43.
72. Keane TM, Caddell JM, Taylor KL. Mississippi scale for combat-related posttraumatic stress disorder: three studies in reliability and validity. J Consult Clin Psychol. 1988;56:85–90.
73. Kessler RC, Ustun TB. The World Mental Health (WMH) survey initiative of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int J Methods Psychiatr Res. 2004;13:93–121.
74. Kimerling R, Ouimette P, Prins A, Nisco P, Lawler C, Cronkite R, Moos RH. BRIEF REPORT: utility of a short screening scale for DSM-IV PTSD in primary care. J Gen Intern Med. 2006;21(1):65–7.
75. Kimerling R, Serpi T, Weathers F, Kilbourne AM, Kang H, Collins JF, Cypel Y, Frayne S, Furey S, Huang G, Reinhard MJ. Diagnostic accuracy of the Composite International Diagnostic Interview (CIDI 3.0) PTSD module among female Vietnam-era veterans. J Trauma Stress. 2014;27:160–7.
76. Kobak KA, Skodol AE, Bender DS. Diagnostic measures for adults. In: Rush AJ, First MB, Blacker D, editors. Handbook of psychiatric measures. 2nd ed. Arlington: American Psychiatric Publishing; 2008. p. 35–60.
77. Koffel E, Polusny MA, Arbisi PA, Erbes CR. A preliminary investigation of the new and revised symptoms of posttraumatic stress disorder in *DSM-5*. Depress Anxiety. 2012;29:731–8.
78. Kubany ES, Haynes SN, Abueg FR, Manke FP, Brennan JM, Stahura C. Development and validation of the Trauma-Related Guilt Inventory (TRGI). Psychol Assess. 1996;8(4):428.
79. Kubany E, Haynes S, Leisen M, Owen J, Kaplan A, Watson S, Burns K. Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: the Traumatic Life Events Questionnaire. Psychol Assess. 2000;12:210–24.
80. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. Trauma and the Vietnam war generation: report of findings from the National Vietnam Veterans Readjustment Study. New York: Brunner/Mazel; 1990.
81. Kulka RA, Schlenger WE, Fairbank JA, Jordan BK, Hough RL, Marmar CR, Weiss DS. Assessment of posttraumatic stress disorder in the community: prospects and pitfalls from recent studies of Vietnam veterans. Psychol Assess. 1991;3:547–60.
82. Lauterbach D, Vrana S, King DW, King LA. Psychometric properties of the Civilian Version of the Mississippi PTSD Scale. J Trauma Stress. 1997;10:499–513.
83. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother. 2011;18:75–9.
84. Lyons JA, Keane TM. Keane PTSD Scale: MMPI and MMPI-2 update. J Trauma Stress. 1992;5:111–7.
85. Lyons JA, Scotti JR. Comparability of two administration formats of the Keane Posttraumatic Stress Disorder Scale. Psychol Assess. 1994;6:209–11.
86. Marmar CR, Weiss DS, Metzler TJ. Peritraumatic dissociation and posttraumatic stress disorder. In: Bremner JD, Marmar CR, editors. Trauma, memory, and dissociation. Washington, DC: American Psychiatric Association; 1998. p. 229–52.
87. Marmar CR, Metzler TJ, Otte C. The Peritraumatic dissociative experiences questionnaire. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guilford Press; 2004. p. 144–67.
88. McDevitt-Murphy ME, Weathers FW, Adkins JW. The use of the Trauma Symptom Inventory in the assessment of PTSD symptoms. J Trauma Stress. 2005;18:63–7.
89. McDevitt-Murphy ME, Weathers FW, Adkins JW, Daniels JB. Use of the Personality Assessment Inventory in assessment of posttraumatic stress disorder in women. J Psychopathol Behav Assess. 2005;27:57–65.
90. McDevitt-Murphy ME, Weathers FW, Flood AM, Benson T, Eakin DE. A comparison of the MMPI-2 and PAI for discriminating PTSD from depression and social phobia. Assessment. 2007;14:181–95.
91. McDonald SD, Beckham JC, Morey RA, Calhoun PS. The validity and diagnostic efficiency of the Davidson Trauma Scale in military veterans who have served since September 11th, 2001. J Anxiety Disord. 2009;23:247–55.
92. Meltzer-Brody S, Churchill E, Davidson JR. Derivation of the SPAN, a brief diagnostic screening test for post-traumatic stress disorder. Psychiatry Res. 1999;88(1):63–70.
93. Miller HR, Goldberg JO, Streiner DL. What's in a name? The MMPI-2 PTSD scales. J Clin Psychol. 1995;51:626–31. doi:10.1002/1097-4679.
94. Morey LC. The Personality Assessment Inventory professional manual. Odessa: Psychological Assessment Resources; 1991.
95. Morey LC. An interpretive guide to the Personality Assessment Inventory. Odessa: Psychological Assessment Resources; 1996.
96. Myers US, Wilkins KC, Allard CB, Norman SB. Trauma-related guilt inventory: review of psychometrics and directions for future research. In: Columbus AM, editor. Advances in psychology research, vol. 91. Hauppauge: Nova Science Publishers; 2012. p. 71–91.
97. National Center for Posttraumatic Stress Disorder. DSM-5 measures. 2016. Retrieved from www.ptsd.va.gov/professional/assessment/DSM_5_Validated_Measures.asp.
98. Norris FH, Hamblen JL. Standardized self-report measures of civilian trauma and PTSD. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guilford Press; 2004. p. 63–102.
99. Norris FH, Perilla J. Reliability, validity, and cross-language stability of the Revised Civilian Mississippi Scale for PTSD. J Trauma Stress. 1996;9:285–98.
100. Norris FH, Perilla JL, Ibañez GE, Murphy AD. Sex differences in symptoms of posttraumatic stress: does culture play a role? J Traumatic Stress. 2001;14:7–28.
101. Peters L, Andrews G, Cottier LB, Chatterji S, Janca A, Smeets R. The composite International diagnostic interview posttraumatic stress disorder module: preliminary data. Int J Methods Psychiatr Res. 1996;6:167–74.
102. Prins A, Ouimette P. The Primary Care PTSD Screen (PC-PTSD): development and operating characteristics. Primary Care Psychiat. 2004;9:151.
103. Robins LN, Helzer JE, Croughan JL, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch gen Psychiatry. 1981;38:381–9.
104. Runtz MG, Roche DN. Validation of the Trauma Symptom Inventory in a Canadian sample of university women. Child Maltreat. 1999;4:69–80.
105. Scheibe S, Bagby RM, Miller LS, Dorian BJ. Assessing posttraumatic disorder with the MMPI–2 in a sample of workplace accident victims. Psychol Assess. 2001;13:369–74.
106. Snyder JJ, Elhai JD, North TC, Heaney CJ. Reliability and validity of the Trauma Symptom Inventory with veterans evaluated for posttraumatic stress disorder. Psychiatry Res. 2009;170:256–61.
107. Steenkamp M, McLean CP, Arditte, Litz BT. Exposure to trauma in adults. In: Anthony MM, Barlow DH, editors. Assessment and treatment planning for psychological disorders. 2nd ed. New York: Guilford Press; 2010. p. 301–43.

108. Stockdale GD, Gridley BE, Balogh DW, Holtgroves T. Confirmatory factor analysis of single- and multiple-factor competing models of the Dissociative Experiences Scale in a nonclinical sample. Assessment. 2002;9:94–106.
109. Sundin EC, Horowitz MJ. Impact of event scale: psychometric properties. Br J Psychiatry. 2002;180:205–9.
110. van Ijzendoorn MH, Schuengel C. The measurement of dissociation in normal and clinical populations: meta-analytic validation of the Dissociative Experiences Scale (DES). Clin Psychol Rev. 1996;16:365–82.
111. Vrevan DL, Gudanowski DM, King LA, King DW. The Civilian Version of the Mississippi PTSD Scale: a psychometric evaluation. J Trauma Stress. 1995;8:91–109.
112. Walters JT, Bisson JI, Shepherd JP. Predicting posttraumatic stress disorder: validation of the trauma screening questionnaire in victims of assault. Psycholog Med. 2007;37:143–50.
113. Weathers FW, Keane TM. The criterion a problem revisited: controversies and challenges in defining and measuring psychological trauma. J Trauma Stress. 2007;20:107–21.
114. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist: reliability, validity, and diagnostic utility. Paper presented at the annual meeting of the International Society for Traumatic Stress Studies, San Antonio; 1993.
115. Weathers FW, Ruscio AM, Keane TM. Psychometric properties of nine scoring rules for the Clinician-Administered Posttraumatic Stress Disorder Scale. Psychol Assess. 1999;11:124.
116. Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: a review of the first ten years of research. Depress Anxiety. 2001;13:132–56.
117. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Interview available from the National Center for PTSD at www.ptsd.va.gov; 2013.
118. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Life Events Checklist for DSM-5 (LEC-5). Instrument available from the National Center for PTSD at www.ptsd.va.gov; 2013.
119. Weiss DS. The impact of event scale – revised. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. 2nd ed. New York: Guilford Press; 2004. p. 168–89.
120. Weiss DS, Marmar CR. The impact of event scale – revised. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guilford; 1997. p. 399–411.
121. Wetzel RD, Murphy GE, Simons A, Lustman P, North C, Yutzy S. What does the Keane PTSD scale of the MMPI measure? Repeated measurements in a group of patients with major depression. Psychol Rep. 2003;92:781–6.
122. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depress Anxiety. 2011;28:596–606.
123. Wise EA. Diagnosing posttraumatic stress disorder with the MMPI clinical scales: a review of the literature. J Psychopathol Behav Assess. 1996;18:71–82.
124. Wittchen H. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res. 1994;28:57–84.
125. Wolf EJ, Miller MW. The Minnesota multiphasic personality inventory-2 restructured form and posttraumatic stress disorder: forensic applications and considerations. Psychol Inj Law. 2014;7:143–52.
126. Wolf, E. J., Mitchell, K. S., Sadeh, N., Hein, C., Fuhrman, I., Pietrzak, R. H., & Miller, M. W.. The dissociative subtype of PTSD scale initial evaluation in a national sample of trauma-exposed veterans. Assessment. 2015. Advance online publication, http://dx.doi.org/ 10.1177/1073191115615212.
127. Wolfe J, Kimerling R, Brown PJ, Chrestman KR, Levin K. Psychometric review of the life stressor checklist – revised. In: Stamm BH, editor. Measurement of stress, trauma, and adaptation. Lutherville: Sidran Press; 1996. p. 198–201.
128. World Health Organization. Composite international diagnostic interview. Geneva: World Health Organization; 1990.
129. Wortmann JH, Jordan AH, Weathers FW, Resick PA, Dondanville KA, Hall-Clark B, Foa EB, Young-McCaughan S, Yarvis JS, Hembree EA Mintz J. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. Psychol Assess. 2016. Advance online publication, http://dx.doi.org/10.1037/pas0000260.
130. Zanarini MC, Frankenburg FR. Attainment and maintenance of reliability of Axis I and II disorders over the course of a longitudinal study. Compr Psychiatr. 2001;42:369–74.

Sleep Disturbances and Sleep Assessment Methods in PTSD

15

Anne Germain, Rebecca Campbell, and Ashlee McKeon

Introduction

Sleep is a universal, biologically driven, and multifaceted state of behavioral quiescence that supports mental and physiological health and well-being. A detailed summary of the multiplicity of neurobiological events that are required to initiate and sustain consolidated and restorative sleep exceeds the scope of this chapter (see [1, 2] for review). Different observable dimensions of sleep, however, are direct expressions of the complex, recurrent, and reversible neurobiological processes that support the experience of sleep. Dimensions such as sleep duration, consolidation, timing, and sleep quality have been proposed as related yet distinct dimensions that contribute to the overall experience of sleep [3]. Healthy sleep, thus, can be defined by regular, predictable, sufficient, and restorative or non-fragmented sleep episodes. All of these dimensions are disrupted in combat-exposed service members and veterans with posttraumatic stress disorder (PTSD).

Self-report and objective sleep measurement methods capture different aspects of these dimensions of sleep. However, none of the available sleep measurement methods can simultaneously capture all dimensions of sleep with high concordance between subjective and objective methods. The discordance between measurement methods is even greater in clinical samples [4]. Unfortunately, this discordance has been misinterpreted as a "misperception" of sleep in individuals with PTSD [5]. Specifically, subjective reports of sleep disturbances are considered to be inaccurate (i.e., "misperceived") as few objective polysomnographic (PSG) anomalies have been consistently found in adults with PTSD, and none are specific to the disorder [6, 7]. However, sleep neuroimaging studies have shown that PSG does not capture subcortical metabolic and blood flow changes that distinguish between healthy and clinical samples with poor sleep. Cortical and subcortical differences between groups of healthy sleepers and groups of individuals with psychiatric or sleep disorders can be detected even when PSG measures fail to distinguish between healthy and clinical groups [8–12]. Thus, the inconsistencies between subjective reports and objective PSG more likely reflect the limitations of PSG, rather than the absence of meaningful changes in brain activity during sleep in individuals with PTSD.

The measurement of sleep and sleep disturbances in PTSD, thus, requires careful considerations of the specific objectives of assessment. For clinical purposes, self-report clinician-administered sleep assessments and clinical sleep evaluations provide sufficient information to accurately define and diagnose insomnia, nightmares, and other parasomnias that are common among trauma-exposed individuals. Other sleep disorders, such as sleep-disordered breathing (SDB), periodic limb movement disorder (PLMD), narcolepsy, rapid eye movement (REM) sleep behavior disorder (RBD), or trauma-associated sleep disorder (TASD), can be diagnosed based on clinical and self-report measures, but require confirmation with specific in-lab polysomnographic studies. For research questions that target sleep-specific mechanisms and correlates of PTSD, more resource-intensive measurement methods such as actigraphy, PSG, or sleep neuroimaging methods must be considered.

In this chapter, the types of sleep disturbances observed in adults with PTSD are first briefly described. Advantages and limitations of assessing sleep disturbances using items extracted from PTSD-specific measures are then discussed. Sleep-specific measures that provide a more detailed evaluation of the nature and severity of sleep disturbances in PTSD and that align more closely with the diagnostic features of sleep disorders are then provided. In this section, self-report instruments, prospective sleep diaries and actigraphy, and objective sleep measurement methods are then described. We conclude by offering specific recommendations for the assessment of sleep disturbances in service members and

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veterans with PTSD that align with clinical and research purposes.

Sleep Disturbances in PTSD

Insomnia and nightmares are two well-recognized core symptoms of PTSD. Both insomnia and distressing dreams are more prevalent in military samples relative to prevalence estimates reported in the general civilian population (e.g., [13–15]). Furthermore, both sleep disorders can first occur during deployment (see Chaps. 6 and 7) and prior to the onset of PTSD. In fact, both insomnia and nightmares increase the risk of developing PTSD following trauma exposure [16]. For example, Gehrman and colleagues showed that service members with insomnia, short sleep duration, or both prior to deployment were at greater risk for developing PTSD post-deployment compared to their peers without insomnia or short sleep duration. These relationships persisted above and beyond the impact of combat exposure during deployment [17]. In another study, van Liempt and colleagues showed that pre-deployment nightmares, but not insomnia, predicted PTSD symptom 6 months post-deployment [16]. Following deployment, Sleep disturbances:insomnia and nightmares insomnia and nightmares also predict the severity of PTSD symptoms at subsequent assessments (e.g., [14, 15, 18]).

Other sleep disturbances common in PTSD but are often overlooked include SDB, sleep-related movement disorders, and other parasomnias. SDB refers to complete cessation of breathing (i.e., apnea) or marked limitations of airflow during sleep. Common risk factors associated with SDB include being male, older in age (i.e., >50 years old), obesity, and endorsing excessive daytime sleepiness. However, the performance of the first three of these indicators in military samples is questionable, as many younger, nonobese, and female service members and veterans are found to have clinically significant SDB. In the context of PTSD, daytime sleepiness due to sleep fragmentation is often masked by hyperarousal. Nevertheless, Colvonen et al. found that over 60% of veterans referred to a PTSD clinic screened positive for obstructive sleep apnea (OSA) and that one's risk for OSA increased as a function of PTSD symptom severity [19]. In another study, PTSD severity did not increase the risk for OSA, but over 70% participants seeking PTSD treatment were at risk for OSA [20].

PLMD has also been observed in veterans and civilians with PTSD [21–24]. This sleep-related movement disorder refers to the recurrent movements of the legs and/or arms at intervals of 20–40 s during non-REM (NREM) sleep [25]. These movements are typically associated with brief arousals that are not remembered upon awakening. As a result, affected individuals report daytime fatigue, difficulty maintaining sleep, and non-restorative sleep.

Mysliewic and colleagues recently identified a new trauma-related REM sleep parasomnia called trauma-associated sleep disorder (TASD; Chap. 18) [26]. Behaviorally, TASD resembles RBD by virtue of complex vocal and motor behaviors occurring during REM sleep that are associated with the loss of muscle atonia. However, TASD is specifically associated with trauma exposure and distinct polysomnographic and physiological features that accompany these episodes. TASD also does not appear to respond to first-line PTSD or RBD treatments [26], but prazosin may be effective.

Surprisingly, little is known about the prevalence of NREM sleep parasomnias, such as nocturnal panic attacks or somnambulism, in relation to PTSD in military samples. In civilian samples, a history of trauma is associated with increased prevalence of nocturnal panic attacks [27]. Similarly, the prevalence of complex motor behaviors or vocalization during NREM sleep in trauma-exposed individuals with or without PTSD is unknown. One case report described 12 military trainees who were honorably discharged due to severe somnambulism [28]. Although the literature on NREM sleep parasomnias is greatly limited, it is likely that trauma exposure and the sleep disruption and/or sleep curtailment associated with PTSD increase the risk of such episodes which, in turn, may be mistaken for nightmares. Similarly, it is likely that individuals with a personal and familial history of NREM sleep parasomnias would be especially at risk for the recurrence or exacerbation of these sleep disorders in the context of PTSD.

Assessing Sleep Disturbances Using Items Extracted from PTSD Measures

Over the past decade, there has been a growing recognition that sleep disturbances may not only reflect secondary symptoms or conditions in PTSD but may also reflect more critical aspects of the pathophysiology underlying this debilitating disorder and/or comorbid sleep disorders that require targeted clinical attention. This has encouraged many clinical investigators to extract sleep item scores from well-established PTSD symptom measures in order to cross-sectionally or prospectively explore the relationship between sleep, the severity of daytime PTSD symptoms, and clinical outcomes [13, 29–32].

This approach has the advantages of (1) limiting the number of additional assessments required to get a broad evaluation of sleep quality or severity of insomnia and nightmares, (2) aligning directly with other scales used to assess daytime symptoms of PTSD, (3) facilitating the collection of sleep data in large samples where additional or more

time-consuming resources are typically impractical, and (4) providing a measure that captures improvements in sleep symptoms with treatments [e.g., 30, 32]. However, this economical approach does not provide well-validated information regarding different dimensions of sleep (i.e., quality, duration, timing, consolidation) nor does it allow for ruling out the presence of sleep disorders that may masquerade as insomnia or nightmares [22, 33].

The gold standard for assessing the presence and severity of PTSD is the Clinician-Administered PTSD Scale (CAPS) [34, 35]. The CAPS for the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th Edition, includes two sleep-related items. Item B-2 states "recurrent distressing or unpleasant dreams of the event," where a frequency of at least once or twice for the period under assessment (i.e., past week, past month, or lifetime), is scored as "1" on this item. The intensity of the nightmare episodes is determined based on associated distress and difficulty returning to sleep. In the revised CAPS for DSM-5 [34], a moderate rating (i.e., clinically significant) requires the endorsement of at least two nightmares per month and the presence of distress and persistence of nightmare-related images or emotions during the day. The difficulty returning to sleep after awakening from unpleasant dreams is no longer specified as an index of nightmare severity.

Former item D-1 inquired about difficulty falling or staying asleep. Additional information was obtained to determine the extent to which difficulties initiating or maintaining sleep or early morning awakenings were present. The number of desired vs. actual hours of sleep was also assessed, presumably to evaluate sleep duration/loss. The intensity score for item D-1 was based on the estimated sleep loss, where a sleep loss of up to 30 min was rated as "mild" (score = 1) and a sleep loss of 90 min to 3 h was considered severe (score = 3). In the CAPS-5, the new sleep item E6 is similar to the former D-1 item in focusing on sleep latency, nocturnal awakening, early morning awakenings, and total sleep or estimated sleep loss. Interestingly, the header to this item now specifies "restless sleep," but a definition is not provided.

While the use of the individual or combined sleep item scores from the CAPS has face validity, a significant problem inherent in this approach is that the anchors provided to determine clinically significant frequency (score = 1) and intensity (score = 2) do not align with the thresholds of clinical significance established for nightmare disorder or insomnia [25]. For instance, a frequency of a least one nightmare per week with any sleep disruption of unspecified duration and at least one instance of sleep disruption, distress, or other daytime impairment would indicate clinically significant nightmares. Thus, the anchors provided with the CAPS may underestimate the severity and clinical relevance of nightmares experienced by individuals with PTSD.

A similar but inverted issue arises when estimating insomnia with item D-1 only. A score of "1" for frequency reflects insomnia that occurs less frequently than three times per week, which represents the threshold established by the International Classification of Sleep Disorders, 3rd edition, and DSM-5 [25, 36]. Furthermore, the cutoff regarding sleep loss provided for scoring the intensity of sleep disturbances is arbitrarily determined; the diagnostic and research criteria for insomnia do not require a range of duration of reported sleep loss. A sleep latency or wake time after the initial onset of sleep of >30 min is considered clinically significant [37]. Furthermore, other indicators of the impact of sleep loss reported in insomnia, such as daytime impairments in occupational or social functioning and cognitive, somatic, or mood symptoms, are not considered in the rating of the intensity of the sleep disturbance. Thus, item D-1 provides an aggregate estimate of insomnia features and sleep loss that can be helpful, but is not a good estimate of insomnia as clinically defined. While the use of these CAPS items can provide a simple global estimate of sleep in PTSD, this approach does not accurately capture the phenomena of interest, nor does it provide sufficient information to detail sleep among different dimensions in PTSD to guide decisions for further sleep assessment of treatment planning. Thus, when used to assess the impacts of treatment of sleep in PTSD [30–32], the use of the CAPS sleep items (individually or in combination) may inaccurately estimate the magnitude of the severity of sleep disturbances as well as treatment-related improvements in sleep. More comprehensive measures should be considered especially in the context of clinical trials.

Extracting sleep items from self-report measures of PTSD symptom severity to evaluate sleep disturbances is also a common practice, and this approach faces similar limitations to extracting sleep items from the CAPS. Self-report PTSD measures with sleep items include teh PTSD Checklist [38, 39], the Davidson Trauma Scale [40], the Impact of Event Scale (IES) [41, 42], and the Mississippi Scale for Combat-Related PTSD (M-PTSD) [43]. Some of these instruments assess distress associated with sleep disturbances and unpleasant dreams, while others assess the frequency and severity of these symptoms [41, 42, 44]. The time frame used as reference to determine the frequency of symptoms varies significantly across instruments (past 2 weeks to past 6 months), which makes it difficult, at best, to determine an adequate sleep-focused intervention plan.

In summary, extracting sleep items from PTSD assessment instruments can provide a broad assessment of some aspects of sleep disturbances, but does not provide information that aligns with the diagnostic criteria for insomnia or nightmares, and only captures certain aspects of sleep-related daytime impairments. To better characterize sleep disturbances in PTSD, validated, sleep-focused instruments are

recommended. Some of the instruments recommended for the assessment of insomnia, unpleasant dreams, and other sleep disturbances are detailed in the next section.

Self-Report Measures of Insomnia, Sleep Quality, and Disruptive Nocturnal Behaviors

A number of self-report measures of sleep and sleep disturbances have been validated in civilian samples and used in military samples. These tools are brief and capture global sleep quality through specific dimensions of sleep or severity of sleep disorders. They typically have cutoff scores to determine the clinical significance of sleep disturbances. It is important to note, however, that only a few studies have assessed the validity of cutoff scores for these instruments in military samples, and none has been validated in active duty military samples, where sleep is often curtailed or disrupted by occupational, operational, and/or environmental demands, and circumstances are common sleep challenges. Nevertheless, they offer a starting point to evaluate overall sleep patterns and disturbances. A handful of the recommended assessment tools and methods are summarized here, but the reader is encouraged to consult expert recommendations for the assessment and management of sleep disorders [45–48].

The Insomnia Severity Index (ISI) [49, 50] is the recommended self-report measure to capture the severity of insomnia. The ISI is a seven-item measure that captures both nighttime and daytime disturbances that characterize insomnia [25, 36]. Scores range from 0 (no insomnia) to 28 (severe insomnia). Scores from 0 to 7 indicate no symptoms of insomnia; 8–14, mild; 15–21, moderate; and scores above 21 severe insomnia. A reduction of eight points (or a decrease by one severity category) has been proposed as a clinically meaningful improvement in insomnia [51]. In clinical trials, remission can be defined as an end-point ISI score of less than or equal to 7. The psychometric properties of the ISI have not been evaluated in military samples.

The Pittsburgh Sleep Quality Index (PSQI; [52]) is the most widely used self-report measure of global sleep quality. The PSQI is an 18-item self-report measure that broadly assesses global sleep quality and includes subscales to evaluate sleep duration, sleep onset latency, sleep efficiency (ratio of total sleep time/total time spent in bed), sleep disturbances, daytime impairments, and use of sleep medications. The time reference is 1 month, and each item and summary subscale are scored from 0 (not in the past month) to 3 (three or more times/week). Total scores range from 0 (good sleep quality) to 21 (poor sleep quality). A cutoff score of greater than or equal to 5 is associated with clinically significant sleep disturbances in civilians. In samples of civilians and military veterans with PTSD, mean PSQI scores typically range from 10 to 15 [29, 33, 53–55]. A reduction in PSQI scores by three points has been suggested as a minimally meaningful difference in sleep-focused clinical trials [56–58].

An addendum to the PSQI was specifically designed to capture trauma-related sleep disturbances and has been validated in civilian [59–61] and military samples [62, 63]. The PSQI Addendum for PTSD (PSQI-A) is a seven-item self-report measure that assesses the frequency of disruptive nocturnal behaviors, including nocturnal panic attacks, night terrors, acting out dreams, night sweats, nightmares or bad dreams related to traumatic events, unpleasant dreams unrelated to traumatic events, intrusive thoughts and images at night, and general nervousness. Like the PSQI, each item of the PSQI-A is rated on a three-point scale. The sum of item scores ranges from 0 (no disruptive nocturnal behaviors) to 21 (severe disruptive nocturnal behaviors). A cutoff score of 4 has shown high specificity and sensitivity to identify individuals with and without PTSD [59, 62]. The PSQI-A has thus been proposed as a brief, sleep-focused screening measure of PTSD. Although the PSQI-A is sensitive to change with sleep treatment, a minimally meaningful difference has not been established.

For a more focused assessment of nightmares and unpleasant dreams, the Disturbing Dream and Nightmare Severity Index (DDNSI) measures the frequency, intensity, and severity of nightmares and unpleasant dreams. For each, an estimate of the number of dreams per night and total number of nights with nightmares/unpleasant dreams per week is assessed. The severity of these episodes is rated on a scale from 0 (no problem) to 6 (extremely problematic). The occurrence of awakening following unpleasant dreams is rated on a four-point scale (0 = never to 4 = always). An index score is obtained by adding the number of nightmares per week and the number of nights with nightmares per week, along with severity of nightmares and frequency of awakening. A score of 10 or greater indicates the presence of nightmare disorder [64, 65].

Other Self-Report Sleep Measures

Because sleep apnea is prevalent in military samples and can be mistaken for insomnia, nightmares, depression, or daytime fatigue, a brief screening measure can be helpful to detect SDB in this at-risk population. The STOP-BANG and Berlin Questionnaire offer well-validated instruments to assess the risk of sleep apnea. The STOP-BANG [66, 67] is a questionnaire that includes eight dichotomous items (yes/no) to assess the risk of clinically significant sleep apnea, based on snoring, tiredness or sleepiness, observed sleep apneas, high blood pressure, body mass index, neck circumference, age, and gender. A positive answer to three of the

eight items suggests the presence of moderate risk of sleep apnea. The Berlin Questionnaire [68] is a ten-item questionnaire that assesses the presence and characteristics of snoring, daytime sleepiness, and hypertension. Positive scores in two of these three categories suggest a high risk of sleep apnea.

Questionnaires to preliminarily assess symptoms of sleep disorders are often lengthy (e.g., Sleep Disorders Questionnaire; [69]) and impractical in research or general clinical settings and offer little advantage over clinical interviews.

Prospective Sleep Assessments

Questionnaires, like clinical interviews, only provide a snapshot of sleep disturbances and different dimensions of sleep. Prospective measurement methods have the advantage of providing longitudinal information that captures both inter- and intraindividual variations over several sleep/wake cycles, sleep duration regularity, efficiency, and sleep quality over extended periods of time.

Sleep diaries are a critical clinical tool in the assessment and treatment of insomnia, nightmares, and other sleep disorders [70]. Multiple versions of sleep diaries exist, and one has been created by consensus of experts [70] (see also [71]). Upon awakening in the morning, individuals are asked to provide information about the previous night's sleep latency, total time in bed and total sleep duration, number and duration of nocturnal awakenings, sleep quality, and restfulness upon final awakening. Other events such as dreams and nightmares can also be logged. For a representative sampling of sleep/wake patterns, completing the diary for 7–14 days is recommended. Sleep diaries can also be augmented by an evening section that is completed prior to bedtime to monitor sleep-impacting behaviors, such as napping, caffeine and alcohol use, use of medications, and stress levels during the day. While a paper diary may not be completed in a timely fashion, several online or electronic diaries are now available and provide time stamps to ascertain the timeliness of entries. Sleep diaries are helpful to capture variations in sleep/wake patterns, provide a more fine-grained portrait of overall sleep habits, and track adherence to treatment recommendations and improvements over time.

On the other hand, actigraphy is an objective and prospective measure of rest-activity patterns. Actigraphs are wristwatch-like devices that use accelerometer to capture motion from the nondominant wrist. Rest-activity patterns are derived from periods of inactivity (used as a proxy for sleep episodes) and activity (used as a proxy for wakefulness).

Actigraphs can be worn for several consecutive 24-h periods, without the need to recharge or download data collected over time. Actigraphy has the advantage of providing a low-burden means to capture the regularity, timing, and duration of rest-activity cycles over time, but do not capture sleep quality. While actigraphy is of low burden for users, the burden on clinician and research resources is not negligible, given each device must be calibrated and have data downloaded and manually processed. Determining the proper acquisition parameters and scoring protocols for actigraphy is also crucial for obtaining reliable and replicable data [72] (e.g., [73, 74]). Concurrent acquisition of actigraphy with an event marker to signal the onset and offset of the rest period and completion of a sleep diary to identify the main rest period can significantly improve the concordance between the two measurement methods [73, 74] but can rapidly become resource intensive. In veterans with PTSD, poor correlations between actigraphy and sleep diary data have been reported [75].

Of note, wearable devices are becoming more widely used and can be helpful to augment the assessments of sleep timing and duration. Although the vast majority of wearable devices have not undergone extensive validation against actigraphy or PSG, they may provide a gross overview of the timing and duration of the rest intervals. Recent findings suggest that the Fitbit® (and similar devices) shows strong validity when compared to research-grade actigraphy [76] and demonstrates the same magnitude of discrepancy between research-grade actigraphy and polysomnographic measures of sleep architecture [77–79].

Polysomnography (PSG)

PSG is the gold standard for the measurement of objective sleep parameters including sleep stages and phasic events that characterize sleep disorders. In addition to electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG), sleep montages include additional sensors to monitor heart rate, respiratory effort, oximetry, and limb movements. The diagnosis of insomnia and nightmares rests on clinical information, and PSG is not recommended for the diagnosis of these comorbid sleep conditions. However, objective assessment of breathing patterns and efficiency during sleep, movement-related disorders, and other parasomnias such as RBD and TASD require in-lab sleep evaluations. For sleep apnea, ambulatory or home-testing methods have become more prevalent in the past decades and provide cost-efficient methods to estimate the risk and severity of SDB and guide treatment planning [80].

In the context of PTSD, PSG has been mainly used for research purposes. As previously mentioned, some modest abnormal PSG parameters have been detected in PTSD [6], and differences in quantitative EEG that may suggest heightened or attenuated central arousal during sleep have been

inconsistently reported [81–83]. Ambulatory PSG has been used to conduct in-home studies of adults with and without PTSD that have yielded similar findings [84, 85]. Some studies have detected indices of heightened autonomic arousal during sleep using heart rate variability measures, and findings suggest an autonomic imbalance during sleep in adults with PTSD [86–88].

Conclusion

Sleep challenges are inherent to military service and deployment (Chaps. 6 and 7) and can contribute to a heightened risk of developing PTSD in trauma-exposed individuals. Objective indices of sleep disruption have been reported in PTSD (See Chap. 16). Sensitive and comprehensive sleep assessment methods are necessary to fully capture the extent of sleep disruption associated with PTSD. The accurate assessment of sleep disturbances is essential in elucidating how sleep disruption contributes to the pathophysiology underlying PTSD and influences treatment outcomes.

The current PTSD assessment measures do not encompass the full breadth of sleep disturbances that are prevalent among service members and veterans with PTSD. While the expertise and tools necessary to conduct extensive clinical sleep interviews are often unavailable, sleep-focused measures can be helpful and require little additional time investment. A number of brief, validated sleep-focused self-report and ambulatory measurement methods can capture several dimensions of sleep and can readily supplement existing PTSD assessment methods and tools, with minimal burden to patients and clinicians.

Although objective sleep measurement methods have failed so far at identifying a unique set of sleep anomalies in PTSD, they remain important in clinical context when comorbid sleep disorders that can exacerbate symptoms and impede treatments are suspected. From a research perspective, novel PSG methods with high-density EEG and the combination of EEG and sleep neuroimaging methods can advance our understanding of the underpinnings of sleep disturbances comorbid with PTSD. Ultimately, comprehensive treatment strategies that address both daytime and nighttime expressions of PTSD are required to promote recovery and sustained resilience.

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References

1. Rosenwasser AM, Turek FW. Neurobiology of circadian rhythm regulation. Sleep Med Clin. 2015;10:403–12.
2. Schwartz MD, Kilduff TS. The neurobiology of sleep and wakefulness. Psychiatr Clin North Am. 2015;38:615–44.
3. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep. 2014;37:9–17.
4. Taibi DM, Landis CA, Vitiello MV. Concordance of polysomnographic and actigraphic measurement of sleep and wake in older women with insomnia. J Clin Sleep med. 2013;9:217–25.
5. Pradono P, Tazawa R, Maemondo M, Tanaka M, Usui K, Saijo Y, Hagiwara K, Nukiwa T. Gene transfer of thromboxane A(2) synthase and prostaglandin I(2) synthase antithetically altered tumor angiogenesis and tumor growth. Cancer Res. 2002;62:63–6.
6. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
7. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry. 1992;49:651–68.
8. Ebdlahad S, Nofzinger EA, James JA, Buysse DJ, Price JC, Germain A. Comparing neural correlates of REM sleep in posttraumatic stress disorder and depression: a neuroimaging study. Psychiatry Res. 2013;214:422–8.
9. Nofzinger EA, Buysse DJ, Germain A, Carter C, Luna B, Price JC, Meltzer CC, Miewald JM, Reynolds CF, Kupfer DJ. Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry. 2004;61:695–702.
10. Nofzinger EA, Price JC, Meltzer CC, Buysse DJ, Villemagne VL, Miewald JM, Sembrat RC, Steppe DA, Kupfer DJ. Towards a neurobiology of dysfunctional arousal in depression: the relationship between beta EEG power and regional cerebral glucose metabolism during NREM sleep. Psychiatry Res. 2000;98:71–91.
11. Germain A, James J, Insana S, Herringa RJ, Mammen O, Price J, Nofzinger E. A window into the invisible wound of war: functional neuroimaging of REM sleep in returning combat veterans with PTSD. Psychiatry Res. 2013;211:176–9.
12. Nofzinger EA, Buysse DJ, Germain A, Price J, Miewald J, Kupfer DJ. Insomnia: functional neuroimaging evidence for hyperarousal. Sleep. 2004;27(Abstract Supplement):A272.

Ref Type: Abstract

13. Ulmer CS, Van VE, Germain AE, Voils CI, Beckham JC. A Comparison of sleep difficulties among Iraq/Afghanistan theater veterans with and without mental health diagnoses. J Clin Sleep Med. 2015;11:995–1005.
14. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. Mil Med. 2010;175:759–62.
15. Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75:546–50.
16. van Liempt S, van Zuiden M, Westenberg H, Super A, Vermetten E. Impact of impaired sleep on the development of PTSD symptoms in combat veterans: a prospective longitudinal cohort study. Depress Anxiety. 2013;30:469–74.
17. Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, Ulmer CS, Smith TC. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. Sleep. 2013;36:1009–18.
18. Koffel E, Polusny MA, Arbisi PA, Erbes CR. Pre-deployment daytime and nighttime sleep complaints as predictors of

post-deployment PTSD and depression in National Guard troops. J Anxiety Disord. 2013;27:512–9.
19. Colvonen PJ, Masino T, Drummond SP, Myers US, Angkaw AC, Norman SB. Obstructive sleep apnea and posttraumatic stress disorder among OEF/OIF/OND veterans. J Clin Sleep Med. 2015;11:513–8.
20. Forbus L, Kelly UA. Screening for obstructive sleep apnea in veterans seeking treatment of posttraumatic stress disorder. ANS Adv Nurs Sci. 2015;38:298–305.
21. Ross RJ, Ball WA, Dinges DF, Kribbs NB, Morrison AR, Silver SM, Mulvaney FD. Motor dysfunction during sleep in posttraumatic stress disorder. Sleep. 1994;17:723–32.
22. Krakow B, Germain A, Tandberg D, Koss M, Schrader R, Hollifield M, Cheng D, Edmond T. Sleep breathing and sleep movement disorders masquerading as insomnia in sexual-assault survivors. Compr Psychiatry. 2000;41:49–56.
23. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry. 2003;54:1092–8.
24. Brown TM, Boudewyns PA. Periodic limb movements of sleep in combat veterans with posttraumatic stress disorder. J Trauma Stress. 1996;9:129–36.
25. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, Darien, IL 2014.
26. Mysliwiec V, O'Reilly B, Polchinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia encompassing disruptive nocturnal behaviors, nightmares, and REM without atonia in trauma survivors. J Clin Sleep Med. 2014;10:1143–8.
27. Freed S, Craske MG, Greher MR. Nocturnal panic and trauma. Depress Anxiety. 1999;9:141–5.
28. Reid WH. Treatment of somnambulism in military trainees. Am J Psychother. 1975;29:101–6.
29. Germain A, Buysse DJ, Shear MK, Rayyad R, Austin C. Clinical correlates of sleep disturbance severity in posttraumatic stress disorder. J Trauma Stress. 2004;17:477–84.
30. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170:1003–10.
31. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63:629–32.
32. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'connell J, Taylor F, Gross C, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61:928–34.
33. Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, Koss M, Warner TD, Schrader R. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry. 2001;49:948–53.
34. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. (2013). The clinician-administered PTSD scale for DSM-5 (CAPS-5). Interview available from the National Center for PTSD at www.ptsd.va.gov.
35. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8:75–90.
36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Arlington: American Psychiatric Association; 2013.
37. Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW. Quantitative criteria for insomnia. Behav Res Ther. 2003;41:427–45.
38. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). Behav Res Ther. 1996;34:669–73.
39. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov; 2013.
40. Davidson JR, Book SW, Colket JT, Tupler LA, Roth S, David D, Hertzberg M, Mellman T, Beckham JC, Smith RD, et al. Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med. 1997;27:153–60.
41. Weiss DS, Marmar CR. Assessing psychological trauma and PTSD. In: Wilson J, Keane TM, editors. The impact of event scale – revised (note: includes measure in its entirety). New York: Guilford; 1996. p. 399–411.
42. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med. 1979;41:209–18.
43. Keane TM, Caddell JM, Taylor KL. Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. J Consult Clin Psychol. 1988;56:85–90.
44. Fos E, Riggs D, Dancu C, Rothbaum B. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J Trauma Stress. 1993;6:459–73.
45. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep med. 2008;4:487–504.
46. Morgenthaler TI, Lee-Chiong T, Alessi C, Friedman L, Aurora RN, Boehlecke B, Brown T, Chesson AL Jr, Kapur V, Maganti R, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. Sleep. 2007;30:1445–59.
47. Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, Coleman J, Kapur V, Lee-Chiong T, Owens J, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American academy of sleep medicine report. Sleep. 2006;29:1415–9.
48. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, Maganti RK, Ramar K, Kristo DA, Bista SR, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6:389–401.
49. Morin CM. Insomnia: psychological assessment and management. New York: The Guilford Press; 1993.
50. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2:297–307.
51. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin. 2009;25:2487–94.
52. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.
53. Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. J Clin Sleep Med. 2011;7:57–68.
54. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. Jama. 2001;286:537–45.
55. Mellman TA, David D, Kulick-Bell R, Hebding J, Nolan B. Sleep disturbance and its relationship to psychiatric morbidity after Hurricane Andrew. Am J Psychiatry. 1995;152:1659–63.
56. Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, Begley A, Houck PR, Mazumdar S, Reynolds CF, et al.

Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch Intern Med. 2011;171:887–95.
57. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. Behav Res Ther. 2007;45:627–32.
58. Germain A, Moul DE, Franzen PL, Miewald JM, Reynolds CF, Monk TH, Buysse DJ. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. J Clin Sleep Med. 2006;2:403–6.
59. Germain A, Hall M, Krakow B, Katherine Shear M, Buysse DJ. A brief sleep scale for Posttraumatic Stress Disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. J Anxiety Disord. 2005;19:233–44.
60. Ait-Aoudia M, Levy P, Bui E, Insana S, de Fouchier C, Germain A, et al. Validation of the French version of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder. Eur J Psychotraumatol. 2013; 4:19298. doi:http://dx.doi.org/10.3402/ejpt.v4i0.19298.
61. Barbosa Neto JB, Germain A, Mattos PF, Serafim PM, Santos RC, Martini LC, Suchecki D, Mello MF. Psychometric properties of the Brazilian version of the Pittsburgh Sleep Quality Index Addendum for PTSD (PSQI-A). Rev Bras Psiquiatr. 2014;36:330–5.
62. Insana SP, Hall M, Buysse DJ, Germain A. Validation of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) in U.S. male military veterans. J Trauma Stress. 2013;26:192–200.
63. Farrahi J, Nakhaee N, Sheibani V, Garrusi B, Amirkafi A. Psychometric properties of the Persian version of the Pittsburgh Sleep Quality Index addendum for PTSD (PSQI-A). Sleep Breath. 2009;13:259–62.
64. Krakow BJ, Melendrez DC, Johnston LG, Clark JO, Santana EM, Warner TD, Hollifield MA, Schrader R, Sisley BN, Lee SA. Sleep dynamic therapy for Cerro Grande fire evacuees with posttraumatic stress symptoms: a preliminary report. J Clin Psychiatry. 2002;63:673–84.
65. Krakow B, Hollifield M, Schrader R, Koss M, Tandberg D, Lauriello J, McBride L, Warner TD, Cheng D, Edmond T, et al. A controlled study of imagery rehearsal for chronic nightmares in sexual assault survivors with PTSD: a preliminary report. J Trauma Stress. 2000;13:589–609.
66. Farney RJ, Walker BS, Farney RM, Snow GL, Walker JM. The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. J Clin Sleep Med. 2011;7:459–65B.
67. Chung F, Abdullah HR, Liao P. STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. Chest. 2016;149:631–8.
68. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131:485–91.
69. Douglass AB, Bornstein R, Nino-Murcia G, Keenan S, Miles L, Zarcone VP, Guilleminault C, Dement WC. The sleep disorders questionnaire. I: creation and multivariate structure of SDQ. Sleep. 1994;17:160–7.
70. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35:287–302.
71. National Sleep Foundation. Sleep Diary. https://sleepfoundation.org/sleep-diary/SleepDiaryv6.pdf. Date accessed: December 2016.
72. Boudebesse C, Leboyer M, Begley A, Wood A, Miewald J, Hall M, Frank E, Kupfer D, Germain A. Comparison of five actigraphy scoring methods with bipolar disorder: an objective/subjective data processing spectrum approach. Behav Sleep Med. 2013;11:1–8.
73. Boudebesse C, Leboyer M, Begley A, Wood A, Miewald J, Hall M, Frank E, Kupfer D, Germain A. Comparison of five actigraphy scoring methods with bipolar disorder. Behav Sleep Med. 2013;11:275–82.
74. Chow CM, Wong SN, Shin M, Maddox RG, Feilds KL, Paxton K, Hawke C, Hazell P, Steinbeck K. Defining the rest interval associated with the main sleep period in actigraph scoring. Nat Sci Sleep. 2016;8:321–8.
75. Westermeyer J, Sutherland RJ, Freerks M, Martin K, Thuras P, Johnson D, Rossom R, Hurwitz T. Reliability of sleep log data versus actigraphy in veterans with sleep disturbance and PTSD. J Anxiety Disord. 2007;21:966–75.
76. Ferguson T, Rowlands AV, Olds T, Maher C. The validity of consumer-level, activity monitors in healthy adults worn in free-living conditions: a cross-sectional study. Int J Behav Nutr Phys Act. 2015;12:42.
77. Blackwell T, Redline S, Ancoli-Israel S, Schneider JL, Surovec S, Johnson NL, Cauley JA, Stone KL. Comparison of sleep parameters from actigraphy and polysomnography in older women: the SOF study. Sleep. 2008;31:283–91.
78. De ZM, Claudatos S, Inkelis S, Colrain IM, Baker FC. Evaluation of a consumer fitness-tracking device to assess sleep in adults. Chronobiol Int. 2015;32:1024–8.
79. De ZM, Baker FC, Colrain IM. Validation of sleep-tracking technology compared with polysomnography in adolescents. Sleep. 2015;38:1461–8.
80. Bruyneel M, Ninane V. Unattended home-based polysomnography for sleep disordered breathing: current concepts and perspectives. Sleep Med Rev. 2014;18:341–7.
81. Cohen DJ, Begley A, Alman JJ, Cashmere DJ, Pietrone RN, Seres RJ, Germain A. Quantitative electroencephalography during rapid eye movement (REM) and non-REM sleep in combat-exposed veterans with and without post-traumatic stress disorder. J Sleep Res. 2013;22:76–82.
82. Cowdin N, Kobayashi I, Mellman TA. Theta frequency activity during rapid eye movement (REM) sleep is greater in people with resilience versus PTSD. Exp Brain Res. 2014;232:1479–85.
83. Woodward SH, Murburg MM, Bliwise DL. PTSD-related hyperarousal assessed during sleep. Physiol Behav. 2000;70:197–203.
84. Germain A, Hall M, Katherine Shear M, Nofzinger EA, Buysse DJ. Ecological study of sleep disruption in PTSD: a pilot study. Ann N Y Acad Sci. 2006;1071:438–41.
85. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Leykin Y, Metzler TJ, Schoenfeld FB, Marmar CR. The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. J Clin Psychiatry. 2003;64:445–50.
86. Kobayashi I, Lavela J, Mellman TA. Nocturnal autonomic balance and sleep in PTSD and resilience. J Trauma Stress. 2014;27:712–6.
87. Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. Biol Psychiatry. 2004;55:953–6.
88. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146:697–707.

Sleep Changes in PTSD

16

Shawn Vasdev, Jasmyn Cunningham, and Colin Shapiro

Introduction

Posttraumatic stress disorder (PTSD) is characterized by exposure to an extreme stressor and subsequent development of four clusters of symptoms, which include intrusive symptoms related to the traumatic event, avoidance of stimuli related to the event, negative alterations in cognition and affect and altered arousal and reactivity. *The Diagnostic and Statistical Manual* 5th Edition (DSM-5) outlines 20 possible symptoms that aid in making the diagnosis [1]. Of these 20 symptoms, only two relate specifically to sleep: the presence of distressing dreams about the event and difficulty staying asleep, falling asleep or experiencing restless sleep. Nevertheless, sleep disturbance remains among the most common symptoms and subjective complaints among people with PTSD. Patients with PTSD frequently report their sleep quality as poor. They may complain of a number of specific symptoms related to sleep including initial and maintenance insomnia, early morning awakening, nightmares and other parasomnias [2].

In this chapter, we begin by describing the scope of the sleep disturbance in PTSD. A point of distinction should be made between subjective sleep complaints (those signs and symptoms that patients express in words) and objective disturbances, which are assessed by polysomnography, actigraphy or other methods such as magnetic resonance imaging. This distinction is particularly relevant in PTSD, as studies have found varying degrees of correlation between subjective complaints and objective measures on polysomnography [3] and actigraphy [4]. Next we will characterize the various objective and subjective sleep changes that have been observed and reported in PTSD. A description of specific symptoms and objective measurement methods can be useful to the clinician or researcher who wishes to assess and treat these symptoms. Given the high degree of psychiatric and medical comorbidity that is seen in PTSD, attention will be given to sleep problems in special populations, as well as common co-occurring sleep disorders. Finally, we will provide a discussion of future directions within the assessment of sleep disturbance in this population.

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Prevalence of Sleep Disturbance in PTSD

Numerous studies point to a high prevalence of sleep complaints among people with PTSD. According to a community sample of adults with PTSD, over two thirds reported complaints related to sleep. An additional 40% met concurrent criteria for primary insomnia [2]. In a sample of combat veterans in the United States, 89% of eligible veterans with a confirmed diagnosis of PTSD also had a diagnosis of insomnia [5]. A community sample of 92 individuals with PTSD in Montreal, Canada, showed that sleep complaints were present in over 88% of the subjects studied [6]. Moreover, sleep quality was not associated with age, gender, marital status, the nature of the trauma or the time since the traumatic event. This finding suggests that sleep disturbance is an enduring and sensitive measure of PTSD.

There is some debate as to whether sleep disturbance is simply a secondary symptom that results from exposure to trauma or whether sleep disturbance is actually the core feature of PTSD; however, the current research mainly supports the latter hypothesis. This distinction does have clinical significance when assessing and treating the subjective sleep changes in PTSD; if sleep disturbance is a core feature of

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PTSD, then its assessment and treatment should be of high priority. Evidence that sleep disturbance is a core feature of PTSD arises from four main findings. First, studies have shown that poor sleep in the aftermath of exposure to trauma predicts the development of PTSD [7–9]. Second, treatment of PTSD that results in residual sleep disturbance is associated with poorer outcomes. Third, treatment that focuses on sleep disturbance improves both sleep and other features of PTSD [10, 11]. Fourth, neuroimaging studies have demonstrated that brain regions impacted by sleep disturbances share large overlap with regions known to be associated with PTSD [12]. At this time, we cannot definitively conclude that sleep is the hallmark feature of PTSD, but we can argue that sleep disturbance is prevalent in patients with PTSD and it certainly merits assessment and treatment. Further research continues in this area.

Although sleep disturbance is a common feature in patients with PTSD, it is important to note the heterogeneity that exists within the diagnosis [5]. Factors that influence the presentation of PTSD include, but are not limited to, (1) the nature, severity and duration of the trauma, (2) the developmental level of the individual affected, (3) the past personal and psychiatric history of the individual affected and (4) the resources and supports available to individuals.

Insomnia

Insomnia is perhaps the most widely reported symptom in PTSD [2]. Insomnia is defined as the inability to initiate or maintain sleep and may encompass elements of non-restorative sleep, i.e. sleep that is considered non-refreshing. All three types of insomnia (initial, maintenance and non-restorative sleep) have been reported in patients with PTSD. The underlying pathophysiology may relate to a constant state of hyperarousal, both physiological and cognitive, which interferes with sleep functioning. It may be perpetuated by maladaptive sleep behaviours that individuals with PTSD adopt to deal with their symptoms (e.g. avoidance of sleep, alcohol use). Chronic insomnia (insomnia of duration greater than 1 month) is clinically significant, as it is associated with increased healthcare use, hypertension, diabetes and mortality [13, 14].

There is ample evidence of sleep disturbance in PTSD following exposure to military combat. One recent study found that 41% of returning service members from Iran and Afghanistan reported insomnia. These initial reports of insomnia were predictive of PTSD at follow-up [15]. Other studies have also shown that insomnia is one of the most common complaints of veterans returning from Operation Enduring Freedom/Operation Iraqi Freedom post-deployment [16]. Based on data from the National Vietnam Veterans Readjustment Study – a large study of veterans who served during the Vietnam War – rates of sleep disturbance are exceedingly high; 44% of veterans with PTSD reported difficulties initiating sleep, and 90% reported difficulties maintaining sleep [17]. In this study, combat exposure was correlated with sleep symptoms, including insomnia and nightmares. Service members returning from military deployments may be reluctant to report other symptoms of PTSD due to stigma; sleep complaints and insomnia may be a more accepted complaint for which one can seek treatment.

Insomnia is found in other types of trauma as well. A study of Holocaust survivors found that although only 3.8% met full criteria for PTSD, sleep disturbance rates reached 62%, a rate significantly higher than the control group [18]. This effect held even after controlling for age, education, religious observance and past-year presence of anxiety and depressive disorders. The significance of this finding is that sleep disturbance can remain long after exposure to trauma and that sleep disturbance may persist even after the other symptoms of PTSD have resolved or when symptoms do not meet full diagnostic criteria for PTSD.

Natural disasters such as hurricanes or earthquakes may precipitate PTSD in both children and adults. For example, studies of children who have survived hurricanes have shown significant rates of sleep disturbance and nightmares. In a study looking at a cohort of children following Hurricane Hugo, 35% of children endorsed sleep difficulties and 9% endorsed nightmares. The sleep difficulties were most prominent in children of a younger age, suggesting that developmental stage does mediate the emergence of sleep symptoms [19]. Another study examined children in the aftermath of Hurricane Katrina and found high rates of PTSD, with specific symptoms of difficulty initiating sleep and fear of sleeping alone. Sleep disturbances were more pronounced in women, those of a younger age and those whose lives continued to be disrupted by the disaster [20].

There is a clear connection between childhood sexual abuse and the development of PTSD. Childhood sexual abuse is correlated with insomnia and nightmares, both with and without comorbid PTSD. One hypothesis that may explain this link is that sleep naturally occurs in a place of safety and security. For victims of childhood sexual abuse, both the bedroom and the night (both the place and the time during which abuse frequently occurs) become associated with fear, thereby limiting sleep. A further consequence of insomnia in this population has to do with the long-term effects of chronic insomnia; adolescents who do not have restorative sleep may experience daytime sleepiness, more emotional dysregulation and difficulties processing unsafe or dangerous situations. Such a state of sleep deprivation may

make them more vulnerable to future re-victimization [21]. See the case vignettes at the end of this chapter for relevant clinical examples.

Nightmares

Nightmares are a common subjective complaint in patients with PTSD, reported by 19–71% of PTSD patients [10, 22], which can persist for many years following exposure to trauma [8], even after the completion of treatment for PTSD [10]. Nightmares can be understood as part of the re-experiencing process seen in PTSD. Nightmares can be defined as "a frightening dream that awakens the dreamer from sleep" [23]. There is controversy over the necessity of the dreamer awakening from sleep in order to define a nightmare, as many people describe disturbing dreams in the absence of awakening; some may only recall the emotional elements (e.g. fear, sadness, dysphoria) that have occurred in the context of a nightmare. The International Classification of Sleep Disorders II captures this distinction by defining nightmares as *disturbing mental experiences* rather than frightening dreams [24].

Nightmares may awaken an individual from sleep with varying degrees of recall and can be quite distressing to the affected individual. Even if the exact content is not recalled, the emotional elements may be present, such as fear, distress and entrapment. The nightmares may be exact replicas of the scenarios or contain varying degrees of symbolization, emotional content and autonomic arousal [8].

Dreams serve an important function after exposure to trauma, specifically in the integration and processing of highly emotional content. Thus, dreams and nightmares may initially be considered as a means of adapting to trauma and integrating it within the psyche. However, the persistence of nightmares months or years after trauma conceptualizes PTSD as a disorder of failed adaptation and/or trauma that overwhelms an individual's coping mechanism. There is conflicting evidence as to whether dream recall is heightened or impaired after exposure to trauma, again reflecting the heterogeneity of the disorder. Some patients report vivid recalls of nightmares, and others report only awakening in a state of panic, without recall of the actual content. In some patients, dream recall may be initially quite vivid, with a gradual decrease over time and with adaptation to the trauma.

The actual content of nightmares can provide useful information in understanding the patient and their traumatic experience (though appropriate caution must be taken when bringing up traumatic memories, especially in the absence of desensitization or other appropriate therapeutic treatments). Most researchers classify nightmares according to the degree to which they are similar to the trauma experienced by a person. Nightmares may be classified as *post-traumatic, modified* or *disguised*, based on their content. Posttraumatic dreams are those that involve content of the actual trauma experienced. A veteran who dreams of actual events he/she experienced during the war would fit in this this category. Modified dreams present content that is not directly related to the trauma, but is closely related. Finally, disguised dreams use symbols, images and emotions to replay the traumatic content [25]. Dreams with posttraumatic content are more prevalent early after exposure to trauma, and ongoing posttraumatic dreams are associated with a higher degree of PTSD. Dreams are more likely to be set in the past in patients with PTSD. A higher level of dream recall and recurrent nightmares is also associated with more symptoms and persistence of PTSD as well as poorer clinical prognosis [8].

One study of World War II veterans and civilians exposed to war found posttraumatic nightmares in 102 out of 124 people with PTSD [26]. Forty-two percent of these nightmares were posttraumatic in nature; that is, their content was replicative of the events experienced. Twenty-eight percent were non-replicative and 35% were a mixture of replicative and non-replicative content. Posttraumatic nightmares that were replicative in nature were associated with fewer hours of sleep, greater fear of going to sleep, depression upon waking and greater PTSD symptom severity. As well, those with replicative posttraumatic nightmares showed a greater frequency of nightmares. Thus, the degree of similarity between the nightmare content and the actual trauma is associated with a higher degree of symptom severity and comorbidity.

Mellman et al. [27] examined 60 patients with exposure to trauma and created dream reports by having patients keep a morning diary to remember their dreams. Thirty percent of these patients were able to remember a dream. Of these, half the dreams contained content related to the trauma. Almost 50% were dreams that closely resembled the traumatic event, while the remainder were either distressing in emotion alone or neutral. Those who experienced trauma dreams were more likely to go on to develop PTSD.

Patients who experience nightmares may actively engage in sleep avoidance. This may take the form of poor sleep hygiene, using stimulants at bedtime, or reversal of circadian rhythms. Sleep avoidance can create further impairments for patients with PTSD as it may worsen mood symptoms, lead to daytime sleepiness and worsen emotional dysregulation in the context of sleep deprivation. Sleep deprivation may also make individuals less able to access resources and support and re-engage in meaningful activities that would otherwise be helpful in coping with trauma.

Nocturnal Panic

Nocturnal panic is another subjective sleep complaint that may present in patients with PTSD [28, 29]. Nocturnal panic is defined as the awakening from sleep in a state of panic. A panic attack consists of both cognitive and physiological responses, usually involving fear or discomfort, along with accompanying somatic or cognitive symptoms. Symptoms of a panic attack may include palpitations, sweating, trembling or shaking, shortness of breath, choking, chest pain or discomfort, nausea, feeling dizzy, derealization, fear of losing control or dying, paraesthesias, chills or hot flashes. Diagnostically, four of the above criteria are required to meet criteria for a panic attack [1].

With respect to symptom description of nocturnal panic, they usually occur within 1–3 h of sleep onset. The episodes last 2–8 min, and are followed by difficulty falling back to sleep, likely because of the intense arousal that such episodes generate. They are distinguished from nightmares, in that they are a non-REM phenomenon. They are also distinguished from panic attacks that may follow a prolonged period of insomnia. Consequences of nocturnal panic disorder include sleep avoidance and anxiety around going to sleep. This interference with sleep can produce excessive daytime sleepiness and fatigue, which can worsen symptoms of anxiety and PTSD.

Polysomnography (PSG)

Numerous studies have been conducted to determine the objective sleep findings in patients with PTSD. One of the methods used to measure objective sleep disturbances is polysomnography, or PSG. There has been a lack of consistent findings in this literature, but PTSD has been associated with increased REM sleep, increased REM density and reductions in slow-wave sleep [10]. Other studies have shown no difference in objective findings between patients with PTSD and controls (see [8, 10] or [30] for a review). Thus, there is no clear consensus on polysomnographic changes that occur in PTSD, which may be due to the heterogeneity of the disorder or other factors yet to be discovered. Nevertheless, the lack of consensus in objective PSG findings highlights the importance of assessing sleep complaints through careful history taking and detailed inquiry, as there is currently no typical "profile" of objective sleep disturbance in PTSD, and there may even be differences in insomnia presentation between PTSD patients with insomnia and sufferers of primary insomnia [10].

Actigraphy

One convenient method of measuring objective sleep disruptions is actigraphy, which is relatively inexpensive to use and can be used in either a lab or home environment (unlike PSG, which must for the most part be completed in a sleep laboratory). While most individuals with PTSD report subjective sleep complaints, far fewer show objective signs of sleep disruption as measured with actigraphy. Additionally, even those individuals who report subjective sleep impairment after a given night may not show signs of objective sleep disruptions in the actigraphy measures from that same night [4]. For example, one study of veterans of the Iran-Iraq War showed no correlation between objective measures of sleep (measured with actigraphy) and self-reported sleep parameters [31]. This is referred to as "paradoxical insomnia", when patients subjectively report insomnia symptoms, with no corresponding objective sleep measurements.

Brain Imaging

While this is not a direct measure of sleep disturbance, recent studies have begun investigating the neural correlates of the sleep disturbances associated with PTSD. One study by Nardo et al. [12] measured changes in brain structure and function related to sleep disturbances in participants developing PTSD, both with magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT). Their findings indicated that increased insomnia and nightmare complaints were associated with decreased grey-matter volume in the amygdala, hippocampus, anterior cingulate cortex and insula. Additionally, they found increased relative blood flow in the midbrain, praecuneus and insula and decreased relative blood flow in the anterior cingulate cortex, also associated with higher nightmare and insomnia complaints. However, it is important to note that sleep disturbances, as reported in this study, were subjectively assessed [12].

Psychiatric Comorbidity

When assessing the subjective sleep complaints in PTSD, it is important to bear in mind the high degree of psychiatric and medical comorbidity that often exists in this population. According to the National Comorbidity Study, rates of panic disorder reach almost 50% in this population, and rates of comorbid depression have been estimated to be as high as 65% [32]. These disorders each have features that would

subjectively affect an individual's sleep. In the case of panic disorder, nocturnal awakening and panic are frequently found. In the case of depression, all phases of insomnia may be seen, and hypersomnia may be present in some patients. While the severity of the sleep disturbance in individuals with PTSD does not seem to be mediated by comorbid psychiatric problems [33], other aspects besides overall severity (e.g. symptom profile) may be altered.

Substance abuse of all kinds (including substance use disorders, SUDs) is also highly prevalent in this population, possibly as a coping mechanism for sleep-related and/or other symptoms of their PTSD, for example, through self-medicating their insomnia complaints [33]. Thus, an assessment of a patient with PTSD should include a careful history about current substances. Information regarding the type of substance and the quantity consumed can allow the clinician to make hypotheses regarding the nature and cause of concurrent sleep disturbances. In the case of alcohol, its use may improve initial insomnia, but it can also result in rebound insomnia, which in turn can further increase alcohol use. Nightmares and vivid dreams can occur in the context of alcohol intoxication and withdrawal and must be inquired about in a patient who has PTSD and is alcohol dependent. Similarly, with other substances, tolerance and withdrawal after extended use as well as other patterns of effects similar to alcohol may end up contributing to more severe sleep disturbances overall [33].

Traumatic brain injury (TBI) is a frequent comorbid condition that is seen in many veterans returning from Afghanistan and Iraq wars, attributed in part to the widespread use of improvised explosive devices. In one study of returning veterans, the co-occurrence of cognitive impairment secondary to TBI and PTSD was 42% [34]. Sleep complaints, both insomnia and hypersomnia, are noted in patients with TBI, and these can overlap with symptoms of PTSD. The aetiology of sleep complaints following mild traumatic brain injury is multifactorial and may result from injury to brain structures responsible for regulating sleep, pain, medication side effects and comorbid PTSD and mood disorders.

A study of returning veterans with concurrent PTSD and mild traumatic brain injury found that 60% reported mild insomnia and 40% reported severe insomnia. Eighty percent reported difficulties with sleep initiation, and 87% reported difficulties with sleep maintenance. Fifty-three percent reported difficulties with early morning awakenings. They also reported higher rates of daytime sleepiness, as measured by the Epworth Sleepiness Scale. Depressive symptoms were present in all patients. There was also a higher incidence of REM and non-REM parasomnias in patients with both PTSD and mild traumatic brain injury, including REM behaviour disorder and nightmares, though these symptoms may have also been affected by medications [16].

Common Comorbid Sleep Disorders

Sleep-related breathing disorders (SRBD) have been reported frequently in conjunction with PTSD, at rates significantly higher than normal samples (40–90% versus 1.2–3.6% respectively [8, 22]). However, one study reported that the typical symptom profile may differ from that displayed by normal clinical SRBD patients; patients with PTSD may demonstrate more upper airway resistance, but less snoring and sleep apnoea [35]. Additionally, PTSD patients who report nightmares and/or comorbid major depressive disorder may also demonstrate faster overall breathing, whereas PTSD patients without nightmares may demonstrate slower than average breathing. This may be found for both REM and non-REM sleep stages, unlike in normal SRBD patients, where breathing rate is associated with these sleep stages [36]. Interestingly, untreated obstructive sleep apnoea (OSA) may exacerbate the sleep-related symptoms of PTSD, including nightmares, nighttime awakenings and daytime sleepiness. However, one study has showed that successfully treating the OSA with a continuous positive airway pressure (CPAP) device can reduce some of these symptoms, including daytime sleepiness and nightmare frequency [37]. It is unclear currently whether the sleep-disordered breathing contributes to the PTSD, the directionality is reversed or bidirectional, or some other factor such as insomnia mediates or moderates the relationship between the two. Research is ongoing in this area [8, 33].

Periodic limb movement disorders (PLMD), generally including restless legs and excessive body movement, have also been reported more frequently in PTSD patients by several studies [10, 22]; however, similarly to SRBD, the directionality and mechanism of this association, its relationship with insomnia, and its origin (psychiatric or medical) are unclear. Interestingly, the amount of movement time has been positively correlated with sleep efficiency, indicating that higher rate of movement leads to better sleep in these patients [8]. Woodward and colleagues posited that this could be a result of a "freezing" motor response, similarly to what one might see as a result of a fear response, and that increased movement time may serve as a protective factor against nocturnal panic attacks in patients who experience this symptom [38].

As of 2016, there has been no comprehensive review of parasomnias in patients with PTSD. However, REM-sleep behaviour disorder (no REM atonia; acting out dreams) and sleep paralysis (inability to move, speak, etc. while falling asleep or waking up; possible presence of hallucinations) have been shown to occur in larger rates in PTSD patients [8].

Conclusion

Sleep complaints are the most common presenting symptoms in PTSD. The most common sleep complaints are insomnia, nightmares and nocturnal panic attacks. These symptoms may seriously impair an individual's functional status, as well as their ability to recover from traumatic events. While there is no consensus on an objective sleep disturbance "profile" of individuals with PTSD, PTSD has been associated with increased REM sleep, increased REM density and reductions in slow-wave sleep. Sleep is essential in recovery from stress and traumatic events in general, and the persistence of sleep disturbance should signal to the clinician the ongoing presence of PTSD. Thus, sleep complaints can be considered to be a core feature of PTSD and should be a focus of inquiry and treatment in all patients, especially given the reduction of PTSD symptomology following sleep-focused treatment.

Additional "Screening" Topics

- Individuals who are suspected of having PTSD (or who have a confirmed diagnosis of PTSD) should be screened for subjective sleep complaints/disturbances. This may be done using the DSM-5 criteria and further with self-report questionnaires (e.g. Epworth Sleepiness Scale, Insomnia Severity Index).
- If parasomnias, disordered breathing or circadian rhythm disruptions are suspected, refer the patient for an overnight sleep study at a sleep laboratory to assess any objective sleep disturbances that may be present [10]. Alternatively, if this is not possible, some objective sleep measurements may be recorded using actigraphy.
- Given the comorbidity with substance use disorders (SUDs), any assessment of an individual with PTSD should include screening for these disorders. Should a patient endorse symptoms of a SUD, the type, amount and timing of substance use should be determined, if possible, in order to assess the contributing factors to any sleep disturbances.
- Given the common comorbidity with depression, individuals presenting with PTSD should also be screened for symptoms of depression if this disorder is suspected, or if patients endorse persistent low mood or loss of pleasure in usual activities.
- History of traumatic brain injury should be considered when accounting for origins and contributing factors to sleep disturbances.

Case Vignette

Mr. K, a 67-year-old recently retired man, presented to a sleep clinic for assessment of chronic insomnia, which had worsened since his retirement. He endorsed difficulties falling asleep and reported it would take him up to 3 h to fall asleep. Once asleep, he frequently woke up earlier than he intended. He endorsed being "keyed up" and on edge for most of the day. He reported experiencing nightmares at least once a week which revealed themes of being chased or attacked, which frequently resulted in him awakening in a state of panic. He began to fear going to sleep.

Further questioning revealed a number of traumatic events in his life. He was attacked and physically assaulted by a stranger at age 12. He experienced a major accident at work that resulted in the loss of his finger. He also described the death of one of his children from a motor vehicle accident.

Objective polysomnography showed prolonged sleep onset, normal REM density, a high level of arousals from sleep and no evidence of sleep-disordered breathing. He was given a diagnosis of PTSD and was recommended for a course of pharmacotherapy and psychotherapy.

Case Vignette

Ms. D was a 38-year-old woman presented to a psychiatrist's office with a number of physical and psychiatric complaints. She reported a significant history of childhood sexual abuse by her father between the ages of 10 and 14, which ended after her father was arrested. She reported that the abuse frequently occurred at night in her bedroom.

One of the difficulties she had at this time is related to her sleep. She would often get anxious at night and avoid going to bed. She spent several hours watching TV, eating or drinking coffee late at night. Often by 3:00 am, she was tired enough to go to sleep and slept until 11:00 am. She was frequently tired in the daytime and also had difficulties regulating her emotions. Her sleeping habits made it difficult to hold a regular job and engage in activities.

She was referred for long-term psychotherapy, which included a behavioural focus to help improve her sleeping habits.

Case Vignette

Mrs. J presented with her 5-year-old son M. who was having difficulties falling asleep since there was a fire in their home. No one was injured during the fire, and the family was able to escape safely.

Since the fire, M. had become increasingly clingy and was reluctant but able to separate from his mother to attend school. At nighttime, he would get even more anxious. He previously had slept in his own bed, but now wanted to co-sleep with his parents. He was more restless during sleep and complained of nightmares. He also talked more in his sleep.

With reassurance, and a brief period of co-sleeping with his parents, he eventually returned to his baseline level of function.

References

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders 5. American Psychiatric Association. Washington, DC.
2. Ohayon MM, Shapiro CM. Sleep disturbance and psychiatric disorders associated with posttraumatic stress in the general population. Compr Psychiatry. 2000;41:469–78.
3. Hurwitz TD, Mahowald MW, Kuskowski M, Engdahl BE. Polysomnographic sleep is not clinically impaired in Vietnam combat veterans with chronic posttraumatic stress disorder. Biol Psychiatry. 1998;44(10):1066–73.
4. Werner KB, Griffin MG, Galovski TE. Objective and subjective measurements of sleep disturbance in female trauma survivors with posttraumatic stress disorder. Psychiatry Res. 2016;240:234–40.
5. Wallace ML, Iyengar S, Bramoweth AD, Frank E, Germain A. Clarifying heterogeneity of daytime and nighttime symptoms of posttraumatic stress in combat veterans with insomnia. Mil Psychol. 2015;27(4):212–22.
6. Belleville G, Guay S, Marchand A. Impact of sleep disturbances on PTSD symptoms and perceived health. J Nerv Ment Dis. 2009;197(2):126–32.
7. Fan F, Zhou Y, Liu X. Sleep disturbance predicts posttraumatic stress disorder and depressive symptoms: a cohort study of Chinese adolescents. J Clin Psychiatry. 2016. doi:10.4088/JCP.15m10206 [e-pub ahead of print].
8. Khazaie H, Ghadami MR, Masoudi M. Sleep disturbances in veterans with chronic war-induced PTSD. J Inj Violence Res. 2016;8(2):99–107.
9. Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. Am J Psychiatry. 2002;159(5):855–7.
10. Koffel E, Khawaja IS, Germain A. Sleep disturbances in posttraumatic stress disorder: updated review and implications for treatment. Psychiatr Ann. 2016;46(3):173–6.
11. Spoormaker VI, Montgomer P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature. Sleep Med Rev. 2008;12:850–9.
12. Nardo D, Hogberg G, Jonsson C, Jacobsson H, Hallstrom T, Pagani M. Neurobiology of sleep disturbances in PTSD patients and traumatized controls: MRI and SPECT findings. Front Psychiatry. 2015;6:134.
13. Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with short sleep duration and mortality: the Penn State cohort. Sleep. 2010; 33(9):1159–64.
14. Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karattaraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. Diabetes Care. 2009;32(11):1980–5.
15. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in US service members returning from military deployments. Mil med. 2010;175(10):759–62.
16. Wallace DM, Shafazand S, Ramos AR, Carvalho DZ, Gardener H, Lorenzo D, Wohlgemuth WK. Insomnia characteristics and clinical correlates in Operation Enduring Freedom/Operation Iraqi Freedom veterans with post-traumatic stress disorder and mild traumatic brain injury: an exploratory study. Sleep med. 2011;12:850–9.
17. Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DJ, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbance in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatr. 1998;155:929–33.
18. Sharon A, Levav I, Brodsky J, Shemesh AA, Kohn R. Psychiatric disorders and other health dimensions among holocaust survivors six decades later. Br J Psychiatry. 2009;195:331–5.
19. Shannon MP, Lonigan CJ, Finch AJ, Taylor CM. Children exposed to disaster: epidemiology of posttraumatic symptoms and symptom profile. J Am Acad Child Adolesc Psychiatry. 1994;33:80–93.
20. Brown TH, Mellman TA, Alfano CA, Weems CF. Sleep fears, sleep disturbance, and PTSD symptoms in minority youth exposed to hurricane Katrina. J Trauma Stress. 2011;24(5):575–80.
21. Noll JG, Trickett PK, Susman EJ, Putnam FW. Sleep disturbances and childhood sexual abuse. J Pediatr Psychol. 2006;31(5):469–80.
22. Mohsenun S, Mohsenin V. Diagnosis and management of sleep disorders in posttraumatic stress disorder: a review of the literature. Prim Care Companion CNS Disord. 2014;16(6): https://doi.org/10.4088/PCC.14r01663.
23. Nielsen TA, Zadra A. Nightmares and other common dream disturbances. Princ Pract Sleep Med. 2005;4:926–35.
24. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester: American Academy of Sleep Medicine; 2005.
25. Germain A, Zadra A. Dreams and nightmares in PTSD. In: Encyclopedia of neuroscience. Oxford: Elsevier; 2009. p. 655–61.
26. Schreuder BJN, Kleijn WC, Rooijmans HGM. Nocturnal re-experiencing more than forty years after war trauma. J Trauma Stress. 2000;13(3):453–63.
27. Mellman TA, David D, Bustamante V, Torres J, Fins A. Dreams in the acute aftermath of trauma and their relationship to PTSD. J Trauma Stress. 2001;14(1):241–7.
28. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatr. 1995;152:110–5.
29. Mellman TA, Uhde TW. Sleep panic attacks: new clinical findings and theoretical implications. Am J Psychiatry. 1989;146(9):1204–7.
30. Sheikh JI, Woodward SH, Leskin GA. Sleep in post-traumatic stress disorder and panic: convergence and divergence. Depress Anxiety. 2003;18:187–97.
31. Ghadami MR, Khaledi-Paveh P, Nasouri M, Khazaie H. PTSD-related paradoxical insomnia: an actigraphic study among veterans with chronic PTSD. J Inj Violence Res. 2015;7(2):54–8.
32. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048–60.

33. Vandrey R, Babson KA, Herrmann ES, Bonn-Miller MO. Interactions between disordered sleep, post-traumatic stress disorder, and substance use disorders. Int Rev Psychiatry. 2014;26(2):237–47.
34. Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. J Rehabil Res Dev. 2009;46(6):697–702.
35. Krakow B, Melendrez D, Warner TD, Clark JO, Sisley BN, Dorin R, Harper RM, Leahigh LK, Lee SA, Sklar D, Hollifield M. Signs and symptoms of sleep-disordered breathing in trauma survivors: a matched comparison with classic sleep apnea patients. J Nerv Ment Dis. 2006;194(6):433–9.
36. Woodward SH, Leskin GA, Sheikh JI. Sleep respiratory concomitants of comorbid panic and nightmare complaint in post-traumatic stress disorder. Depress Anxiety. 2003;18:198–204.
37. Tamanna S, Parker JD, Lyons J, Ullah MI. The effect of continuous positive air pressure (CPAP) on nightmares in patients with posttraumatic stress disorder (PTSD) and obstructive sleep apnea (OSA). J Clin Sleep Med. 2014;10(6):631–6.
38. Woodward SH, Leskin GA, Sheikh JI. Movement during sleep: associations with posttraumatic stress disorder, nightmares, and comorbid panic disorder. Sleep. 2002;25(6):669–76.

Actigraphy and PTSD

17

Imran S. Khawaja, Joseph J. Westermeyer, and Thomas D. Hurwitz

Introduction

Insomnia and nightmares are common symptoms of posttraumatic stress disorder (PTSD) in addition to wakeful symptoms of reexperiencing traumatic events and avoidance of stimuli associated with the trauma. Sleep disturbance is frequently, though not often, the principal focus of therapy in PTSD [1]. Emergence of insomnia following trauma may predict subsequent development of PTSD [2].

Evaluation of insomnia is challenging because it is a subjective experience. Patients can inaccurately perceive sleep due to dissociation and other memory distortions [3]. Clinical history, including collateral information, is valuable for evaluation of sleep. However, many individuals with PTSD do not have bed partners. Sleep diaries are useful for evaluation of insomnia, but they lack objective information. Because polysomnography (PSG) is generally not useful for evaluation of insomnia in PTSD, a simpler objective measure has been used to complement subjective reporting. The most usual technique is electronic activity monitoring, or actigraphy. This chapter will describe this technique, its reported use in studies of PTSD, and its clinical applicability.

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Clinical advantages of actigraphy include its coverage of extended periods of time, cost effectiveness, and ease of use in the natural environment. Actigraphy cannot clearly describe cerebral sleep-wake state as can EEG; its nonspecific finding can be a disadvantage.

Description of Actigraphy

Actigraphy, a technique of recording and quantifying body or extremity movements, can be used to assess sleep in conjunction with sleep diaries [4]. Activity monitors are small-computerized devices that record and store data generated by movements. Most can record continuously for up to a few weeks. Actigraphy systems usually include a recording device, an interface for transferring data to a computer, and software for setting recording parameters and analyzing the digital data. There are several systems available commercially, some including light sensors. Event markers can be used to indicate events such as "lights out" or "awakening." The device is typically worn on the nondominant wrist for a week or two. Subsequent computer download produces a graphic and quantitative report of movements per unit time that can be designated as sleep or wakefulness with reasonable reliability. The devices do not tolerate submersion in water, so it must be removed for bathing or swimming.

Assessment of validity and reliability of measures from the various devices, recording modes, and scoring algorithms are not typically available. Generally they are regarded as reliable for estimation of sleep duration, but not for quantification of sleep onset latency or daytime sleepiness [4]. Actigraphy does not capture central nervous system (CNS) arousals and absent significant movement. Actigraphy is most useful for description of timing of multiple sleep-wake cycles, which can be useful in evaluation of circadian rhythm disorders and treatment outcomes. Typically, individuals collect subjective data each day in a sleep-wake diary to complement the activity data from the device. This permits determination of time of retiring to bed and rising during the

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night and in the morning. This information can be used to define the intervals used for calculation of periods of sleep or wakefulness by movement count data. The diary can also provide assistance for distinguishing relatively motionless wakeful periods from sleep. Other relevant information may also be collected, such as medication administration, exercise, or daytime naps.

Figure 17.1 shows actigraphic data depicting periods of inactivity (i.e., low-amplitude tracing) suggesting time spent asleep. Figure 17.2 shows an actigraphic tracing of a person with insomnia complaints showing increased activity during the night suggestive of wakeful periods.

Figure 17.3 shows a typical recording device, which looks like a wristwatch and is worn on a nondominant wrist.

Clinical utility of actigraphy has been established gradually over time. Practice parameters established by the American Academy of Sleep Medicine cite evidence supporting actigraphy for evaluation of circadian rhythm sleep disorders, insomnia, hypersomnia, and obstructive sleep apnea [5]. This has resulted in allotment of Current Procedural Terminology (CPT) category 1 status as of 2009.

Over the past few years, there has been a quick growth in commercially available devices to measure activity and sleep. For example, the Fitbit Ultra (Fitbit Inc., San Francisco, CA, 1012) costs approximately $100 with no fee to use the online software.

These devices have great potential because they are accessible and affordable. While the usual clinically utilized devices have been shown to provide reliable estimate of sleep-wake patterns, the validity of the consumer-grade devices like the Fitbit is not proven. When compared to PSG and clinical actigraphy for adults, the Fitbit has shown good intra-device reliability, and both Fitbit and actigraphy overestimated sleep compared to PSG. Fitbit overestimation was 24 min more than actigraphy [6]. Therefore, Fitbit could possibly serve in a limited fashion when actigraphy is unavailable for normal adults, but further validation was recommended for clinical use.

Review of Literature Addressing Use of Actigraphy in Studies of PTSD

Polysomnographic studies of patients with PTSD have produced variable findings [7]. Based on meta-analysis, Kobayahi et al. report an association between PTSD and increased rapid eye movement (REM) density (a measure of rapid eye movement frequency during REM sleep), decreased stage N3 ("deep") sleep, and increased stage N1 (light) sleep compared with healthy comparison subjects [7]. These nonspecific findings are not uniformly documented in all studies. Consequently routine polysomnography is not indicated in the clinical assessment of PTSD unless other sleep disorders such as obstructive sleep apnea are suspected. Indeed, many individuals with PTSD find that they sleep more comfortably in a sleep laboratory, which is perceived as safe and "guarded" by the technologists [8]. Abnormal subjective sleep as perceived by patients with PTSD may also vary greatly over time, so that one or a few nights of data collection may be insufficient. That suggests that in-home monitoring with actigraphy may be helpful in documenting objective sleep disturbance in these patients.

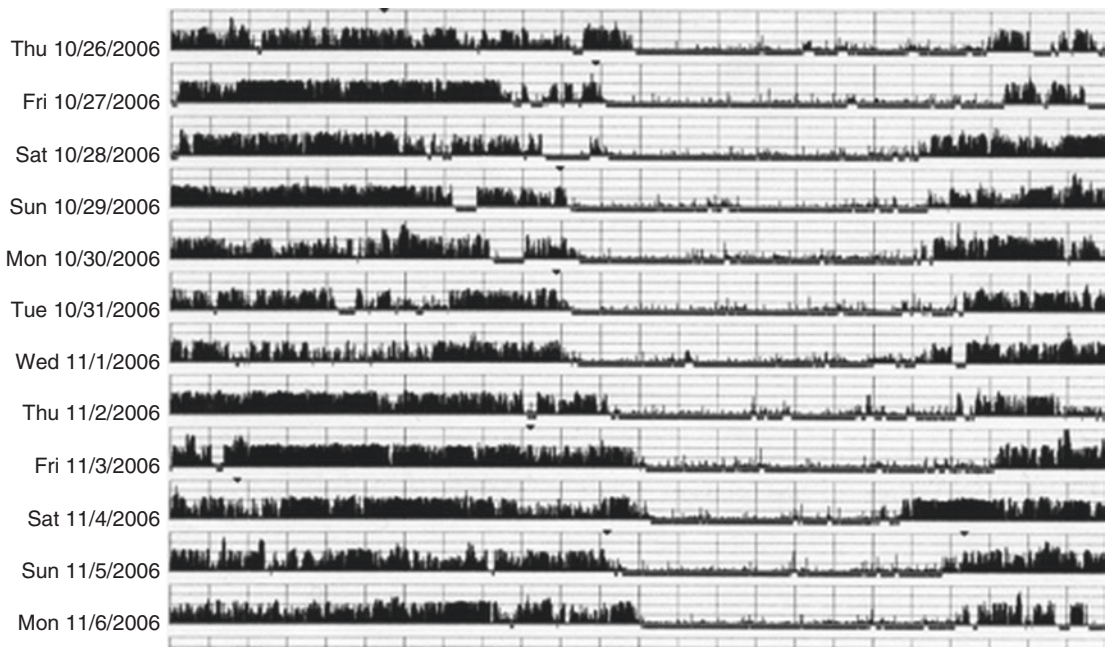

Fig. 17.1 A normal actigraph

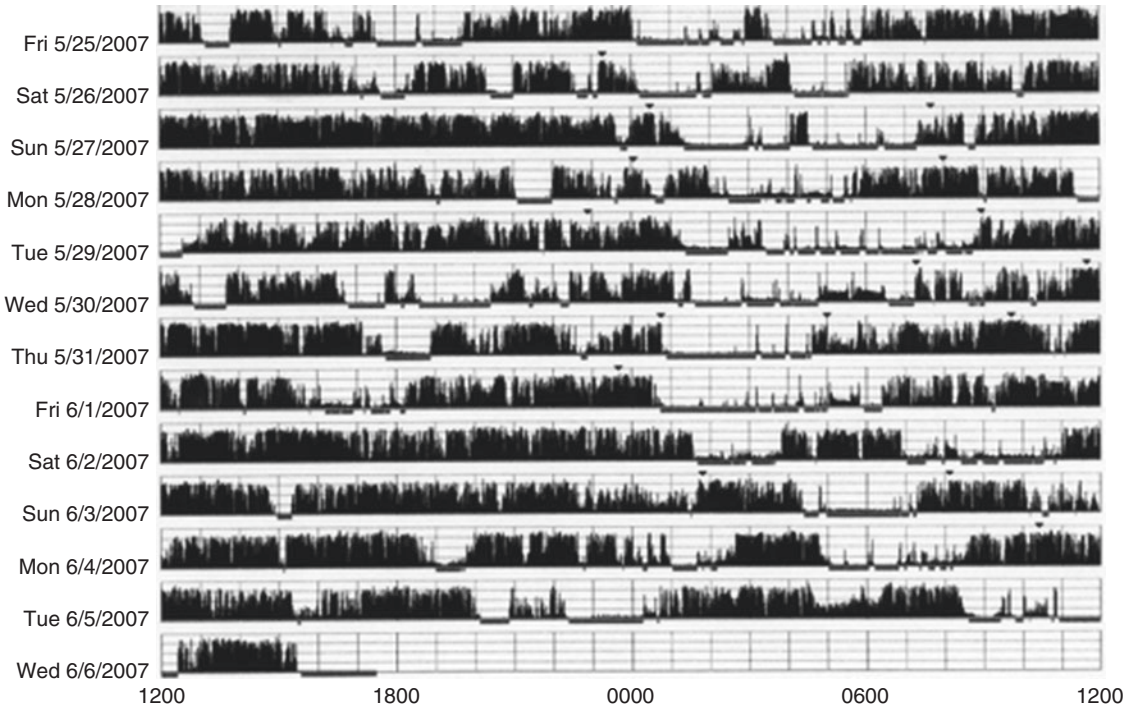

Fig. 17.2 An actigraph of a person with insomnia showing periods of activity in the middle of the night

Fig. 17.3 A basic actigraph

Dagan et al. [3] studied actigraphic findings during sleep at home in 16 men with DSM III-R-defined PTSD and 11 male non-PTSD controls. The PTSD group included randomly selected Lebanon war veterans. The control group included veterans of that conflict without diagnosed PTSD. Interestingly, PTSD patients did not have poorer actigraphic sleep (sleep time) than controls, despite reporting poorer subjective sleep. The authors suggested that PTSD patients might fail to correctly estimate their sleep, such as "sleep state misperception" or "paradoxical insomnia," in the newer nosology of International Classification of Sleep Disorders (ICSD II and III).

Westermeyer and colleagues [9] compared actigraphic and subjective sleep diary data for 241 nights among 21 veterans with lifetime PTSD. Actigraphic sleep minutes per night were, on average, 51 min longer than self-reported sleep minutes on sleep logs. Total intra-class correlation between actigraphy and sleep logs was 0.588. In the same study, correlation between self-reported awakenings on the sleep diary and apparent actigraphic awakenings was conducted after excluding nights when there was failure to indicate sleep duration in the diaries. There was a major difference with the number of awakenings reported on sleep diary never exceeding the number of apparent awakenings on actigraphy. For 241 nights of monitoring, actigraphy indicated 3.6 times more awakening episodes than did sleep diary information. This odds ratio differed greatly from one person to another, ranging from 2 to 12 times, leading the authors to suggest that self-reported awakenings are not reliable for scientific studies of individuals with PTSD. It is possible that patients moved sufficiently in their sleep to produce an appearance of an "awakening response" in the actigraphy. This study was limited by the inclusion of veterans receiving care for lifetime as opposed to current PTSD with sleep symptoms and cannot inform a concern about all patients with PTSD and insomnia. Interestingly, in contrast, Woodward et al. [10] have reported that veterans with PTSD tend to move less during sleep than normal controls.

In another paper, Westermeyer et al. [11] examined the same cohort to assess sleep symptoms in patients with lifetime PTSD. In this report, Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), Clinician-Administered PTSD Scale (CAPS), and PTSD Checklist were used. Posttraumatic avoidance, hypervigilance, and depressive symptoms were all associated with poor sleep quality on PSQI. Trends of borderline statistical significance were noted between worse sleep quality and more severe clinician-rated PTSD, more self-rated awakenings, and greater actigraphically determined sleep duration. Using linear regression, only PTSD hypervigilance symptoms were associated with impaired sleep quality. PSQI sleep disturbance showed no correlation with actigraphic awakening or with sleep log awakening. Shorter sleep duration on actigraphy revealed a borderline association with poor sleep quality on PSQI at $p = 0.08$. Awakenings per night were not associated with mean PSQI scores. Neither sleep duration nor awakenings per night were associated with the mean Epworth Sleepiness Scale score in this population.

These studies by Westermeyer et al. are severely limited with a small number of only 21 veterans with chronic "stable PTSD" in an active outpatient treatment setting. Women and nonwhites were minimally represented. In addition, clinical or sleep laboratory evaluations were not conducted to rule out other sleep disorders like obstructive sleep apnea (OSA) or restless legs syndrome (RLS) with periodic limb movements of sleep. However, several cases of OSA were identified during the screening process and referred for OSA evaluation.

Woodward and colleagues [12] used a novel approach to monitor movement in bed during sleep. Large and small movements of the sleeping individual activated accelerometers embedded in the mattress topper. With additional kinetocardiogram technology, they were able to evaluate movement and autonomic variability (autonomic activity is not recorded during a normal actigraphy). They reported on 59 nonveterans divided into groups with PTSD alone, PTSD and panic disorder, panic disorder alone, and normal controls. Screening for other sleep disorders was performed by PSG. In patients with PTSD with and without comorbid panic disorder, heart rate during sleep was higher than in control subjects ($p < 0.05$). Heart rates of those with panic disorder alone did not differ from controls. PTSD patients exhibited significantly longer periods of actigraphic sleep time and time in bed as compared to either panic disorder group or PTSD and panic disorder group. The PTSD-only participants showed contradictory indicators, i.e., tonically elevated sympathetic tone with extended sleep periods.

Overall the study showed that among nonveteran participants meeting criteria for PTSD alone, there was evidence of increased autonomic activation (not relevant to general actigraphy) co-occurring with prolonged actigraphic sleep periods, a finding which seems counterintuitive.

More recently, Ghadami et al. [13] assessed sleep disturbances in veterans with chronic PTSD, using both subjective and objective measures. Thirty-two patients with chronic PTSD and complaints of insomnia underwent two consecutive overnight actigraphic assessments. For subjective assessments, authors utilized Clinician-Administrated PTSD Scale (CAPS) version 1 and PSQI. In this study, the veterans underestimated total sleep time (TST), sleep efficiency (SE), as well as nocturnal awakenings in the subjective questionnaire compared to the actigraphic assessment. The authors concluded that self-reported disturbance in veterans with chronic PTSD is not reliable, and objective sleep assessments are necessary to compliment clinical evaluation as these patients have PTSD-related paradoxical insomnia.

Discussion

Actigraphy can assist in the evaluation of insomnia and circadian rhythm sleep disorders, such as advanced sleep phase type, delayed sleep phase type, shift work disorder, jet lag disorder, and non-24 h sleep/wake syndrome.

The use of actigraphy to evaluate sleep disturbances in clinical psychiatric settings is uncommon but can provide valuable information. It is commonly unavailable in most psychiatric clinics. There is not yet ample evidence to support any specific actigraphic findings related to PTSD. Those patients who are experiencing sleep disturbances should have a formal clinical assessment to evaluate possible comorbid sleep disorders.

In patients with PTSD and comorbid insomnia, actigraphy in conjunction with sleep diary may help to characterize circadian rhythm and sleep patterns. Even if the diary information is not available, actigraphy can reveal information covering extended periods in a graphic form. This can also allow patients to see their own sleep pattern, e.g., sleeping during the daytime. This could aid their capacity to appreciate poor sleep habits and can foster ownership of their own nonadaptive sleep patterns.

References

1. Spoonmaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12:169–84.
2. Koren D, Amon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year study of injured survivors of motor vehicle accidents. Am J Psychiatry. 2002;159:855–7.
3. Dagan Y, Zinger Y, Lavie P. Actigraphic sleep monitoring in posttraumatic stress disorder (PTSD) patients. J Psychosom Res. 1997;42(6):577–81.
4. Martin J, Hakim A. Wrist actigraphy. Chest. 2011;139(6):1514–27.

5. Morgenthaler T, Alessic, Freidman, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep. 2007;30(4):519–29.
6. Montgomery-Downs HE, Insana SP, Bond JA. Movement toward a novel activity monitoring device. Sleep Breath. 2012;16:913–7.
7. Kobayahi I, Boarts JM, Delahanty D, et al. Polysomnographically measured sleep abnormalities in TSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
8. Levie. Ecological study of sleep disturbance in PTSD: a pilot study. Ann N Y Acad Sci. 2006;1071:438–41.
9. Westermeyer J, Sutherland RJ, Freerks M, et al. Reliability of sleep log data vs. actigraphy in veterans with sleep disturbance and PTSD. J Anxiety Disord. 2007;21(7):966–75.
10. Woodward SH, Leskin GA, Sheikh JI. Movements during sleep: associations with post traumatic stress disorder, nightmares, and co morbid panic disorder. Sleep. 2002;25(6):681–8.
11. Westermeyer J, Khawaja IS, Freerks M et al.. Correlates of daytime sleepiness in patients with posttraumatic stress disorder and sleep disturbance. Prim Care Companion J Clin Psychiatry. 2010; 12(2). Pii: PCC.07m00563.
12. Woodward SH, Arsenault NJ, Veolker K, et al. Estimating heart rate and RSA from the mattress-recorded kinetocardiogram. Psychophysiology. 2007;44:635–8.
13. Ghadami MR, Khaledi-Paveh B, Nasouri M, et al. PTSD-related paradoxical insomnia: an actigraphic study among veterans with chronic PTSD. J Inj Violence Res. 2015;7(2):54–8.

The Extreme Nocturnal Manifestation of Trauma: Trauma Associated Sleep Disorder

18

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Illustrative Case of TSD

A 31-year-old active duty soldier presented with a 10-year history of restless sleep and disturbing nightmares occurring three to four times per week. He reluctantly discussed the content of his nightmares which involved experiences from his first deployment to Iraq. During his deployment, he had multiple prolonged missions without sleep. His combat-related nightmares primarily related to his duties as a medic when he encountered mutilated bodies and ensured enemy combatants were killed. Other nightmares involved life-threatening situations he experienced; however, in his nightmare he would not survive. The patient's wife reported he frequently acted out his dreams with violent punching, slapping, rolling, and kicking that have injured her on multiple occasions. During some of his nightmares, he vocalized with sounds ranging from crying out to panicked or angry speech related to his combat experiences. His past medical history was notable for PTSD that is treated with bupropion, and he suffers from daytime symptoms including flashbacks and visual hallucinations of enemy snipers or roadside bombs. Diagnostic polysomnography revealed a reduced sleep efficiency (77%), increased arousal index (25/h), and REM without atonia associated with thrashing body movements and increases in heart rate. He was diagnosed with trauma associated sleep disorder (TSD). Treatment with 10 mg of nightly prazosin and imagery rehearsal therapy decreased nightmare frequency (less than once per week) without changing nightmare severity. His disruptive nocturnal behaviors persisted.

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Introduction

Sleep disturbances are frequent following a traumatic experience [1, 2]. Ross and colleagues originally described sleep disturbances, with an emphasis on REM sleep disturbances and nightmares, as the hallmark of posttraumatic stress disorder (PTSD) [3]. There is now substantial evidence that both REM and NREM sleep are dysregulated following trauma [4]. Additionally, a variety of sleep disturbances arise in trauma survivors with and without PTSD including insomnia, trauma-related nightmares (TRN), autonomic hyperarousal, and disruptive nocturnal behaviors (DNB) consisting of dream enactment, vocalizations, and complex motor behaviors [3, 5–10]. Many of these disturbances, such as TRN or trauma-induced insomnia, do not conform to currently accepted sleep disorders; however, they are sometimes recognized as distinct nosological entities with novel neurobiological models [5]. More often, patients who present with the symptoms of posttraumatic nightmares and DNB are considered to have symptoms of PTSD or variants of existing sleep disorders such as nightmare disorder or REM sleep behavior disorder (RBD) [11, 12]. For these reasons, and because TRN and DNB are rarely captured during polysomnography, these posttraumatic sleep disturbances remain relatively poorly characterized [6].

Trauma associated sleep disorder (TSD) is a proposed parasomnia that encompasses the TRN, sympathetic activation, and DNB occurring during sleep in patients following trauma [13]. Though TSD may be associated with PTSD in some (but not all cases), its symptomatology is confined to sleep. Clinical features of TSD differentiate it from other sleep disorders, including established parasomnias. This chapter will discuss the clinical characteristics of TSD and distinguish it as a unique sleep disorder. Historical findings consistent with TSD and potential neurobiological

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mechanisms of TSD will also be described. Recognition of TSD as a unique parasomnia that develops after trauma is critical to furthering our understanding of this disorder and developing effective therapies.

The onset of profound sleep disturbances after trauma has long been recognized. In their historical account of psychotraumatology, Crocq and Crocq [14] detail multiple distinct accounts of TRN and DNB. They noted the following in Lucretius' poem, De Rerum Natura, which was written in 50 BC (Book IV, translation William Ellery Leonard):

"Again, the minds of mortals …
Often in sleep will do and dare the same
In manner like. Kings take the towns by storm,
Succumb to capture, battle on the field,
Raise a wild cry as if their throats were cut
Even then and there. And many wrestle on
And groan with pains, and fill all regions round
With mighty cries and wild, as if then gnawed
By fangs of panther or of lion fierce.
Many amid their slumbers talk about Their mighty enterprises…
Many meet death; many, as if headlong
From lofty mountains tumbling down to earth
With all their frame, are frenzied in their fright;
And after sleep, as if still mad in mind,
They scarce come to…

This historical account details many of the characteristic features of TSD to include TRN, vocalizations, dream enactment behavior, and frequent lack of dream recall. Similar symptoms have long been reported and continue to be reported by trauma survivors and their bed partners; however, as noted such profound clinical manifestations are only rarely documented during PSG. Based on the existing literature, there are 11 cases to date that have PSG-documented abnormalities consistent with TSD (see Table 18.1). The reasons for this lack of documentation

Table 18.1 Previous cases of polysomnographic documentation of patients with findings consistent with TSD

Article	Patients consistent with TSD	Demographic	PSG findings	Self-reported DNB	Nightmare content
Mysliwiec et al. [13]	4 ($N = 4$)	Male soldiers (ages 22–34)	Patient 1: defensive limb movements and repeated vocalizations, "oh f***, leave me alone!" Sleep stage: REM All patients: RWA, phasic bursts	Patient 1: screaming and combative movements Patient 2: thrashing movements; episode of choking wife Patient 3: somnambulism, combative movements Patient 4: "screaming, crying, throwing pillows, and cursing" and witnessed punching/kicking wall with vocalization of "I am going to kill you"	Patient 1: assailants pursued and threatened him Patient 2: combat-related experiences Patient 3: flashbacks to combat environment Patient 4: related to personal relationship
Hefez [10]	2 ($N = 11$)	Male maritime disaster survivors (ages 20 and 25)	Patient 1: violent body movement and vocalizations; 2 reports of falling out of bed Sleep stage: REM Patient 2: REM-related motor activity and vocalizations Sleep stage: REM	None reported	Patient 1: reliving sea disaster Patient 2: nightmares related to disaster
Schlosberg and Benjamin [19]	3 ($N = 3$)	Male soldiers (ages 25–35)	Patient 1: "awoke particularly violently, jumping out of bed screaming and hallucinating" Sleep stage: N2 All patients: numerous body movements with RWA	None reported	All patients reported recurrent nightmares; descriptions not provided
Van der Kolk et al. [8]	2 ($N = 15$)	Male Vietnam veterans (ages not reported)	Patient 1: removed electrodes and walked around the room; later reporting thinking he was in an ambush Sleep stage: REM Patient 2: body movements and thrashing Sleep stage: REM	Reported body movements accompanying nightmares with occasional physical attacks on bed partners	Patient 1: thought he was in an ambush Patient 2: memory of being in gunfight; coming upon mutilated bodies

Abbreviations: *DNB* disruptive nocturnal behaviors, *PSG* polysomnogram, *RWA* REM without atonia, *TSD* trauma associated sleep disorder

remain speculative, with some suggesting that being watched/monitored while sleeping decreases nocturnal hyperarousal, which is likely part of the pathophysiologic mechanism for TSD.

Besides the patient's symptomatology and PSG, there is a clinical instrument which evaluates posttraumatic sleep disturbances. The Pittsburgh Sleep Quality Index Addendum (PSQI-A) assesses the DNB that occur in trauma survivors with and without PTSD [6]. This instrument was initially developed to evaluate DNB in patients with PTSD but is now recognized as a better measure of trauma-related sleep disturbances as opposed to PTSD [15]. One study assessed 375 combat veterans using the PSQI-A and reported 59.1% had a score of >4, consistent with PTSD [16]. Nightmares were one of the most frequent symptoms, and participants reported abnormal movements during sleep, potentially suggestive of TSD. More recently, Thordardottir et al. evaluated the sleep of avalanche survivors 16 years after the inciting trauma using the PSQI-A [2]. They reported that compared to matched controls, survivors who were children at the time of the trauma had increased DNB, whereas adult survivors had TRN. Based on the previous cases consistent with TSD, the reports using the PSQI-A, and our clinical experience, the following features of TSD are outlined below.

Clinical Features of TSD

There are distinct clinical characteristics that define TSD and differentiate it from existing sleep disorders. See Table 18.2 for the proposed diagnostic criteria for TSD:

Table 18.2 Proposed diagnostic criteria for TSD

1. Onset after combat or other traumatic experiences (often in the setting of sleep deprivation/disruption)
2. A history of altered dream mentation that is related to prior traumatic experience
3. Self- or witnessed reports of disruptive nocturnal behaviors to include at least one of the following:
(a) Abnormal vocalizations
(i) Screaming or yelling
(b) Abnormal motor behaviors in sleep
(i) Tossing, turning, or thrashing
(ii) Combative behaviors such as striking bed partner
4. Symptoms of autonomic hyperarousal or PSG monitoring demonstrates one of the following:
(a) Tachycardia
(b) Tachypnea
(c) Diaphoresis
(d) If documented on PSG, these findings are not due to sleep-disordered breathing
5. PSG may demonstrate:
(a) REM sleep without atonia (variable amounts of RWA)
(b) Dream enactment behavior in REM sleep
6. Absence of EEG epileptiform activity on PSG

Adapted from Mysliwiec et al. [13]; with permission

1. *Onset/precipitating factors*: Every previously described case that is consistent with TSD developed following a traumatic experience [8, 17, 18]. In most cases, combat was the inciting event [8, 13, 19], though maritime disasters have also been described [10] and exposure to natural disasters [2] or other traumatic experiences are a potential trigger. These experiences typically occurred under extreme duress and more than likely lasted for a prolonged period of time, suggesting that the traumatic experience must be extremely stressful to induce TSD. Sleep deprivation or disruption also appears to contribute to the onset of TSD [19]. Military personnel serving in combat are exposed to disrupted, insufficient sleep or total sleep deprivation [20], and sailors likely experience similar conditions. Notably, sleep after trauma exposure appears to decrease the intensity and frequency of traumatic memories [21]. After the inciting trauma, symptoms including nightmares and DNB typically develop relatively acutely, within weeks to months [10, 13, 19]. In some cases, nightmares of the traumatic experience may precede DNB, or repeated exposure to trauma is required to unmask DNB [13].
2. *Patient demographics*: In the majority of cases consistent with TSD, patients were young adult males [8, 10, 13, 17, 19]. This is likely due to increased combat exposure in males and under-recognition of TSD. To date, we have diagnosed TSD in two females, both of whom had substantial combat exposure. In the study by Thordardottir et al. [2], children ages 2–12 who had trauma exposure during their developmental years had more severe nocturnal symptoms (i.e., DNB) than adults. This finding suggests that the development of TSD in the pediatric population may not necessarily require concomitant sleep disturbance as this cohort likely had normal sleep prior to their traumatic exposure. Though further research is required, it is conceivable that TSD could develop at any age in individuals with trauma exposure and concurrent sleep disruption.
3. *Nightmares*: Patients with TSD suffer from nightmares that are related to their traumatic experience. Nightmare content varies depending on the nature of the trauma [22], but may include elements of death or dying, combat, and imminent threat to the patient's safety. Associated symptoms of anxiety, fear, or emotions felt at the time of the trauma may accompany the nightmare. Nightmares in TSD appear to occur primarily in REM sleep [3, 8, 10], but nightmares in NREM sleep [19, 23] have also been reported. The occurrence of nightmares in NREM sleep may account for the fact that some patients lack specific dream recall [24–26]. In those cases, the patient may vocalize or act out the dream, as reported by the bed partner, which results in the patient seeking clinical care.

4. *Disruptive nocturnal behaviors*: Perhaps the most distinctive characteristic of TSD is the DNB that can accompany TRN. These symptoms, often reported by the bed partner, range from gross body movements to vocalizations. Some patients have limb movements or thrash and toss about [8, 17], whereas others report more purposeful movements consistent with dream enactment behavior (DEB) including combative behaviors such as striking or choking a bed partner [13]. A smaller number of patients experience vocalizations ranging from grunts and groans to yelling out expletives and frank screaming [8, 13, 19]. In documented cases, vocalizations are often related to the content of the nightmare and may occur repeatedly. Unfortunately, the patient's nightmares and DNB that are reported to frequently occur in the habitual sleeping environment are difficult to characterize due to rare capture on PSG. One potential explanation for this phenomenon is that the monitored environment and presence of another person in the vicinity of the patient afford a feeling of safety which may reduce the probability of having a nightmare [27]. In the few cases that have documented DNB in the sleep lab, movements were typically purposeful and ranged from defensive posturing to escaping from the room [8, 10, 13, 19].
5. *Autonomic hyperarousal*: Symptoms consistent with sympathetic nervous system activation including tachycardia, tachypnea, and night sweats are common in patients with TSD. Similar findings have been reported acutely and chronically in combat veterans with and without PTSD [17, 19]. Stress and sleep disruption are closely associated with physiologic hyperarousal in humans [28]. The hyperarousal physiology likely results from specific trauma exposure, such as that experienced during combat [29]. In TSD, the hyperarousal is likely a reflection of increased autonomic and limbic activity with dysfunctional processing of memories and emotions similar to PTSD [30], though occurring exclusively during sleep. Relative tachycardia during REM sleep, which is associated with phasic RWA, is the most common finding of autonomic hyperactivity on PSG.
6. *REM sleep without atonia*: Patients with TSD have increased phasic EMG activity during REM sleep on PSG. Using the Sleep Innsbruck Barcelona criteria for "any" mentalis EMG activity [31], the amount of RWA may vary. It is suspected that the RWA coincides with the occurrence of nightmares with or without associated DNB. For this reason, the RWA may appear intermittently in REM with phasic bursts, and the overall "any" EMG activity may not be pathologically increased [13]. Figure 18.1 demonstrates a characteristic finding of RWA and DNB in a previously unreported patient with TSD.
7. *Associated illnesses and comorbid sleep disorders*: Posttraumatic stress disorder appears to frequently co-occur with TSD. Though trauma incites both disorders, they are distinct and can be mutually exclusive; only one of four patients with TSD had PTSD in our initial report [13]. Sleep disorders, including insomnia and obstructive sleep apnea (OSA), are also commonly comorbid with TSD. Multiple authors have reported insomnia in up to 74% of combat veterans with nightmares and symptoms of PTSD [19, 32]. Additionally, approximately half of patients with TSD have OSA, with the majority having mild sleep-disordered breathing. A similar association of OSA with PTSD has been posited, noting that in a review of sleep studies in PTSD patients, over half met clinical criteria for sleep-disordered breathing [33].
8. *Therapy*: Potential therapies for TSD should target the core symptoms of the parasomnia. Enhanced sympathetic activity may be counteracted using prazosin, an alpha-1 adrenergic receptor antagonist that is active in the central nervous system (CNS). This medication has been effective in reducing nightmares in veterans with PTSD [34] and the nightmares and DNB of patients suffering from TSD [13]. Imagery rehearsal therapy may also have a therapeutic role in TSD given its efficacy in treating nightmares [35], but this remains to be determined. Clonazepam, a medication effective in controlling movements in RBD [18, 36], does not appear to be effective in counteracting the DNB of TRN in combat veterans [37]. Counseling regarding a safe sleep environment is essential for both the patient and his/her bed partner. Further research is required to determine additional treatment options, but a multidisciplinary approach including pharmacotherapy and behavioral therapy will likely be required to address the spectrum of TSD symptomatology.
9. *Clinical course*: The nightmares and DNB of TSD appear to be most severe early in the disease course. In close proximity to the trauma (i.e., weeks to months), symptoms may occur nightly and sometimes more than once per night [13]. While nightmares and DNB persist over time, their frequency and severity tends to diminish. In a study of 59 elderly men with and without PTSD who had combat experiences 28–50 years prior to their evaluation, sleep was similar between the groups with the exception of increased REM sleep and decreased arousals in those with PTSD [38]. Notably, recrudescence of nightmare symptomatology can result from increased stress [39]. The clinical course of TSD likely follows a similar pattern, though longitudinal studies are required to determine the chronic nature of this disease.

Differentiating TSD from Established Parasomnias and Other Sleep Disorders

TSD has characteristics that overlap with other sleep disorders including the established REM parasomnias, RBD, and nightmare disorder. However, TSD has features that distinguish it from these diagnoses, and TSD fulfills the necessary

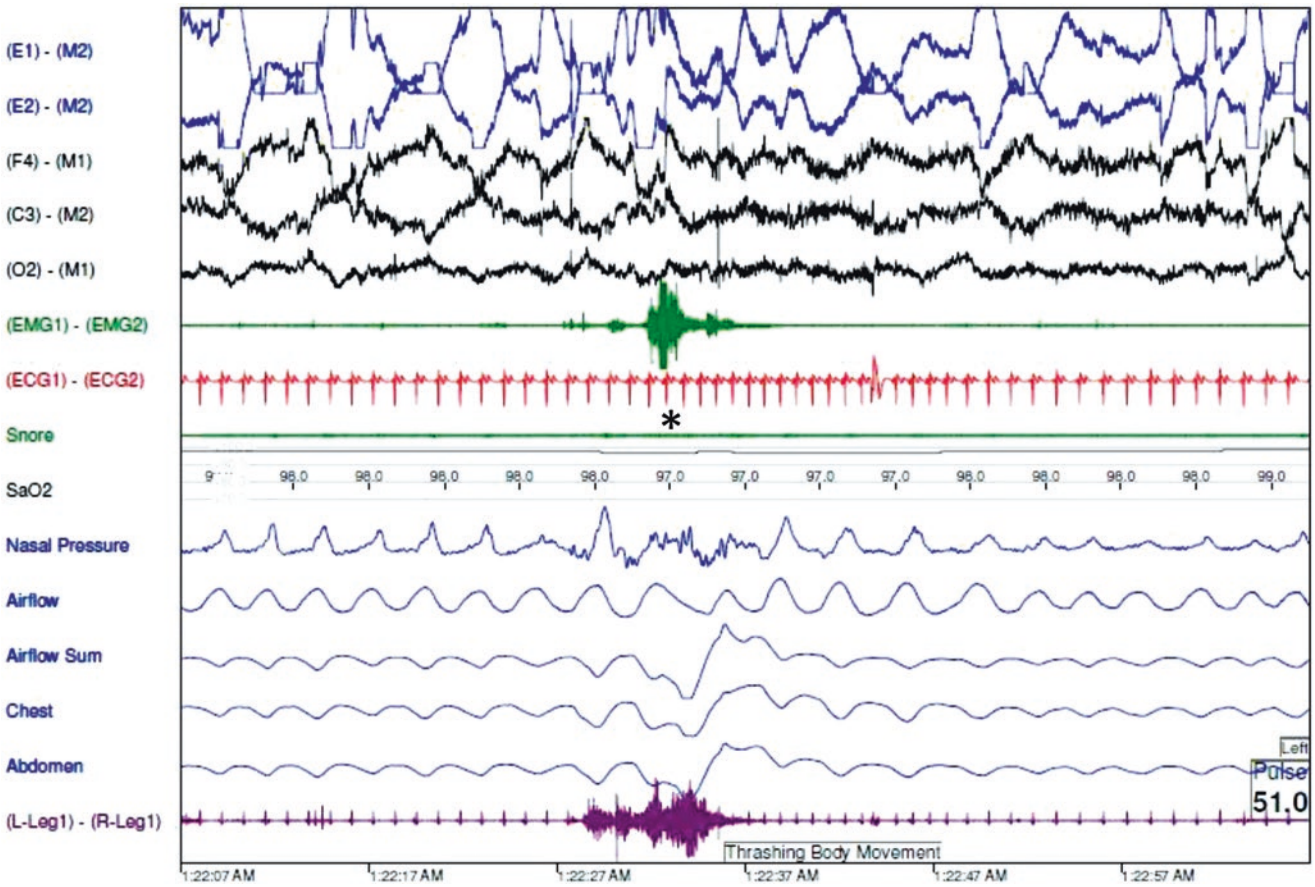

Fig. 18.1 Epoch of REM sleep depicting characteristic findings of TSD. A 60-s epoch of REM sleep in a 31-year-old male with posttraumatic stress disorder who presented with nightmares and disruptive nocturnal behaviors. These symptoms developed after deployment to Iraq. His nightmares occurred >3 times per week and entailed reenactments of combat. The nightmares were accompanied with thrashing and falling out of bed. His episodes of thrashing included slapping, kicking, and rolling into his spouse. The epoch demonstrates REM without atonia (*RWA*) with increased electromyogram (*EMG*) tone in the submental and left lower extremity corresponding with a thrashing body movement. A 15-beat increase in heart rate was associated with this event (onset at *). His PSG was otherwise normal except for multiple similar occurrences of RWA

criteria of a parasomnia with abnormal dreams, sleep-related movements and behaviors, and autonomic nervous system activity that are not better explained by another disorder [12]. Comparing and contrasting TSD with RBD and nightmare disorder bolsters its recognition as a distinct parasomnia (see Table 18.3).

REM Sleep Behavior Disorder

Vivid dreams with DNB, nightmares, and DEB that may be injurious are the presenting symptoms for RBD, and similar symptoms are present in patients with TSD [18, 36]. However, the relatively acute onset of DNB and nightmares in close temporal proximity to trauma is not consistent with the presentation of RBD [19]. There are reports of stressful situations such as being the victim of robbery or fraud, receiving a cancer diagnosis, or having a surgical procedure, which have been associated with the onset of idiopathic RBD (IRBD). Yet, these patients had clinical features which were otherwise consistent with IRBD [40]. RBD is associated with α-synucleinopathies, whereas TSD appears to have an association with PTSD [13, 41, 42]. Clinically, despite the report of frequent DNB by patients with TSD, it is rarely captured on PSG [6, 24, 43]. In contrast, DEB is frequently documented in RBD with two studies reporting a single PSG with video monitoring confirms the diagnosis of RBD in >80% of patients [40, 44]. Another distinguishing characteristic of TSD is the increased sympathetic output reported, most notably tachycardia [13, 19]. Conversely, even with vigorous DNB, there is a relative absence of autonomic activity in patients with RBD [36, 45]. In RBD, sleep quality is usually undisturbed, with 70% of patients reporting good sleep quality [40]. Disturbed sleep is present in all patients with TSD, with most patients meeting diagnostic criteria for insomnia. Regarding treatment, clonazepam, the drug of

Table 18.3 Characteristics of TSD compared to other parasomnias

Characteristics	TSD	RBD	Nightmare disorder
Onset/precipitating factors	Following traumatic experience Associated sleep deprivation or disturbance Rapid onset (weeks to months)	No specific precipitating factors Insidious onset	May be reactive to life stressors, but generally ubiquitous in general population Variable onset
Patient demographic (typical)	Young adults	Older males	May be seen in any age or gender
Nightmares	Related to prior trauma	Defense of sleeper against attack	Content may be stereotyped, but often random
Disruptive nocturnal behaviors	Gross body movements, defensive posturing Vocalizations Recorded in REM and NREM Rarely recorded in sleep lab	Dream enactment with combative, injurious behaviors Exclusive to REM Frequently recorded in sleep lab	Absent
Autonomic hyperarousal	Profound and concordant with dream content	Uncommon	Minor, even in highly disturbing dreams
REM sleep without atonia	Present, but "any" EMG index often normal	Present and "any" EMG activity index >18.2%	Absent
Associated illnesses	Posttraumatic stress disorder	Alpha synucleinopathies (Parkinson's disease, Lewy body dementia, multiple system atrophy) Narcolepsy	Anxiety PTSD Personality disorders
Comorbid sleep disorders	Insomnia and OSA frequent	Periodic limb movements	Insomnia
Therapy	Prazosin	Clonazepam Melatonin	Prazosin Imagery rehearsal therapy Lucid dreaming
Clinical course	Frequency and severity of symptoms diminish over time	Dependent upon underlying etiology, but typically slowly progressive	Frequency and severity of nightmares diminish over time

Abbreviations: *EMG* electromyogram, *OSA* obstructive sleep apnea, *PTSD* posttraumatic stress disorder, *RBD* REM sleep behavior disorder, *TSD* trauma associated sleep disorder

choice for RBD, does not have any efficacy in treating either the nightmares or DNB associated with TSD. In our experience, prazosin results in clinical improvement in >50% of patients with TSD.

The possibility that RBD could be precipitated by trauma was first posited by Husain et al. [46]. In their study of male veterans with ages ranging from 46 to 78 years, of 22 patients with PTSD, 15 also had RBD. The nightmare content of all 22 patients was trauma related. Notably, none of the patients with RBD had either Parkinson's disease or dementia with Lewy bodies. Dallam et al. conducted a retrospective review of elderly military veterans [47] and found 16 of 197 (8%) patients, all of whom had PTSD and dementia, reported war-related nocturnal vocalizations. Seven of their patients reported combative nocturnal behaviors. Another study assessed 12 patients with PTSD, 10 of whom had DEB [48]. In this study, phasic RWA on PSG was reported in 80%. The absence of a clinical course describing the onset of symptoms after trauma in these studies leaves open the question as to whether these patients initially had unrecognized TSD, although it appears more likely that the patients in these reports developed RBD with some incorporation of PTSD symptoms later in life.

Medication-associated RWA and cases of secondary RBD are reported with the use of antidepressants, specifically serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants (TCA) [49, 50]. As with classic RBD, one study postulated that antidepressants may expose an impending neurodegenerative disorder [51]. Yet, there is a different hypothesis which is supported by more robust research suggesting that psychiatric disease itself may increase the risk of RBD independent of antidepressant usage [50]. Additionally, a recent study reported that while RWA was significantly increased in patients taking SSRI or SNRI, patients on these medications were not at increased risk for RBD [52]. In our initial report of TSD, two patients were taking SSRIs. Notably, in both cases, the patients reported DNB and nightmares prior to initiating therapy. In another study, which assessed combat veterans with an average age of 30 years, Wallace et al. reported four patients with RWA, DEB, and sleep-related injury. All of these patients were taking SSRIs and were classified as having secondary RBD [9]. Given their young age and symptom onset after combat exposure, it is possible these patients had TSD. Ultimately, the use of antidepressants, which is fre-

quent in trauma survivors, could confound or potentially exacerbate the underlying diagnosis of TSD.

Nightmare Disorder

Nightmare disorder is a REM-related parasomnia characterized by recurrent disturbing dreams that generally involve a threat to an individual's safety and often result in awakening with the ability to recall the nightmare's contents. Nightmares may be reactive to life stressors but are rather ubiquitous in the general population, affecting males and females of any age [12]. TSD is primarily distinguishable from nightmare disorder by the symptoms of excessive nocturnal movements and DNB, which do not occur with this established parasomnia. In nightmare disorder, autonomic hyperarousal is nearly always absent or at most minor, even in highly disturbing dreams [12]. This contrasts sharply with the profound sympathetic output experienced by TSD patients. Further, although nightmares in TSD are hypothesized to occur primarily in REM sleep [24], they have been reported in NREM [23]. An additional aspect is that TSD patients may not recall their nightmares; this finding has also been reported in PTSD patients with TRN [53]. However, as nightmares are a core symptom of TSD, a better understanding of this component of TSD is required.

Dream content can be classified as replicative/replay, non-replicative/symbolic, or mixed [53]. The nightmares of TSD tend to be replicative of the patient's traumatic experience. Studies evaluating combat veterans and survivors of World War II Japanese prison camps and the Holocaust indicate TRN can persist for more than 40 years [23, 25]. While nightmares tend to decrease in frequency and intensity over time, a study which evaluated Vietnam veterans demonstrated a relationship between the frequency of daytime stressors and increased nightmares as well as nightmare-related distress [39]. The clinical course of TSD is not yet well established; it is likely that the symptoms persist in a manner similar to the aforementioned studies on nightmares.

Other Sleep Disorders

There are several other disorders which may present with symptoms potentially suggestive of TSD. Severe OSA has been reported to mimic RBD with symptoms of DEB, nightmares, and vocalizations [54]. These patients were not reported to have RWA and sleep-disordered breathing preceded the onset of DNB. Further, treatment with CPAP resolved their RBD-like symptoms [54]. While some patients with TSD have OSA, we have not observed DNB emanating from arousals due to sleep-disordered breathing. Periodic limb movement disorder (PLM) is frequently reported in patients with PTSD, and the movements of either the arms or legs could be interpreted by a bed partner as DNB. In our experience, the palpable rage and graphic vocalization of TSD make it clinically distinguishable from PLM. Nocturnal epilepsy can present with DEB which are at times violent; however, the DNB in nocturnal epilepsy are stereotypical and an EEG would document epileptic activity [55]. Polysomnography, potentially on several nights, may be required to differentiate these sleep disorders from TSD. This could also acclimate the patient to the lab environment and potentially increase the likelihood of a patient exhibiting DNB.

Neurobiological Hypothesis of TSD

The neurobiological correlates of TSD remain largely unexplored [56]. However, the growing body of preclinical and clinical research on trauma and PTSD provides insight into how traumatic experiences and disrupted sleep may trigger TSD. The stress of trauma leads to metabolic and structural changes in the brain that can be demonstrated with functional neuroimaging [57, 58]. Sleep deprivation and disruption appear to be priming factors for these changes and the development of TSD.

There is substantial evidence that REM and NREM sleep are dysregulated following trauma (see review by Germain [4]), which is consistent with observations that TSD symptoms can occur in both REM and NREM [9, 50, 65]. However, disturbances in REM sleep physiology, in particular, appear crucial in the development of TSD. Additionally, the characteristic features of TSD, including phasic RWA, occur in REM. In trauma survivors, disturbed REM sleep portends a higher risk for developing PTSD [92] as resilience is compromised and emotional reactivity is amplified [51]. Individual variability in REM sleep propensity and childhood exposure to stressors or trauma may impact REM physiology [57]. Insana et al. showed in combat veterans that REM sleep fragmentation and DNB were associated with adverse childhood experiences [59]. Similar findings were reported by Thordardottir et al. who reported that childhood trauma exposure was associated with DNB later in life [2]. Thus, trauma, particularly at a young age, may affect the development of CNS structures that control REM sleep, particularly those responsible for atonia.

In normal sleep, neurons in the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) excite neurons of the nucleus reticularis magnocellularis in the medulla, which in turn hyperpolarize spinal and brainstem motor neurons producing skeletal muscle atonia, a REM defining feature [60, 61]. Another characteristic of REM sleep is that sympathetic tone is markedly reduced [62, 63] as monoaminergic nuclei, including the locus coeruleus (LC) and dorsal

raphe (DR), are silent [64]. The suppression of central adrenergic neurotransmitters such as norepinephrine (NE) during REM "may be one of the most fundamental and functionally important aspects of this state" [65]. Monoamine nuclei inactivity also contributes to muscle atonia as NE and serotonin, the products of the LC and DR, respectively, excite motor neurons to increase muscle tone [66, 67]. Following trauma, hyperadrenergic activity can be visualized on functional neuroimaging as increased cerebral blood flow and hypermetabolism in the LC [7, 17, 58, 68]. Excess NE creates a nocturnal state of sympathetic hyperactivity that can cause symptoms of tachycardia and DNB as well as objective PSG findings of RWA that are characteristic of TSD [58, 69, 70].

Traumatic nightmares, a hallmark of TSD, likely occur during both NREM [17] and REM sleep, but are conceptualized as exclusively REM phenomena [12]. Despite the emotional and distressing content of nightmares, autonomic activation, as measured by heart rate and respiratory rate, is low or absent during a nightmare [71]. Based on the less than expected sympathetic activity during nightmares, Fisher and colleagues postulated dreaming possessed a mechanism for modulating anxiety and "desomatizing the physiologic response to it" in order to emotionally cope with traumatic experiences [27]. Along these lines, a recent neurocognitive model for nightmares proposed by Nielsen et al. [72] suggests the purpose of dreaming is to facilitate extinction of fearful memories. During normal dreaming there are four regions of the brain [amygdala, medial prefrontal cortex (mPFC), hippocampus complex, and anterior cingulate cortex (ACC)] that synergistically control emotional processes [72]. Stress precipitates dysfunction in this interactive network which can result in nightmares. Supporting this model is research demonstrating high activity levels in these structures during REM sleep and dreaming [73, 74]. Further, lesioning these structures or their connections results in frequent nightmares [75].

The amygdala is active during REM sleep and processes fearful experiences, decreasing their disturbing nature [73, 76–78]. Amygdalar projections are responsible for sympathetic nervous system activation leading to hyperarousal and abnormal motor activity during REM [79–81]. Additional projections to the trigeminal and facial motor nuclei facilitate fearful expressions, and connections with the nucleus reticularis pontis caudalis are involved in the startle reflex. Based on animal studies, stimulation of the amygdala results in locomotor activity [82], whereas amygdala outputs to the striatum may mediate escape behavior [83] and projections to the central gray facilitate freezing and vocalizations associated with fear [80, 84]. Trauma, especially when associated with sleep disturbances, increases amygdalar activity [58]. Increased output to its many projections substantiates the role of the amygdala in generating DNB and vocalizations in patients with TSD.

Sleep deprivation is hypothesized as a predisposing factor to the development of TSD in adults. Some CNS structures are uniquely vulnerable to the effects of sleep deprivation, and the associated dysfunction likely contributes to the development of TSD. The mPFC within the frontal lobes controls fear extinction during dreaming and regulates the amygdala [85]. Impairment of the dorsal mPFC following trauma is linked to nightmare generation. Additionally, sleep deprivation can contribute to nightmares by causing mPFC hypoactivity and increasing amygdala activation [56, 57]. Frontal lobe impairment results in an uninhibited limbic system that may trigger violent/aggressive impulses manifesting as DNB [86]. Another key structure in dreaming as well as the consolidation of memories is the hippocampus, which regulates fear expression and the extinction of fearful memories [87]. The ACC is integral in the neural circuitry of pain [88], including emotional pain [89], and likely mediates affect distress, whereas the insular cortex processes emotions and is involved in autonomic control [77]. Sleep deprivation/disturbances and trauma result in volume loss in all of these structures [90–92] which can result in persistent fear, REM sleep disruption, and TRN [74]. Innovative clinical and preclinical models are required to ferret out the effects of trauma on these CNS structures and their contribution to TSD [93].

Conclusion

Trauma and sleep deprivation/disturbance result in complex physiologic changes in CNS structures that are integral to dream processing and REM sleep. These changes result in autonomic hyperactivity and DNB, the defining characteristics of TSD. Current clinical guidelines do not suggest that sleep disturbances, most notably nightmares, should necessarily be considered a distinct disorder in patients with PTSD. TSD represents a unique parasomnia, distinct from PTSD as well as other established sleep disorders (i.e., parasomnias) based on etiological, clinical, and treatment-based responses. While both PTSD and TSD are incited by trauma, TSD is exclusively a nocturnal disorder. Trauma-related nightmares, which are found in up to 80% of patients with PTSD, transcend the established nightmare definition when they have autonomic hyperactivity and disruptive nocturnal behaviors to include REM without atonia. REM sleep behavior disorder which also has nightmares and dream enactment behaviors is not incited by trauma, nor does it have the symptoms of autonomic hyperactivity or disturbed sleep present in patients with TSD. Treatment regimens for PTSD typically consist of SSRIs and prazosin and clonazepam for RBD. The treatment of TSD remains anecdotal, with a lack of response to clonazepam but clinical improvement with prazosin, noting that RWA may be exacerbated by SSRIs.

Recognizing that TSD has these distinct features and classifying it as a unique parasomnia are paramount to treating the extreme nocturnal distress associated with this disorder.

To date the understanding of TSD is based on limited scientific literature. Given the frequent occurrence of sleep disturbances after trauma and their multifactorial nature, trauma survivors should be specifically asked about TRN and DNB. For those with symptoms suggestive of TSD, a clinical evaluation and PSG are recommended. This could facilitate characterization of this novel disorder to include aspects such as the occurrence of DNB during PSG and RWA. Longitudinal evaluation of patients is needed to thoroughly characterize symptom persistence and the impact of confounding variables such as medications, stress, or recurrent trauma. Therapeutic options for TSD are limited at this time, and randomized controlled trials are required to determine optimal pharmacologic and behavioral interventions. Additionally, understanding how sleep deprivation/disturbances in the peri-traumatic period contributes to the development of TSD may lead to policies that make sleep a priority in professions such as military service or first responders.

References

1. Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med. 2001;345(25):1825–32.
2. Thordardottir EB, Hansdottir I, Valdimarsdottir UA, Shipherd JC, Resnick H, Gudmundsdottir B. The manifestations of sleep disturbances 16 years post-trauma. Sleep. 2016;39:1551.
3. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbances as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
4. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170:372–82.
5. Sinha SS. Trauma-induced insomnia: a novel model for trauma and sleep research. Sleep Med Rev. 2016;25:74–83.
6. Germain A, Hall M, Krakow B, Shear MK, Buysse DJ. A brief sleep scale for posttraumatic stress disorder: Pittsburgh sleep quality index addendum for PTSD. J Anxiety Disord. 2005;19(2):233–44.
7. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. Biol Psychiatry. 1995;38(3):174–9.
8. Van der Kolk B, Blitz R, Burr W, Sherry S, Hartmann E. Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry. 1984;141(2):187–90.
9. Wallace D, Shafazand S, Ramos A, Carvalho D, Gardener H, Lorenzo D, et al. Insomnia characteristics and clinical correlates in Operation Enduring Freedom/Operation Iraqi Freedom veterans with post-traumatic stress disorder and mild traumatic brain injury: an exploratory study. Sleep Med. 2011;12(9):850–9.
10. Hefez A. Long-term effects of extreme situational stress. Am J Psychiatry. 1987;1:44.
11. American Psychiatric Association. Diagnosis and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
12. Darien, IL: American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed; 2014.
13. Mysliwiec V, O'Reilly B, Polchinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia encompassing disruptive nocturnal behaviors, nightmares, and REM without atonia in trauma survivors. J Clin Sleep Med. 2014;10(10):1143.
14. Crocq M-A, Crocq L. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. Dialogues Clin Neurosci. 2000;2(1):47–55.
15. Mysliwiec V, Brock MS, O'Reilly B, Roth BJ, Germain A. Further evidence for a parasomnia incited by trauma. Sleep. 2016;39:2223–4.
16. Plumb TR, Peachey JT, Zelman DC. Sleep disturbance is common among service members and veterans of Operations Enduring Freedom and Iraqi Freedom. Psychol Serv. 2014;11(2):209.
17. Mellman T, Kulick-Bell R, Ashlock L, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(1):110–5.
18. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000;123(2):331–9.
19. Schlosberg A, Benjamin M. Sleep patterns in three acute combat fatigue cases. J Clin Psychiatry. 1978;39:546–9.
20. Luxton D, Greenburg D, Ryan J, Niven A, Wheeler G, Mysliwiec V. Prevalence and impact of short sleep duration in redeployed OIF soldiers. Sleep. 2011;34(9):1189–95.
21. Kleim B, Wysokowsky J, Schmid N, Seifritz E, Rasch B. Effects of sleep after experimental trauma on intrusive emotional memories. Sleep. 2016;39:2125–32.
22. Ziarnowski A, Broida DC. Therapeutic implications of the nightmares of Vietnam combat veterans. VA Practitioner. 1984;1:63–8.
23. Kramer M, Kinney L, Scharf M. Sleep in delayed stress victims. Sleep Res. 1982;11:113.
24. Greenberg R, Pearlman CA, Gampel D. War neuroses and the adaptive function of REM sleep. Br J Med Psychol. 1972;45(1):27–33.
25. Kaminer H, Lavie P. Sleep and dreaming in holocaust survivors dramatic decrease in dream recall in well-adjusted survivors. J Nerv Ment Dis. 1991;179(11):664–9.
26. Kramer M, Schoen LS, Kinney L. Psychological and behavioral features of disturbed dreamers. Psychiatr J Univ Ott. 1984;9:102–6.
27. Fisher C, Byrne J, Edwards A, Kahn E. A psychophysiological study of nightmares. J Am Psychoanal Assoc. 1970;18:747–82.
28. Hall M, Thayer JF, Germain A, Moul D, Vasko R, Puhl M, et al. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. Behav Sleep Med. 2007;5(3):178–93. doi:10.1080/15402000701263221.
29. Naifeh JA, North TC, Davis JL, Reyes G, Logan CA, Elhai JD. Clinical profile differences between PTSD-diagnosed military veterans and crime victims. J Trauma Dissociation. 2008;9(3):321–34.
30. Cohen DJ, Begley A, Alman JJ, Cashmere DJ, Pietrone RN, Seres RJ, et al. Quantitative electroencephalography during rapid eye movement (REM) and non-REM sleep in combat-exposed veterans with and without posttraumatic stress disorder. J Sleep Res. 2013;22(1):76–82. doi:10.1111/j.1365-2869.2012.01040.x.
31. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep. 2012;35(6):835–47.
32. Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75(6):546–50.
33. Krakow BJ, Ulibarri VA, Moore BA, McIver ND. Posttraumatic stress disorder and sleep-disordered breathing: a review of comorbidity research. Sleep Med Rev. 2015;24:37–45.
34. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, et al. A trial of prazosin for combat trauma PTSD with nightmares

in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170:1003–10.
35. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
36. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in sleep. Sleep. 2002;25(2):120–38.
37. Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395–9.
38. Engdahl BE, Eberly RE, Hurwitz TD, Mahowald MW, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. Biol Psychiatry. 2000;47(6):520–5.
39. Gehrman PR, Harb GC, Cook JM, Barilla H, Ross RJ. Sleep diaries of Vietnam war veterans with chronic PTSD: the relationships among insomnia symptoms, psychosocial stress, and nightmares. Behav Sleep Med. 2015;13(3):255–64.
40. Fernandez-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. Sleep. 2015;39(1):121–32.
41. Postuma R, Gagnon J, Vendette M, Fantini M, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology. 2009;72(15):1296–300.
42. Schenck C, Bundlie S, Mahowald M. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and an analysis of the minimum & maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep. 26:A316;2003.
43. Lavie P, Hefez A, Halperin G, Enoch D. Long-term effects of traumatic war-related events on sleep. Am J Psychiatry. 1979;136:175.
44. Zhang J, Lam SP, Ho C, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? Sleep. 2008;31(8):1179–85.
45. Schenck CH, Mahowald M. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. Cleve Clin J Med. 1990;57:S9–S23.
46. Husain AM, Miller PP, Carwile ST. REM sleep behavior disorder: potential relationship to post-traumatic stress disorder. J Clin Neurophysiol. 2001;18(2):148–57.
47. Dallam DL, Mellman TA, Bhatnagar A, Nguyen S, Kurukumbi M. Trauma reenactments in aging veterans with dementia. J Am Geriatr Soc. 2011;59(4):766.
48. Melendez J, Hesselbacher S, Sharafkhaneh A, Hirshkowitz M. Assessment of REM sleep behavior disorder in veterans with posttraumatic stress disorder. Chest. 2011;140(4_MeetingAbstracts):967A-A.
49. Ju Y-ES. Rapid eye movement sleep behavior disorder in adults younger than 50 years of age. Sleep Med. 2013;14(8):768–74.
50. McCarter SJ, St Louis EK, Sandness DJ, Arndt K, Erickson M, Tabatabai G, et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. Sleep. 2014;38(6):907–17.
51. Postuma RB, Gagnon JF, Tuineaig M, Bertrand JA, Latreille V, Desjardins C, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal. Sleep. 2013;36(11):1579–85.
52. Lee K, Baron K, Soca R, Attarian H. The prevalence and characteristics of REM sleep without atonia (RSWA) in patients taking antidepressants. J Clin Sleep Med. 2016;12(3):351–5. doi:10.5664/jcsm.5582.
53. Schreuder BJ, van Egmond M, Kleijn WC, Visser AT. Daily reports of posttraumatic nightmares and anxiety dreams in Dutch war victims. J Anxiety Disord. 1998;12(6):511–24.
54. Iranzo A, Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep. 2005;28(2):203–6.
55. Boller F, Wright DG, Cavalieri R, Mitsumoto H. Paroxysmal "nightmares" sequel of a stroke responsive to diphenylhydantoin. Neurology. 1975;25(11):1026.
56. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.
57. Germain A, James J, Insana S, Herringa RJ, Mammen O, Price J, et al. A window into the invisible wound of war: functional neuroimaging of REM sleep in returning combat veterans with PTSD. Psychiatry Res Neuroimaging. 2013;211(2):176–9.
58. Nardo D, Högberg G, Jonsson C, Jacobsson H, Hällström T, Pagani M. Neurobiology of sleep disturbances in PTSD patients and traumatized controls: MRI and SPECT findings. Front Psychol. 2015;6:134.
59. Insana SP, Kolko DJ, Germain A. Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. Biol Psychol. 2012;89(3):570–9.
60. Boissard R, Gervasoni D, Schmidt MH, Barbagli B, Fort P, Luppi PH. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. Eur J Neurosci. 2002;16(10):1959–73.
61. Sakai K. Anatomical and physiological basis of paradoxical sleep. In: Brain mechanisms of sleep. New York: Raven Press; 1985, p. 111–37.
62. Reiner PB. Correlational analysis of central noradrenergic neuronal activity and sympathetic tone in behaving cats. Brain Res. 1986;378(1):86–96.
63. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol. 2011;21(23):2029–32.
64. Saper CB. The neurobiology of sleep. Continuum. 2013;19(1, Sleep Disorders):19–31.
65. Siegel J. Mechanisms of sleep control. J Clin Neuophysiol. 1990;7:49–65.
66. Lai Y-Y, Kodama T, Siegel JM. Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: an in vivo microdialysis study. J Neurosci. 2001;21(18):7384–91.
67. Fedirchuk B, Dai Y. Monoamines increase the excitability of spinal neurones in the neonatal rat by hyperpolarizing the threshold for action potential production. J Physiol. 2004;557(2):355–61.
68. Geracioti TD Jr, Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158:1227–30.
69. Berridge CW. The locus coeruleus-noradrenergic system and stress: implications for post-traumatic stress disorder. In: Post-traumatic stress disorder. New York: Humana Press. 2009;213–30.
70. Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. Biol Psychiatry. 2004;55(9):953–6.
71. Nielsen TA, Zadra A. Nightmares and other common dream disturbances. Princ Pract Sleep Med. 2005;4:926–35.
72. Nielsen T, Levin R. Nightmares: a new neurocognitive model. Sleep Med Rev. 2007;11(4):295–310.
73. Braun AR, Balkin TJ, Wesensten NJ, Carson RE, Varga M, Baldwin P, et al. Regional cerebral blood flow throughout the sleep-wake cycle. An H2 (15)O PET study. Brain. 1997;120(7):1173–97.
74. Maquet P, Péters J-M, Aerts J, Delfiore G, Degueldre C, Luxen A, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature. 1996;383(6596):163–6.

75. Solms M. The neuropsychology of dreams: a clinico-anatomical study. Mahwah: L. Erlbaum; 1997.
76. Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC, et al. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain. 2002;125(5):1105–15.
77. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage. 2002;16(2):331–48.
78. Maren S, Quirk GJ. Neuronal signalling of fear memory. Nat Rev Neurosci. 2004;5(11):844–52.
79. Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. Neurosci Biobehav Rev. 2006;30(2):188–202.
80. LeDoux JE, Iwata J, Cicchetti P, Reis D. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci. 1988;8(7):2517–29.
81. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001;6(1):13–34.
82. Wiersma A, Bohus B, Koolhaas J. Corticotropin-releasing hormone microinfusion in the central amygdala enhances active behaviour responses in the conditioned defensive burying paradigm. Stress. 1996;1(2):113–22.
83. Amorapanth P, LeDoux JE, Nader K. Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. Nat Neurosci. 2000;3(1):74–9.
84. Fanselow MS. The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety. The midbrain periaqueductal gray matter. Springer US. 1991;151–73.
85. Silvestri A. REM sleep deprivation affects extinction of cued but not contextual fear conditioning. Physiol Behav. 2005;84(3):343–9.
86. Pressman M. Disorders of arousal from sleep and violent behavior: the role of physical contact and proximity. Sleep. 2007;30(8):1039–47.
87. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005;437(7063):1272–8.
88. Nishida M, Pearsall J, Buckner RL, Walker MP. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex. 2009;19(5):1158–66.
89. van Liempt S. Sleep disturbances and PTSD: a perpetual circle? Eur J Psychotraumatol. 2012;3:19142.
90. Frodl T, O'Keane V. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol Dis. 2013;52:24–37. doi:10.1016/j.nbd.2012.03.012.
91. Mohlenhoff BS, Chao LL, Buckley ST, Weiner MW, Neylan TC. Are hippocampal size differences in posttraumatic stress disorder mediated by sleep pathology? Alzheimers Dement. 2014;10(3 Suppl):S146–54. doi:10.1016/j.jalz.2014.04.016.
92. Herringa R, Phillips M, Almeida J, Insana S, Germain A. Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans. Psychiatry Res. 2012;203(2–3):139–45. doi:10.1016/j.pscychresns.2012.02.005.
93. Mysliwiec V, Brock MS, Creamer JL, O'Reilly B, Germain A, Roth BJ. Trauma associated sleep disorder: a parasomnia induced by trauma. Sleep Med Rev. 2017. doi: http://dx.doi.org/10.1016/j.smrv.2017.01.004

PTSD, Arousal, and Disrupted (REM) Sleep

19

Victor I. Spoormaker

Introduction

Already in 1989, Ross et al. proposed that sleep disturbances, and in particular REM sleep disturbances, are the hallmark of post-traumatic stress disorder (PTSD) [1]. A quarter of a century later, evidence from clinical studies, experimental human studies, and animal models is converging that sleep disturbances may represent more than secondary PTSD symptoms and may be the hallmark of "a heightened vulnerability to maladaptive stress responses" [2]. Clinical data are unequivocal and show a high incidence of a wide range of subjective sleep disruptions in PTSD patients [3, 4], from repetitive nightmares to insomnia [5] and also more "physiological" sleep disorders as sleep apnea and periodic limb movements [6]. Objective sleep disturbances have been less pronounced, but disentanglement of confounding factors such as comorbid depression and substance abuse, as well as gender and age, has revealed small-to-moderate effects with increased density of rapid eye movement (REM) sleep and reduced slow-wave sleep (SWS) [7]. However, high prevalence does not tell us anything about the causality of such sleep disturbances regarding the development or maintenance of PTSD, and longitudinal studies are relatively rare. Mellman et al. has shown that REM sleep fragmentation in the month after a motor vehicle accident predicted PTSD severity weeks later [8] and reports that insomnia is a frequent residual symptom after effective PTSD treatment [9] and that specific treatment for nightmares alleviates PTSD symptom severity [10] suggests that sleep disturbances may indeed play a critical role in the development of PTSD. To explore the possible mechanisms and neural circuitry, this chapter will focus on the proposed role of heightened arousal.

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Arousal and the Locus Coeruleus Noradrenalin System

The Research Domain Criteria (RDoC) project of the National Institute of Mental Health (NIMH) provides a framework for the study of psychiatric disorders, which comprises five domains containing multiple constructs. These currently include positive and negative valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems. The latter domain includes sleep and circadian rhythms, with arousal being a related but separate construct: it is naturally related to sleep and wakefulness as arousal differs throughout the circadian rhythm, yet there are also relevant arousal shifts within wakefulness, which are defined as "a continuum of sensitivity of the organism to stimuli, both external and internal" within the RDoC framework.

The inclusion of stimuli into this definition of arousal highlights that the construct extends mere vigilance and incorporates context- and task-related information processing. This is highly relevant since there is now a large body of work supporting the notion that the noradrenergic system, with the locus coeruleus (LC) in the brainstem as the main output center projecting throughout cortical and subcortical regions, does more than just regulating arousal and is in fact a critical system for optimal task performance and neural gain [11]. This is best illustrated by the inverted U shape associated with increased tonic activity of the LC as shown in Fig. 19.1. Low tonic LC activity results in inattentive, non-alert behavior, whereas high tonic LC activity results in reduced attention through increased orienting behavior, distractibility, and scanning of the environment. Optimal performance is achieved at intermediate levels of tonic LC activity, with phasic LC activity in response to relevant stimuli preceding the required motor responses [11].

Increased central noradrenergic concentrations have been observed in PTSD patients in wakefulness [13], as well as in 24-h urinary measures in larger samples [14]. If this is related to increased tonic LC output, PTSD patients should show impaired performance in tasks probing for attention and/or

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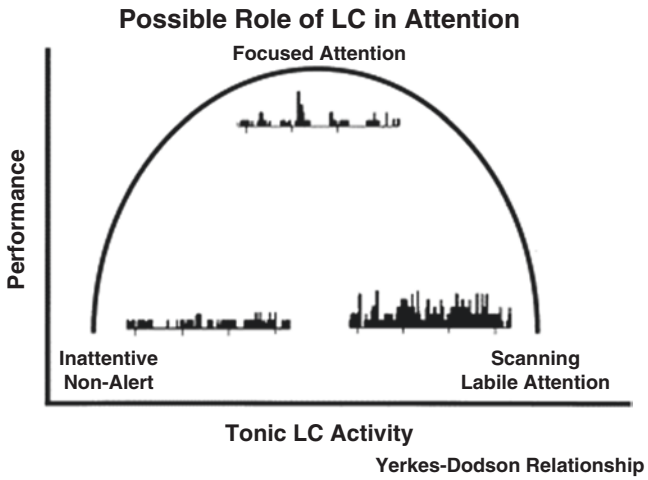

Fig. 19.1 Inverted *U shape* describing the relationship between tonic LC activity and task performance, showing optimal performance at intermediate levels of tonic LC activity, allowing phasic LC activity in response to cued targets requiring a motor response (From Aston-Jones et al. [12], reproduced with kind permission from Elsevier)

general information processing speed. This is indeed the case: a recent meta-analysis on 4108 PTSD patients, trauma-exposed controls, and healthy controls has revealed a Cohen's d of around −0.5 for attention and working memory tasks and a Cohen's d of around −0.6 for information processing speed (both reduced in PTSD patients) [15]. Moreover, another meta-analysis on the P3 response as measured with EEG in PTSD revealed that the P3a to trauma-related distractor stimuli was higher in PTSD patients [16]. One study has provided evidence that the (frontal) P3 to irrelevant distractor stimuli is also increased with PTSD, which would indicate higher distractibility and tonic LC activity as in Fig. 19.1, and that this was related to both hyperarousal and re-experiencing symptom clusters [17].

The LC-Noradrenalin System and Sleep

Another important role for the LC-noradrenalin system is related to the transitioning of stages within sleep: noradrenergic output of the LC is highest in wakefulness and lower in non-REM sleep and reaches its nadir in REM sleep [18]. REM sleep discontinues the moment noradrenergic LC cells (and serotonergic cells in the dorsal raphe nucleus) start firing [19], reason why the LC is also referred to as a REM off switch. It is also worth noting that firing of just 10% of neurons in LC suffices to maintain normal cortical function [20]. This suggests that also minor increases in noradrenalin levels during REM sleep, which may not even be detectable peripherally, could already have an effect on REM sleep and potentially, the SWS-REM cycles seen throughout the night.

A blunted circadian rhythm of 3-methoxy-4-hydroxyphenylglycol (MHPG) [21], the central metabolite of noradrenalin, has also been reported in PTSD. Regarding sleep, although nightmares and insomnia are frequently reported symptoms in PTSD [6], polysomnographic studies on PTSD (a combination of EEG, electromyography, and electrooculography) have been rather inconclusive up until recently. Inconsistencies in the data were largely resolved by a meta-analysis that controlled for confounding factors that affect sleep (gender, age, comorbid depression, and substance abuse) and demonstrated that the amount of slow-wave sleep (SWS) amount is reduced, whereas light sleep stage 1 and REM density are increased in PTSD [7]. Note, however, that effects are modest at best. The question is whether increased REM density is due to an increased number of phasic REM bursts or disrupted fragments of tonic REM sleep; but having shorter and more frequent REM sleep periods within 2 weeks after a motor vehicle accident has been reported to be a significant predictor of PTSD symptomatology months later [8]. Finally, also in line with a role for the LC-noradrenalin system in dysregulating (REM) sleep in PTSD is the relative success of the noradrenergic alpha1-antagonist prazosin. When administered before sleep, prazosin seems to have positive effects on total and REM sleep length (and nightmare amelioration) [22], although these effects have not yet been observed with polysomnographic recordings [23].

Furthermore, increased noradrenergic output may in parallel affect SWS. Using microinjections in cholinergic nuclei in the basal forebrain in rodents, Cape and Jones were able to show that noradrenalin microinjections, compared to serotonergic and Ringer's microinjections, decreased both SWS and REM percentages (both time and transitions into this stage) while increasing wakefulness [24]. Noradrenalin caused an increase in gamma and a reduction in delta activity in the EEG, with electromyography (EMG) being similarly affected by both serotonin and noradrenalin [24].

In a comprehensive review on the role of noradrenalin in sleep mentation, Gottesmann [25] proposed that it is the near absence of noradrenalin in the forebrain, specifically the nucleus accumbens, that gives rise to the maximal dopamine release taking place in REM sleep [26], which could explain increased levels of hallucinatory mental activity typical for REM sleep. A speculation worth mentioning is that increased noradrenergic levels in this region and adjacent subcortical structures such as amygdala and hypothalamus may result in increased physiological arousal and trigger emotional memory traces. However, the role of noradrenalin heavily depends on receptor subtypes (e.g., postsynaptic α1 or β, or presynaptic – inhibitory – α2 receptor function). See Berridge et al. [18] and Broese et al. [27] for reviews on noradrenergic modulation of arousal and sleep.

A Role for Cortisol in the Relationship Between Arousal and the LC System?

Closely linked to both sleep regulation and PTSD symptomatology is the hypothalamus-pituitary-adrenal gland (HPA) axis that orchestrates the stress response and releases glucocorticoids into the bloodstream that provide negative feedback to the hippocampus. Corticotropin-releasing hormone (CRH) is released by the hypothalamus and causes an increase in adrenocorticotropic hormone (ACTH) in the pituitary, which in turn release glucocorticoids from the adrenal gland. Peripheral cortisol is at its trough during early sleep, slowly rises during the progression of the night, peaks in a cortisol-awakening response, and declines during the day. It is of note that cortisol levels are highest in the second half of the night [28] that is richest in REM sleep.

Reduced nocturnal cortisol levels have been observed in PTSD, albeit not consistently [6]. However, there is also evidence from animal models [29] and from a study in motor vehicle victims [30] that blunted cortisol responses after trauma exposure are a risk factor for PTSD. It has been proposed that, in case of reduced cortisol responses to acute stress, the noradrenergic system consequently becomes hyperactive as a homeostatic consequence, increasing the probability of PTSD development [31]. Closer to the central processes regulated by CRH is ACTH, and increased ACTH levels during the night and the awakening response were observed in PTSD and, importantly, correlated to sleep fragmentation and reduced SWS activity [32]. Interestingly, different ACTH/cortisol ratios have been shown in PTSD throughout the circadian cycle [32]. Such variability adds to the complex process of disentangling the multiple modulations of cortisol and reconciling the opposing findings; a meta-analysis on this topic seems warranted. In the meantime, continuous blood sampling during sleep in PTSD [32] appears helpful for extracting more information on ACTH and catecholamines, which might provide more unambiguous effects.

Disrupted Sleep and Disrupted Emotional Memory Consolidation/Homeostasis

The next question is then if the disruption of REM sleep impairs the consolidation of certain memories, given the role of non-REM sleep in declarative memory consolidation [33], and/or emotional homeostasis [34]. Both animal and human models have started to experimentally test this notion by employing analogous models that probe for core disrupted processes in PTSD, i.e., fear conditioning and extinction.

Fear extinction is an associative learning process central to PTSD [35, 36]. In an experimental setting, this is modeled by pairing neutral stimuli with an aversive event (fear conditioning). Subsequently presenting these stimuli alone elicits a fear response that normally extinguishes over time (fear extinction). Extinction learning and consolidation is impaired in PTSD patients [37–39]. As a result, fear conditioning and extinction has been a robust model for scientific advancement on neurocognitive mechanisms underlying PTSD in both preclinical and clinical studies, leading authoritative reviews to conclude that this is one of the most successful models for translating data from animal models to human subjects and psychiatric patients (see review by Milad et al. [40]). Moreover, using functional magnetic resonance imaging (fMRI), limbic and paralimbic regions such as the amygdala, hippocampus, dorsal anterior cingulate cortex (dACC), and ventromedial prefrontal cortex (vmPFC) have been repeatedly demonstrated to subserve fear extinction in healthy individuals (for a systematic review, see Sehlmeyer et al. [41]). Critically, these regions show abnormal fMRI activity in PTSD patients during symptom provocation [42] and during extinction and recall of extinction [38]. The dACC (excitatory influence over amygdala) and the more ventrally located vmPFC (inhibitory influence over amygdala) activity ratio during fear conditioning and extinction, as well as recall of extinction, has been identified in an extensive review on biological studies of PTSD as a promising functional imaging marker of PTSD [43].

There is a large body of preclinical data showing that the amygdala, hippocampus, and medial prefrontal cortex (mPFC) interact through (intracranially recorded) theta oscillations during fear conditioning and extinction [35]. Research in humans has shown abnormal event-related potentials during fear conditioning and extinction in PTSD patients with surface EEG [39], and excess of frontal midline oscillations (in vmPFC) in the theta range (4–8 Hz) during affectively loaded stimuli has recently been proposed as a novel marker of PTSD [44]. One unanswered question is whether hippocampal theta in rodents translates to hippocampal theta in humans – or to hippocampal rhythmic slow activity in the 1.5–3 Hz range as shown by Bodizs et al. [45] with intracranial foramen ovale electrodes in epilepsy patients.

Recent work has shown that sleep benefits memory consolidation [33] and that REM sleep may play an essential role in emotional memory consolidation [34]. Critically, animal studies and studies on human subjects have demonstrated that specific REM deprivation impairs fear extinction consolidation [46, 47], see Fig. 19.2. Moreover, theta coherence in REM sleep predicted subsequent fear expression at recall of conditioning in rodents [48], whereas pontine wave quality in REM sleep in rodents was highly correlated with subsequent extinction memory recall [49]. This makes REM sleep, characterized by theta oscillations and pontine waves

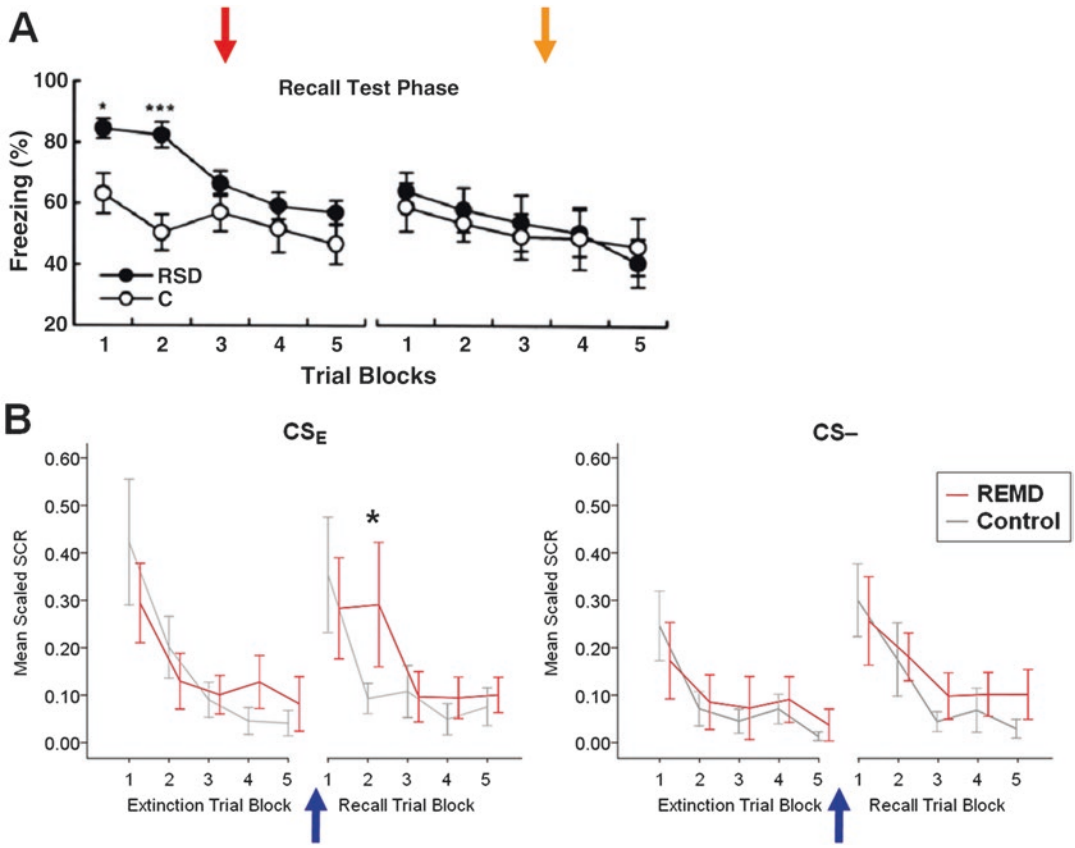

Fig. 19.2 Relevance of REM sleep deprivation for fear extinction consolidation. (**a**) In rats, REM sleep deprivation (*RSD*) immediately after extinction learning (0–6 h, *red arrow*) impaired extinction consolidation manifest in increased freezing to light stimuli that acted as the extinguished stimulus. This was not seen in the control group (*C*), and REM sleep deprivation later after extinction learning (6–12 h, *orange arrow*, different groups) did not have the same effects (From Fu et al. [46], reproduced with kind permission from Elsevier). (**b**) A whole night of REM sleep deprivation (*blue arrows*) in young human subjects specifically affected the consolidation of the extinguished stimulus in the REM sleep deprivation (*REMD*) group, but not of the safety stimulus (or the unextinguished stimulus – not depicted). Note that the trials per task were a priori binned into blocks to reduce analysis flexibility and that a group × time interaction over all blocks had a trend for significance in this small pilot study, suggesting rather large effect sizes (From Spoormaker et al. [47], reproduced with kind permission from John Wiley and Sons)

(or the human equivalents), relevant for plasticity [50], an important brain state for PTSD.

Quantitative EEG and Neuroimaging in PTSD Patients

The reduction in delta sleep and increase in REM density (and the tendency for REM fragmentation) in PTSD patients are in accord with heightened arousal during sleep; however quantitative EEG findings have not been unequivocal in this regard. High-frequency beta (16–30 Hz) and gamma (>40 Hz) can be taken as indices of central arousal [51], but the handful studies conducted on this topic have shown conflicting results, varying from increased to decreased beta and increased to decreased delta (for a review, see [2]). Quantitative EEG may not be optimal to evaluate group differences due to either an increased amount of artifacts (e.g., different EMG tone in PTSD) or to the fact that differences may be more subcortically pronounced. Moreover, arousals may not constitute a single entity with a well-defined neural pathway; intracranial work in epileptic patients has shown that the neural correlates of arousals widely differ dependent on sleep stage and whether they were spontaneous or nociceptive induced [52]. The thalamus showed more stereotypical responses, but these were related to different patterns of cortical arousals [52].

Other neuroimaging approaches may also be helpful to characterize sleep and understand the neurobiology of REM disruptions in sleep in PTSD patients. In a pilot study employing positron-emission tomography, Ebdlahad et al. observed widespread activity increases in REM sleep in PTSD patients compared to depressed patients, among others, in thalamus, limbic, and paralimbic circuitry [53]. In wakefulness, depressed patients showed increased metabolism in several subcortical and (para)limbic regions.

Interestingly, the dorsal anterior cingulate was increased during both wakefulness and REM sleep in PTSD compared to depressed patients [53]. In a small proof-of-concept study, we showed that EEG/fMRI data of subjects falling asleep were also feasible to acquire PTSD patients ($N = 6$ in both the PTSD group and in the trauma-exposed control group), with extra care to be taken for EEG data quality given a seemingly high number of arousals and EMG events in both groups (Vermetten, van Liempt et al. unpublished data).

Conclusion

Objective readouts are converging that in PTSD, both sleep and wakefulness are characterized by heightened arousal. Sleep characteristics of PTSD are reduced SWS and increased stage 1 sleep and REM density, whereas reduced attention, increased distractibility, and reduced information processing speed may well reflect heightened arousal during wakefulness. Animal and human models of PTSD employing fear extinction have revealed that REM sleep causally affects the ability to consolidate extinction, suggesting that disturbed sleep through increased arousal may play a causal role in the development or maintenance of PTSD. Future work should focus on advanced neuroimaging methodology to more closely examine the effects of noradrenalin and imbalances in subcortical circuitry on sleep and arousal in PTSD.

References

1. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146:697–707.
2. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170:372–82.
3. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev. 2003;23:377–407.
4. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep: what a nightmare! Sleep Med Rev. 2000;4:183–200.
5. Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155:929–33.
6. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12:169–84.
7. Kobayashi I, Boarts JM, Delahanty D. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
8. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatry. 2002;159:1696–701.
9. Nappi CM, Drummond SP, Hall JM. Treating nightmares and insomnia in posttraumatic stress disorder: A review of current evidence. Neuropharmacology. 2012;62:576–85.
10. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001;286:537–45.
11. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28(1):403–50.
12. Aston-Jones G, Rajkowski J, Cohen J. Role of locus coeruleus in attention and behavioral flexibility. Biol Psychiatry. 1999;46(9):1309–20.
13. Geracioti TDJ, Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158:1227–30.
14. Wingenfeld K, Whooley MA, Neylan TC, Otte C, Cohen BE. Effect of current and lifetime posttraumatic stress disorder on 24-h urinary catecholamines and cortisol: results from the mind your heart study. Psychoneuroendocrinology. 2015;52:83–91.
15. Scott JC, Matt GE, Wrocklage KM, Crnich C, Jordan J, Southwick SM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. Psychol Bull. 2015;141(1):105–40.
16. Johnson JD, Allana TN, Medlin MD, Harris EW, Karl A. Meta-analytic review of P3 components in posttraumatic stress disorder and their clinical utility. Clin EEG Neurosci. 2013;44(2):112–34.
17. Shucard JL, McCabe DC, Szymanski H. An event-related potential study of attention deficits in posttraumatic stress disorder during auditory and visual go/NoGo continuous performance tasks. Biol Psychol. 2008;79(2):223–33.
18. Berridge CW, Schmeichel BE, Espana RA. Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev. 2012;16:187–97.
19. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat Rev Neurosci. 2002;3:679–93.
20. Berridge CW, Page ME, Valentino RJ, Foote SL. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. Neuroscience. 1993;55:381–93.
21. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. Biol Psychiatry. 1995;38:174–9.
22. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63:629–32.
23. Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. J Psychosom Res. 2012;72:89–96.
24. Cape EG, Jones BE. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep-wake state by noradrenaline and serotonin microinjections into the region of cholinergic basalis neurons. J Neurosci. 1998;18:2653–66.
25. Gottesmann C. The involvement of noradrenaline in rapid eye movement sleep mentation. Front Neurol. 2011;2:81.
26. Léna I, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, et al. Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep – wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res. 2005;81:891–9.
27. Broese M, Riemann D, Hein L, Nissen C. α-adrenergic receptor function, arousal and sleep: mechanisms and therapeutic implications. Pharmacopsychiatry. 2012;45:209–16.
28. Steiger A, Kimura M. Wake and sleep EEG provide biomarkers in depression. J Psychiatr Res. 2010;44:242–52.
29. Cohen H, Zohar J, Gidron Y, Matar MA, Belkind D, Loewenthal U, et al. Blunted HPA axis response to stress influences susceptibility to posttraumatic stress response in rats. Biol Psychiatry. 2006;59:1208–18.

30. Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol Psychiatry. 2000;48:940–7.
31. Zohar J, Juven-Wetzler A, Sonnino R, Cwikel-Hamzany S, Balaban E, Cohen H. New insights into secondary prevention in post-traumatic stress disorder. Dialogues Clin Neurosci. 2011;13:301–9.
32. van Liempt S, Arends J, Cluitmans PJ, Westenberg HG, Kahn RS, Vermetten E. Sympathetic activity and hypothalamo-pituitary-adrenal axis activity during sleep in post-traumatic stress disorder: a study assessing polysomnography with simultaneous blood sampling. Psychoneuroendocrinology. 2013;38:155–65.
33. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11:114–26.
34. Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. Psychol Bull. 2009;135:731–48.
35. Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev. 2010;90:419–63.
36. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. Biol Psychiatry. 2006;60:376–82.
37. Blechert J, Michael T, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behav Res Therapy. 2007;45:2019–33.
38. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66:1075–82.
39. Wessa M, Flor H. Failure of extinction of fear responses in post-traumatic stress disorder: evidence from second-order conditioning. Am J Psychiatry. 2007;164:1684–92.
40. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012;63:129–51.
41. Sehlmeyer C, Schöning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, et al. Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS One. 2009;4:e5865.
42. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. Prog Brain Res. 2008;167:151–69.
43. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012;13:769–87.
44. Cohen JE, Shalev H, Admon R, Hefetz S, Gasho CJ, Shachar LJ, et al. Emotional brain rhythms and their impairment in post-traumatic patients. Hum Brain Mapp. 2013;34:1344–56.
45. Bódizs R, Kántor S, Szabó G, Szûcs A, Erõss L, Halász P. Rhythmic hippocampal slow oscillation characterizes REM sleep in humans. Hippocampus. 2001;11:747–53.
46. Fu J, Li P, Ouyang X, Gu C, Song Z, Gao J, et al. Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. Neuroscience. 2007;144:1186–92.
47. Spoormaker VI, Schröter MS, Andrade KC, Dresler M, Kiem S, Goya-Maldonado R, et al. Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. Hum Brain Mapp. 2012;33:2362–76.
48. Popa D, Duvarci S, Popescu AT, Léna C, Paré D. Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc Natl Acad Sci U S A. 2010;107:6516–9.
49. Datta S, O'Malley MW. Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. J Neurosci. 2013;33:4561–9.
50. Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsáki G. REM sleep reorganizes hippocampal excitability. Neuron. 2012;75:1001–7.
51. Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neurosci. 1998;10:1826–34.
52. Peter-Derex L, Magnin M, Bastuji H. Heterogeneity of arousals in human sleep: a stereo-electroencephalographic study. NeuroImage. 2015;123:229–44.
53. Ebdlahad S, Nofzinger EA, James JA, Buysse DJ, Price JC, Germain A. Comparing neural correlates of REM sleep in post-traumatic stress disorder and depression: a neuroimaging study. Psychiatry Res Neuroimaging. 2013;214(3):422–8.

The Psychophysiology of PTSD Nightmares

20

Steven H. Woodward, Geoff Michell, and Craig Santerre

Nightmares have long offered the promise of privileged access to the kernel pathophysiology of posttraumatic stress disorder (PTSD). This follows from the fact that (excepting nightmare disorder, per se) nightmares are uniquely associated with PTSD in the DSM [1]. Moreover, while prevalent in PTSD [2], and specifically associated with trauma exposure [3], nightmares are conspicuously absent from other anxiety spectrum disorders and from the diagnoses commonly comorbid with PTSD, major depression, and alcohol and substance abuse/dependence. Unfortunately, this promised access has been hobbled by the resistance of nightmares to our principal route of approach to investigating sleep, the laboratory-based nocturnal polysomnogram (PSG). In fact, laboratory studies of sleep in PTSD published since 1990 have observed nightmares on less than 1% of nights [4]. For reasons that are not clear, no one since has approached the feat of Fisher et al. [5] who reported recording 72 nightmares from 18 subjects in the laboratory, including 50 from stage IV c.f [6].

Nightmares are formally similar to the "recurrent, involuntary, and intrusive recollections" classified under criterion B of the diagnosis. These episodes typically comprise some combination of trauma-related mentation and increased arousal. Due to relative ease of measurement and interpretation, heart rate (HR) has been the overwhelming favorite among researchers interested in collecting an objective index of physiological arousal when experimentally provoking symptoms of PTSD. HR is also easily measured during sleep. For these reasons, HR has figured prominently in our own efforts to overcome the impediments to empirical investigation of nightmare phenomena in PTSD.

Unable to record the PSG before, during, or after trauma-related nightmares, the guiding hypothesis of our initial efforts was that nightmares would be associated with chronic increases in sleep HR. We employed a cross-sectional design to compare the sleep physiologies of U.S. military veterans meeting criteria for PTSD but reporting different patterns of chronic nightmare complaint. This study led to some surprising results that were embedded in a pattern common across a number of studies: more severe nightmare complaint is consistently associated with increased wake after sleep onset (WASO). This latter association emerges when persons with primary nightmare disorder are compared to healthy controls [7], when those with trauma-related nightmares are compared to persons with ideographic nightmares [8], and when PTSD patients reporting trauma-related nightmares are compared to those reporting non-trauma-related nightmares [4]. Notwithstanding effects on arousals out of sleep, we have found no evidence in our laboratory data gathered from veterans (Woodward et al. unpublished data), or in the published literature using either laboratory or ambulatory PSG, that nightmare propensity is associated with elevation of basal sleep HR. This negative result has held in our relatively large sample of 81 unmedicated, non-apneic, combat-related PTSD patients studied for three nights in the laboratory no matter what method of indexing nightmare symptomology was used. In addition, in an overlapping sample of combat veterans, sleep HR also failed to correlate with PTSD-related hyperarousal as indexed by the criterion D score from the Clinically Administered PTSD Scale (CAPS [9]) [10]. However, in this same veteran sample, sleep HR correlated with dysphoria as indexed by the Beck Depression Inventory [11].

In response to this failure to uncover any autonomic signature of nightmares reminiscent of the other episodic symptomology of PTSD, we embarked on an investigation of naturalistic sleep using ambulatory PSG in a mixed civilian-veteran sample of persons meeting criteria for PTSD

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and reporting frequent nightmares. The aim of this work was to record sleep continuously over many nights in order to capture trauma-related nightmares and their concomitant PSG indices. The "recording" of spontaneous dreams and nightmares rests on the assumption that subjective reports made immediately after spontaneous awakenings accurately reflect sleep mentation leading to the awakening. There is, as yet, no methodology for validating this assumption; however, some support may be inferred from studies showing that memory for both external and internal events during the sleep period decays rapidly (reviewed in [12]). The implication of these observations is that mentation reports made immediately after spontaneous awakenings should be predominantly influenced by recent mental events rather than by those occurring earlier in the night.

Combat-related PTSD inpatient subjects were recruited from the Men's Trauma Recovery Program at the VA Palo Alto Health Care System. Community-residing survivors of civilian trauma were recruited via print advertisements seeking persons with nightmares which they judged to be related to traumatic experiences. All indicated that they experienced trauma-related nightmares at least once per week. PTSD was confirmed through administration of the CAPS [9]. As in the laboratory studies, subjects were screened for sleep apnea on night one. They were terminated if, after five nights of recording, they had reported no mentation associated with arousals. The final study sample consisted of 33 subjects from whom 146 spontaneous mid-sleep arousals were recording which met the following inclusion criteria: (1) they were preceded by at least 15 min of PSG-verified sleep which could be interrupted by single epochs of movement but not by unambiguous wake and (2) taped mentation reports exhibited unambiguous temporal correspondence with the associated PSG arousals. This requirement effectively constrained our analysis to arousals producing mentation reports exceeding 10 s in length as the mini-cassette recorders required recordings of at least that length in order to encode an electronic time stamp onto the audio tape.

Subjects slept up to 15 nights in their regular sleeping environments. For inpatients, this was their shared dormitory room on the inpatient unit in which they had resided for at least 30 days. For community-residing participants, this was their regular bedroom. Sleep recordings were made using Oxford Instruments MR95 ambulatory physiologic data recorders. Application of electrodes was performed in the early evenings in participants' sleep environments in an effort to promote relatively normal pre-sleep behavior and robust electrode application. The PSG montage included two channels of bipolar electrooculogram (EOG), two channels of scalp electroencephalogram (EEG, Cz, and Pz referred to linked mastoids), mentalis and left anterior tibialis electromyograms (EMG), and electrocardiogram (ECG). Arousal reports were transcribed from tape and scored for presence/absence of dreaming/mentation, symptomatic dream content (including trauma-related content, life threat, and/or interpersonal conflict), autonomic activation (sweating or heart racing), bladder distension, and/or external arousing stimulus. Dream reports were also categorized according to the amount of content recalled. The categories were "none" ("I know I was dreaming but I can't remember what about."), "typical" (one to two sentences comprising one or two actors, objects, and events), and "extensive" (elaborated multi-scene and/or multi-character narratives).

This methodology produced two sets of results. The first comprised a set of non-orthogonal graphical contrasts demonstrating, in sum, that sleep physiology associated with mentation reports following spontaneous arousals from persons who have been diagnosed with PTSD is generally compatible with what has been known about the psychophysiology of dreaming [13]. Figure 20.1a, b provides a comparison of sleep stage proportions leading up to arousals with and without reports of mentation. (To aid legibility, these and subsequent plots contain only REM, non-REM, and wake staging with time collapsed to a 15-min sample period.) It is apparent that arousals without dream reports were predominantly preceded by non-REM sleep, whereas those with dream reports were preceded by REM and non-REM sleep in approximately equal proportions. Furthermore, as illustrated in Figures 20.2a–c, a gradient was apparent within arousals including dream reports such that greater dream content recall (none vs typical vs extensive) was preceded by proportionally more REM sleep. Conversely, the 14 arousals triggered by an "external stimulus," plotted in Fig. 20.3, exhibited no increase in the proportion of REM sleep leading up to them despite the fact that they occurred, on average, later in the night when REM predominates. Instead, such arousals were preceded by an excess of wake relative to other the stages. Figure 20.4a–c contrasts non-symptomatic arousals, symptomatic arousals without trauma-related life-threat content, and symptomatic arousals with trauma-related life-threat content. In this sample, increased dream distress was accompanied by a trend toward an increased proportion of REM leading up to the arousals. It is noteworthy, however, that arousals with life-threat content were still occasionally preceded by non-REM sleep rather than by REM sleep. Figure 20.5 plots sleep staging prior to arousals attributed to bladder distention necessitating use of the bathroom. This last class of arousals was preceded by the highest preponderance of non-REM versus REM sleep observed.

A second set of analyses compared participants' sleep HRs over symptomatic versus non-symptomatic arousals (See Fig. 20.6). Surprisingly, HRs tended to be *lower* prior to symptomatic arousals than non-symptomatic arousals; however, when aggregated over the full 90-min pre-arousal epoch, this difference was not statistically significant ($t(12) = 1.07$, $p = 0.305$). This result was not modified by

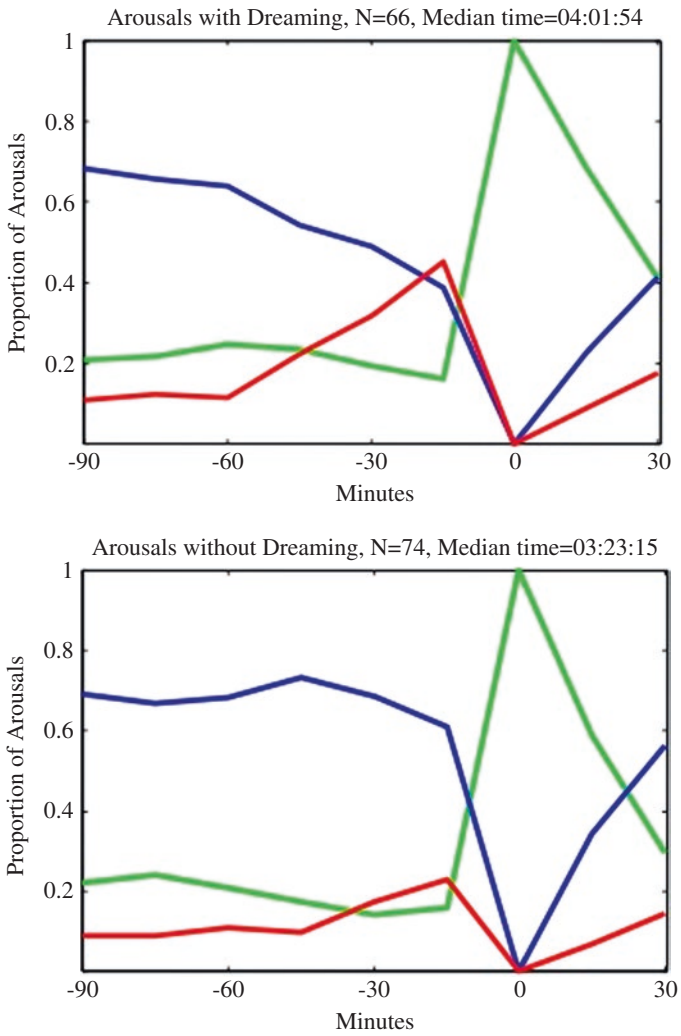

Fig. 20.1 (**a**, **b**) Plot proportion of sleep stages by time for 90 min leading to and 30 min following a verified arousal from sleep. *Blue line* corresponds to non-REM sleep, *red* to REM sleep, and *green* to waking. The median clock time of plotted arousals is also indicated. Data aggregated over 140 arousals from 33 participants. Note marked increase in REM sleep leading up to arousals associated dream mentation versus those without

adjustment for the circadian influence on heart rate. (This adjustment was performed by regressing all pre-arousal HRs against arousal clock time and then residualizing each individual pre-arousal HR by reference to the HR predicted for that time by the model. The linear regression model was highly significant, $F(1138) = 32.6$, $p < 0.001$, with pre-arousal HR lowering at a rate of 2.18 BPM per hour of sleep.) Not surprisingly, HRs were higher after symptomatic than after non-symptomatic arousals; however, this difference was again not significant ($t(12) = 1.07$, $p = 0.305$). The interaction of arousal type and time of measurement (pre- vs post-) was statistically significant ($F(1,12) = 8.12$, $p = 0.015$) as was the main effect of time ($F(1,12) = 5.26$, $p = 0.041$) with post-arousal HRs being higher than pre-arousal.

The sleep preceding different classes of nocturnal arousals in this small mixed sample of persons with PTSD manifested a familiar relationship between the presence and volume of reportable dream mentation and the preponderance of REM sleep leading up to the arousal. An association between longer dream reports and a preponderance of REM versus other stages of sleep was recently reconfirmed in a large naturalistically acquired sample by Stickgold et al. [14]. Increasingly distressful dream content was also associated with increasing proportions of REM sleep. Again, it is noteworthy that though the most disturbing arousals containing life-threat content exhibited the highest preponderance of REM sleep, a minority of such arousals were preceded by non-REM sleep. This latter observation supports the conclusion of Wittman et al. [15] that trauma-related nightmares are not exclusive to REM sleep. Nocturnal arousals associated with external stimuli or interoceptive alarms were *not* preceded by increased proportions of REM sleep. Instead, arousals attributed to external stimuli were preceded by increased waking, while those attributed to an interoceptive alarm were preceded by relatively high amounts of NREM sleep. It seems entirely plausible that reports of external triggering of arousal would be associated with sleep interrupted by waking. As well, the relative paucity of REM sleep leading up to interoceptive alarms is compatible with the fact that the nucleus locus coeruleus (LC), which mediates such internal alarms, is quies-

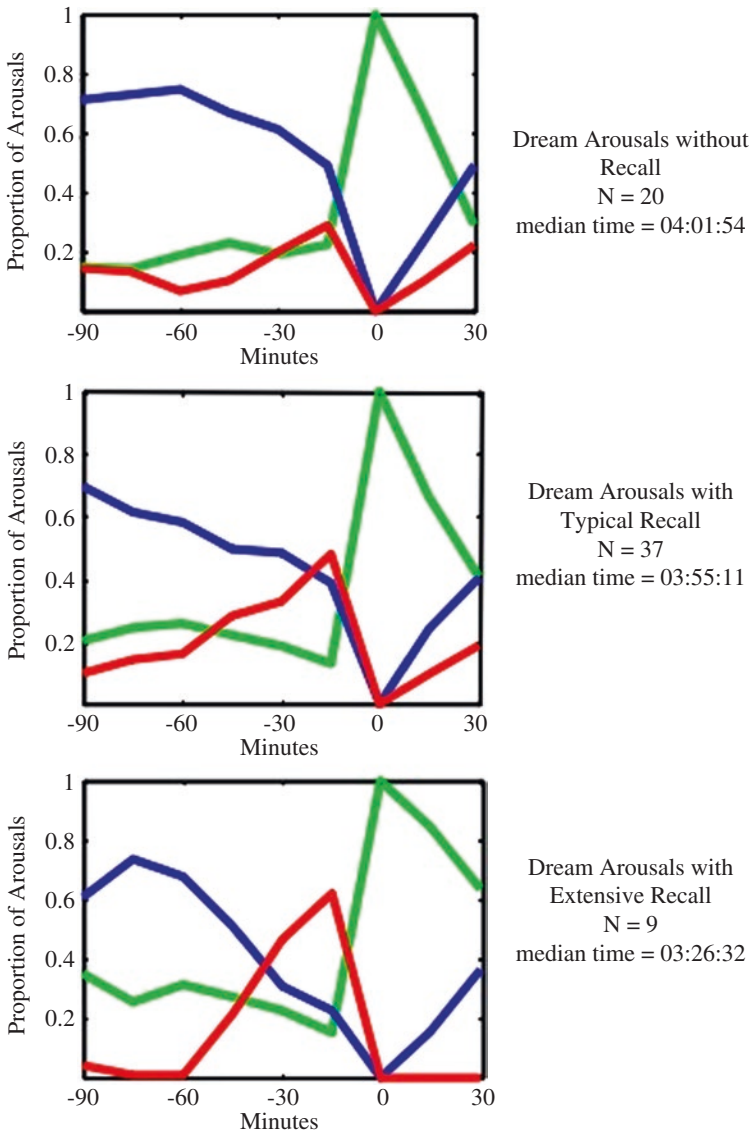

Fig. 20.2 (**a**–**c**) Plot proportion of sleep stages by time leading to and following a verified arousal from sleep that included a dream report. Color coding as before. Data aggregated over 67 arousals. Note marked increase in REM sleep leading up to arousals associated with more extensive dream mentation

cent during REM [16, 17]. This is because interoceptive alarms such as bladder distention are routed through the LC [18] and so should be gated by LC quiescence.

The results of this study are limited by the small size of the corpus of criterial mid-sleep arousals. In particular, this prevented comparisons of symptomatic versus non-symptomatic arousals within subjects and within sleep stages, especially within REM-preceded arousals, of objective indices of EEG spectral composition c.f. [19] and EOG activity c.f [20, 21]. Nevertheless, it is noteworthy that no prodromal elevation of sleep HR was observed in advance of symptomatic versus non-symptomatic arousals evaluated within subjects given the relatively larger HR excursions following the former. Adjusting for circadian effects on HR did not modify this result. This observation contrasts with the earlier reports of Fisher et al. [5] suggesting that nightmares are anticipated by autonomic arousal and instability. (It is unknown if Fisher's subjects met criteria for PTSD as the diagnosis had not yet been incorporated into psychiatric nosology). Any effort to understand this result in light of our knowledge of waking intrusive or reexperiencing symptoms confronts our lack of knowledge regarding their autonomic correlates, as well. While ambulatory HR has been recorded in persons with PTSD [22–26] with reference to certain discrete events such as cigarettes smoked and episodes of hostility, this work has not extended to examinations of the psychophysiological concomitants of phasic symptoms such as intrusive thoughts, flashbacks, and trauma-cue-elicited distress. Hence, it is altogether unknown whether such events are preceded by prodromal autonomic arousals, as has recently been found for panic attacks [27].

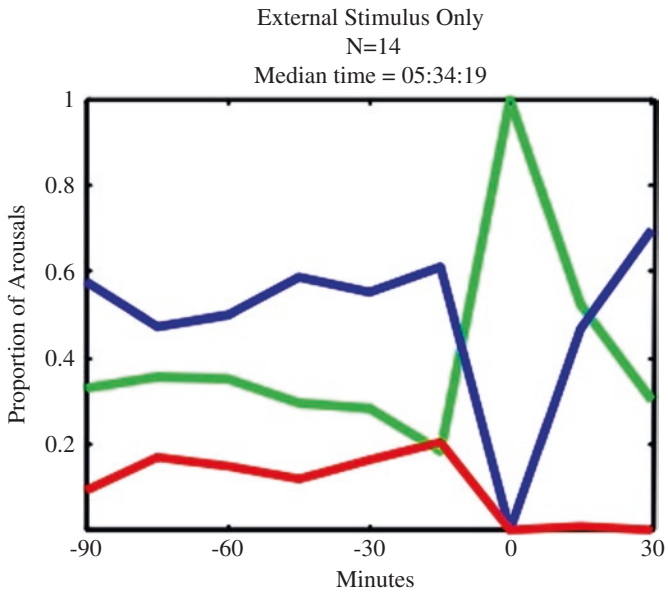

Fig. 20.3 Plot proportion of sleep stages by time leading to and following arousals attributed to external stimuli. Color coding as before. Data aggregated over 14 arousals. Note marked increase in waking prior to these arousals (with the exception of the immediately preceding 15 min per criteria)

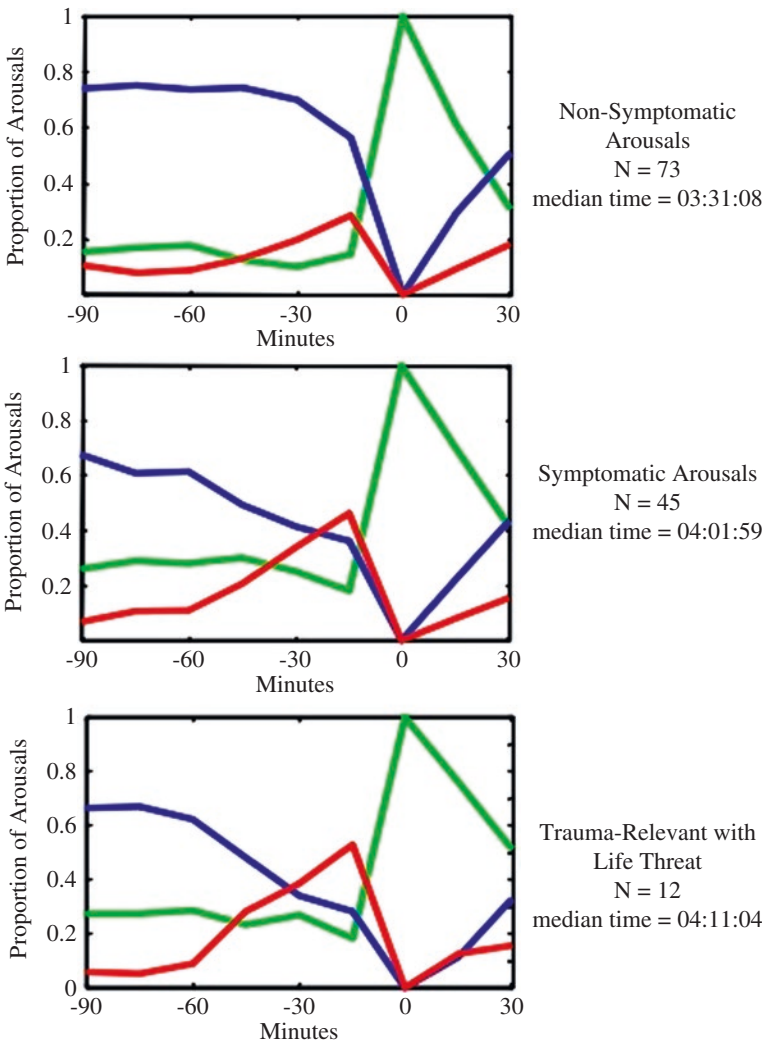

Fig. 20.4 (**a**–**c**) Plot proportion of sleep stages by time leading to and following a verified arousal from sleep categorized according to absence/presence/severity of distressing mentation. Color coding as before. Data aggregated over 130 arousals. (Ten arousals were not clearly categorizable on this dimension.) Note increase in REM sleep leading up to arousals associated with more distressing dream mentation

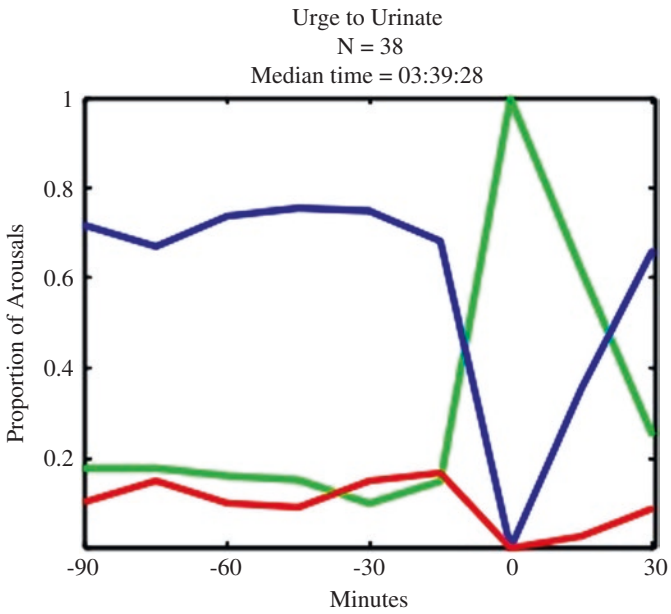

Fig. 20.5 Plot proportion of sleep stages by time leading to and following arousals attributed to an interoceptive stimulus (bladder distention). Color coding as before. Data aggregated over 38 arousals. Note predominance of non-REM sleep prior to these arousals

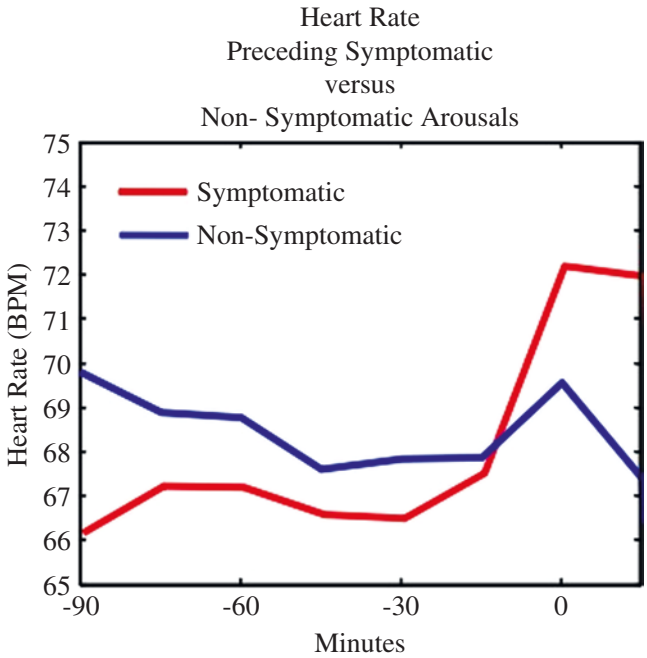

Fig. 20.6 Plot mean HR by time leading to and following arousals associated with or without distressing mentation. Data are from 13 participants who provided examples of both types along with adequate sleep ECG. Within-subject within-category data were averaged and then quantified for statistical analysis (see text). *Red* and *blue lines* plot mean HRs associated with symptomatic and non-symptomatic, respectively

The absence of autonomic activation prior to symptomatic arousals in PTSD is reminiscent of another finding from our laboratory that self-reported nightmare symptom severity is associated with *reduced* all-night movement time in Vietnam combat veterans with PTSD studied in the laboratory [28]. While "thrashing movements during sleep" [29] are reported by veterans with PTSD, objective verification of such episodes and their association with nightmares has been limited. Evidence of autonomic and motoric *quiescence* in association with nightmares has prompted us to revisit a basic question: how do other animals living in dangerous environments, or with histories of exposure to acute stress, sleep? If PTSD is broadly understood as a "failure of recovery" from a state adapted to conditions of extreme threat [30], how might nightmares function as a component of such adaptation?

Humans are not unique in their need to achieve sleep despite the current or recent experience of life threat. The impacts of acute and chronic stress on sleep in laboratory species have been covered in Chap. 12. Here, we will consider ethological investigations of animals sleeping in the wild, work that includes the seminal studies of Zepelin and Rechtschaffen [31] and Allison and Ciccetti [32], the fieldwork of Anderson [33], and a recent series of papers by Lima, Lesku, and colleagues [34–38] (see also [39]). First and foremost, a critical finding across these studies is that sleep in mammals and birds is sensitive to predation threat. That sensitivity is expressed through two main strategies, first, concealment [33] and, second, the preservation of arousability through the de-emphasis of sleep states associated with elevated arousal thresholds, slow wave sleep (SWS), and REM sleep. Into this broad framework, aspects of the sleep of humans unrecovered from traumatization already fit fairly neatly. The Kobayashi et al. [40] meta-analysis concluded that sleep in PTSD is associated with both an increase in stage N1 sleep and a reduction in SWS (or stage N3), adaptations which would result in lower

arousal thresholds throughout the night. To this complex may be added the impact of nightmares, per se, which are, by definition, dreams that awaken the sleeper. It is also noteworthy that the DSM-V (307.47) criteria for primary nightmares includes the following language, "On waking from the nightmare, the person becomes oriented and alert" [41]. Rapid orientation distinguishes nightmares from sleep terrors which are typically associated with impaired consciousness and impaired memory for the event. If nightmare-related awakenings are also behaviorally subtle and devoid of autonomic activation, this would be in line with the conserved strategy of concealment. While concealment during sleep is not a concept with which modern humans are familiar, it is worth considering that hominins ground-slept without benefit of protective shelter, within close range of large nocturnal predators, from at least 2.6 MYA up to approximately 380,000 years ago. (This period is bracketed by the emergence of *H. erectus*, who was devoid of any arboreal skeletal adaptations, and the *Terra Amata* Shelter in southern France, among the earliest sites with evidence of shelter construction, probably built by *H. heidelbergensis*.)

An alternative framework within which formulates this discussion has been variously referred to as the predator imminence or defensive cascade model [42, 43]. In the terminology of this framework, our strategy was to look for evidence of "circa-strike" psychophysiology during sleep in persons with trauma-related nightmares. In fact, our own data may be more suggestive of "post-encounter" psychophysiology. While highly contrastive behaviorally, both circa-strike (aka fight/flight) and post-encounter defensive modes are orchestrated by the amygdala operating through specific effector subsystems, especially, in the latter case, the bed nucleus of the stria terminalis and the periaqueductal gray [44]. The post-encounter pattern combines "freezing" or "movement suppression" [45] with focused attention directed toward the threat. The presumed goal of post-encounter behavior is the avoidance of detection by a predator combined with sustained vigilance to the latter's location, movement, gaze, etc. The freezing component has a long history of use as an index of fear in the animal literature but has been little studied in humans because it has, until recently, been difficult to operationalize in the laboratory [46–49]. Importantly for the model we are proposing, freezing is associated, at least acutely, with a HR *deceleration* sometimes termed "fear bradycardia" [45, 50] instead of the phasic and/or chronic HR accelerations we expected to observe during sleep in PTSD.

Implicit in the above discussion is the proposition that the pre-encounter mode of defensive behavior, in contrast to circa-strike, is somehow compatible with sleep. A recent study by Cano et al. [51] suggests that such a proposition is not far-fetched. In that study, the investigators devised an experimental paradigm that resulted in simultaneous co-activation of sleep-promoting and arousal-promoting subsystems in the brainstem, midbrain, and forebrain. The paradigm involved placing a male rat in a cage previously occupied by another male with no intervening cleaning/deodorization. By instituting a large number of experimental controls and surveying a wide range of brain regions using the intermediate-early gene *c-Fos* to index neuronal activation, these investigators documented, in the cage-exchange condition, concurrent activation of sleep-promoting regions such as the median and ventrolateral preoptic nuclei of the hypothalamus and arousal-promoting regions such as the locus coeruleus (LC), tuberomammillary nucleus (TMN), and extended amygdala. In some sleep-promoting regions, cage-exchange animals exhibited substantially *more* activation than controls. Nevertheless, in these animals, cerebral cortex also exhibited increased *c-Fos* induction, especially the infralimbic and anterior cingulate cortices, regions of the rat brain thought to correspond, respectively, to subgenual and dorsal anterior cingulate cortices in humans [52], both implicated in PTSD [53, 54]. Cano and colleagues aimed to provide a model of "stress-induced insomnia" rather than of PTSD-related sleep disturbance. Nevertheless, viewed from the perspective of defensive adaptation, the Cano et al. model demonstrates that downgraded versions of sleep and arousal can coexist in the rat brain, perhaps representing a "solution" to the conundrum faced by all animals sleeping under threat, the simultaneous requirements to sleep and remain vigilant.

Perhaps the most descriptive term applied to the post-encounter state is "attentive immobility" [55]. In the rat, attentive immobility has been associated with elevated gamma-band EEG similar to both active wake and REM sleep [56]. Gamma-band EEG is normally much lower in amplitude in NREM; however, Cano et al. found amplification of gamma-band EEG in NREM sleep in cage-exchange rats versus controls, an effect which could be reversed either by lesion of LC (by ibotenic acid) or inhibition of the TMN (by the H_3 autoreceptor agonist immepip). Thus, in their preparation, NREM gamma-band EEG appeared to be a specific index of arousal-promoting systems co-activated during sleep.

The Cano et al. findings suggest that gamma-band EEG might provide positive signs of PTSD-related sleep adaptations where sleep HR has not. A direct translation to PTSD-related insomnia would predict the observation of elevated gamma in NREM or SWS. In normals, gamma-band EEG has also been reported elevated in REM sleep, especially when rapid eye movements are present [57]. A possible association with REM density is attractive, here, as this microstructural feature of sleep has been reported to be elevated in PTSD in the studies of Ross and colleagues [20, 58] and confirmed in the Kobayashi meta-analysis [40]. It must be acknowledged that recording gamma-band EEG from the human scalp is more difficult than recording it from the *dura mater* in laboratory animals. Gamma-band EEG represents

only 1% of total EEG power at the scalp. Under baseline conditions, scalp gamma-band EEG is contaminated by both scalp EMG [59, 60] and extraocular EMG [61, 62]. Intracranial recordings in epileptics suggest that the cortical sources of gamma-band activity are spatially restricted and may require dense electrode arrays to resolve optimally [63–65]. Gamma-band EEG may also be primarily event-related [66]. Of particular interest, here, is the evidence that in sleep, gamma-band EEG is phase-locked to the "UP" states within delta-band EEG [67]. These "UP" states should be uncorrelated temporally with potential EMG contaminations. While, to date, this delta phase-locked gamma has been recorded only intracranially, statistical aggregation over space and time employing source-modeled slow waves at the scalp should increase the effective signal-to-noise of this process [68], as would any amplification of gamma related to coactive arousal.

Unfortunately, the researcher employing gamma-band EEG in this context would still face the low-to-zero appearance rate of PTSD nightmares in the sleep laboratory. One untried approach to this challenge would be to exploit prazosin withdrawal. Many PTSD patients experience reductions in nightmares when treated with prazosin [69–71]; however, because of this drug's very short half-life (2–3 h), nightmares can reemerge quickly if it is withdrawn (Raskind, personal communication). In principal, a prazosin withdrawal design could render the laboratory study of nightmares feasible. Needless to say, strong justifications would need to be in place to support the ethicality of such a study, including, the above discussion would suggest, a high degree of certainty that gamma-band EEG can be recorded from the human scalp during sleep. But what of ethical justifications driven by morbidity? If many PTSD patients' nightmares can be attenuated by prazosin, or by behavioral interventions [71–73], why continue to pursue a deeper understanding of the pathophysiology of these events? First, of course, these treatments do not work for everyone [74–77]. Second, we have no strong explanations for why these treatments work at all. In particular, it is remarkable that prazosin, an alpha-adrenergic receptor antagonist, has exhibited therapeutic impact on PTSD symptoms that emerge preferentially from REM sleep, an arousal state characterized by an absence of adrenergic modulation [17]. Third, recent data have recast nightmares in a more serious light. There is now excellent evidence that nightmare complaints are independently associated with suicidal ideation in medical patients [78] and college students [79], with both suicidal ideation [80] and self-harm in adolescents [81], with suicide attempts in psychiatric outpatients [82–84], and with completed suicides in the Finnish population [85]. The weight of evidence suggests that the risk for suicidality conferred by nightmares is independent of both insomnia and depression [86, 87]. The risk of suicidality is known to be elevated in PTSD independent of depression (reviewed in [88]) and to be high in military personnel with mental disorders [89]. Studies are now underway to assess the role of trauma-related nightmares in suicidality in military samples (Pigeon, personal communication). The association of nightmares with suicidality mandates that we push ahead in our efforts to better understand both the psychophysiology and neurobiology of these events, to more aggressively screen for them [90], and to treat them [70, 91–94].

References

1. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for the DSM-IV axis-I disorders. New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.
2. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS Drugs. 2006;20(7):567–90.
3. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
4. Woodward SH, Arsenault NJ, Murray C, Bliwise DL. Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry. 2000;48(11):1081–7.
5. Fisher C, Byrne J, Edwards A, Kahn E. A psychophysiological study of nightmares. J Am Psychoanal Assoc. 1970;18(4):747–82.
6. Hartmann E. The nightmare. The psychology and biology of terrifying dreams. New York: Books, Inc.; 1984.
7. Simor P, Horvath K, Gombos F, Takacs KP, Bodizs R. Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares. Eur Arch Psychiatry Clin Neurosci. 2012;262:687.
8. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry. 2003;54(10):1092–8.
9. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Charney DS, Keane TM. Clinician-administered PTSD scale for DSM-IV: current and lifetime version. Behavioral Science Division, Boston VA Medical Center, Boston, MA/Clinical Neurosciences Division, West Haven VA Medical Center, West Haven, CN; 1997.
10. Woodward SH, Murburg MM, Bliwise DL. PTSD-related hyperarousal assessed during sleep. Physiol Behav. 2000;70(1–2):197–203.
11. Woodward SH, Friedman MJ, Bliwise DL. Sleep and depression in combat-related PTSD inpatients. Biol Psychiatry. 1996;39(3):182–92.
12. Roth T, Roehrs T, Zwyghuizen-Doorenbos A, Stepanski E, Wittig R. Sleep and memory. Psychopharmacol Ser. 1988;6:140–5.
13. Rechtschaffen A. The psychophysiology of mental activity during sleep. In: McGuigan FJ, Schoonover RS, editors. The psychophysiology of thinking. New York: Academic; 1973. p. 153–205.
14. Stickgold R, Malia A, Fosse R, Propper R, Hobson JA. Brain-mind states: I. Longitudinal field study of sleep/wake factors influencing mentation report length. Sleep. 2001;24(2):171–9.
15. Wittmann L, Schredl M, Kramer M. Dreaming in posttraumatic stress disorder: a critical review of phenomenology, psychophysiology and treatment. Psychother Psychosom. 2007;76(1):25–39.
16. Page ME, Akaoka H, Aston-Jones G, Valentino RJ. Bladder distention activates noradrenergic locus coeruleus neurons by an excitatory amino acid mechanism. Neuroscience. 1992;51(3):555–63.

17. Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci. 1981;1(8):876–86.
18. Rickenbacher E, Baez MA, Hale L, Leiser SC, Zderic SA, Valentino RJ. Impact of overactive bladder on the brain: central sequelae of a visceral pathology. Proc Natl Acad Sci U S A. 2008;105(30):10589–94.
19. Marzano C, Ferrara M, Mauro F, et al. Recalling and forgetting dreams: theta and alpha oscillations during sleep predict subsequent dream recall. J Neurosci. 2011;31(18):6674–83.
20. Ross RJ, Ball WA, Dinges DF, et al. Rapid eye movement sleep disturbance in posttraumatic stress disorder. Biol Psychiatry. 1994a;35(3):195–202.
21. Mellman TA, Nolan B, Hebding J, Kulick-Bell R, Dominguez R. A polysomnographic comparison of veterans with combat-related PTSD, depressed men, and non-ill controls. Sleep. 1997;20(1):46–51.
22. Beckham JC, Feldman ME, Barefoot JC, et al. Ambulatory cardiovascular activity in Vietnam combat veterans with and without posttraumatic stress disorder. J Consult Clin Psychol. 2000;68(2):269–76.
23. Beckham JC, Flood AM, Dennis MF, Calhoun PS. Ambulatory cardiovascular activity and hostility ratings in women with chronic posttraumatic stress disorder. Biol Psychiatry. 2009;65(3):268–72.
24. Beckham JC, Gehrman PR, McClernon FJ, Collie CF, Feldman ME. Cigarette smoking, ambulatory cardiovascular monitoring, and mood in Vietnam veterans with and without chronic posttraumatic stress disorder. Addict Behav. 2004;29(8):1579–93.
25. Beckham JC, Taft CT, Vrana SR, et al. Ambulatory monitoring and physical health report in Vietnam veterans with and without chronic posttraumatic stress disorder. J Trauma Stress. 2003;16(4):329–35.
26. Buckley TC, Holohan D, Greif JL, Bedard M, Suvak M. Twenty-four-hour ambulatory assessment of heart rate and blood pressure in chronic PTSD and non-PTSD veterans. J Trauma Stress. 2004;17(2):163–71.
27. Meuret AE, Rosenfield D, Wilhelm FH, et al. Do unexpected panic attacks occur spontaneously? Biol Psychiatry. 2011;70(10):985–91.
28. Woodward SH, Leskin GA, Sheikh JI. Movement during sleep: associations with posttraumatic stress disorder, nightmares, and comorbid panic disorder. Sleep. 2002;25(6):681–8.
29. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(1):110–5.
30. Rothbaum BO, Davis M. Applying learning principles to the treatment of post-trauma reactions. Ann N Y Acad Sci. 2003;1008:112–21.
31. Zepelin H, Rechtschaffen A. Mammalian sleep, longevity, and energy metabolism. Brain Behav Evol. 1974;10(6):425–70.
32. Allison T, Cicchetti DV. Sleep in mammals: ecological and constitutional correlates. Science. 1976;194(4266):732–4.
33. Anderson JR. Sleep, sleeping sites, and sleep-related activities: awakening to their significance. Am J Primatol. 1998;46(1):63–75.
34. Lesku JA, Bark RJ, Martinez-Gonzalez D, Rattenborg NC, Amlaner CJ, Lima SL. Predator-induced plasticity in sleep architecture in wild-caught Norway rats (Rattus norvegicus). Behav Brain Res. 2008;189(2):298–305.
35. Lesku JA, Roth TC 2nd, Amlaner CJ, Lima SL. A phylogenetic analysis of sleep architecture in mammals: the integration of anatomy, physiology, and ecology. Am Nat. 2006;168(4):441–53.
36. Lesku JA, Roth TC, Rattenborg NC, Amlaner CJ, Lima SL. Phylogenetics and the correlates of mammalian sleep: a reappraisal. Sleep Med Rev. 2008;12(3):229–44.
37. Lima SL, Rattenborg NC, Lesku JA, Amlaner CJ. Sleep under the risk of predation. Anim Behav. 2005;70:723–36.
38. Roth TC 2nd, Lesku JA, Amlaner CJ, Lima SL. A phylogenetic analysis of the correlates of sleep in birds. J Sleep Res. 2006;15(4):395–402.
39. Capellini I, Barton RA, McNamara P, Preston BT, Nunn CL. Phylogenetic analysis of the ecology and evolution of mammalian sleep. Evolution. 2008;62(7):1764–76.
40. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44(4):660–9.
41. Association AP. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
42. Lang PJ, Bradley MM, Cuthbert BN. Motivated attention: affect, activation and action. In: Lang PJ, Simons RF, Balaban MF, editors. Attention and orienting: sensory and motivational processes. Hillsdale: Lawrence Erlbaum Associates; 1997. p. 97–135.
43. Fanselow M. Neural organization of the defensive behavior system responsible for fear. Psychon Bull Rev. 1994;1:429–38.
44. Jhou T. Neural mechanisms of freezing and passive aversive behaviors. J Comp Neurol. 2005;493(1):111–4.
45. Lang PJ, Davis M, Ohman A. Fear and anxiety: animal models and human cognitive psychophysiology. J Affect Disord. 2000;61(3):137–59.
46. Hillman CH, Rosengren KS, Smith DP. Emotion and motivated behavior: postural adjustments to affective picture viewing. Biol Psychol. 2004;66(1):51–62.
47. Stins JF, Beek PJ. Effects of affective picture viewing on postural control. BMC Neurosci. 2007;8:83.
48. Facchinetti LD, Imbiriba LA, Azevedo TM, Vargas CD, Volchan E. Postural modulation induced by pictures depicting prosocial or dangerous contexts. Neurosci Lett. 2006;410(1):52–6.
49. Azevedo TM, Volchan E, Imbiriba LA, et al. A freezing-like posture to pictures of mutilation. Psychophysiology. 2005;42(3):255–60.
50. Blanchard RJ, Flannelly KJ, Blanchard DC. Defensive behavior of laboratory and wild Rattus norvegicus. J Comp Psychol. 1986;100(2):101–7.
51. Cano G, Mochizuki T, Saper CB. Neural circuitry of stress-induced insomnia in rats. J Neurosci. 2008;28(40):10167–84.
52. Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol. 2003;460(3):425–49.
53. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164(10):1476–88.
54. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry. 2006;59(7):582–7.
55. Marks IM. Fears, phobias, and rituals. New York: Oxford University Press; 1987.
56. Maloney KJ, Cape EG, Gotman J, Jones BE. High-frequency gamma electroencephalogram activity in association with sleep-wake states and spontaneous behaviors in the rat. Neuroscience. 1997;76(2):541–55.
57. Abe T, Matsuoka T, Ogawa K, Nittono H, Hori T. Gamma band EEG activity is enhanced after the occurrence of rapid eye movement during human REM sleep. Sleep Biol Rhythms. 2008;6:26–33.
58. Ross RJ, Ball WA, Sanford LD, et al. Rapid eye movement sleep changes during the adaptation night in combat veterans with posttraumatic stress disorder. Biol Psychiatry. 1999;45(7):938–41.
59. Freeman WJ, Holmes MD, Burke BC, Vanhatalo S. Spatial spectra of scalp EEG and EMG from awake humans. Clin Neurophysiol. 2003;114(6):1053–68.
60. Whitham EM, Pope KJ, Fitzgibbon SP, et al. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. Clin Neurophysiol. 2007;118(8):1877–88.

61. Hassler U, Barreto NT, Gruber T. Induced gamma band responses in human EEG after the control of miniature saccadic artifacts. NeuroImage. 2011;57(4):1411–21.
62. Schwartzman DJ, Kranczioch C. In the blink of an eye: the contribution of microsaccadic activity to the induced gamma band response. Int J Psychophysiol. 2011;79(1):73–82.
63. Ray S, Niebur E, Hsiao SS, Sinai A, Crone NE. High-frequency gamma activity (80–150Hz) is increased in human cortex during selective attention. Clin Neurophysiol. 2008;119(1):116–33.
64. Crone NE, Sinai A, Korzeniewska A. High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res. 2006;159:275–95.
65. Gross DW, Gotman J. Correlation of high-frequency oscillations with the sleep-wake cycle and cognitive activity in humans. Neuroscience. 1999;94(4):1005–18.
66. Pockett S, Holmes MD. Intracranial EEG power spectra and phase synchrony during consciousness and unconsciousness. Conscious Cogn. 2009;18(4):1049–55.
67. Valderrama M, Crepon B, Botella-Soler V, et al. Human gamma oscillations during slow wave sleep. PLoS One. 2012;7(3):e33477.
68. Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G. Source modeling sleep slow waves. Proc Natl Acad Sci U S A. 2009;106(5):1608–13.
69. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61(8):928–34.
70. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.
71. Germain A, Richardson R, Moul DE, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. J Psychosom Res. 2012;72(2):89–96.
72. Krakow B, Hollifield M, Johnston L, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001;286(5):537–45.
73. Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. Behav Sleep Med. 2006;4(1):45–70.
74. Cook JM, Harb GC, Gehrman PR, et al. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. J Trauma Stress. 2010;23(5):553–63.
75. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. J Trauma Stress. 2010;23(5):645–8.
76. Reardon CL, Factor RM. Bizarre behavior in a patient treated with prazosin for PTSD. Am J Psychiatry. 2008;165(6):774–5.
77. Nuzhat SS, Osser DN. Chest pain in a young patient treated with prazosin for PTSD. Am J Psychiatry. 2009;166(5):618–9.
78. Krakow B, Ribeiro JD, Ulibarri VA, Krakow J, Joiner TE Jr. Sleep disturbances and suicidal ideation in sleep medical center patients. J Affect Disord. 2011;131(1–3):422–7.
79. Nadorff MR, Nazem S, Fiske A. Insomnia symptoms, nightmares, and suicidal ideation in a college student sample. Sleep. 2011;34(1):93–8.
80. Liu X, Buysse DJ. Sleep and youth suicidal behavior: a neglected field. Curr Opin Psychiatry. 2006;19(3):288–93.
81. Wong MM, Brower KJ, Zucker RA. Sleep problems, suicidal ideation, and self-harm behaviors in adolescence. J Psychiatr Res. 2011;45(4):505–11.
82. Li SX, Lam SP, Yu MW, Zhang J, Wing YK. Nocturnal sleep disturbances as a predictor of suicide attempts among psychiatric outpatients: a clinical, epidemiologic, prospective study. J Clin Psychiatry. 2010;71(11):1440–6.
83. Sjostrom N, Hetta J, Waern M. Persistent nightmares are associated with repeat suicide attempt: a prospective study. Psychiatry Res. 2009;170(2–3):208–11.
84. Sjostrom N, Waern M, Hetta J. Nightmares and sleep disturbances in relation to suicidality in suicide attempters. Sleep. 2007;30(1):91–5.
85. Tanskanen A, Tuomilehto J, Viinamaki H, Vartiainen E, Lehtonen J, Puska P. Nightmares as predictors of suicide. Sleep. 2001;24(7):844–7.
86. Ribeiro JD, Pease JL, Gutierrez PM, et al. Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal ideation and behavior in young adults in the military. J Affect Disord. 2012;136(3):743–50.
87. Bernert RA, Joiner TE. Sleep disturbances and suicide risk: a review of the literature. Neuropsychiatr Dis Treat. 2007;3(6):735–43.
88. Panagioti M, Gooding PA, Tarrier N. A meta-analysis of the association between posttraumatic stress disorder and suicidality: the role of comorbid depression. Compr. Psychiatry. 2012;53:915.
89. Bachynski KE, Canham-Chervak M, Black SA, Dada EO, Millikan AM, Jones BH. Mental health risk factors for suicides in the US Army, 2007–8. Inj Prev. 2012;18(6):405–12.
90. Nadorff MR, Nadorff DK, Germain A. Nightmares: underreported, undetected, and therefore untreated. J Clin Sleep Med. 2015;11(7):747–50.
91. Nadorff MR, Lambdin KK, Germain A. Pharmacological and non-pharmacological treatments for nightmare disorder. Int rev Psychiatry. 2014;26(2):225–36.
92. Balliett NE, Davis JL, Miller KE. Efficacy of a brief treatment for nightmares and sleep disturbances for veterans. Psychol Trauma. 2015;7(6):507–15.
93. Davis JL, Wright DC. Randomized clinical trial for treatment of chronic nightmares in trauma-exposed adults. J Trauma Stress. 2007;20(2):123–33.
94. Raskind MA, Dobie DJ, Kanter ED, Petrie EC, Thompson CE, Peskind ER. The alpha1-adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. J Clin Psychiatry. 2000;61(2):129–33.

Sleep-Disordered Breathing and Posttraumatic Stress Disorder

21

Barry Krakow, Bret Moore, and Victor A. Ulibarri

Introduction

Sleep-disordered breathing is one of the most common sleep disorders, affecting as many as 9–24% of the adult population [1]. The most common form of sleep breathing problem is termed obstructive sleep apnea (OSA), which comprises three precisely defined obstructive breathing events known as apneas, hypopneas, and respiratory effort-related arousals (RERA) (Fig. 21.1), each of which generally collapses the airway for 10 s or longer [2]. Apneas reflect total or near cessation of airflow, hypopneas reflect approximately a 50% reduction in airflow, and the RERA, which also goes by the name flow limitation event (FLE) or upper airway resistance syndrome (UARS), entails an approximately 25% reduction in airflow. Apneas and hypopneas are often accompanied by some degree of oxygen desaturations or fluctuations, whereas the RERA usually shows limited or no changes in oxygenation. All three events usually trigger brain arousals or awakenings after which normal breathing resumes, but then this pattern repeats itself for most of the night (i.e., breathing event, then arousal, then normal breathing, then breathing event, and so on). One additional breathing event that may prove particularly relevant to patients with posttraumatic stress disorder (PTSD) is the central apnea (Fig. 21.1), which refers to changes in the central nervous system that induce a cessation in breathing while asleep despite an unobstructed airway [3]. Recent research indicates anxiety patients [4] as well as traumatic brain injury patients [5] show greater risks for central apneas. All these types of breathing events are linked to a wide array of physical health symptoms and disorders that worsen morbidity and in some cases increase mortality risks (Table 21.1 [6–21]).

Defined theories on clinically relevant relationships between OSA as well as UARS and PTSD appear to have been introduced into the scientific literature in 1998. In a study involving 156 female sexual assault survivors with nightmares and PTSD [22], 52% reported the combination of symptoms of snoring and daytime sleepiness, meeting screening criteria to test for sleep apnea based on the standards of the American Sleep Disorders Association (subsequently American Academy of Sleep Medicine) [23]. At the time, we suggested that the concept of posttraumatic insomnia appeared to be a marker for much more complex and intrinsic sleep disorders in this cohort of PTSD patients. Using a more in-depth analysis of symptom reports, we discovered a strong potential for sleep breathing and/or sleep movement disorders among these sexual assault survivors complaining of nightmares and insomnia. When we compared those patients with these likely sleep physical disorders to those without such symptoms, the presumptive sleep disorders groups correlated significantly with PTSD symptom severity. We speculated that treatment of physiological sleep disorders might be associated with improvement in PTSD severity [22]. And, in that same year, Youakim, Doghramji, and Schutte reported a single case of OSA in a PTSD patient, whose PTSD symptoms remitted when treated with positive airway pressure therapy (PAP-T) [24]. Earlier works had reported objective data on sleep breathing events in PTSD patients without suggesting a broader clinical relevance to posttraumatic stress [25, 26]. And some works had reported relationships between partner-assessed snoring or objective sleep apnea and posttraumatic anxiety dreams [27, 28].

From 2000 to 2002, our research team published six articles on the specific topic of sleep-disordered breathing and PTSD, developing a number of hypotheses as well as presenting key objective data [22, 29–33]. The main thrusts of these works showed that among female sexual assault survivors with nightmares and posttraumatic stress symptoms or diagnoses:

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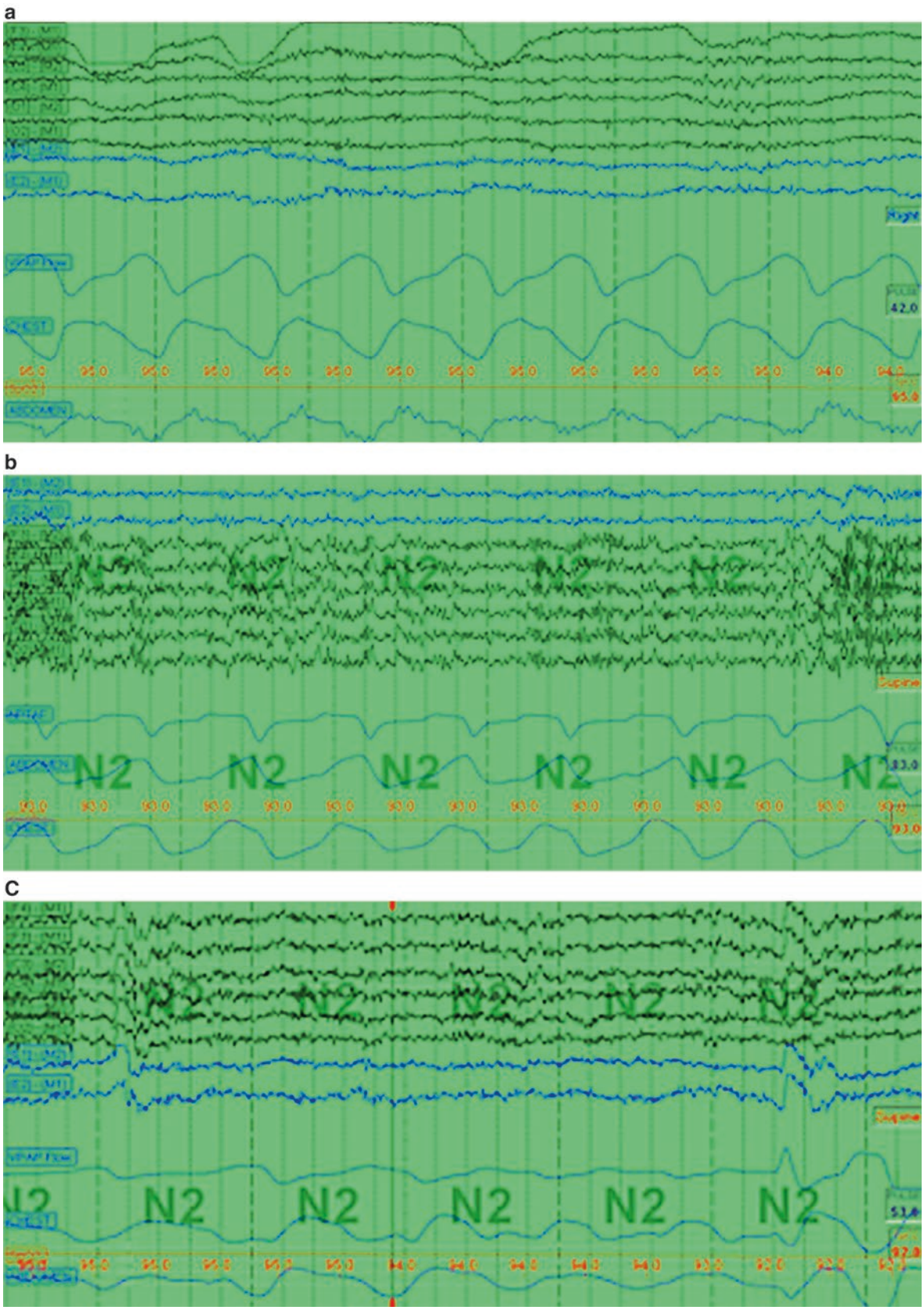

Fig. 21.1 Thirty-second polysomnography epochs showing normal breathing (**a**), upper airway resistance syndrome (UARS) (**b**), hypopnea (**c**), obstructive sleep apnea (OSA) (**d**), central sleep apnea (CSA) (**e**), and expiratory pressure intolerance (EPI) (**f**)

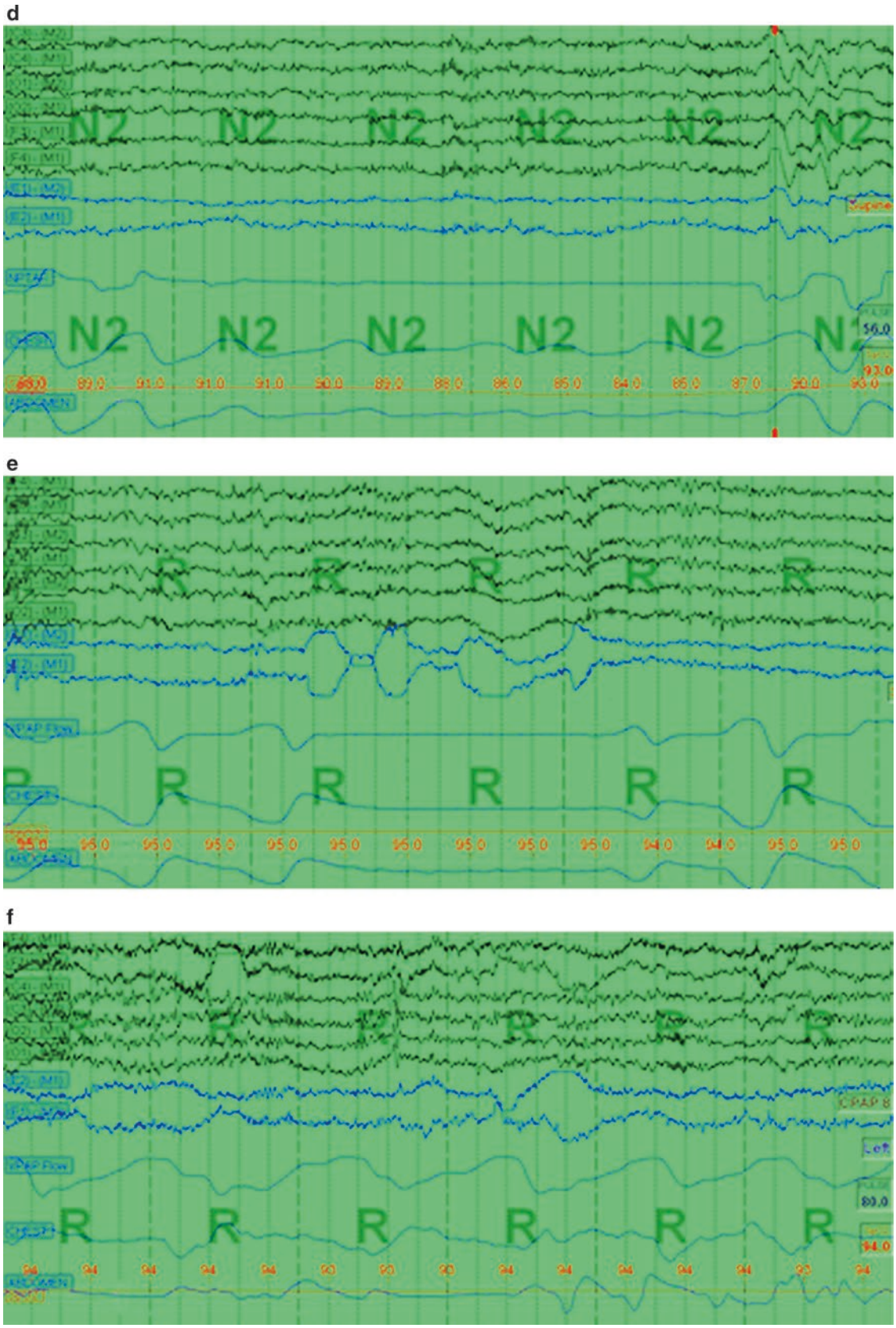

Fig. 21.1 (continued)

Table 21.1 Common medical comorbidity associated with either PTSD or OSA

Cardio/cerebrovascular
Cardiac arrhythmia [6–10]
Congestive heart failure [7–10]
Heart disease [7–10]
Hypertension [7, 8, 10–12]
Myocardial infarction [7–9]
Stroke [7–10]
Pain
Arthritis [7, 9, 13]
Chronic pain [9, 13]
Fibromyalgia [14–17]
Headache [9, 11, 20]
Endocrine/metabolic
Diabetes mellitus [6, 7, 9, 18, 19]
Lipid metabolism [7, 11, 19]
Obesity [11, 18]
Thyroid disease [6, 21]

No reference examined these conditions in a sample with comorbid PTSD and OSA

- Sleep breathing symptoms were surprisingly common, often present in greater than 50% of the sample [22, 30, 31, 33].
- Presumptive sleep breathing disorders presented more likely an insomnia disorder rather than classic sleep apnea [22, 30, 31].
- Sleep-disordered breathing symptoms and disorders were associated with worse psychiatric distress [30, 31, 33].
- Treatment of sleep breathing disorders in PTSD patients was associated with decreases in nightmares, insomnia, and posttraumatic stress [29].

The most important work from our initial effort to describe this phenomenon included a study objectively testing 44 consecutive crime victims with posttraumatic stress who were seeking treatment for nightmares and insomnia; 40 of the 44 patients were diagnosed by polysomnography (PSG) with OSA or UARS [32]. From these results, we coined the term "complex insomnia" to describe patients who present with insomnia as their primary complaint while also suffering comorbid and usually covert sleep-disordered breathing [32]. Subsequent to this work, we completed a review article to describe our hypotheses about the surprisingly high rates of sleep breathing problems among trauma survivors, which we were observing both in research and clinical practice [34]. In particular, we hypothesized about the possibility of a bidirectional pathway (Fig. 21.2) in which posttraumatic stress creates sleep fragmentation, which is known to adversely impact the human airway and increase vulnerability to the subsequent development of OSA or UARS [35] and how sleep breathing problems, in turn, might worsen PTSD symptoms through further sleep fragmentation [34].

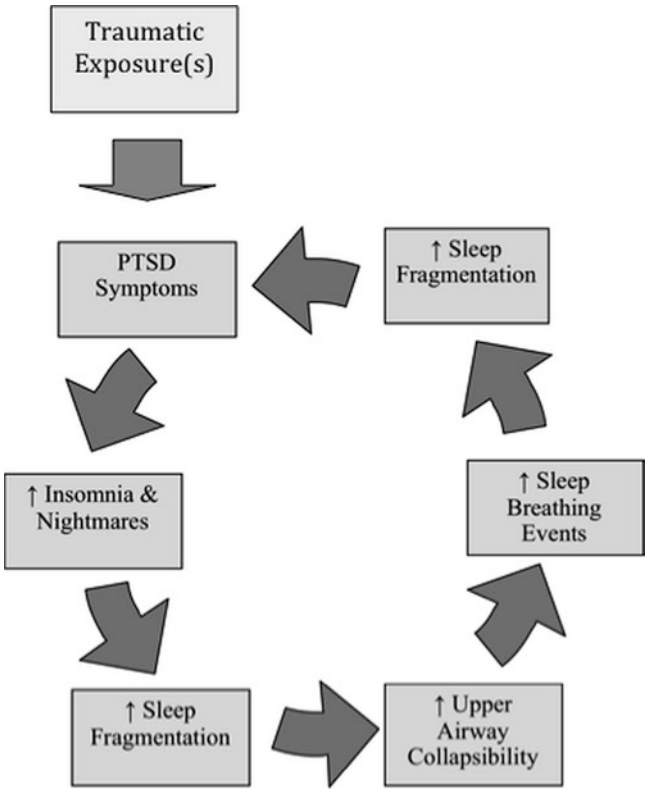

Fig. 21.2 A bidirectional theory in which PTSD increases susceptibility to SDB, which in turn may increase PTSD symptoms [16]

In the ensuing decade since the publication of these works, there has been a slow but steady increase in the interest in this unusual relationship. This chapter will review and highlight extant literature to provide current information about assessment and prevalence, potential clinical relevance, treatment options, and recommendations for future research on the relationship between PTSD and sleep-disordered breathing.

Assessment

Two entrenched paradigms have diluted research on the relationships between sleep breathing disorders and PTSD, and both reflect problems of conventional wisdom inhibiting the adoption of new perspectives and with technology to assess trauma survivors with sleep complaints [34]. Foremost among these barriers is the predominant view that PTSD is strictly a psychological or psychiatric disorder [36–38]. Despite efforts several years ago to introduce concepts about sleep and PTSD into the scientific literature [39–42], a clinical sleep medicine perspective on PTSD has only

emerged during the past decade [43–55]. But these efforts have not pervaded the psychiatric literature, where most PTSD research excludes any primary interest in sleep, and only rare mention is made of sleep breathing problems. In fact, if one completes a Medline search with the single term, "PTSD," the results generate more than 20,000 citations, but if the terms "PTSD and sleep" are used, there are fewer than 1000 entries; and of these thousands, the vast majority do not assess sleep as a primary variable of interest.

More specific to our discussion is the second entrenched paradigm that adversely influences research on sleep and PTSD in which diagnostic PSG is conducted rarely even when sleep is a variable of interest. When PSG was performed, it was unusual that breathing was formally assessed. Finally, even when breathing was assessed, not until 2001 was a study conducted using the now current standard technology in the field, known as nasal cannula pressure transducer [32]. This gap in technology produces a substandard level of assessment—based on the nosology of the American Academy of Sleep Medicine [56, 57]—which is best exemplified in Breslau et al.'s widely cited study on objective sleep findings in patients with chronic PTSD [58]. This study measured breathing solely with thermistor technology, a qualitative tool that can only measure one (apnea) of the three common types of obstructive breathings. Yet, 5 years prior to the Breslau study, the American Academy of Sleep Medicine gave thermistors a "D" grade for its capacity to measure hypopneas accurately, and it was incapable of measuring RERAs, both of which require pressure transducer technology [56, 57]. Another unusual element of the Breslau et al. study was the use of the threshold AHI (apnea-hypopnea index) of ten or greater, which is double the standard set in the field of sleep medicine of five events or greater [57]. The authors reported only 7–10% received such a diagnosis (Breslau 2004). Yet, based on our research 3 years earlier, which used the standard sensors for respiratory assessment, we found that 91% of PTSD patients were diagnosed with either OSA or UARS. Thus, the absence of appropriate technology in Breslau's study would appear to have vastly underestimated both hypopneas and RERAs, leading to a clear-cut underestimation in the number of patients diagnosed with sleep breathing disorders in their PTSD sample.

This barrier to assessment persists. As recently as 2007 [59] and 2010 [60], two research studies using polysomnography in PTSD cohorts did not adopt the appropriate technology to measure hypopneas and RERAs, and both reported the absence of breathing disorders in their samples, an unlikely possibility in light of other research using the appropriate technology.

Prevalence and Clinical Relevance

Prevalence rates for the comorbidity of SDB and PTSD are difficult to discern as the literature reflects highly mixed results. However, there is a general agreement that individuals with PTSD have a disproportionately higher rate of SDB as compared to the general population [47]. In a study of elderly war veterans (n = 59) with and without PTSD, the PTSD group reported poorer sleep quality, but PSG showed minimal differences. However, in the recruitment for this study, many in the PTSD group were excluded due to positive screens for sleep apnea [61]. In a sample of 156 female sexual assault victims with PTSD, Krakow and colleagues (2000) hypothesized that 52% suffered from some form of SDB [22], but this study was limited by relying on self-report only.

Several uncontrolled studies utilizing objective measures of SDB also support increased prevalence of SDB in PTSD patients. In a sample of 105 Vietnam-era veterans with PTSD, 69% had an apnea-hypopnea index >10 despite the fact this study used only thermistor technology [62]. Dagan and colleagues found that 13 out of 24 combat veterans diagnosed with PTSD had sleep apnea [25]. In a study of 44 crime victims with PTSD or clinically significant PTSD symptoms, 55% were found to have OSA and 45% were noted as having UARS [32].

To date, two controlled studies have used objective measures of SDB in patients with comorbid PTSD. In one study, nearly half of combat veterans with PTSD compared with 13% of a nonclinical sample were found to have apneas and hypopneas, although index scores were <10 [63]. In a similar study, ten healthy controls were matched against ten combat veterans diagnosed with PTSD. Although no apneas or hypopneas were observed, more frequent arousals were present in the first half of the night in association with decreased slow-wave sleep in the PTSD group, which may indicate a potential for RERAs in this protocol that used only thermistor technology [64].

And from a different perspective in a review of the Veterans Health Administration healthcare database, a higher rate of PTSD was found in a group with sleep apnea compared to a group without sleep apnea (11.85% vs. 4.74%). However, similar findings were noted for mood and anxiety disorders, psychosis, and dementia indicating a potential general association between psychiatric disorders and sleep apnea [65]. In a similar type of study, Raper et al. found a PTSD rate of 28% among combat veterans with sleep apnea [66].

The comorbidity of PTSD and SDB is more than just an academic issue. There are various clinical implications. Past studies have shown that both SDB and PTSD lead to a variety of physical health consequences (Table 21.1). For example, the medical literature provides clear and overwhelming evidence that SDB is linked to hypertension, dys-

lipidemia, and insulin resistance [8, 19]. OSA in particular is believed to put the individual at greater risk for diabetes and cardiovascular disease [67]. Similarly, individuals with PTSD are more likely to suffer from diabetes, noncirrhotic liver disease, angina pectoris, gastritis, arthritis, and other various physical ailments [7, 68].

Less clear in the literature is the combined impact of comorbid PTSD and SDB on physical health and functioning. Although there are virtually no data to support the idea that physical health problems are exacerbated in individuals with comorbid PTSD and SDB and vice versa, one can reasonably assume, based on studies of depression and chronic pain [69] and stress and cardiovascular disease [70], that a bidirectional process may occur leading to increased symptom severity, decreased global functioning, and less than robust treatment effects.

One study indirectly addressed this issue in 187 sexual assault survivors with posttraumatic stress symptoms (majority with PTSD) who were divided into two groups: those with likely sleep apnea (n = 168) and those unsuspected of having a sleep breathing disorder (n = 19) [33]. Of the 168 suspected SDB cases, all 21 participants from this group who had completed objective tests were confirmed to be suffering an SDB diagnosis. Thus, as all their demographic, sleep, and psychiatric histories were no different than the remaining 147 who did not complete objective testing, an assumption was made that likely all 168 from this group of suspected cases suffered from sleep breathing disorders. When using the SF-36 health scales [71] to compare the SDB group with the 19 women for whom SDB was unsuspected, all eight physical and mental health scales showed significantly worse outcomes (lower scores) for the SDB group with medium to large effects (Cohen's d):

- Physical functioning: 67.53 (27.51) vs. 83.42 (16.92); d = 0.59
- Role physical: 40.06 (41.09) vs. 65.79 (40.15); d = 0.62
- Bodily pain: 47.47 (26.09) vs. 63.37 (19.27); d = 0.61
- General health perception: 47.69 (25.03) vs. 69.95 (18.58); d = 0.88
- Energy/vitality: 26.63 (19.02) vs. 50.53 (21.53); d = 1.16
- Social functioning: (%) 48.87 (24.84) 67.76 (26.46); d = 0.74
- Role emotional: 21.28 (30.74) vs. 52.63 (39.00); d = 0.95
- Mental health: 57.86 (12.89) vs. 64.63 (9.45); d = 0.52

Whether separate processes are involved (e.g., high levels of cortisol in PTSD; sympathetic nervous system activation in SDB) leading to increased physical health problems or some unknown syngergistic effect, future studies will need to be undertaken to address these questions. Certainly, the interesting comorbidity associated with either OSA or PTSD warrants further research (Table 21.1).

Treatment Adherence and Outcomes

Treatment of OSA/UARS among PTSD patients follows standard practice parameters in so far as the use of evidence-based medical technology or procedures [72], but there are scant data on samples of trauma survivors undergoing treatment for sleep apnea.

In a case-controlled prospective design, El-Solh et al. (2010) showed at 30-day follow-up, PAP adherence was significantly lower in a PTSD group compared to a control group (41% versus 70%). Greater sleepiness at intake appeared to promote adherence, whereas more frequent reports of nightmares diminished adherence. Mask comfort and claustrophobia were also reported as barriers to care as well as too little or too much air pressure [73]. In a study by Means and colleagues, black veterans with mental health diagnoses (of which nearly 60% included those with PTSD) showed significantly worse adherence to CPAP than white veterans with similar mental health diagnoses [74]. In a randomized controlled study by Lajos et al. (2004), there were no differences in CPAP adherence between the PTSD and non-PTSD group, but anxiety was the strongest predictor of difficulty with CPAP adaptation [75]. In another study, adherence rates measured by number of nights was not different between PTSD patients and controls, but the actual number of hours of PAP usage was markedly lower in the PTSD group [76].

Adherence rates and outcomes data are also limited in scope and duration, but preliminary studies point to potential problems among trauma survivors in learning to adapt to the device and possibly receiving suboptimal responses to standard PAP therapy. Like all PAP therapy patients, there are always a series of adjustments involving mask fit and comfort, adjusting to pressurized airflow, and global acceptance of learning to sleep with a cumbersome and foreign device attached to one's face all night long for years on end. See Bollig (2010) for an outstanding review on the factors that contribute most to the barriers and enhance the compliance with PAP therapy in the general population [77].

In PTSD patients, mask-triggered claustrophobia is a potential barrier to treatment, but in recent years, the technological expansion in the types of masks along with specific comfort enhancements has created opportunities for virtually every patient with rare exception to find a usable, well-fitting, and comfortable mask. There is little research conducted about masks, perhaps due to such rapid changes in this essential component of PAP therapy, but the general consensus or research findings are as follows:

- Full face masks alleviate mouth breathing.
- Chinstraps may alleviate mouth breathing in patients using nasal masks; and in some cases chinstraps help patients using full face masks.
- Nasal pillow masks (inserted into nostrils) may yield the most comfort by the limited contact with the facial surface.
- Various cushions and pads now marketed for use between the face and mask may further alleviate irritation or sores due to masks tightened down onto the skin, but these same tools may increase air leak.

In our clinical experience, we have found that the most distinctive adaptation problem for PTSD patients in particular and those with other forms of anxiety in general is the problem of expiratory pressure intolerance (Fig. 21.1) [78, 79], wherein the patient tends to either report direct discomfort when breathing out against fixed pressure devices (CPAP) [72] or engages in attention amplification when first learning to use CPAP and thereby develops an adverse psychosomatic response to the sensation of pressurized airflow (almost exclusively on exhalation) [78–80]. This sensation usually can only be eliminated by either a change in pressure delivery mode (e.g., dual pressure devices that utilize lower pressure on expiration) [81] or specific distraction coaching to learn to divert attention away from the sensation itself [78, 79].

To address many of these issues in our insomnia or anxiety patients, we developed the PAP-NAP procedure, a daytime desensitization or "test-drive" of the PAP device, which provides a less stressful experience to initiate usage to patients with greater complexity [82]. Our original paper on the PAP-NAP was conducted on a sample of chronic insomnia patients with elevated psychiatric distress and sleep-disordered breathing, who showed a much greater percentage of adherence to the PAP device compared to a historical control group of insomnia patients with SDB who did not undergo a PAP-NAP. The PAP-NAP is conducted without most of the typical sensors of polysomnography, but instead it focuses on having the patient try out various styles of masks and most importantly try out various modes of pressure delivery, which in most situations leads to a more comfortable or palatable introduction to this unique therapeutic modality. By working one on one with a sleep technologist for upward of 3–4 h, the vast majority of patients build self-efficacy for having worn the mask for an hour or two and experienced pressurized airflow for a similar time interval [83].

Medical and psychiatric comorbidity is another area of concern about PAP therapy, because there are so many potential ways in which another health condition can adversely interfere with the use of the device [84]. In fact, this comorbidity argues against the unrealistic position taken by Medicare policy-makers who imagine, quite fancifully we would add, that there exists something called "the typical sleep apnea patient." Such patients are extremely rare when the issue of comorbidity is appreciated. Consider just a few anecdotal examples from a potential list of hundreds of co-occurring conditions:

- Diabetic patients are at high risk for facial skin abrasions, sores, and infections due to mask pressures.
- Eye disorder patients report blurred vision and dry eyes from air leaks.
- Back and neck pain patients experience difficulties in positioning themselves to use the device, and some report worsening of conditions ironically due to higher quality of sleep leading to less motion during the night.
- Sinus disorders and nonallergic rhinitis patients are at considerable risk for worsening of their conditions solely due to the effects of pressurized airflow.
- Reflux disease is one of the leading causes of aerophagia (air swallowing induced by PAP-T) that in many patients leads to excessive and often times painful bloating and cramping as well as annoying burping and flatulence.
- Of no small significance to a PTSD cohort, traumatic brain injury patients are at high risk for the development of central apneas, which require a much more advanced and expensive form of PAP therapy known as adaptive servo-ventilation (ASV).

Many if not all the conditions listed above may manifest higher prevalence in PTSD patients compared to the general population. Thus, it would not be surprising to anticipate considerable comorbidity in the treatment of PTSD patients with sleep breathing disorders (Table 21.1). Also, there are considerable numbers of PTSD patients who suffer various disabling conditions in addition to traumatic brain injuries, such as schizophrenia [85], upper limb paralysis, and amputations [86], who might have greater difficulty using PAP therapy without receiving consistent aid from another person on a daily (cleaning) and nightly (applying) basis, not to mention in the early going the need for middle of the night strategies for patients who unconsciously remove the mask or who cannot replace it on their own.

Finally, there is a paucity of data on the impact of SDB treatment on PTSD patients [87]. The most remarkable case reports described a patient essentially eliminating the PTSD diagnosis with the treatment of sleep apnea [24]. In two studies by our group, one retrospective [29] and the other prospective [88], the use of PAP therapy in trauma survivors with posttraumatic stress symptoms (PSS) or the PTSD diagnosis was associated with either improvement in PSS or various sleep variables. In the prospective study of 17 crime victims with insomnia and history of criminal victimization, treatment with SDB therapies including PAP therapy, oral appliance therapy, or surgery yielded marked improvements in insomnia and quality of life [88].

Research Recommendations and Conclusions

While data are sparse on the relationships between PTSD and sleep-disordered breathing and even rarer on the treatment of SDB in PTSD patients, emerging literature indicates these areas may have considerable clinical relevance for a sizeable proportion of patients who have not been evaluated for this poorly understood comorbidity. The pathophysiological relationship between SDB and PTSD appears to be a difficult one to appreciate, in particular because we cannot say with any certainty whether the finding of SDB is something that is present in trauma survivors before they develop PTSD, something that develops in a PTSD patient at some point after traumatization, or whether the finding is coincidental or an epiphenomenon. Regardless, considering the emerging research indicating much stronger associations between insomnia and sleep-disordered breathing (i.e., "complex insomnia") [89], the clinical relevance of SDB in PTSD is anticipated to be very high, given the enormously high prevalence of insomnia complaints in trauma survivors.

With this view in mind, both epidemiological and treatment research studies are urgently needed to clarify the exact prevalence of the problem and the best means for treatment. Epidemiological studies must be designed to use the most advanced respiratory technology so that all sleep breathing events can be accurately measured: most notably sensors for measuring UARS are essential. Likewise, treatment studies including those using PAP therapy, oral appliance therapy, surgery, or other emerging modalities must develop appropriate models to manage the anxiety problems likely to inhibit PTSD patients from engaging and following through with treatment.

In conclusion, in our own clinical experiences, treating PTSD patients with sleep-disordered breathing has proven challenging, but anecdotally, many of these patients report noticeable improvements in their sleep, and some report improvements in posttraumatic stress symptoms. These experiences have motivated us to continue investigating the unusual relationship between PTSD and sleep-disordered breathing.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230–5.
2. Iber C A-ISCAQS. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester: American Academy of Sleep Medicine; 2007.
3. Sanner B, Schafer T. Central sleep apnea syndrome. Dtsch Med Wochenschr. 2008;133(14):722–6.
4. Krakow B, Romero EA, Ulibarri VA, Kikta S, Thomas RJ. ASV therapy in anxious or insomnia patients with complex sleep apnea. Sleep. 2010;33:A146. Abstract
5. Webster JB, Bell KR, Hussey JD, Natale TK, Lakshminarayan S. Sleep apnea in adults with traumatic brain injury: a preliminary investigation. Arch Phys Med Rehabil. 2001;82(3):316–21.
6. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004;1032:141–53.
7. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Physical health conditions associated with posttraumatic stress disorder in U.S. older adults: results from wave 2 of the National Epidemiologic Survey on alcohol and related conditions. J Am Geriatr Soc. 2012;60(2):296–303.
8. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA. 2003;290(14):1906–14.
9. Sledjeski EM, Speisman B, Dierker LC. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the National Comorbidity Survey-Replication (NCS-R). J Behav Med. 2008;31(4):341–9.
10. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american college of cardiology foundation scientific statement from the American Heart Association Council for high blood pressure research professional education committee, Council on clinical cardiology, stroke Council, and Council on cardiovascular nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on sleep disorders research (National Institutes of Health). Circulation. 2008;118(10):1080–111.
11. Nazarian D, Kimerling R, Frayne SM. Posttraumatic stress disorder, substance use disorders, and medical comorbidity among returning U.S. veterans. J Trauma Stress. 2012;25(2):220–5.
12. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342(19):1378–84.
13. Kang JH, Lin HC. Obstructive sleep apnea and the risk of autoimmune diseases: a longitudinal population-based study. Sleep Med. 2012;13(6):583–8.
14. Ablin JN, Cohen H, Eisinger M, Buskila D. Holocaust survivors: the pain behind the agony. Increased prevalence of fibromyalgia among Holocaust survivors. Clin Exp Rheumatol. 2010;28(6 Suppl 63):S51–6.
15. Raphael KG, Janal MN, Nayak S. Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. Pain Med. 2004;5(1):33–41.
16. Gold AR, Dipalo F, Gold MS, Broderick J. Inspiratory airflow dynamics during sleep in women with fibromyalgia. Sleep. 2004;27(3):459–66.
17. Shah MA, Feinberg S, Krishnan E. Sleep-disordered breathing among women with fibromyalgia syndrome. J Clin Rheumatol. 2006;12(6):277–81.
18. Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. J Clin Endocrinol Metab. 2010;95(2):483–95.
19. Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. J Intern Med. 2003;254(1):32–44.
20. Rains JC, Poceta JS. Headache and sleep disorders: review and clinical implications for headache management. Headache. 2006;46(9):1344–63.
21. Bahammam SA, Sharif MM, Jammah AA, Bahammam AS. Prevalence of thyroid disease in patients with obstructive sleep apnea. Respir Med. 2011;105(11):1755–60.
22. Krakow B, Germain A, Tandberg D, Koss M, Schrader R, Hollifield M, et al. Sleep breathing and sleep movement disorders

masquerading as insomnia in sexual-assault survivors. Compr Psychiatry. 2000;41(1):49–56.
23. Krakow B, Tandberg D, Sandoval D, Cutchen L, Schrader R. Severity of sleep disturbances in sexual assault survivors. Sleep. 1998:3(6):583–8.
24. Youakim JM, Doghramji K, Schutte SL. Posttraumatic stress disorder and obstructive sleep apnea syndrome. Psychosomatics. 1998;39(2):168–71.
25. Dagan Y, Lavie P, Bleich A. Elevated awakening thresholds in sleep stage 3-4 in war-related post-traumatic stress disorder. Biol Psychiatry. 1991;30(6):618–22.
26. Lavie P, Katz N, Pillar G, Zinger Y. Elevated awaking thresholds during sleep: characteristics of chronic war-related posttraumatic stress disorder patients. Biol Psychiatry. 1998;44(10):1060–5.
27. de Groen JH, Op den Velde W, Hovens JE, Falger PR, Schouten EG, van Duijn H. Snoring and anxiety dreams. Sleep. 1993;16(1):35–6.
28. Guilleminault C. Sleep disorders. In: Handbook of clinical neurology: clinical neuropsychology. Amsterdam: Elsevier; 1985. p. 129–45.
29. Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M, et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. J Psychosom Res. 2000;49(5):291–8.
30. Krakow B, Artar A, Warner TD, Melendrez D, Johnston L, Hollifield M, et al. Sleep disorder, depression, and suicidality in female sexual assault survivors. Crisis. 2000;21(4):163–70.
31. Krakow B, Germain A, Warner TD, Schrader R, Koss M, Hollifield M, et al. The relationship of sleep quality and posttraumatic stress to potential sleep disorders in sexual assault survivors with nightmares, insomnia, and PTSD. J Trauma Stress. 2001;14(4):647–65.
32. Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry. 2001;49(11):948–53.
33. Krakow B, Melendrez D, Johnston L, Warner TD, Clark JO, Pacheco M, et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. J Nerv Ment Dis. 2002;190(7):442–52.
34. Krakow B, Melendrez D, Warner TD, Dorin R, Harper R, Hollifield M. To breathe, perchance to sleep: sleep-disordered breathing and chronic insomnia among trauma survivors. Sleep Breath. 2002;6(4):189–202.
35. Series F, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. Am J Respir Crit Care Med. 1994;150(2):481–5.
36. Lopez-Ibor JJ. The classification of stress-related disorders in ICD-10 and DSM-IV. Psychopathology. 2002;35(2–3):107–11.
37. Pearn J. Traumatic stress disorders: a classification with implications for prevention and management. Mil Med. 2000;165(6):434–40.
38. Yufik T, Simms LJ. A meta-analytic investigation of the structure of posttraumatic stress disorder symptoms. J Abnorm Psychol. 2010;119(4):764–76.
39. Pagel JF Jr. Nightmares. Am Fam Physician. 1989;39(3):145–8.
40. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
41. Benca RM. Sleep in psychiatric disorders. Neurol Clin. 1996;14(4):739–64.
42. Mellman TA. Psychobiology of sleep disturbances in posttraumatic stress disorder. Ann N Y Acad Sci. 1997;821:142–9.
43. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep-what a nightmare! Sleep Med Rev. 2000;4(2):183–200.
44. Singareddy RK, Balon R. Sleep in posttraumatic stress disorder. Ann Clin Psychiatry. 2002;14(3):183–90.
45. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev. 2003;23(3):377–407.
46. Caldwell BA, Redeker N. Sleep and trauma: an overview. Issues Ment Health Nurs. 2005;26(7):721–38.
47. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS Drugs. 2006;20(7):567–90.
48. Mellman TA, Hipolito MM. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. CNS Spectr. 2006;11(8):611–5.
49. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44(4):660–9.
50. Lamarche LJ, De Koninck J. Sleep disturbance in adults with posttraumatic stress disorder: a review. J Clin Psychiatry. 2007;68(8):1257–70.
51. van Liempt S, Vermetten E, de Groen JH, Westenberg HG. Sleep disturbances in post-traumatic stress disorder. An overview of the literature. Tijdschr Psychiatr. 2007;49(9):629–38.
52. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.
53. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12(3):169–84.
54. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
55. Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: a critical review of the empirical literature. J Anxiety Disord. 2010;24(1):1–15.
56. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of sleep medicine task force. Sleep. 1999;22:667–89.
57. American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic & Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
58. Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch Gen Psychiatry. 2004;61(5):508–16.
59. Habukawa M, Uchimura N, Maeda M, Kotorii N, Maeda H. Sleep findings in young adult patients with posttraumatic stress disorder. Biol Psychiatry. 2007;62(10):1179–82.
60. Yetkin S, Aydin H, Ozgen F. Polysomnography in patients with post-traumatic stress disorder. Psychiatry Clin Neurosci. 2010;64(3):309–17.
61. Engdahl BE, Eberly RE, Hurwitz TD, Mahowald MW, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. Biol Psychiatry. 2000;47(6):520–5.
62. Yesavage JA, Kinoshita LM, Kimball T, Zeitzer J, Friedman L, Noda A et al. Sleep-disordered breathing in Vietnam veterans with posttraumatic stress disorder. Am J Geriatr Psychiatry. 2010:3(6):583–8.
63. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(1):110–5.
64. Fuller KH, Waters WF, Scott O. An investigation of slow-wave sleep processes in chronic PTSD patients. J Anxiety Disord. 1994;8(3):227–36.
65. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005;28(11):1405–11.
66. Raper TB, Li J, Desai NR, Hayek H, Thammasitboon S. Posttraumatic stress disorder is highly prevalent in veterans with obstructive sleep apnea. Sleep. 2010;33:A235. Abstract
67. Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. Nutr Metab Cardiovasc Dis. 2007;17(3):233–40.

68. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Medical comorbidity of full and partial posttraumatic stress disorder in US adults: results from wave 2 of the National Epidemiologic Survey on alcohol and related conditions. Psychosom Med. 2011;73(8):697–707.
69. Ohayon MM, Schatzberg AF. Chronic pain and major depressive disorder in the general population. J Psychiatr Res. 2010;44(7):454–61.
70. Garrido M, Hash-Converse J, Leventhal H, Leventhal E. The handbook of stress science: biology, psychology, and health [e-book]. Internet, 487–500. 2011. Springer Publishing Co. Electronic Citation.
71. Ware JE, Koskinski M, Keller SD. SF-36 physical and mental health summary scales: a user's manual. Boston: The Health Institute; 1994.
72. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006;29(3):375–80.
73. El Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. Sleep. 2010;33(11):1495–500.
74. Means MK, Ulmer CS, Edinger JD. Ethnic differences in continuous positive airway pressure (CPAP) adherence in veterans with and without psychiatric disorders. Behav Sleep Med. 2010;8(4):260–73.
75. Lajos LE, Molina PE, Im SS, Gonzales PA, Garza PC, Ingmundson PT. Continuous positive airway pressure adherence among veterans with and without posttraumatic stress disorder. Sleep. 2004;27:A228.
76. Hoffman M, Lettieri C. Adherence to continuous positive airway pressure treatment of obstructive sleep apnea in patients with posttraumatic stress disorder. Sleep. 2010;33:A237. Abstract
77. Bollig SM. Encouraging CPAP adherence: it is everyone's job. Respir Care. 2010;55(9):1230–9.
78. Self guided imagery enhances PAP therapy adaptation. 08 June; 2008.
79. McIver ND, Krakow B, Romero EA, Trujillo LL. Subjective effects of self-guided imagery on PAP therapy adaptation. Sleep. 2008;31. Abstract.
80. Krakow B. Sound sleep, sound mind: 7 keys to sleeping through the night. New York: Wiley; 2007.
81. Krakow B, Ulibarri VA, Romero EA, Thomas R, Togami L. Adaptive servo-ventilation therapy for expiratory pressure intolerance and complex sleep apnea in patients with co-morbid insomnia: a retrospective case series. (in submission). J Sleep Disor Treat Care. 2013;2:1–10.
82. Krakow B, Ulibarri V, Melendrez D, Kikta S, Togami L, Haynes P. A daytime, abbreviated cardio-respiratory sleep study (CPT 95807-52) to acclimate insomnia patients with sleep disordered breathing to positive airway pressure (PAP-NAP). J Clin Sleep Med. 2008;4(3):212–22.
83. Krakow B. Paving the way to optimal titrations. The PAP-NAP: a titration by any other name. Sleep Rev J Sleep Specialists. 2011;11:14–21.
84. Eastwood PR, Malhotra A, Palmer LJ, Kezirian EJ, Horner RL, Ip MS, et al. Obstructive sleep apnoea: from pathogenesis to treatment: current controversies and future directions. Respirology. 2010;15(4):587–95.
85. Hamner MB, Frueh BC, Ulmer HG, Huber MG, Twomey TJ, Tyson C, et al. Psychotic features in chronic posttraumatic stress disorder and schizophrenia: comparative severity. J Nerv Ment Dis. 2000;188(4):217–21.
86. Reiber GE, McFarland LV, Hubbard S, Maynard C, Blough DK, Gambel JM, et al. Service members and veterans with major traumatic limb loss from Vietnam war and OIF/OEF conflicts: survey methods, participants, and summary findings. J Rehabil Res Dev. 2010;47(4):275–97.
87. Hurwitz TD, Khawaja I. Treatment of obstructive sleep apnea may be an important adjunct to therapy of posttraumatic stress disorder not to be overlooked. Sleep. 2010;33(11):1435–6.
88. Krakow B, Melendrez D, Lee SA, Warner TD, Clark JO, Sklar D. Refractory insomnia and sleep-disordered breathing: a pilot study. Sleep Breath. 2004;8(1):15–29.
89. Krakow B, Ulibarri VA. Prevalence of sleep breathing complaints reported by treatment-seeking chronic insomnia disorder patients on presentation to a sleep medical center: a preliminary report. Sleep Breath. 2012. Epub (Ahead of Print). 3(6):583–8.

Heart Rate Variability, Sleep, and the Early Detection of Post-traumatic Stress Disorder

22

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Introduction

The prevalence of combat-related post-traumatic stress disorder (PTSD) and the severity of its symptoms increase with time after return from deployment, from 5% to 6% immediately after return to 27–42% 3–6 months later [12]. In addition, not even half of the veterans diagnosed with a mental health problem seek professional help care in the year after their return from deployment (23–40% in a study reported by [16]). These findings indicate that the early recognition and treatment of PTSD are still underestimated, at least by the affected veterans themselves. This review is concerned with a possible biological marker of PTSD, heart rate variability (HRV), which has the potential to detect PTSD early in its development. HRV parameters might thus be used as an early warning system that can discriminate veterans with high or low risks for developing PTSD.

DSM-5 criteria for PTSD include a state of constant hyperarousal, a state that has a strong physiological component, as can be measured by various peripheral measures such as increased heart rate, blood pressure, breathing rate, and sweating activity (e.g., [20]). The parameters of these peripheral measures are to a large extent determined by activity of the autonomic nervous system at two distinct levels: the basal tone and the phasic reaction to stress-inducing (e.g., combat-related) stimuli. Heart rate variability predominantly reflects the more tonic (i.e., resting state) activation of the autonomic nervous system, which is the focus of the present review. Because sleep disturbances are reported by the majority of PTSD patients and because sleep is also characterized by a distinct pattern of autonomic nervous system activity, the relationship between HRV, an index of autonomic functioning, sleep quality, and PTSD is also reviewed here.

Anatomical and Physiological Background

The Autonomic Nervous System

The autonomic nervous system consists of two anatomically distinct branches: the sympathetic and parasympathetic (vagal) systems, which both project to most of the internal organs with opposing (complementary) effects. The effects of the sympathetic system are fast and directed toward activation ("fight-flight"); they involve an increase in heart rate, respiration, blood pressure, and pupil dilation, and a decrease in digestive activity. By contrast, activity of the parasympathetic nervous system is thought to act more slowly and is related to relaxation and digestion, involving a decrease in heart rate and respiration and an increase in digestive activity such as peristaltic activity. Anatomically, the sympathetic and parasympathetic branches of the autonomic nervous system are distinct in that the former originates from thoracic

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and lumbar spinal cord (T1 to L2) and the latter from the brain stem (cranial nerves III, VII, IX, X) and sacral spinal cord (S2–S4). The efferent connections to the organs consist of two nerve fibers in both branches (pre- and postganglionic), but in the sympathetic branch, the first efferent nerve fiber is short and the second long, whereas the converse is true for the parasympathetic branch. Pharmacologically, the preganglionic fibers of both branches release the neurotransmitter acetylcholine, but whereas the short postganglionic fibers of the parasympathetic system also release acetylcholine, the long postganglionic fibers of the sympathetic branch release norepinephrine (noradrenaline). Thus, the sympathetic branch of the autonomic nervous system is said to be *adrenergic* and the parasympathetic branch *cholinergic*.

The sympathetic and parasympathetic branches of the autonomic nervous system both innervate the heart, more specifically the sinoatrial (SA) node, which results in contraction of the heart. The adrenergic sympathetic branch (originating from the T1-T4 segments of the spinal cord) increases SA rate, thereby increasing heart rate, while the cholinergic parasympathetic branch (originating from cranial nerve X – vagus nerve) decreases it. Activity of the SA node, located at the top of the heart, is the first event in the characteristic electrical record of the heart beat – the electrocardiogram (ECG or EKG).

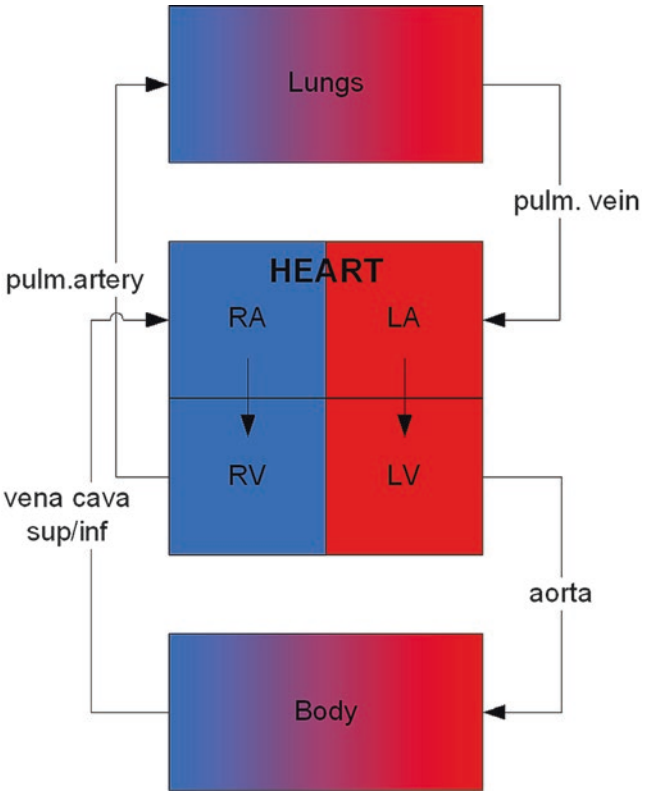

Fig. 22.1 Schematic representation of cardiovascular circulation. *Red*, oxygen-rich blood; *blue*, desaturated blood

Cardiac Anatomy and Circulation

The heart consists of four chambers surrounded by muscle tissue, the myocardium. Under normal conditions, blood cannot flow directly from right to left or vice versa. The upper right chamber or right atrium (RA) receives low-oxygen blood from the body through the superior and inferior vena cava. Conversely, the left atrium (LA) receives oxygen-rich blood from the lungs through the pulmonary veins. The lower right chamber or right ventricle (RV) receives blood by contraction of RA and similarly the left ventricle (LV) is filled by contraction of LA. When the ventricles contract on their turn, the blood is driven to the two major arteries that originate from the heart: RV serves the pulmonary artery (PA) to allow O_2-CO_2 gas exchange in the lungs. Finally, LV drives the oxygen-rich blood to the aorta which supplies all vital organs and other types of tissue with blood. Figure 22.1 summarizes the circulation; compartments with oxygen-rich blood are red, and compartments with desaturated blood are blue. Valves between left/right atria and ventricles as well as between the ventricles and the PA and aorta prevent blood to flow back into atria and ventricles, respectively.

Each heart cycle consists of three phases. During the first phase, the atria contract and empty their contents into the ventricles. After a short delay, the second phase is initiated during which the ventricles contract and drive their blood content into the pulmonary artery and aorta, respectively. During the third phase, the myocardium recovers from contraction. After this period a new heart cycle can start.

Electrical Innervation of the Heart

The mechanical contraction of individual heart cells is initiated by action potentials (APs), electrical impulses that travel across a physiologically determined pathway across the cardiac muscle. In a healthy heart, the trigger for each cardiac cycle is in the upper right area of the right atrium, the sinoatrial (SA) node (Fig. 22.2). This area contains cells that spontaneously can generate APs. The frequency at which action potentials are generated by this natural pacemaker has a natural baseline value, but this frequency usually is controlled by the autonomic nervous system. From the SA node, APs travel across a pre-programmed pathway to adjacent cardiac cells; first, the atrial myocardial cells are activated in such a way that they contract from the top to the atrioventricular areas. Contrary to the mechanical barrier that prevents blood to flow from right to left, APs travel from right to left atria and ventricles. However, there is an electrical barrier between both atria and the ventricles: APs cannot cross the

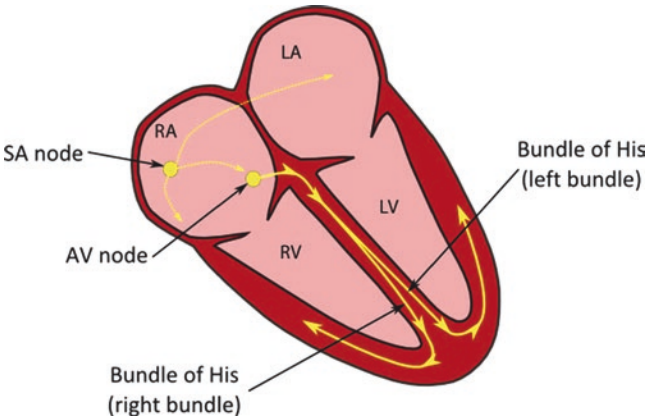

Fig. 22.2 Neural innervation pathways across the heart (*yellow*)

atrioventricular junction, except in one area called the atrioventricular (AV) node. This structure is located in the muscle wall between the two atria and consists of specialized tissue that introduces a delay in the conduction of APs. Once passed through the atrioventricular barrier, APs are conducted via the bundle of His and the bundle branches to the bottom of the right and left ventricles, respectively. Through small branches called Purkinje fibers, the ventricular myocardium is innervated, basically from bottom to the atrioventricular areas. After the electrophysiological innervation of cardiac muscle cells, there is always a resting or refractory period which needs to be finished in other to initiate a new AP.

Spreading of Electrophysiological Activity in the Surrounding Tissue

Action potentials not only act as a trigger for the mechanical contraction of cardiac muscle cells but also cause electrical currents that spread across all conductive tissues surrounding the heart. Most pericardial tissue can be considered as a bioelectrical universe that instantaneously conducts the local currents generated in and around individual cardiac cells toward the natural electrical conductive barrier that surround every subject: skin that is surrounded by air. Because air cannot conduct electrical current, the currents that are generated in the myocardium also cause currents that flow across the skin. Because skin has a finite electrical resistance, Ohms law applies, and voltage differences are generated across different locations at the skin. Because of the highly collective and synchronized manner, many cardiac cells are activated and deactivated during each heart cycle; all the small contributions of individual cells add up and generate a measurable signal at the skin surface, in particular at skin positions close to the heart. This signal, the electrocardiogram (ECG), varies over time because the activation of the various heart regions varies over time and consequently the distance between active and "silent" cardiac regions is time-varying. The basic rule of thumb is that the closer an active region is to any skin position, the larger its contribution in the net electrical voltage that can be measured at such a location. This typically is done using adhesive sensors called electrodes.

ECG: Morphology and Other Characteristics

Figure 22.3 shows an example of a 10-s episode of an ECG recording obtained at nine different skin positions. A detailed description is beyond the scope of this text, but one can easily see that the morphology of the various recordings differs significantly. Nevertheless there are a number of common characteristics: each recording shows a characteristic prominent sequence of sharp peaks and valleys, some recordings having the opposite polarity when compared to others. This is the QRS complex, which is associated with the electrical activation of the ventricles. Although the amplitude (peak-to-peak value) may differ remarkably, its time of occurrence for each recording is exactly the same. This is a result of the laws of physics.

A second characteristic that regularly appears in ECG recordings and is of relevance for HRV analysis is illustrated by the large, slow fluctuations that occur in all recordings around 5 s from the beginning of this trace and in the lower three recordings at the end of this epoch depicted in Fig. 22.3. This is an example of the many types of artifacts that may be encountered during ECG recordings: such large fluctuations are usually a consequence of movement, poor electrode contact, or even loose electrodes. Other manifestations of artifacts may be presence of irregular waveforms (usually referred to as noise), flat recordings, or extremely high amplitudes.

Because different skin areas have different relative positions to the bioelectric heart activity, the morphology of an ECG strongly depends on the position of an electrode. This becomes apparent from illustrated in Fig. 22.3. Two standard electrode configurations, or montages, are commonly used in clinical practice. The oldest electrode configuration was defined by the first pioneer in ECG recordings, Willem Einthoven, who in the early 1900s used four basins filled with saline in which the two lower arms and legs where immersed. The basins acted as electrodes and were connected to a galvanometer that recorded the voltage differences between the four "leads." Today, adhesive electrodes are used that directly are wired to modern polygraphs, but the leads still are referred to as RA, LA, RL, and LL for right and left arm/leg, respectively (sometimes the term "foot" is used instead of "leg"). Any electrophysiological recording requires a reference voltage; often the right leg electrode is used for this purpose, but many alternatives can be found in literature. For standard extensive cardiological assessments,

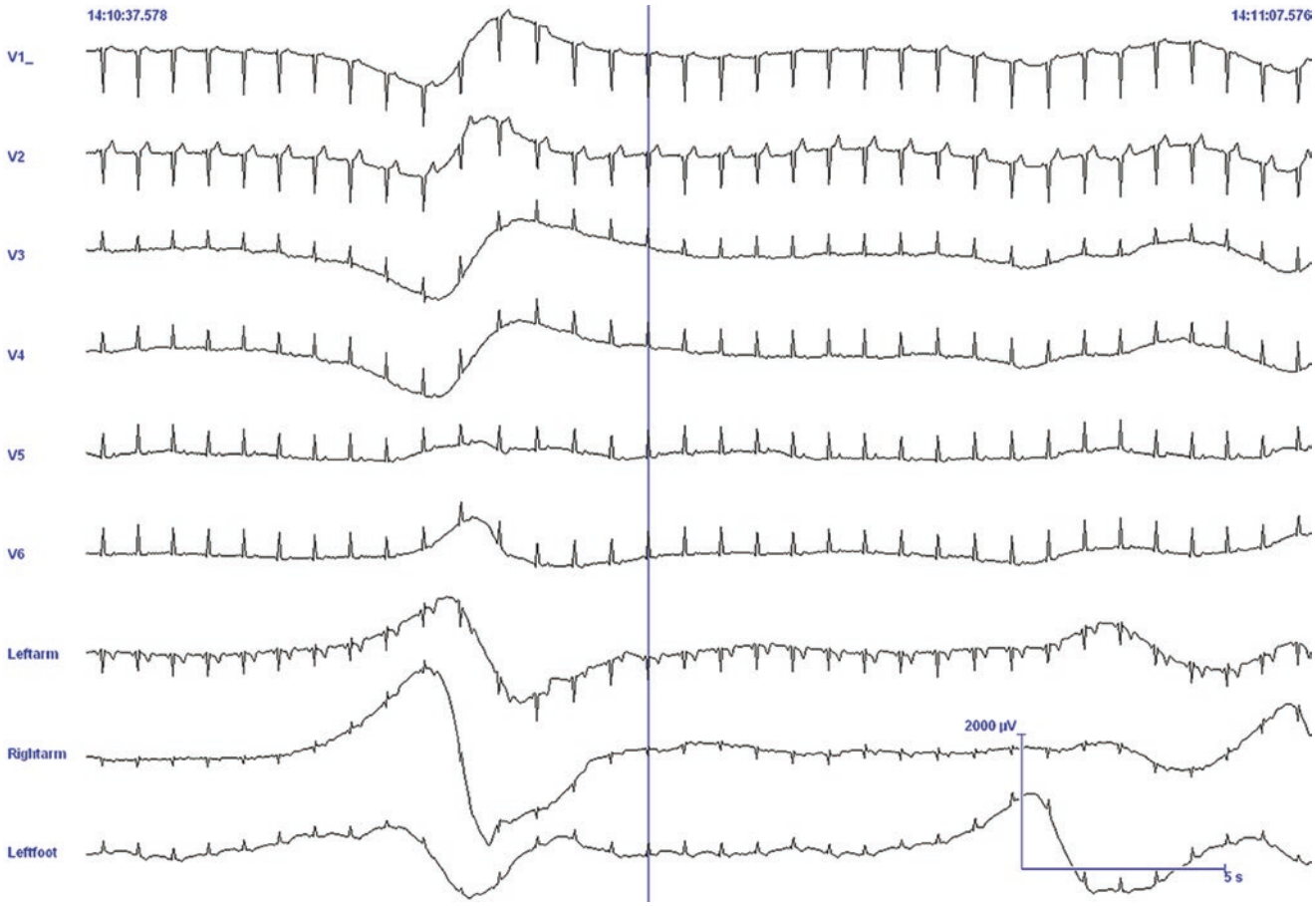

Fig. 22.3 Example of a 10 s ECG recording from different electrode positions

the wrists and ankles still are used, but for clinical studies the positions of the four Einthoven leads often are chosen at more convenient positions such as just below the left/right claviculae and at left and right upper legs or hips. In addition to the voltage difference between the "active" leads and the reference (RL) electrode, one also can determine the difference between two active leads, e.g., LA-RA, LL-RA, and LL-LA. In compliance with Einthoven's naming conventions, these three signals are coded with roman numerals: I, II, and III, respectively.

The second type of electrode montage uses six electrodes which are placed at the so-called precordial positions, skin locations close to the heart at well-defined positions at the chest. The positioning is not only chosen such that they can be used for any gender but also allow observation of the electrical heart activity from different directions. The naming convention for these electrode positions is V1…V6. Figure 22.3 also shows example of the signals acquired from these electrodes.

In most clinical and health HRV assessments, a subset of the ten standard electrode positions is used; the precordial positions usually are preferred because these ECG recordings have the most prominent QRS complex and consequently allow the most robust R-peak detection. When a minimal number of electrodes is required, often lead LA-RA is used (positions at left and right front shoulders, just below the claviculae) or V1–V6, the latter having the largest amplitudes [22] but are not always practical considering client-friendliness.

R-Peak Detection for HRV

In cardiology, ECG recordings are indispensable for the initial diagnostic of a host of cardiac diseases. HRV, however, can only be done reliably and in a sensible manner when no clear deficits of heart rate control by the autonomic nervous system and AP conduction problems across the myocardium exist. Under these conditions, each QRS complex can always be associated with one single "trigger" in the SA node. Therefore, the first step in ECG-based HRV analysis is the detection of each individual and consecutive QRS complex and careful determination of its time of occurrence and detection of the next QRS complex.

From a signal analysis perspective, QRS detection is a pattern recognition task. Trained human experts are known to be extremely skilled in such a task, but automation using

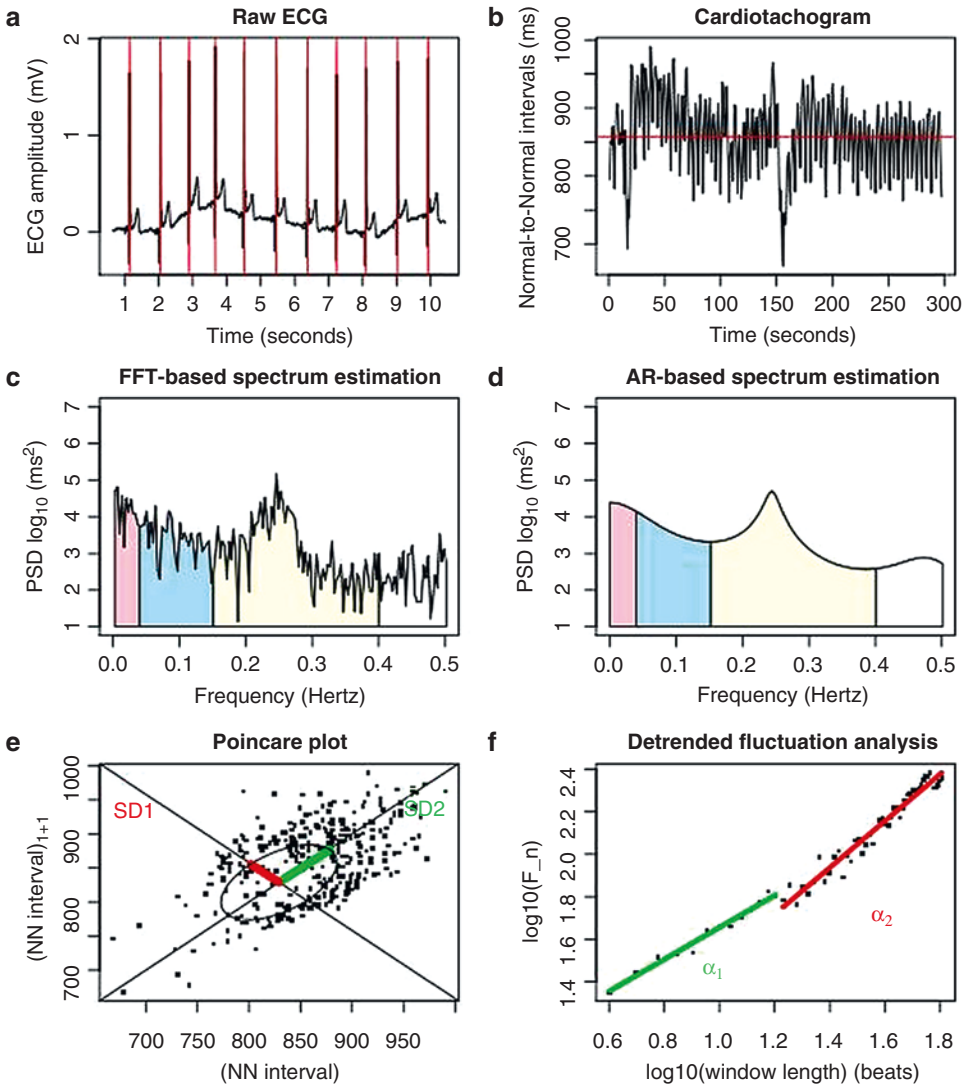

Fig. 22.4 Example of a raw ECG with fiducial R-peaks (**a**); the associated cardiotachogram (**b**); FFT-based (**c**) and autoregressive-based (**d**) spectra showing the VLF (*pink*), LF (*blue*), and HF (*yellow*) bands; Poincaré plot (**e**); and detrended fluctuation analysis (**f**)

computer algorithms in practice turns out to be a very difficult task, in particular when dealing with long-duration and/or ambulatory conditions. A host of proposals have been made, but to our experience no algorithm has shown to be as good or even superior to human pattern recognition. A useful and recommended strategy is to preprocess the data by a modern QRS detection algorithm, such as the one based on filter banks proposed by Afonso et al. [1], and subsequently inspect, and if necessary correct, the algorithmically determined fiducial points.

Measuring Heart Rate Variability

Given accurate determination of the fiducial QRS complex points, the R-R (inter-beat) intervals can be calculated. These intervals are also referred to as *normal-to-normal (NN) intervals* or *heart periods.* Actually, a more correct term for what is usually referred to as heart *rate* variability would be heart *period* variability, because usually most calculations are performed on heart periods not rates.[1] The heart periods can be plotted against time in the *cardiotachogram* (Fig. 22.4b). The calculations on heart periods can be classified into four categories: time domain measures, frequency domain measures, time-frequency domain methods, and nonlinear measures. Software for many of these measures is freely available in several packages such as Kubios (http://kubios.uku.fi/), Physionet (http://www.physionet.org/), and RHRV (http://cran.r-project.org/web/packages/RHRV/).

Time Domain Methods

The most common time domain methods of HRV are listed in Table 22.1, along with normative values and some values that have been found in cases of PTSD. Mean NN intervals in seconds or milliseconds, or mean heart rate in beats per

[1]We will use the terms heart rate variability and heart period variability interchangeably. Focus is on the *concept* of variability, irrespective of the measure that is used or whether the measures have been derived from heart rates or heart periods.

Table 22.1 Normative values for commonly used variables of HRV

Name	Description	Unit	Normative values
Mean R-R	Mean of R-R intervals	ms	926 ± 90[a]
SD R-R (SDNN)	Standard deviation of R-R intervals	ms	50 ± 16[a]
RMSSD	Root mean square of successive differences	ms	42 ± 15[a]
HRV triangular index	Triangular index of HRV histogram		37 ± 15[b]
LF	Power in the low-frequency band (0.04–0.15 Hz)	log10(ms[b])	5.01 ± 1.76[a]
LFnu	LF power in normalized units (divided by total power – VLF power)	n.u.	54 ± 4[b]
HF	Power in the high-frequency band (0.15–0.40 Hz)	log10(ms^2)	4.76 ± 1.78[a]
HFnu	HF power in normalized units (divided by total power – VLF power)	n.u.	29 ± 3[b]
LF/HF	Ratio between LF and HF power		2.8 ± 2.6[a]; 1.5–2.0[b]

[a]Nunan et al. [24]
[b]Task Force [32]

minute, are obvious global indicators of heart functioning that can be analyzed in various situations like rest, sleep, task performance, etc. The most straightforward measure of overall HRV is the standard deviation of NN intervals (SDNN). To obtain stable measures, a period of approximately 5 min is recommended, and the duration must be kept constant in case comparisons under different conditions are made, because the standard deviation depends on the length of the recording period. In case of 24-h recordings, the total duration is often divided into 5-min segments, and the standard deviation of the segment averages is reported (SDANN). This value reflects very slow periodicities, i.e., longer than 5 min. The most commonly used time domain measures for short (beat-to-beat) variations are the Root Mean Square of Successive Differences (RMSSD), calculated as the square root of the mean squared differences of successive NN intervals; NN50, the number of NN intervals greater than 50 ms; and pNN50, the proportion of number of intervals greater than 50 ms. Obviously, because the latter measures all reflect relatively fast fluctuations, they are highly correlated.

A histogram of frequency distribution of all NN intervals forms the basis of *geometrical* time domain measures. If the frequency distribution is narrow and high, then all NN intervals lie within a small range of values, and HRV is low. If, on the other hand, the distribution is low and broad, then variability is high. Based on this notion, the *HRV triangular index* is the ratio between the integral of the NN density distribution (i.e., the total number of NN intervals) and its height. Because the resulting value depends on the bin width of the frequency histogram, this bin width has been standardized to 1/128 = 7.8125 ms). The *triangular interpolation of the NN interval histogram* (TINN) reflects the baseline width of the NN interval histogram in milliseconds. The HRV triangular index and TINN correlate with SDNN, as they reflect overall variability. Note that a sufficient number of NN intervals should be available for reliable calculation of the geometric measures of HRV. Therefore, these measures are usually only employed for 24-h recordings.

Frequency Domain Measures

The power spectral density function (PSD) relates variance (power) to specific frequencies in the heart period series. It can be calculated nonparametrically (usually by the fast Fourier transform; FFT), or parametrically by autoregressive (AR) methods. The nonparametric FFT-based approach is fast and straightforward, but may result in "spiky" spectra for relatively short recordings (although this can be alleviated somewhat by using Welch's periodogram). In addition, the results may depend on choices made with respect to tapering of the raw series to avoid spectral leakage (a 10% cosine window is often used) and to the smoothing of the periodogram. AR spectra are smoother and more suitable for short recordings, but it is not straightforward to determine the optimal AR model order. Irrespective of the method used to calculate the PSD, its calculation assumes an equidistantly spaced time base, as opposed to an NN interval base. Therefore, the NN intervals should be interpolated to a real-time axis. Usually, cubic splines are used for interpolating values, and a sampling frequency of 4 Hz is recommended for the time base.

Overall power as calculated by the PSD corresponds to overall variation in the time domain as calculated by SDNN. If short (5-min) recordings are used, three sources of variance can be distinguished: very low frequency (VLF; <0.04 Hz; period >25 s), low frequency (LF; 0.04–0.15 Hz, period ~7–25 s), and high frequency (HF; 0.15–0.4 Hz; period 2.5 –

~7 s). If 24-h recordings are analyzed, the VLF band is usually further subdivided into an ultralow frequency band (ULF; <0.003 Hz, period >333 s ~5 min) and a VLF band (VLF; 0.003–0.04 Hz, period 25 s – 5 min). An example of the PSD in which these frequency bands were marked is presented in Fig. 22.4c (FFT method) and Fig. 22.4d (AR method); normal values are given in Table 22.1. Power in the HF band correlates with the RMSSD, NN50, and pNN50 in the time domain, because these variables all reflect relatively fast fluctuations in the NN series. There is no clear correlate of the LF and VLF bands in the time domain, but the ULF band in 24-h recordings is related to SDANN.~

Power values can be calculated in absolute or normalized units (n.u.), i.e., divided by the total power minus power in the VLF band. The idea behind normalized power in the LF and HF bands is that these values are thought to reflect the activity of the sympathetic and parasympathetic branches of the autonomic nervous system, respectively. Consequently, the LF/HF ratio has been suggested to reflect autonomic balance. Much can and has been written about this interpretation. The relation between power in the HF band and parasympathetic activity seems to be established beyond doubt and is supported by pharmacological, clinical, and physiological evidence such as vagal stimulation (e.g., [18]). The interpretation of the LF component, by contrast, is more controversial and has been interpreted both as reflecting sympathetic activation and as reflecting both sympathetic and parasympathetic activation (see Task [32], for a discussion). Although this discussion has not been settled definitely, it constitutes a viable working model for many clinical and nonclinical applications, and it also fits with findings in sleep and PTSD (see following sections). On a more functional level, the HF band can be said to be primarily related to respiratory variations, whereas the LF band is thought to mainly reflect baroreceptor (blood pressure) changes (e.g., [2]).

Time-Frequency Domain Measures

Frequency domain measures as discussed above all rely on estimation of the PSD, which assumes (quasi-)stationarity of the underlying time series. Obviously, this assumption is not always met in HRV recordings, and the very deviations from stationarity are interesting in their own right. Time-frequency domain methods such as the wavelet transform may be an alternative in cases in which stationarity is questioned. These methods have good frequency as well as time resolution and would allow the distinction between slow and fast periodicities just like the frequency domain methods. Instead of relying on sinusoidal functions in FFT-based approaches, wavelet transforms use a "mother" waveform that can have various shapes (usually the "Daubechies 4" mother wavelet is used) to decompose the time series. Pichot et al. [25] have shown that sudden changes in the HRV as a result of administering atropine (an acetylcholine antagonist used as a parasympathetic inhibitor) and propranolol (a "beta-blocker" or (nor) epinephrine antagonist and used as an inhibitor of the sympathetic system) could be modeled better by wavelet analysis compared to FFT-based methods.

Time-frequency domain methods are relatively new in the analysis of HRV and are as yet not employed widely. There are no reliable normative values for time-frequency domain measures.

Nonlinear Measures

Another relatively recent development in the analysis of HRV is the use of nonlinear measures. These measures attempt to detect recurring patterns in the data. Unfortunately, the physiological interpretation of many nonlinear measures is unclear, so it remains to be seen whether they add something meaningful to overall time or frequency domain measures such as SDNN or total power. In addition, many methods require large amounts of data (~ 10,000 data points; [31]), which is not always feasible.

There are two noteworthy examples of nonlinear techniques that do not require large amounts of data and that allow the distinction between fast and slow fluctuations: the Poincaré plot (Fig. 22.4e) and detrended fluctuation analysis (Fig. 22.4f). In the Poincaré plot, NN interval i is plotted against NN interval $i+1$. This will result in an ellipsoid scatter plot through which two orthogonal lines are fitted: x_2 at an angle of roughly 45° with respect to the X-axis and x_1 perpendicular to x_2. The standard deviations along these lines denoted by SD2 and SD1 reflect short-term (HF) and long-term (LF) variability, respectively. In detrended fluctuation analysis, the NN interval series is integrated and divided into segments of equal lengths. Least squares regression is then used to detrend the local segments, and a root mean squared fluctuation is calculated, which depends on segment length. Then, short-term (α_1) and long-term (α_2) fluctuations can be calculated that correlate with the HF and LF power bands, respectively.

Heart Rate Variability in Post-traumatic Stress Disorder

Psychophysiological variables have long since been suspected to differ between PTSD and normal controls. In an extensive review and meta-analysis, Pole [26] summarized that PTSD is characterized by elevated psychophysiologic measures of facial electromyography (EMG), heart rate, skin conductance, and blood pressure. Increased mean heart rate has been viewed as a

correlate of PTSD since many years (e.g., [10]). Blanchard, Kolb, Pallmeyer, and Gerardi [4] also found increased mean heart rate in PTSD patients ($N = 11$) compared to controls, along with changes in blood pressure, forehead EMG, skin resistance level, and peripheral temperature. In addition, they found an increase in mean heart rate while listening to combat sounds in the PTSD group not in the normal controls. Findings such as these can be interpreted by assuming that PTSD is characterized both by a state of heightened tonic (resting state) arousal and phasic (reaction to stressors) hyperreactivity, both brought about by changes in autonomic activity (cf. [27]). Most researchers assume that the elevated heart rate and blood pressure arise from increased sympathetic activity [7]. However, it cannot be established whether these changes involve an increase in sympathetic activity and/or a decrease in parasympathetic activity, because cardiovascular changes are known to involve both branches of the autonomic nervous system, either working reciprocal to one another, or in parallel, or even uncoupled [3].

Cohen and colleagues [8, 9] were the first to study HRV in PTSD patients. They compared HRV parameters in nine PTSD patients to nine matched controls and distinguished between tonic (basal tone) and phasic (reaction to stress-related cues) measurements. After 20 min of recording while resting, the participants were asked to recount a significant traumatic event during another measurement of 20 min, which was followed by another resting measurement of 15 min. They found that PTSD patients had a mean heart rate that was about 10 beats per minute higher than controls, which did not change as a function of the experimental manipulation in either group. Overall heart rate variability was smaller in PTSD compared to controls and like mean heart rate did not differ between experimental stages. A different picture emerged when distinguishing between HF and LF components of HRV, however. PTSD patients had a higher LF component *and* a lower HF component compared to controls in the resting measurements, but not while recounting the traumatic event. In the control participants, by contrast, the LF component rose and the HF component dropped as a response to recalling a stressful life event and returned to baseline values in the second resting measurement. Thus, PTSD appeared to be characterized tonically both by increased sympathetic *and* by decreased parasympathetic activity compared to normal controls, while in addition, they exhibited less phasic cardiovascular reactivity to stressors. The latter result deviated from earlier findings (e.g., [4]). It should be noted, however, that the values reported for the LF/HF ratio in this study, approximately five in normal controls and ten in PTSD, were atypical and deviated from the normative values listed in Table 22.1.

Since these early studies on HRV in PTSD, similar results have been reported many times. However, specific details differ between the studies, and the factors influencing these differences have not yet been identified. For instance, Sahar, Shalev, and Porges [30] did not find tonic resting state differences in HRV between PTSD patients ($N = 14$) and a group with traumatic experiences without PTSD ($N = 15$), but did find phasic differences in response to a stressor (an arithmetic task). The PTSD patients in their study showed a decrease both in the LF and in the HF components compared to the non-PTSD group. Sahar et al. [30] noted that the study of Cohen et al. [9] reported atypical LF/HF values and also pointed to subtle differences in calculating the HRV frequency bands, which could possibly account for the differences between these studies. Sack, Hoppert, and Lamprecht [29] noted that the number of patients involved in all of these studies were too small to draw firm conclusions. They reported on 31 PTSD patients and speculated that reactivity might be different for individuals with high versus low vagal tone, as indexed by the HF component of HRV. Thus, they specifically related the tonic and phasic aspects of cardiovascular measures to PTSD. Script-driven imagery of personalized traumatic or neutral events was used to assess cardiovascular reactivity. Mean heart rate increased, and the HF component of HRV decreased from the neutral to the trauma script, in line with earlier findings. These effects were prolonged in patients with low parasympathetic tone compared to patients who exhibited higher parasympathetic tone at baseline, and they suggested that low tonic vagal tone may account for the deficient phasic arousal regulation capacity in PTSD. Similarly, Hopper and co-workers [17] found that when PTSD patients ($N = 59$) were classified according to vagal tone at baseline (low, middle, high), only the subgroup with low vagal tone exhibited elevated mean heart rate as commonly found in PTSD patients.

In sum, it seems that PTSD patients are characterized by low tonic parasympathetic activity in resting situations and that this low vagal tone is associated with elevated mean heart rates and reduced cardiac responsiveness in PTSD patients relative to controls. A recent study involving 26 PTSD patients, 26 trauma-exposed controls, and 18 non-trauma-exposed controls confirmed these relations based on a correlation analysis [15].

Sleep, Cardiovascular Control, and PTSD

Sleep and Cardiovascular Control

From a neurophysiological point of view, sleep can be described as an unconscious state characterized by lower cortical activity. Because cardiac activity is also associated with states of relaxation and cortical activity, it is no surprise that sleep and cardiovascular control are linked.

Results of studies that monitored heart rate over a period of 24 h showed a relative sympathetic dominance in cardiac control during daytime and a relative parasympathetic dominance during sleep [11]. This diurnal rhythm in cardiac activity can be seen as the result of modulation by a circadian component and as such is under control of the suprachiasmatic nucleus and by a homeostatic component, merely reflected the time being awake during daytime. These modulations result in episodes of sleep or wakefulness coinciding with relatively low or elevated cardiac activity, respectively [34].

Sleep is not a uniform state throughout the night. During the night, different sleep stages can be observed. After the lights go off, while attempting to fall asleep, we shift from an awake state to N1 sleep and subsequently to N2, N3, and rapid eye movement (REM) sleep. A single sequence of a cascade from light sleep (N1 and N2) to deep sleep (N3, also referred to as slow-wave sleep (SWS)) and followed by an episode of REM is called a sleep cycle, and one sleep cycle has a duration of approximately 90 min. Sleep stages N1 to N3 are also referred to as non-REM (NREM) sleep. It should be mentioned that during normal sleep, small bursts of cortical activity can be observed in all of the sleep stages. Although these periods of arousal hardly impact sleep stage classification, they do clearly impact cardiac activity [34].

The interplay between cardiovascular activity and sleep is concisely described by Trinder and co-workers [34]. During the process of sleep onset, a drop in cardiac activity can be observed. The high-frequency (HF) activity is clearly getting more dominant, and the LH/HF ratio is progressively declining from light to deep NREM sleep, indicating an increased parasympathetic drive during NREM sleep. In REM sleep both HF and LF/HF ratio approximate values that are observed during relaxed wakefulness, indicative of an increased sympathetic drive [33]. The cortical activity periods, present in every sleep stage, coincide with a strong increase in cardiac activity and sympathetic tone.

It needs to be mentioned that sleep and cardiac activity are linked in a bidirectional fashion. Not only does sleep exert a regulatory control over cardiac activity, but, conversely, changes toward a more parasympathetic dominance also facilitate sleep. Thus, changes in cardiac activity related to sleep initiation pave the way to progress toward deeper sleep. This view is supported by the observation that the change in vagal tone precedes the development of deep sleep during the night and also the brief arousals from sleep are preceded by slight changes in cardiac activity. As a consequence, increased cardiac activity during nighttime is likely to lead to sleep disruption. Sleep disruption in turn frequently leads to sleep loss, and if this sleep loss built up during a couple of nights of disrupted sleep, it can be called sleep deprivation. Sleep deprivation in turn causes a shift toward higher sympathetic tone.

Sleep and PTSD

Subjective sleep complaints, including nightmares, are prevalent in an average of 70% of patients diagnosed with PTSD [35]. Around 40% of patients diagnosed with PTSD report having problems with falling asleep. Ninety percent of PTSD patients also report more difficulties to maintain sleep during the night and end of the night. Also nightmares are reported to be more prevalent (52%) in PTSD patients as compared to healthy controls. These reported sleep disturbances were shown to have strong prognostic value [14].

The findings on the relation between objective sleep measures and PTSD are mixed. Some studies show significantly more disturbed sleep (shorter total sleep time, lower sleep efficiency), whereas other studies show that the objective sleep measure fall into the normal range. A meta-analysis performed by Kobayashi and co-workers [19] showed that the sleep of PTSD patients contains relatively more N1 sleep and less SWS sleep. Moreover, REM density, a measure of the actual amount of REM brain activity within a REM episode, was higher in patients with PTSD. The authors also showed moderating effects of age, gender, comorbid depression, and comorbid substance abuse on sleep. Trauma-related nightmares were also associated with more fragmented sleep and more nocturnal awakenings. Also motor dysfunction both in REM sleep and in NREM sleep has been associated with PTSD [28].

It has been pointed out by several authors that the subjective evaluation of sleep by the patient might indicate a more severe sleep problem than the actual objectively measured sleep [14]. This phenomenon called sleep state misperception is not unique to PTSD patients, but also prevalent in patients with insomnia. To date, it cannot be concluded whether objective sleep measures prevail over subjective sleep measures for quantifying a sleep complaint; sleep state misperception by the patient may as well be sleep state misinterpretation by the sleep researcher or sleep clinician.

Sleep, Cardiovascular Control, and PTSD

Acute stressors have been shown to have a profound effect on cardiac activity and sleep in the night following the acute stressor. As a result of the stressor, decreased levels of parasympathetic drive (decreased HF) during NREM and REM and increased sympathovagal balance (increased LF/HF ratio) during NREM were observed. It was concluded that changes in HRV associated with acute stress are likely a cause of the disturbed sleep [13]. Within 30 days after the trauma, an increased sympathovagal balance (increased LF/HF ratio) during NREM sleep in subjects that were positive for PTSD symptoms was observed by Mellman and co-workers, and they concluded that the change in cardiac activity (as a consequence of increased noradrenergic activity) contributes to the development of PTSD [21].

As concluded before, it seems that PTSD patients are characterized by low tonic parasympathetic activity in resting situations and that this low vagal tone is associated with elevated mean heart rates and reduced cardiac responsiveness in PTSD patients relative to controls. From the sparse results that are reported in sleep studies, it is suggested PTSD patients are characterized by the increased sympathetic activation during sleep, mainly observed during REM sleep. Thus, a disturbed sympathovagal balance can be observed both in daytime and during sleep in all phases following the exposition to the trauma event and continuing months after. The acute stressor during a traumatic event might trigger a cascade of changes that will disturb healthy autonomic cardiac regulation: a stressor might lead to an elevated activation of the sympathetic nervous system during sleep, especially REM sleep. As a consequence sleep is likely to be disturbed. Due to this sleep disturbance and the sleep deprivation as a result, the sympathetic dominance might increase even further, which in turn will hamper the process of falling asleep and sound progression to deeper, restorative sleep [34]. As a possible intervention to improve sleep, one might aim to lower the sympathetic tone. It has been shown that HRV biofeedback intervention in PTSD will lead a decreased sympathetic activity and subsequently to reduced PTSD symptoms and sleep disturbances [23].

To summarize, sleep and cardiac activity are linked in a bidirectional manner. The disturbance in the sympathovagal balance, with a shift toward elevated activation of the sympathetic nervous system, due to the exposure to a traumatic event, might start a chain reaction that affects sleep and cardiac activity negatively and might lead to severe sympathovagal imbalance.

Early Detection of PTSD

Based on the above review of the literature, it can be expected that cardiovascular markers, especially those indicative of low parasympathetic tone at rest and an increased sympathetic tone during sleep, especially REM sleep, should be able to facilitate the early detection of PTSD. Note that it is unlikely, in our view, that a single cardiovascular marker will be able to detect PTSD with a high degree of sensitivity and specificity. The disorder is far too diverse to allow this, and different subtypes seem to exist, even characterized by differences in cardiovascular reactivity (e.g., [15]). Rather, measures of cardiovascular activity may be indicative of a certain risk in developing PTSD, and people at high risk may be selected for programs aimed at preventing PTSD.

The work of Bryant [5, 6] was specifically geared at the early detection of PTSD based on cardiovascular markers. Bryant [5] reviewed ten prospective studies that indexed the acute reactions to trauma indicative of chronic PTSD, and did not find consistent predictors in symptomatology or in cognitive style. It was suggested, however, that mean heart rate in the resting state could be such a marker, and Bryant [6] followed up on this by reviewing ten further studies, eight of which indeed indicated that elevated heart rate in the acute phase was associated with the risk of developing PTSD. It was also noted, however, that variability in heart rate levels and in symptoms of subsequent PTSD was quite high and that there seemed multiple pathways to PTSD development. In a prospective study involving 161 acutely injured surgical patients, by contrast, Zatzick and colleagues [36] determined that mean resting heart rate above 95 beats per minute was predictive of subsequent PTSD symptoms, albeit with modest specificity (60–65%) and sensitivity (49–63%).

Thus it seems that the issue of predicting PTSD symptoms from mean resting heart rate is not yet settled. More data are necessary to establish the relations more firmly. Based on the available literature, we suggest that such future studies also incorporate measures of baseline vagal tone (HF component of HRV, RMSSD), in addition to mean heart rate levels. We are unaware of any studies on this topic up to now, but this seems to be a fruitful area for future research.

References

1. Afonso VX, Tompkins WJ, Nguyen TQ, Luo S. ECG beat detection using filter banks. IEEE Trans Biomed Eng. 1999;46(2):192–202.
2. Berntson GG, Bigger J Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 1997;34:623–48.
3. Berntson GG, Cacioppo JT, Quigley KS. Autonomic determinism: the modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. Psychol Rev. 1991;98:459–87.
4. Blanchard EB, Kolb LC, Pallmeyer TP, Gerardi RJ. A psychophysiological study of post-traumatic stress disorder in Vietnam veterans. Psychiatry Q. 1982;54:220–9.
5. Bryant RA. Early predictors of posttraumatic stress disorder. Biol Psychiatry. 2003;53:789–95.
6. Bryant RA. Longitudinal psychophysiological studies of heart rate: mediating effects and implications for treatment. Ann N Y Acad Sci. 2007;1071:19–26.
7. Buckley TC, Kaloupek DG. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom Med. 2001;63:585–94.
8. Cohen H, Kotler M, Matar MA, Kaplan Z, Miodownlik H, Cassuto Y. Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. Biol Psychiatry. 1997;41:627–9.
9. Cohen H, Kotler M, Matar MA, Kaplan Z, Loewenthal U, Miodownlik H, Cassuto Y. Analysis of heart rate variability in posttraumatic stress disorder patients in response to a trauma-related reminder. Biol Psychiatry. 1998;44:1054–9.
10. Dobbs D, Wilson WP. Observations on persistence of war neurosis. Disord Nerv Syst. 1961;21:40–6.
11. Carrington M, Walsh M, Stambas T, Kleiman J, Trinder J. The influence of sleep onset on the diurnal variation in cardiac activity and cardiac control. J Sleep Res. 2003;12:213–21.

12. Ginsberg JP, Berry ME, Powell DA. Cardiac coherence and posttraumatic stress disorder in combat veterans. Altern Ther Health Med. 2010;16:52–60.
13. Hall M, Vasko R, Buysse D, Ombao H, Chen Q, Cashmere JD, Kupfer D, Thayer JF. Acute stress affects heart rate variability during sleep. Psychosom Med. 2004;66:56–62.
14. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev. 2003;23:377–407.
15. Hauschildt M, Peters MJV, Moritz S, Jelinek L. Heart rate variability in response to affective scenes in posttraumatic stress disorder. Biol Psychol. 2011;88:215–22.
16. Hoge CW, Castro CA, Messner SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351:13–22.
17. Hopper JW, Spinazzola J, Simpson WB, Van der Kolk BA. Preliminary evidence of parasympathetic influence on basal heart rate in posttraumatic stress dosorder. J Psychosom Res. 2006;60:83–90.
18. Kamath MV, Upton ARM, Talalla A, Fallen EL. Effect of vagal nerve electrostimulation on the power spectrum of heart rate variability in man. Pacing Clin Electrophysiol. 1992;15:235–43.
19. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
20. Kolb LC. A neuropsychological hypothesis explaining posttraumatic stress disorders. Am J Psychiatr. 1987;144:989–95.
21. Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. Biol Psychiatry. 2004;55:953–6.
22. Mulder LJM. Assessment of cardiovascular reactivity by means of spectral analysis. Unpublished doctoral dissertation, University of Groningen; 1988.
23. Nishith P, Duntley SP, Domitrovich PP, Uhles ML, Cook BJ, Stein PK. Effect of cognitive behavioral therapy on heart rate variability during REM sleep in female rape victims with PTSD. J Trauma Stress. 2003;16:247–50.
24. Nunan D, Sandercock GRH, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing Clin Electrophysiol. 2010;33:1407–17.
25. Pichot V, Gaspoz J-M, Molliex S, Antoniadis A, Busso T, Roche F, Costes F, Quintin L, Lacour J-R, Bartélémy J-C. Wavelet transform to quantify heart rate variability and to assess its instantaneous changes. J Appl Physiol. 1999;86:1081–91.
26. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. Psychol Bull. 2007;133:725–46.
27. Rosen J, Fields R. The long-term effects of extraordinary trauma: a look beyond PTSD. J Anxiety Disord. 1988;2:179–91.
28. Ross RJ, Ball WA, Dinges DF, Kribbs NB, Morrison AR, Silver SM, Mulvaney FD. Motor dysfunction during sleep in posttraumatic stress disorder. Sleep. 1994;17:723–32.
29. Sack M, Hoppert JW, Lamprecht F. Low respiratory sinus arrhythmia and prolonged psychophysiological arousal in posttraumatic stress disorder: heart rate dynamics and individual differences in arousal regulation. Biol Psychiatry. 2004;55:284–90.
30. Sahar T, Shalev AY, Porges SW. Vagal modulation of responses to mental challenge in posttraumatic stress disorder. Biol Psychiatry. 2001;49:637–43.
31. Seker R, Saliu S, Birand A, Kudaiberdieva G. Validity test for a set of nonlinear measures for short data length with reference to short-term heart rate variability signal. J Syst Integr. 2000;10:41–54.
32. Task Force. Heart rate variability; standards of measurement, physiological interpretation, and clinical use. Eur Heart J. 1996;17:354–81.
33. Toscani L, Gangemi PF, Parigi A, Silipo R, Ragghianti P, Sirabella E, Morelli M, Bagnoli L, Vergassola R, Zaccara G. Human heart rate variability and sleep stages. Ital J Neurol Sci. 1996;17:437–9.
34. Trinder J, Waloszek J, Woods MJ, Jordan AS. Sleep and cardiovascular regulation. Arch Eur J Physiol. 2012;463:161–8.
35. Van Liempt S, Vermetten E, de Groen JHM, Westenberg HGM. Slaapafwijkingen bij posttraumatische stressstoornis. Overzicht van onderzoeksbevindingen [Sleep anomalies in posttraumatic stress disorder. Survery of Research findings]. Tijdschr Psychiatr. 2007;49:629–38.
36. Zatzick DF, Russo J, Pitman RK, Rivara F, Jurkovich G, Roy-Byrne P. Reevaluating the association between emergency department heart rate and the development of posttraumatic stress disorder: a public health approach. Biol Psychiatry. 2005;57:91–5.

Sleep, Declarative Memory, and PTSD: Current Status and Future Directions

23

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- Healthy sleep is critical for successful memory consolidation.
- Both SWS and REM sleep play distinct but important roles in sleep-dependent memory consolidation.
- PTSD-diagnosed individuals have poor neutral declarative memory in comparison with control individuals.
- SWS and/or REM sleep disruptions may contribute to neutral declarative memory deficits in PTSD.
- The empirical evidence for this hypothesis is examined as well as possible mechanisms underlying the hypothesis.

Healthy sleep plays a vital role in the encoding and consolidation of newly acquired memories. As noted elsewhere in this volume, individuals diagnosed with posttraumatic stress disorder (PTSD) do not, typically, experience healthy sleep, with disruptions at both REM and NREM stages. Furthermore, from a clinical neuropsychological perspective, the diagnosis of PTSD is also associated with marked memory impairment. Few empirical studies have, however, explored possible associations between disrupted sleep and impaired memory in PTSD. In this chapter, we will review (a) models of memory processing during sleep in healthy individuals and (b) characteristics of sleep- and declarative memory-related impairments in PTSD-diagnosed individuals. We will propose that disrupted sleep is a critical mechanism underlying memory impairments in PTSD.

Because much of the literature on the neuropsychology of combat-related PTSD is concerned with performance deficits on tests of neutral, non-affective declarative memory, we have chosen to focus here on the processing of such memories during sleep in veterans with the diagnosis. Other chapters in this volume focus on recent research into the consolidation of memories with affective or emotionally laden content, which is, of course, integral to our overall understanding of the neuropsychology of PTSD.

We begin our review by examining declarative memory processing during sleep in healthy individuals. This section focuses primarily on consolidation processes during sleep but also makes reference to the relationship between healthy sleep and optimal encoding. Next, we review, briefly, the characteristics of declarative memory impairment in combat veterans diagnosed with PTSD. Finally, we will propose that this particular profile of memory deficits might result from disrupted sleep interrupting encoding and consolidation processes.

Healthy Sleep Enhances Encoding and Consolidation of Declarative Memories

Memory traces can evolve from unstable initial representations (formed at the encoding stage, where a representation of an experience is registered in the brain) to fully fledged and stable images and narratives that may persist for years [46, 58]. The process of memory consolidation is responsible for this evolution; it ensures that the initial representation is resistant to decay (forgetting), and it may even be responsible for enhanced strength of the memory trace [54, 79]. In healthy individuals experiencing uninterrupted sleep, consolidation of declarative memories appears to occur throughout the night [22, 36]. In fact, it appears that the successive

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progression of sleep stages, from early-night slow-wave-rich sleep to late-night REM-rich sleep, promotes encoding as well as consolidation [20, 63, 80, 81].

Consolidation During SWS

Two different theoretical models have, from a neurophysiological basis, attempted to explain how declarative memory consolidation occurs during SWS. The *active system consolidation* theory (for reviews, see [12, 80]), incorporating findings from both the animal [61–64] and human [19, 43, 65] literatures, suggests that the same brain regions and functional connective systems active during encoding in wakefulness are reactivated during sleep. Specifically, this theory posits that memory traces encoded initially in both the hippocampus and neocortex are reactivated during subsequent episodes of SWS. During those stages of sleep, slow electrophysiological oscillations generated by the neocortex drive repeated reactivations of memory traces in the hippocampus. The upstate (represented as the peak of the wave formation on EEG recordings) of these slow oscillations synchronizes with sharp-wave ripple from hippocampal- and thalamic-driven spindles [34, 82]. This synchronization promotes the formation of ripple-spindle events, which in turn promote effective transfer of reactivated memory traces from the hippocampus to neocortical structures [41]. Hence, the initially unstable and relatively weak memory traces based in the hippocampus are incorporated increasingly strongly into preexisting networks of knowledge stored in neocortical circuits; during later waking activation, these memory traces are therefore less reliant on hippocampal activation [20].

Various studies support these findings. Healthy participants asked to encode word pairs and then recall them later perform better when the delay is filled with the SWS-rich first half of the night than when it is filled with the REM-rich second half of the night or with normal waking activity [21, 47, 48]. Additionally, when waves specific to SWS (i.e., very slow cortical oscillations of <1 Hz) are induced in the prefrontal cortex (PFC) using direct current stimulation, participants in the stimulation condition have greater word-pair retention than no-stimulation controls [2, 44].

In contrast to the active system consolidation theory, the *synaptic homeostasis* theory [67, 68] suggests that the slow oscillations during SWS act to decrease, rather than increase, neural connections or synaptic strength. Specifically, this theory posits that whereas during waking, learning and memory processes act to increase synaptic strength, during sleep synaptic connections are downscaled so that circuits do not become saturated and therefore unable to encode information successfully the next day. A result of this downscaling is that while weakly potentiated synapses are eliminated, strongly potentiated synapses remain, thus ensuring better recall of relevant information.

Recent studies focusing on biological markers of synaptic strength such as long-term potentiation (LTP) and long-term depression (LTD) have provided some support for this theory. LTP is one key mechanism explaining long-lasting synaptic strengthening in neural networks; LTD, in contrast, is a process that selectively weakens specific synaptic connections over a period of hours, thus clearing them of old memory traces and allowing the potentiation of new traces [32]. Glutamatergic AMPA receptors containing the subunit GluR1 have been found to play an important role in mediating LTP and LTD processes [42]. Vyazovskiy et al. [77], studying the rat hippocampus and cortex, showed that, during wakefulness, the levels of this receptor were high; during sleep, however, they were low. Further, changes in the expression of this receptor were consistent with LTP during the day and with LTD during the night. Importantly, changes in slow-wave activity in the rat brain during sleep were associated with changes in synaptic efficacy, further supporting the hypothesis that SWS is associated with LTD and therefore with synaptic downscaling.

Are these two different models of the neurophysiological mechanisms underlying memory consolidation during SWS sleep compatible with one another? On the face of it, they are not: The active system consolidation model suggests a strengthening of synaptic connections, and therefore of memory traces, whereas the synaptic homeostasis theory suggests an overall decrease in synaptic connections. Nonetheless, several authors (e.g., [12, 80]) have suggested that these models are in fact complementary and together may explain discrete aspects of the consolidation process during SWS sleep. That is to say, the processes can operate simultaneously: While active system consolidation may strengthen memory traces and integrate them into wider and preexisting networks of information, synaptic downscaling may eliminate superfluous neural connections and refresh synaptic potential for encoding. Furthermore, and with specific regard to memory consolidation, one set of hypotheses [80] suggests that these processes work together to improve signal-to-noise ratio: When superfluous neural connections are eliminated, the connections that remain have greater overall strength, thus ensuring optimal consolidation. In a recent update on the state of the art, Genzel et al. [23] suggest that these two models of sleep-dependent consolidation can be further reconciled by understanding the distinction between light NREM sleep (NREM 1 and NREM 2) and deep NREM (SWS). These authors argue that slow oscillations, sharp-wave ripples generated in the hippocampus, and surface EEG indicators (such as K-complexes and spindles) represent global markers of active system consolidation which is strongly (but not exclusively) associated with light

NREM sleep. They furthermore propose that slow-wave activity and delta waves are local markers of synaptic homeostasis, which dominates over replay mechanisms related to active system consolidation in SWS. Each successive cycle of lighter and deeper NREM sleep results in the reorganization of information and removal of superfluous connections, respectively, which leads to optimal memory consolidation. Further research is still needed to demonstrate exactly how these processes may work alongside each other.

Consolidation During REM

There is evidence for two distinct memory consolidation processes, each based on discrete electrophysiological events, during REM. The first process involves pontogeniculo-occipital (PGO) waves. In rats, PGO density during REM increases following learning [10, 11, 69]. This increase is associated with post-sleep task performance improvements. Furthermore, PGO waves are associated with the expression of immediate early genes (IEGs), which express during LTP in REM sleep and result in long-term synaptic strengthening in the brain [11]. Following learning, IEG activity is localized to brain regions which were involved in the acquisition of new material [52, 53, 69]. A recent study also demonstrated that if REM sleep is selectively deprived after learning in rats, both memory consolidation and LTP are impaired [50].

The second electrophysiological process that promotes memory consolidation during REM is the expression of the theta rhythm [3, 12]. During waking, theta activity occurs during the encoding of hippocampal-dependent memories [9]. During sleep, there is evidence of neuronal replay, associated with theta activity, of this encoded information in the hippocampus [40, 49]. Furthermore, in mice, silencing of REM-specific theta rhythms only (i.e., leaving intact those rhythms during other stages of sleep) selectively impairs consolidation of, for instance, neutral information related to novel object place recognition [3]. In humans, theta activity during REM increases after the learning of word pairs before sleep [17]. Current research shows that theta rhythm and PGO waves are related, in that PGO waves are phase-locked to theta rhythm [51]. In animal models, eliciting theta waves during REM sleep in the medial septum entrains PGO waves to the theta rhythm. In humans, PGO waves are impossible to measure given the current technology because they occur in medial regions of the brain and are not easily detected via surface EEG [29]. Hence, the relationship between theta rhythm and PGO waves, and their distinct or overlapping contribution to memory consolidation, remains unclear in humans.

In summary, these theoretical frameworks and empirical data help explain why the progression of sleep stages over the night results in optimal memory consolidation. During early-night SWS, relevant memory traces are selected (by the strength of their potentiation at synapses; weak connections are eliminated) and integrated into preexisting networks of knowledge. During REM sleep, these traces are strengthened so that they form long-lasting representations in the brain. Of note here is that IEG activity is correlated with EEG spindle activity during the preceding SWS. One hypothesis, then, is that SWS primes networks for later IEG expression [55].

Encoding Following Sleep

Numerous empirical studies have shown that acquisition of newly-presented declarative information is more efficient after a session of uninterrupted sleep than after a period of sleep deprivation or after a session of fragmented sleep. For instance, Harrison and Horne [28] showed that healthy participants who had been sleep deprived for 36 h performed significantly more poorly on a face recognition task than those who had slept for the normal 8 h prior to testing. Even when a subgroup of the sleep-deprived participants was administered caffeine to combat non-specific effects of lower alertness, the sleep-refreshed group performed better.

There is a clear neural basis for these between-group differences. Functional MRI studies exploring the sleep deprivation and memory testing paradigm described above have shown that, compared to those who sleep normally, sleep-deprived individuals have less medial temporal lobe (and, specifically, hippocampal) activation and greater (perhaps compensatory) PFC and parietal activation [13, 86]. Because, in these studies and in others (e.g., [14, 59, 87]), successful encoding is associated with extent of hippocampal activation, it appears that healthy sleep is important in preparing the appropriate neural circuits for next-day acquisition of novel information.

These empirical data are consistent with the theoretical frameworks outlined above. By the active consolidation model, one proposed result of the dialogue between the neocortex and hippocampus during SWS is that retrieval of "old" memories is less reliant on hippocampal involvement during subsequent (daytime) reactivations. Similarly, the synaptic homeostasis model posits that, upon waking, hippocampal networks are refreshed as a result of synaptic downscaling during SWS. Both theories, then, predict that the hippocampus will be refreshed and ready for new encoding after a night of healthy, uninterrupted sleep.

Declarative Memory and Sleep in Combat-Related PTSD

A key feature of the neurocognitive profile of PTSD is declarative memory impairment (for reviews, see, e.g., [6, 31, 60]). These impairments are (a) independent of performance on tests of attention (i.e., impaired memory is not a secondary effect of impaired attention) and (b) not significantly associated with level of depression or with degree of past alcohol abuse [26, 30]. Furthermore, neuroimaging studies suggest that, in PTSD, decreased hippocampal volume is associated with degree of declarative memory impairment [4, 66, 78, 85] and that individuals with PTSD show altered patterns of hippocampal/parahippocampal and PFC activation during associative learning and memory tasks [25, 83].

There are critical nuances to the pattern of declarative memory impairment in PTSD, however. Veterans diagnosed with PTSD tend to show deficits in the encoding of novel information, as well as in the delayed free recall of that information [5, 7, 57, 74–76]. These deficits in recall are not deficits in *retention* of information, however; that is to say, individuals diagnosed with PTSD perform more poorly at the encoding stage of list learning, word association, or story memory tasks and continue to perform poorly at delayed free recall, but they do not lose more information over the delay interval than do control participants (i.e., there tend to be no significant between-group differences when one uses percentage retention (the amount recalled after a delay as a proportion of what was learned initially) as an outcome variable) ([56, 74, 76, 78] but see [4, 5]).

The implication here, then, is that PTSD-diagnosed individuals have relatively stable memory performance after they have learned information during waking: They do not forget any more than controls do. One runs into a conundrum here: Retention ability is reliant on hippocampal activation [14, 15, 70]; PTSD-diagnosed individuals have decreased hippocampal volume and compromised hippocampal functioning [4, 78]; yet they do not forget previously learned information more readily than controls do [74, 76].

One possible way to explain this conundrum involves considering the patterns of sleep disruption present in PTSD. As other chapters in this volume note, SWS percentage tends to be lower in PTSD patients than in healthy controls [1, 35]. As explained in the preceding sections of this chapter, normal SWS acts to strengthen memories encoded during the preceding waking hours. It does so by replaying the functional connectivity of neural circuits involved in (a) the encoding of information and (b) the transfer of that information from the hippocampus to neocortical sites. This active consolidation process, along with the synaptic downscaling detailed by the synaptic homeostasis theory, leaves the hippocampus refreshed for next-day encoding as previous-day memory traces no longer rely heavily on hippocampal activation. In PTSD, however, SWS disruption may leave hippocampal networks saturated during next-day learning and memory tasks; hence, one observes the characteristic PTSD-related pattern of declarative memory (and especially encoding) deficits on these tasks.

Currently, however, there is little data directly addressing the role of disrupted REM sleep in explaining impaired consolidation of declarative memories in combat-related PTSD. As noted above, empirical studies have shown that, in healthy individuals, REM is also important for the consolidation of neutral non-affective declarative memories [52, 69]. Additionally, PTSD-diagnosed individuals have a different quality of REM sleep to controls; for instance, they have increased REM density [35] and REM fragmentation [24, 45]. Although SWS is strongly associated with the restoration of memory networks through active system consolidation and synaptic homeostasis that leave hippocampal and other brain networks refreshed for next-day encoding, a recent study showed that REM sleep is also implicated in restorative processes. Grosmark et al. [27] showed that firing rates are unexpectedly decreased during REM sleep in contrast with NREM sleep in the rat hippocampus, suggesting a downscaling of neuronal activity in preparation for next-day encoding [16]. These results indicate that restorative processes which leave the hippocampus refreshed for next-day encoding might not be isolated to SWS (i.e., that REM sleep might also play a role in restoration). From this point of view, REM sleep disruptions may also contribute to the specific neutral declarative memory impairments demonstrated in PTSD-diagnosed individuals, which are characterized by poor daytime immediate and delayed recall.

In summary, the hypothesis here is that (a) disrupted consolidation in PTSD-diagnosed individuals occurs during nighttime rather than daytime, and that (b) a consequence of this disruption is the saturation of hippocampal networks, so that (c) these individuals have significant difficulty learning (but not retaining after learning) novel information during waking hours.

Empirical Studies

Only three recent studies, from three different laboratories, have directly investigated memory processing during sleep in PTSD. First, van Liempt et al. [73] showed that combat veterans with PTSD (n = 13) experienced more fragmented sleep during the first, SWS-rich, half of the night than did trauma controls (i.e., veterans who had experienced trauma but who did not meet diagnostic criteria for PTSD; n = 15) and healthy controls (i.e., individuals who had never experienced a DSM-IV A1 criterion traumatic event; n = 15). Furthermore, relative to healthy controls, veterans with

PTSD showed significantly lower plasma levels of growth hormone (GH) during the night. This latter finding is important because:

(a) GH assists in the survival, maintenance, and flourishing of target neurons, including those in the hippocampus [18, 37, 38, 71].
(b) GH has a peak during the first, SWS-rich, half of the night [72].
(c) A recent study in rats showed a mediating relationship between sleep, GH, and normal synaptic function of the hippocampus [33], hence suggesting that GH secretion during sleep is closely associated with optimal memory processing.

Additionally, van Liempt and colleagues demonstrated that morning recall of a word list learned 3 h before sleep was poorer in the PTSD group than in the healthy control group, and that GH secretion and number of awakenings were independent predictors of this delayed recall performance. Clearly, the findings from this study are consistent with the theoretical accounts presented above: It appears that early-night SWS-rich sleep is critical for consolidation of declarative information acquired during waking hours, and that this consolidation process during sleep is centered on biological events occurring in the hippocampus and related brain regions.

Second, Brownlow et al. [8] examined the relationship between sleep and performance within several cognitive domains in 18 men and 26 women who had experienced a variety of traumas, including sexual assault, violent crime, accident, or unexpected death of someone close to them. The sample included 14 participants with no PTSD diagnosis, 14 participants with a lifetime PTSD diagnosis, and 16 participants with a current PTSD diagnosis. The authors did not report any between-group differences in polysomnographically monitored sleep or in verbal memory performance, but showed that the latter was positively correlated with REM sleep quantity ($r = 0.43$). This finding suggests that individuals who experienced more REM sleep also had better verbal memory performance, although the analyses did not detect any significant difference between those with trauma exposure only versus those with a PTSD diagnosis. Furthermore, the study did not include a healthy control group, which limits its capacity to make distinctions between those that have a trauma experience and those that do not.

Third, Lipinska et al. [39] recruited three groups of women: PTSD-diagnosed survivors of sexual assault ($n = 16$), trauma-exposed controls ($n = 15$), and healthy controls ($n = 14$). They administered a declarative memory task and a procedural memory task before and after a full night (8 h) of sleep. The authors recorded sleep variables using sleep-adapted EEG. Results showed that PTSD-diagnosed individuals experienced less sleep efficiency and REM sleep percentage, and experienced more awakenings and wake percentage, in the second half of the night than did participants in the other two groups. Furthermore, participants in the PTSD group, in comparison with those in the other two groups, retained less declarative information, but not procedural ability, over the night. Most importantly, lower REM percentage predicted poorer retention in PTSD-diagnosed individuals, suggesting that memory consolidation was compromised by REM sleep disturbance.

All three studies reviewed above suggest, at least indirectly, that consolidation during sleep is central to the declarative memory deficits observed in PTSD. Future studies need to provide more direct evidence for the abovementioned theory (e.g., by imaging hippocampal activation during sleep in PTSD-diagnosed individuals and controls, by ascertaining longitudinally the temporal relationship between sleep and memory disorders in PTSD, or by conducting intervention studies that examine the specific effects of medication on the relationship between sleep and memory in PTSD). Additionally, various questions regarding the mechanisms governing the consolidation process during sleep in PTSD need to be addressed (e.g., whether the hippocampus is unable to effectively transfer information to neocortical sites or whether synaptic downscaling of hippocampal networks during sleep is impaired).

Furthermore, future studies should aim to evaluate whether disruptions in either SWS or REM sleep, or in a combination of the two, is associated with memory consolidation difficulties in PTSD. The results of the three studies examining sleep and memory in PTSD differed with respect to both SWS- and REM-related sleep disruption and their associations with neutral declarative memory after sleep. Where van Liempt and colleagues found SWS-related changes in sleep-dependent neutral declarative memory consolidation, both Brownlow et al. and Lipinska et al. found associations between REM sleep and declarative memory in PTSD-diagnosed individuals. Considering that both SWS and REM sleep are known to enhance memory consolidation in healthy individuals via discrete neurobiological mechanisms, more research is needed to clarify the contribution of these different sleep stages to neutral declarative memory impairment in PTSD.

Another question that deserves the attention of future research in this field is why, in PTSD, memory consolidation seems differentially affected at different times of the day (i.e., why it appears to be more disrupted during sleep than during waking). One possible answer to this question is that, under normal circumstances, memory consolidation happens more effectively during sleep, when there are no external stimuli; during waking, the brain is constantly receiving new input. Hence, impairments in consolidation may be most prominent at night, when this aspect of memory processing is most active.

There is little research comparing waking to sleep consolidation processes directly; more empirical enquiry around this question may be crucial to our understanding of the neuropsychology of PTSD. One recent study [84] found that increased cortisol affected nighttime, but not daytime, memory consolidation processes in healthy individuals. Specifically, the authors reported that retention of information on a relational memory task (a sensitive measure of hippocampal functioning) improved with increased cortisol during the day but was impaired at night. These results point toward fundamentally different mechanisms of hippocampal memory consolidation, depending on the brain state. What these mechanisms might be still needs to be elucidated, however.

Summary and Conclusion

Subjective complaints about sleep disturbances and objectively measured memory deficits are common features of posttraumatic stress disorder. Few studies focus directly on the association between these features, however, and so the ways in which one might drive the other are neither well understood nor precisely elucidated. In this review, we have begun to clarify the relationship between the two. We described the powerful ways in which sleep acts on memory processes in healthy individuals; there are strong suggestions, from a growing body of literature, that sleep is critical to both consolidation of newly acquired memories and to next-day encoding of novel information. Because disturbed sleep is a hallmark of the PTSD diagnosis, and because declarative memory problems are widely documented in combat-related PTSD, we proposed that sleep disturbance may be a mechanism explaining declarative memory deficits in this population. We reviewed recent studies supporting this hypothesis, and we highlighted areas that should be investigated in future studies. Overall, this line of inquiry shows that disordered sleep in PTSD goes beyond the simple inability to fall asleep and to maintain sleep, and it provides some preliminary support for findings showing that, as disordered sleep abates, so do other symptoms of PTSD.

References

1. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: a meta-analysis of polysomnographic research. Psychol Bulletin. 2016; 142(9):969–90.
2. Barham MP, Enticott PG, Conduit R, Lum JA. Transcranial electrical stimulation during sleep enhances declarative (but not procedural) memory consolidation: evidence from a meta-analysis. Neurosci Biobehav Rev. 2016;63:65–77.
3. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science. 2016;352(6287):812–6.
4. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152:973–81.
5. Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR, et al. Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry. 1993;150:1015–9.
6. Brewin CR, Kleiner JS, Vasterling JJ, Field AP. Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. J Abnorm Psychol. 2007;116:448–63.
7. Brewin CR. The nature and significance of memory disturbance in posttraumatic stress disorder. Annu Rev Clin Psychol. 2011;7:203–27.
8. Brownlow JA, Brown TS, Mellman TA. Relationships of posttraumatic stress symptoms and sleep measures to cognitive performance in young-adult African Americans. J Trauma Stress. 2014;27(2):217–23.
9. Buzsaki G. Theta oscillations in the hippocampus. Neuron. 2002;33:325–40.
10. Datta S. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. J Neurosci. 2000;20:8607–13.
11. Datta S, Li G, Auerbach S. Activation of phasic pontine-wave generator in the rat: a mechanism for expression of plasticity-related genes and proteins in the dorsal hippocampus and amygdala. Eur J Neurosci. 2008;27:1876–92.
12. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11:114–26.
13. Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB. Altered brain response to verbal learning following sleep deprivation. Nature. 2000;403:655–7.
14. Eichenbaum H. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron. 2004;44:109–20.
15. Eichenbaum H, Otto T, Cohen N. Two functional components of the hippocampal memory system. Behav Brain Sci. 1994;17:449–72.
16. Feld GB, Diekelmann S. Sleep smart-optimizing sleep for declarative learning and memory. Front Psychol. 2015;6:622.
17. Fogel SM, Smith CT, Cote KA. Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. Behav Brain Res. 2007;180:48–61.
18. Frago LM, Paneda C, Dickson SL, Hewson AK, Argente J, Chowen JA. Growth hormone (GH) and GH-releasing peptide-6 increase brain insulin-like growth factor-I expression and activate intracellular signaling pathways involved in neuroprotection. Endocrinology. 2002;143:4113–22.
19. Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci. 2005;6:119–30.
20. Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, et al. Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A. 2007;104:18778–83.
21. Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem. 2004;11:679–85.
22. Gais S, Lucas B, Born J. Sleep after learning aids memory recall. Learn Mem. 2006;13:259–62.
23. Genzel L, Kroes MC, Dresler M, Battaglia FP. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends Neurosci. 2014;37(1):10–9.
24. Germain A, James J, Insana S, Herringa RJ, Mammen O, Price J, Nofzinger E. A window into the invisible wound of war: functional neuroimaging of REM sleep in returning combat veterans with PTSD. Psychiatry Res. 2013;211(2):176–9.
25. Geuze E, Vermetten E, Ruf M, de Kloet CS, Westenberg HG. Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. J Psychiatr Res. 2008;42:659–69.

26. Gilbertson MW, Gurvits TV, Lasko NB, Orr SP, Pitman RK. Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. J Trauma Stress. 2001;14:413–32.
27. Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsaki G. REM sleep reorganizes hippocampal excitability. Neuron. 2012;75(6):1001–7.
28. Harrison Y, Horne JA. Sleep loss and temporal memory. Q J Exp Psychol. 2000;53:271–9.
29. Hutchison IC, Rathore S. The role of REM sleep theta activity in emotional memory. Front Psychol. 2015;6:1439. doi:10.3389/fpsyg.2015.01439.
30. Jelinek L, Jacobsen D, Kellner M, Larbig F, Biesold KH, Barre K, Moritz S. Verbal and nonverbal memory functioning in posttraumatic stress disorder (PTSD). J Clin Exp Neuropsychol. 2006;28:940–8.
31. Johnsen GE, Asbjornsen AE. Consistent impaired verbal memory in PTSD: a meta-analysis. J Affect Disord. 2008;111:74–82.
32. Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. Science. 2001;294:1030–8.
33. Kim E, Grover LM, Bertolotti D, Green TL. Growth hormone rescues hippocampal synaptic function after sleep deprivation. Am J Physiol Regul Integr Comp Physiol. 2010;298:R1588–96.
34. Klinzing JG, Molle M, Weber F, Supp G, Hipp JF, Engel AK, Born J. Spindle activity phase-locked to sleep slow oscillations. NeuroImage. 2016;134:607–16.
35. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44:660–9.
36. Lahl O, Wispel C, Willigens B, Pietrowsky R. An ultra short episode of sleep is sufficient to promote declarative memory performance. J Sleep Res. 2008;17:3–10.
37. Lai Z, Emtner M, Roos P, Nyberg F. Characterization of putative growth hormone receptors in human choroid plexus. Brain Res. 1991;546:222–6.
38. Lai Z, Roos P, Zhai O, Olsson Y, Fhölenhag K, Larsson C, Nyberg F. Age-related reduction of human growth hormone-binding sites in the human brain. Brain Res. 1993;621:260–6.
39. Lipinska G, Timol R, Kaminer D, Thomas KG. Disrupted rapid eye movement sleep predicts poor declarative memory performance in post-traumatic stress disorder. J Sleep Res. 2014;23(3):309–17.
40. Louie K, Wilson MA. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron. 2001;29:145–56.
41. Maingret N, Girardeau G, Todorova R, Goutierre M, Zugaro M. Hippocampo-cortical coupling mediates memory consolidation during sleep. Nat Neurosci. 2016;19:959–64.
42. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004;44:5–21.
43. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci. 2007;11:442–50.
44. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444:610–3.
45. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatr. 2002;159(10):1696–701.
46. Paller KA, Wagner AD. Observing the transformation of experience into memory. Trends Cogn Sci. 2002;6:93–102.
47. Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci. 1997;9:534–47.
48. Plihal W, Born J. Memory consolidation in human sleep depends on inhibition of glucocorticoid release. Neuroreport. 1999;10:2741–7.
49. Poe GR, Nitz DA, McNaughton BL, Barnes CA. Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res. 2000;855:176–80.
50. Ravassard P, Hamieh AM, Joseph MA, Fraize N, Libourel PA, Lebarillier L, et al. REM sleep-dependent bidirectional regulation of hippocampal-based emotional memory and LTP. Cereb Cortex. 2016;26(4):1488–500.
51. Reinoso-Suarez F, de Andres I, Rodrigo-Angulo ML, Garzon M. Brain structures and mechanisms involved in the generation of REM sleep. Sleep Med Rev. 2001;5(1):63–77.
52. Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C. Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci. 2002;22:10914–23.
53. Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, et al. Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci. 2007;1:43–55.
54. Robertson EM, Pascual-Leone A, Miall RC. Current concepts in procedural consolidation. Nat Rev Neurosci. 2004;5:576–82.
55. Rosanova M, Ulrich D. Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci. 2005;25:9398–405.
56. Samuelson KW, Metzler T, Rothlind J, Choucroun G, Neylan TC, Lenoci M, Henn-Haase C. Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. Neuropsychology. 2006;20:716–26.
57. Samuelson KW. Post-traumatic stress disorder and declarative memory functioning: a review. Dialogues Clin Neurosci. 2011;13(3):346–51.
58. Schacter DL, Reiman E, Uecker A, Polster MR, Yun LS, Cooper LA. Brain regions associated with retrieval of structurally coherent visual information. Nature. 1995;376:587–90.
59. Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus. 1999;9:7–24.
60. Scott JC, Matt GE, Wrocklage KM, Crnich C, Jordan J, Southwick SM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. Psychol Bull. 2015;141(1):105–40.
61. Sirota A, Buzsaki G. Interaction between neocortical and hippocampal networks via slow oscillations. Thalamus Relat Syst. 2005;3:245–59.
62. Sirota A, Csicsvari J, Buhl D, Buzsaki G. Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci U S A. 2003;100:2065–9.
63. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005;437:1272–8.
64. Stickgold R, Walker MP. Memory consolidation and reconsolidation: what is the role of sleep? Trends Neurosci. 2005;28:408–15.
65. Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, et al. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci USA. 2006;103:756–61.
66. Tischler L, Brand SR, Stavitsky K, Labinsky E, Newmark R, Grossman R, et al. The relationship between hippocampal volume and declarative memory in a population of combat veterans with and without PTSD. Ann N Y Acad Sci. 2006;1071:405–9.
67. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull. 2003;62:143–50.
68. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev. 2006;10:49–62.
69. Ulloor J, Datta S. Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. J Neurochem. 2005;95:418–28.

70. Vago DR, Bevan A, Kesner RP. The role of the direct perforant path input to the CA1 subregion of the dorsal hippocampus in memory retention and retrieval. Hippocampus. 2007;17:977–87.
71. Van Cauter CE, Caufriez A, Kerkhofs M, Van Onderberger A, Thorner MO, Copinschi G. Sleep, awakenings, and insulin-like growth factor-1 modulate the growth hormone (GH) secretory response to GH-releasing hormone. J Clin Endocrinol Metab. 1992;74:1451–9.
72. Van Cauter E, Latta F, Nedeltcheva A, Spiegel K, Leproult R, Vandenbril C, et al. Reciprocal interactions between the GH axis and sleep. Growth Horm IGF Res. 2004;14(Suppl. A):S1–7.
73. van Liempt S, Vermetten E, Lentjes E, Arends J, Westenberg H. Decreased nocturnal growth hormone secretion and sleep fragmentation in combat-related posttraumatic stress disorder; potential predictors of impaired memory consolidation. Psychoneuroendocrinology. 2011;36:1361–9.
74. Vasterling JJ, Brailey K, Constans JI, Sutker PB. Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology. 1998;12:125–33.
75. Vasterling JJ, Constans JI, Hanna-Pladdy B. Head injury as a predictor of psychological outcome in combat veterans. J Trauma Stress. 2000;13:441–51.
76. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN Jr, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology. 2002;16:5–14.
77. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci. 2008;11:200–8.
78. Vythilingam M, Luckenbaugh DA, Lam T, Morgan CA 3rd, Lipschitz D, Charney DS, Southwick SM. Smaller head of the hippocampus in Gulf War-related posttraumatic stress disorder. Psychiatry Res. 2005;139:89–99.
79. Walker MP. A refined model of sleep and the time course of memory formation. Behav Brain Sci. 2005;28:51–104.
80. Walker MP. The role of sleep in cognition and emotion. Ann N Y Acad Sci. 2009;1156:168–97.
81. Walker MP, Brakefield T, Hobson JA, Stickgold R. Dissociable stages of human memory consolidation and reconsolidation. Nature. 2003;425:616–20.
82. Wei Y, Krishnan GP, Bazhenov M. Synaptic mechanisms of memory consolidation during sleep slow oscillations. J Neurosci. 2016;36(15):4231–47.
83. Werner NS, Meindl T, Engel RR, Rosner R, Riedel M, Reiser M, Fast K. Hippocampal function during associative learning in patients with posttraumatic stress disorder. J Psychiatry Res. 2009;43:309–18.
84. Wilhelm I, Wagner U, Born J. Opposite effects of cortisol on consolidation of temporal sequence memory during waking and sleep. J Cogn Neurosci. 2011;23:3703–12.
85. Woon FL, Sood S, Hedges DW. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2010;34:1181–8.
86. Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP. A deficit in the ability to form new human memories without sleep. Nat Neurosci. 2007;10:385–92.
87. Zeineh MM, Engel SA, Thompson PM, Bookheimer SY. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. Science. 2003;299:577–80.

Part V

Treatments of Sleep Disturbances in PTSD

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Post-traumatic stress disorder (PTSD) is a complicated syndrome arising from a specific incident or sets of incidents whereby an individual experiences either a direct, indirect, or perceived threat to their personal safety. It is estimated that between 2% and 12% of the population will experience at least transient PTSD throughout the course of their lives [1, 2]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), four clusters of symptoms must be present to confirm the diagnosis: (1) recurrent mental imagery reexperiencing the traumatic event, (2) a pattern of avoidance behaviors, (3) negative alterations in cognitions and mood, and (4) alterations in arousal and reactivity such as hypervigilance [3].

Both sleep complaints and sleep disorders are common in those with PTSD. Polysomnographic recordings of patients with PTSD noted changes in sleep efficiency, sleep latency, rapid eye movement (REM) latency, and REM density [4]. The amygdala and medial prefrontal cortex, known to facilitate emotional processing and fear conditioning, may have an additional modulating role with respect to the sleep-wake cycle [5]. The associated sleep disorders seen with PTSD are intimately linked to each of the four symptom clusters that define this disorder. Recurrent images and reexperiencing the traumatic event can cause difficulty initiating sleep and nightmares. The development of avoidance behaviors may lead to alterations in physical activity, social interactions, and daily routines that can lead to circadian phase shifts and inconsistent sleep-wake schedules. Negative alterations in cognition and mood commonly manifest as anxiety and depression, which further contribute to insomnia and circadian rhythm disruptions. Further, medications used to treat these symptoms may contribute to altered sleep architecture. Finally, heightened arousal and vigilance seen with PTSD reflect the core association between this disorder and disturbed sleep, manifesting as difficulty initiating sleep, maintaining sleep, diminished sleep efficiency, and sleep disordered breathing.

Insomnia is the most common sleep disorder associated with PTSD. The presence of insomnia following a traumatic event greatly increases the likelihood for the subsequent develop-

ment of PTSD [6–8]. In addition, persistent insomnia portends worse outcomes, with a greater risk for recurrent major depressive episodes, hospitalizations, substance abuse, and suicidality [7–12]. Treatment of PTSD-associated insomnia includes pharmacotherapy as well as cognitive behavioral therapy (CBT-I). Meditation and relaxation techniques have also been shown to improve sleep quality, decrease symptoms of depression, and improve quality of life in patients with PTSD [13]. While a potentially promising primary or alternative therapy, the evidence is not nearly as robust as with pharmacotherapy and CBT-I and warrants further exploration.

Nightmares are reported in 50–90% of patients with PTSD, and many develop nightmare disorder [14, 15]. Nightmares not only diminish quality of life, they contribute to insomnia, sleep avoidance, and sleep fragmentation. As such, they represent a target of therapy that may greatly improve outcomes. Imagery rehearsal therapy and dream rescripting can greatly reduce the frequency and severity of nightmares [16]. In addition, several pharmaceutical agents may improve sleep-related symptoms in PTSD. Most notably, the alpha-antagonist prazosin can reduce nightmare frequency and severity [17–19].

It is becoming increasingly apparent that OSA may contribute to both the underlying sleep disturbances and persistence of symptoms in many patients with PTSD [20]. There appears to be a bidirectional relationship between the risks of OSA and PTSD, with each increasing the risk of the other [21–24]. Not only is this association common, it has been shown to have additive pathologic impact, and the combination negatively impacts the response to therapy [25].

It is clear that sleep comorbidities are common, contribute to worse outcomes, and must be treated as separate disorders in parallel with treatment of PTSD. The following chapters will review data assessing the success of sleep-focused cognitive behavioral therapies, nightmare deconstruction and reprocessing, imagery rehearsal therapy, and associated pharmacotherapy. Future directions and gaps in the evidence base will also be acknowledged.

References

1. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048–60.
2. Stein MB, McQuaid JR, Pedrelli P, Lenox R, McCahill ME, et al. Posttraumatic stress disorder in the primary care medical setting. Gen Hosp Psychiatry. 2000;22:261–9.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5). Washington, DC: American Psychiatric Association; 2013.
4. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep-what a nightmare! Sleep Med Rev. 2000;4(2):183–200.
5. Germain A, Buysse D, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.
6. Lavie P. Current concepts: sleep disturbances in the wake of traumatic events. N Engl J Med. 2001;345(25):1825–32.
7. Clum GA, Nishith P, Resick PA. Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. J Nerv Ment Dis. 2001;189:618–22.
8. Jacobs-Rebhun S, Schnurr PP, Friedman MJ, et al. Posttraumatic stress disorder and sleep difficulty. Am J Psychiatry. 2000;157:1525–6.
9. Krakow B, Artar A, Warner TD, et al. Sleep disorder, depression, and suicidality in female sexual assault survivors. Crisis. 2000;21:163–70.
10. Krakow B, Melendrez D, Johnston L, et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. J Nerv Ment Dis. 2002;190:442–52.
11. Saladin ME, Brady KT, Dansky BS, et al. Understanding comorbidity between PTSD and substance use disorders: two preliminary investigations. Addict Behav. 1995;20:643–55.
12. Nishith P, Resick PA, Mueser KT. Sleep difficulties and alcohol use motives in female rape victims with posttraumatic stress disorder. J Trauma Stress. 2001;14:469–79.
13. Rosenthal JZ, Grosswald S, Ross R, Rosenthal N. Effects of transcendental meditation in veterans of operation enduring freedom and operation Iraqi freedom with posttraumatic stress disorder: a pilot study. Mil Med. 2011;176(6):626.
14. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
15. Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75:546–50.
16. Casement MD, Swanson LM. A meta-analysis of imagery rehearsal for post-trauma nightmares: effects on nightmare frequency, sleep quality, and posttraumatic stress. Clin Psychol Rev. 2012;32(6):566–74.
17. Raskind MA, Peskind ER, Kanter ED, Petrie EC, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.

18. Germain A, Richardson R, Moul DE, Mammen O, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military veterans. J Psychosom Res. 2012;72(2):89–96.
19. Raskind MA, Peterson K, Williams T, Hoff DJ, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170(9):1003–10.
20. Jaoude P, Vermont LN, Porhomayon J, El-Solh AA. Sleep-disordered breathing in patients with post-traumatic stress disorder. Ann Am Thorac Soc. 2015;12:259–68.
21. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005;28:1405–11.
22. Mysliwiec V, Gill J, Lee H, et al. Sleep disorders in US military personnel a high rate of comorbid insomnia and obstructive sleep apnea. Chest. 2013;144(2):549–57.
23. Colvonen P, Masino T, Drummond S, Myers U, Angkaw A, Norman S. Obstructive sleep apnea and posttraumatic stress disorder among OEF/OIF/ OND veterans. J Clin Sleep Med. 2015;11:513–8.
24. Forbus L, Kelly UA. Screening for obstructive sleep apnea in veterans seeking treatment of posttraumatic stress disorder. ANS Adv Nurs Sci. 2015;38(4):298–305.
25. Lettieri CJ, Williams SG, Collen JF. OSA syndrome and posttraumatic stress disorder: clinical outcomes and impact of positive airway pressure therapy. Chest. 2016;149(2):483–90.

Psychotherapy Interventions for Comorbid Sleep Disorders and Posttraumatic Stress Disorder

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Difficulty in sleep onset and maintenance is the most frequently reported symptom of posttraumatic stress disorder (PTSD) [1, 2]. Indeed, estimates indicate that as many as 70% of trauma survivors with PTSD suffer from significant sleep impairment [3]. There is evidence that insomnia and nightmares related to trauma may not completely remit with PTSD treatment interventions, despite general improvements in PTSD symptom severity [4–8]. This chapter provides an overview of evidence-based treatments for PTSD and psychotherapy interventions targeting sleep disturbance. The question of how sleep symptoms (i.e., insomnia and nightmares) are addressed within the context of treatment for PTSD and considerations for treatment interventions are discussed. It should be noted that our use of the term "insomnia" does not refer to the formal diagnosis of insomnia as specified in the *Diagnostic and Statistical Manual of Mental Disorders*-5 [9] or the *International Classification of Sleep Disorders* (ICSD-2) [10]. Rather, we refer to "insomnia" as the hyperarousal-related sleep difficulties experienced in PTSD.

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Evidence-Based Interventions for PTSD

The most widely supported evidence-based interventions for the treatment of PTSD include exposure treatments such as prolonged exposure (PE), cognitive therapies such as cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR).

Prolonged Exposure

Exposure therapy is characterized by prolonged exposure to anxiety-provoking stimuli without use of relaxation or other anxiety-reducing methods. The PE protocol developed by Foa and colleagues [11] includes four main components: (1) psychoeducation about trauma reactions and PTSD, (2) breathing retraining, (3) in vivo exposure to anxiety-provoking stimuli and situations, and (4) imaginal exposure to the trauma memory through detailed description of the trauma for prolonged periods of time, followed by discussion with the therapist. An analysis of four RCTs exploring the efficacy of PE for military-related trauma revealed large within-group posttreatment effect sizes with PE surpassing control and treatment-as-usual conditions in the reduction of PTSD symptoms [12].

Among existing randomized trials of PE, most have included civilian samples, most often female survivors of sexual assault. Results of these studies indicated that PE was superior to waitlist conditions in reductions of PTSD symptomatology [13]. One landmark study [14] included a large sample of female veterans and active-duty personnel to compare PE to a present-centered therapy. Results indicated that women who received PE experienced a greater reduction in symptoms immediately following treatment and at 3-month follow-up, and they were less likely to meet diagnostic criteria for PTSD. However, the significant differences between groups diminished at 6-month follow-up.

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Exposure therapy has been compared with several other CBT treatments, and a number of studies have examined whether adding other CBT interventions to exposure enhances outcome. Generally, the research has shown that treatment outcomes for exposure are comparable to that of other CBT treatments and that adding additional treatment components (such as cognitive therapy) does not significantly improve the efficacy of imaginal plus in vivo exposure although the sample sizes in these studies tended to be too small to detect differences [13].

Cognitive Processing Therapy

CPT is predominantly a cognitive therapy for PTSD and can be implemented as an individual or group therapy [15]. CPT is comprised of three components: education, trauma processing, and cognitive challenging. First, the client is educated about the symptoms of PTSD, the treatment model, and the connection between thoughts and feelings. In addition, the client begins to examine the meaning he or she has made of the traumatic event and how the traumatic event has affected beliefs about self, others, and the world. The client is taught to identify "stuck points," or distorted thoughts and faulty interpretations of the event, and to challenge through Socratic questions and modify these distorted thoughts to arrive at more accurate balanced cognitions. CPT may be delivered with or without a component involving a written account of the trauma.

CPT has been widely studied in a number of gold standard randomized controlled trials (RCTs) and, along with PE, is one of the leading empirically supported treatments for PTSD. The first RCT of CPT found that both CPT and PE showed significant improvements in PTSD symptoms compared to a waitlist control group [16]. A later dismantling study of CPT compared the full CPT protocol to a cognitive-only version of CPT (CPT-C) and a written account-only (WA) condition [17]. Participants in all three treatment conditions showed significant improvements in PTSD symptoms during treatment and at follow-up. Surprisingly, the combination of cognitive therapy and written accounts did not improve upon the results of either component. In fact, when examining PTSD symptoms over the course of treatment, the CPT-C group had significantly lower scores than the WA condition, while the CPT condition did not differ significantly from CPT-C or WA. This finding suggests that cognitive therapy alone may be at least as effective as exposure in the treatment of PTSD. Multiple RCTs [15, 18–22] have shown CPT to be effective for reducing PTSD symptoms in veteran [21] and active military [22] samples.

Eye Movement Desensitization and Reprocessing

EMDR is another treatment for traumatic stress that has been increasingly researched and supported [23]. Following assessment and preparation stages of treatment, EMDR includes rhythmic eye movements to address trauma symptoms. In this desensitization and reprocessing stage of the treatment, the client is asked to hold a distressing image in mind, along with associated negative cognitions and bodily sensations, while tracking the therapist's fingers in rhythmic sweeps across the client's field of vision. After a set of eye movements, the client is asked to report on any changes in the image, sensations, thoughts, or emotions. The therapist then directs the client as to what to attend to next, and the eye movement process is repeated. Once the disturbing images have been desensitized (assessed by patient report of low distress), the client is instructed to hold a positive or desired cognition in mind while tracking the therapist's fingers. The client then reports on changes in the validity of the positive cognition. Next, the client is asked to report any continuing bodily tensions or discomfort and to attend to each of them during additional sets of eye movements. Finally, the client is provided with information and support, such as coping techniques or relaxation skills to address emerging distressing thoughts or memories. The client is reevaluated at the next session and the process is repeated.

Shapiro suggests that through the use of eye movements, EMDR facilitates information processing, relieving the patient of distress, distorted cognitions, and dysfunctional reactions [24]. Although initial studies examining EMDR had significant methodological limitations [25], there has been a substantial improvement in the quality of research on the efficacy of EMDR. Several RCTs have compared EMDR to exposure therapy and found that both treatments demonstrated significant improvements in PTSD and other symptoms compared to a waitlist control condition (see Spates et al. [26] for a review).

Interventions for PTSD-Related Sleep Problems

Although the therapies above have been shown to be effective in addressing most symptoms of PTSD, these treatments do not specifically target nighttime symptoms. However, treatment protocols directly targeting sleep difficulties in individuals with PTSD have been developed. These include treatments targeting nightmares, insomnia, or both. In recent years, several meta-analyses and systematic reviews have been conducted to examine the impact of

cognitive behavioral interventions targeting sleep disturbances on insomnia and nightmares in individuals with PTSD symptoms [27–32]. Overall, these reviews tend to find that not only do sleep-focused interventions reduce nightmares and insomnia, but they also improve overall sleep quality and daytime symptoms of PTSD and depression. However, this finding has not been consistent across all studies. A challenge for the literature is that there are various approaches to addressing sleep disturbances with varying degrees of overlap. For instance, Casement and Swanson [28] included 13 studies in their meta-analysis and identified eight variations of nightmare treatment components (described below) and varying degrees of focus on cognitive behavioral approaches for insomnia. Research is needed to guide the field on the optimal approaches for addressing sleep disturbances. Because treatments for nightmare and insomnia are the focus of other chapters in this volume, they are only briefly discussed here.

Nightmare Treatments

Treatments for nightmares were first systematically studied starting in the late 1960s [33, 34]. However, because PTSD was not included in the DSM until 1980, assessment of trauma exposure in early nightmare treatment studies generally was not included. The extent to which these early reports addressed trauma-related nightmares is unclear.

Among the most widely researched approaches for treating trauma-related nightmares are imagery rehearsal therapy (IRT) and exposure, relaxation, and rescripting therapy (ERRT), a trauma-focused variation of IRT. Nightmare treatments are brief, typically ranging from one [35] to six [36] sessions. As noted above, gains have been demonstrated in PTSD symptoms, depression, and sleep quality in addition to reduced nightmares. Relaxation procedures for treating nightmares and exposure to nightmares also have been examined [37–40]. Here, we focus primarily on IRT and ERRT and highlight those studies that have been conducted in military populations.

Imagery Rehearsal Therapy

It is theorized that nightmares are the result of disruption of the imagery system and that imagery rehearsal can address this disruption. Furthermore, nightmares are conceptualized as originating as a result of a traumatic experience that becomes a learned habit over time. Through IRT, clients are taught that they can modify the habit of having nightmares [41]. IRT can be conducted in group or individual format. In general, clients in IRT are instructed to write down a nightmare, to change the nightmare in some way, to write down the changed version, and to practice imagining the changed version while relaxed [42]. The protocol tends to vary across studies, particularly with regard to the degree of exposure to the nightmare. Some protocols emphasize minimizing exposure to the nightmare and trauma-related material [43]. For example, clients may be discouraged from focusing on the worst nightmare or nightmares that replay the trauma [44]. Other protocols allow participants to choose which nightmare to target and then instruct them to write the nightmare in detail and to change it any way they wish based on discussion of their nightmare with the group and/or the therapist [45, 46].

A number of RCTs of IRT have been conducted. In a RCT comparing IRT to a waitlist among civilian assault survivors ($N = 168$), 95% of whom met criteria for PTSD, the treatment group exhibited significant improvements in nightmare frequency, sleep quality, and self-reported and clinician-rated PTSD symptoms [43]. However, in a more recent study of IRT in 124 male Vietnam war veterans with PTSD [36], participants were randomized to either IRT or a control group (sleep and nightmare management). Unlike studies conducted in civilian samples, results found no improvements in nightmares. Only the Pittsburgh Sleep Quality Index [47] (which does not directly assess nightmares) demonstrated a significant reduction across time. To explain the findings, the authors propose that veterans with chronic, severe PTSD may be less responsive to nightmare treatment. Additionally, the majority of veterans reported experiencing replicative nightmares, which may be less responsive to IRT. Also, this study included only men, whereas other RCTs included mostly women [43, 48–50], who may be more responsive to treatment. The authors suggest that IRT may be more suitable as an adjunctive treatment to other PTSD treatments in veterans rather than as a stand-alone treatment. Thus, the efficacy of IRT may be limited in veteran samples.

Nonrandomized trials of IRT have also been conducted among military personnel including open trials [45, 51, 52] and chart reviews [40] among veterans and one case series of 11 soldiers deployed to Iraq within 30 days of trauma [53] (see Table 24.1). Although these studies generally find support for IRT, conclusions are limited due to significant methodological limitations of noncontrolled trials. Some studies demonstrated positive effects immediately posttreatment [45], whereas others indicated significant improvements that were not evident until 3–6 months later [52]. There is also indication that treatment gains were maintained up to 1 year after treatment among veterans [54]. Although improvements were generally noted, only a minority of participants across these trials exhibited complete elimination of nightmares. For example, in their chart review, Nappi et al. [40] found that only 23% achieved ≤1 nightmare per week. These nonrandomized trials provide preliminary evidence that IRT is

Table 24.1 Studies of interventions targeting sleep disturbance in military personnel

Intervention	Design	Population	Treatments/control	Main outcome measure	Major findings/conclusions
Sleep intervention					
Balliett et al. (2015) [60]	Pilot study	19 veterans	4 sessions of individual, in pairs, or individual and in pairs ERRT-M	CAPS BDI-II PSQI TRNS ISI	ERRT-M was found to significantly improve sleep disturbances and related psychopathy. No significant change in PTSD symptoms was reported
Berlin et al. (2010) [68]	Case study	1 male Vietnam veteran	6 sessions of individual CBT-I and IRT (1 assessment session, 1 session of CBT-I, and 4 sessions of IRT)	Sleep and nightmare diaries	Number of nightmares per week decreased from 17 at pretreatment to 5 at posttreatment. Sleep quality and nighttime awakening improved
Cook et al. (2010) [36]	RCT	124 male Vietnam war veterans	6 group sessions of IRT vs. 6 group sessions of sleep and nightmare management control group	CAPS SCID-IV-P PSQI NFQ	Participants in the IRT condition did not improve significantly more than the comparison condition on primary and secondary outcome measures
Gellis and Gehrman (2011) [66]	Uncontrolled pilot study	11 male veterans older than 50 years of age	5 sessions of individual CBT-I	Sleep diaries ISI Actigraphy CAPS NFQ	Improvements were demonstrated in self-reported wake time after sleep onset, total sleep time, sleep efficiency, and overall insomnia. There were no pre-post differences for the actigraphy, PTSD symptoms, or nightmare frequency
Harb et al. (2009) [51]	Open trial	11 male Iraq war veterans	7–8 individuals sessions of CBT-I combined with IRT (3 sessions of CBT-I, 4–5 sessions of IRT)	CAPS NFQ PSQI PCL-M Sleep and nightmare diaries	Pre- to posttreatment, moderate effect sizes were found for improvements in nightmare frequency, global sleep quality, and PTSD symptom severity. Sleep diaries found large effects for increased sleep time and sleep onset latency. Sleep diaries found no change in nightmare frequency but a trend toward less intense dreams
Long et al. (2011) [61]	Open trial	37 male veterans	6 sessions of imagery rescripting and exposure therapy (IRET) – group treatment	PCL-M Daily sleep activity log	IRET significantly (statistically and clinically) decreased nightmare frequency, increased quantity of sleep, and reduced PTSD symptoms
Lu et al. (2009) [52]	Open trial	15 male veterans	6 group sessions of IRT	Nightmare effects survey PTSD dream rating scale PSQI PCL BDI-II	There were no improvements at posttreatment. At 3- and 6-month follow-up, trauma-related nightmare frequency (nights/week) significantly decreased. Non-trauma-related nightmares did not decrease. The number of trauma-related nightmares and total nightmares per week and PTSD symptoms significantly decreased at 3-month follow-up but was not maintained at the 6-month follow-up. The impact of nightmares, sleep quality, and depression did not improve
Margolies et al. (2013) [70]	RCT	40 combat veterans	4 sessions of CBT-I with adjunctive IRT or a waitlist control	Sleep diary Actigraphy PSQI ISI DBAS PSS-SR PHQ-9 POMS	The CBT-I and IRT group displayed improvements in insomnia and PTSD symptoms compared to the waitlist control

(continued)

Table 24.1 (continued)

Intervention	Design	Population	Treatments/control	Main outcome measure	Major findings/conclusions
Moore and Krakow (2007) [53]	Case series	11 active-duty Iraq war soldiers	4 sessions of IRT	Number of nightmares PDS ISI	The majority of soldiers (7/11) experienced large clinical improvements in nightmares, posttraumatic stress symptoms, and insomnia at the 1-month follow-up. Among the four nonresponders, one had an increase in nightmares and two had an increase in posttraumatic stress symptoms
Nappi et al. (2010) [40]	Chart review	58 male and female veterans	5 sessions of individual or group IRT	Daily nightmare log ISI PSQI PCL	Treatment completers experienced significant decreases in weekly frequency and maximum intensity of nightmares, insomnia severity, and PTSD symptoms. No change was found for the PSQI. 23% of treatment completers experienced one or fewer nightmares per week and 11% experienced no nightmares at the end of treatment. Posttreatment, PCL and ISI were below cutoffs. Participants in the individual treatment had significantly greater reductions on the ISI
Swanson et al. (2009) [73]	Open trial	10 male Vietnam and Gulf War veterans	10 sessions of group treatment (5 sessions of CBT-I, 2 sessions of ERRT, 2 sessions of discussion/trouble-shooting, and 2 sessions of relapse prevention)	ISI PSQI PDS Sleep and dream diaries	Nightmare frequency and distress decreased by half. Following treatment, average insomnia was in the subthreshold range. Although at posttreatment, sleep quality had significantly improved, the mean score was still in the clinically significant range. PTSD symptom reduction was nonsignificant
Talbot et al. (2014) [67]	RCT	45 adults with PTSD	8 sessions of individual CBT-I vs. monitor-only waitlist control	CAPS Sleep diaries PSG ISI PSQI PCL BDI WSAS Actigraphy	CBT-I significantly improved sleep and psychosocial functioning in adults with PTSD
Ulmer et al. (2011) [69]	Randomized parallel group experiment	22 male and female veterans	Usual care condition vs. 6 individual sessions of sleep intervention for PTSD (SIP) (3 sessions of CBT-I followed by 3 sessions of IRT)	ISI Sleep diary PSQI PSQI-A PCL-M	Intent-to-treat analyses found that individuals in SIP had substantial improvements on insomnia severity, PTSD symptoms, and sleep quality. The SIP group had improvements on all sleep diary outcomes. Groups did not differ on depression or the PTSD-specific sleep measure

(continued)

Table 24.1 (continued)

Wanner et al. (2010) [62]	Case studies	2 male Vietnam veterans	4–5 individual sessions of ERRT	PCL-M DSAL BDI-II	Veteran 1 experienced clinically significant reductions in PTSD and depressive symptoms from pre- to posttreatment; these improvements remained at 3-month follow-up. However, depressive symptoms remained in the severe range. At 3-month follow-up, the frequency of trauma-related nightmares decreased by half. Quantity of sleep increased by an hour from pre- to follow-up. Veteran 2 achieved clinically significant reductions in PTSD symptoms from pre- to 3-month follow-up. Depressive symptoms clinically decreased between pre- and post- but were not maintained at follow-up. From pre- to follow-up, trauma-related nightmares decreased by one third and he gained an average of 1 h of sleep per night
Ho et al. (2016) [30]	Meta-analysis of 11 RCTs	Trauma-exposed individuals, veterans, sexual assault survivors, and adults with PTSD and insomnia	Sleep-specific CBT vs. waitlist control	Various PTSD, depression, and sleep measures	Sleep-specific CBT showed significant reduction in PTSD symptoms, depressive symptoms, and insomnia severity
Sleep intervention followed by CBT for PTSD					
None					
CBT for PTSD followed by sleep intervention					
Forbes et al. (2001) [45]	Open trial	12 male Australian Vietnam veterans	6 group sessions of IRT at least 6 months following inpatient treatment of PTSD	Nightmare diaries IES-R BDI-I	Significant improvements from pre- to posttreatment on measures of nightmares, PTSD, and depression. 7 patients reported cessation of the target nightmare and 11 patients reported improved frequency and/or intensity of the target nightmare
Galovski et al. (2016) [76]	RCT	108 female assault survivors	Either 3 weeks of hypnosis or symptom monitoring control before standard CPT	CAPS BDI-II PSQI ISI	Hypnosis significantly improved sleep disturbances but, however, did not augment PTSD recovery during CPT
Forbes et al. (2003) [54]	12-month follow-up to Forbes et al. (2001) study	”	”	Nightmare diaries IES-R BDI-I	Treatment gains (reported above) were maintained at 12-month follow-up. At the 12-month follow-up, 60% reported cessation of the nightmare targeted in treatment
Integrated PTSD and sleep intervention					
None					

Abbreviations for interventions utilized in more than one study in the table are as follows: *CBT-I* cognitive behavioral therapy for insomnia, *ERRT* exposure, relaxation, and rescripting therapy, *IRT* imagery rehearsal therapy

Measures are abbreviated as follows: *BDI* Beck Depression Inventory, *BDI-II* Beck Depression Inventory, Second Edition, *CAPS* Clinician-Administered PTSD Scale, *DBAS* Dysfunctional Beliefs and Attitudes about Sleep Scale, *DSAL* daily sleep activities log, *IES-R* Revised Impact of Events Scale, *ISI* Insomnia Severity Index, *NFQ* Nightmare Frequency Questionnaire, *PCL* PTSD Checklist, *PCL-M* PTSD Checklist – Military, *PDS* Posttraumatic Diagnostic Scale, *PHQ-9* Patient Health Questionnaire, *POMS* Profile of Mood States, *PSG* polysomnography, *PSQI* Pittsburgh Sleep Quality Index, *PSQI-A* Pittsburgh Sleep Quality Index Addendum for PTSD, *PSS-SR* PTSD Symptom Scale Self-Report, *TRNS* Trauma-Related Nightmare Survey, *SCID-IV-P* Structured Clinical Interview for DSM IV-Patient Version, *WSAS* Weinberg Screening Affective Scales

efficacious for reduction of nightmares in veterans. However, the extent to which IRT works similarly in military and non-military samples is unclear as evidenced by inconsistent results between RCTs of IRT conducted to date [33, 43].

Among civilians, noncontrolled trials and case studies have been conducted among crime victims with PTSD [35, 55], in a large group of fire evacuees as part of a larger treatment protocol [56], adjudicated adolescent girls in a residential facility [57], and in a community sample of individuals with idiopathic nightmares and individuals with trauma-related nightmares [58]. In general, results suggest IRT has a positive impact on nightmares and related distress, although findings are limited by lack of controlled design.

Exposure, Relaxation, and Rescripting Therapy

ERRT for trauma-related nightmares was developed to incorporate imagery rehearsal with evidence-based techniques from treatments for insomnia and PTSD. Specifically, ERRT combines rescripting and imagery rehearsal with sleep hygiene education and relaxation from anxiety and insomnia treatments. A key difference between ERRT and IRT is that ERRT emphasizes exposure to the nightmare and trauma-related material and integrates identification of trauma-related themes. Exposure and trauma-related themes are key components of the evidence-based PTSD treatments discussed above [13]. To incorporate exposure, the ERRT protocol instructs participants to write out their most frequent or distressing nightmare (regardless of similarity to a traumatic event) in the present tense and with as much sensory detail as possible. Participants next read the nightmares aloud, and trauma-related themes are discussed prior to rescripting. Participants then are instructed to write their rescription according to the most prominent trauma-related theme or themes. For example, if the nightmare includes a prominent sense of powerlessness, the rescripted content would specifically include increased power in whichever way the participant chooses. In ERRT, several mechanisms of change are purported, including emotional processing through exposure to the nightmare (similar to PE for PTSD), cognitive changes through discussing trauma-related themes inherent in nightmare content (similar to CPT for PTSD), and rescription of the nightmare content. Nightmares may also change through modification of sleep behaviors. Taking steps to improve sleep quality and quantity may increase the individual's coping resources and decrease distress. Utilization of relaxation techniques may reduce cognitive and physiological arousal close to bedtime, which may reduce the likelihood of experiencing a nightmare and also may improve sleep.

To date, two RCTs comparing ERRT to a waitlist control group have been conducted in community-based samples, and a pilot study has been conducted in a veteran sample. In the first study examining a community sample of traumatized adults, the ERRT group (n = 21) demonstrated positive effects on self-report measures of nightmares, sleep, and PTSD compared to control (n = 22) [48]. A second study was conducted to replicate these findings and to assess changes in physiological responses to nightmare content through a script-driven imagery paradigm [49, 50], a method shown to adequately evoke emotional and psychological reactions to nightmare cues [59]. In addition to replicating the findings from the first RCT, results showed the treatment group demonstrated significant reductions on all measures of physiological arousal (skin conductance, heart rate, and facial electromyogram) associated with the personal nightmare scripts at 1-week posttreatment, whereas the control group did not change [50]. The pilot study evaluating ERRT among veterans [60] (N = 19) also found improvements in nightmare frequency and severity, depression, sleep quality, and insomnia severity at the 1-week and 2-month follow-ups with 50% of the sample reporting no nightmares in the previous week at the follow-up. Thus, evidence suggests that treatments specifically targeting nightmares have positive impacts on nightmares, sleep problems, and daytime PTSD symptoms in relatively few sessions. However, only limited research has been conducted to examine the extent to which these treatments are effective in military populations.

Among veterans, two case studies and an open trial have been reported on a variant of ERRT, called imagery rescripting and exposure therapy (IRET) [61, 62] (see Table 24.1). IRET was developed specifically to address the needs of the veteran population by allocating more time to sleep management, exposure to the nightmare, and rescripting for a total of six sessions. Wanner and colleagues [62] report on two case studies for veterans participating in the open trial reported by Long et al. [61]. The open trial examined IRET in a sample of 33 veterans, primarily from the Vietnam Era. Both studies found significant and clinically meaningful improvements in nightmare frequency, sleep, and PTSD symptoms.

Cognitive Behavioral Therapy for Insomnia Combined with Nightmare and PTSD Treatments

Additional studies combining nightmare treatments with insomnia treatments also have been conducted. Research supports the use of several behavioral techniques for treating primary and secondary insomnia. The American Academy of Sleep Medicine provides a review of 48 studies utilizing these approaches from 1970 to 1997 [63], 37 studies from

1998 to 2004 [64], and practice parameters for psychological and behavioral approaches based on the literature [65]. The most widely studied and supported approaches for insomnia include stimulus control (using the bed and bedroom for sleep and sexual activity only), relaxation training, sleep restriction (limiting time in bed to more closely approximate the individual's sleep ability), sleep hygiene education, and cognitive therapy. Treatment packages of cognitive behavioral therapy for insomnia (CBT-I) may include any combination of these elements. Research has examined CBT-I combined with nightmare treatment and broader treatments for PTSD.

CBT-I in PTSD

Gellis and Gehrman [66] conducted a pilot study of five sessions of CBT-I in eight veterans with chronic PTSD. The authors found that insomnia severity and sleep parameters measured with the sleep diary demonstrated significant improvements. Objectively measured sleep with actigraphy (small, wrist-worn devices that monitor movement and provide estimates of sleep continuity) did not show improvements. Although statistically significant improvements in depression were observed, there were no improvements in nightmares or other PTSD symptoms. The authors hypothesize that although subjectively reported sleep improved, the presence of PTSD and nightmares may limit the effectiveness of CBT-I in individuals with PTSD.

In an RCT with 45 veterans with PTSD, Talbot and colleagues [67] compared CBT-I with a monitor-only waitlist control. They found that CBT-I improved insomnia among these veterans with PTSD. Large changes were found with the sleep diary, polysomnography with regard to total sleep time, several other self-report sleep measures, as well as social and work functioning. Although PTSD improved it did not improve more than the monitoring group. All participants were required to be enrolled in treatment for PTSD (medications or psychotherapy), and so the impact of CBT-I alone is unclear.

CBT-I Combined with Nightmare Treatments

More recently, researchers have proposed that treatment approaches that combine elements of nightmare treatments (i.e., exposure, rescripting, and imagery rehearsal) and CBT-I (i.e., sleep restriction) may be optimal for treating sleep disturbances in trauma-exposed adults. One case study [68], one noncontrolled trial [51], and a randomized parallel group experiment [69] of IRT combined with CBT-I in veterans have been reported. Another study implemented CBT-I and included IRT only as an adjunctive intervention for some participants [70] (see Table 24.1). In the case study [68], a 69-year-old Vietnam veteran who had been experiencing nightmares for 35 years completed two sessions of CBT-I followed by three sessions of IRT. At the end of treatment, his nightmare frequency reduced from 17 per week to 5 per week. He also reported decreased nightmare intensity and improved sleep. In an open trial, Harb et al. [51] examined a six-session treatment protocol that combined CBT-I and IRT in seven veterans of the Iraq war. The treatment included three sessions of psychoeducation, progressive muscle relaxation, and sleep hygiene (including stimulus control) followed by three sessions of IRT (one session for writing the target nightmare, one session for brainstorming changes to the nightmare, and one session for rescripting the nightmare). Overall, improvements were found in nightmare frequency, sleep quality, and PTSD symptom severity. Further, the authors divided the sample into responders (n = 4) and nonresponders (n = 3). The authors noted that the nonresponders were experiencing certain issues that may have impacted treatment outcome including pending redeployment, traumatic brain injury, alcohol use, nightmares of perpetration, and guilt. Thus, research is needed to examine potential predictors of response to IRT.

In the randomized parallel group study [69], 22 veterans with PTSD from a variety of eras were randomized to either the treatment condition (three sessions of CBT-I followed by three sessions of IRT) or to care as usual (including a variety of mental health treatments such as medication management/supportive therapy and unspecified individual therapy sessions). From baseline to immediate posttreatment, veterans in the CBT-I with IRT condition demonstrated greater improvements in nightmare frequency, sleep parameters, insomnia severity, sleep quality, and PTSD symptoms than the control group, providing additional support for the efficacy of treatments targeting sleep disturbances in veterans with PTSD.

ERRT also has been combined with CBT-I to treat trauma-related nightmares. From its inception, the ERRT manual has included components to improve sleep directly, including relaxation training (e.g., diaphragmatic breathing and progressive muscle relaxation), sleep hygiene, and stimulus control [71, 72]. However, participants typically have been asked to select any poor sleep hygiene habit to modify during the course of treatment and any positive sleep hygiene habit to maintain. Thus, stimulus control and sleep restriction, which are considered integral components of CBT-I [65], are not always selected as an integral component of ERRT.

Swanson et al. [73] modified ERRT to include five sessions of CBT-I (including stimulus control and sleep restriction for every patient) prior to nightmare rescripting for a total of ten sessions of therapy. This protocol was evaluated in an open trial with a sample of nine combat veterans with PTSD (see Table 24.1). Results demonstrated an average reduction in nightmares per week of 50% and an average reduction in total nightmare distress of 46%. Interestingly, data indicate a substantial decrease in nightmare frequency prior to implementation of exposure or rescription of the nightmare followed by continuing improvements. Furthermore, the average

insomnia ratings were in the subthreshold range at the conclusion of treatment. However, PTSD symptom ratings did not demonstrate a significant decrease. Further research is needed to determine the optimal combinations of treatment components and to determine for which symptom presentations the treatments are needed.

Another study conducted by Margolies et al. [70] randomized 40 veterans with PTSD into either CBT-I with adjunctive IRT or a waitlist control. IRT was implemented with 13 participants who reported nightmares but only 6 of those participants opted to continue IRT in subsequent sessions. Veterans who were placed into the CBT-I/IRT group reported significant increases in overall sleep quality and decreased nighttime PTSD symptoms, PTSD symptom severity, and depressed mood when compared to the control. These results support the use of sleep-based treatments for individuals experiencing sleep and PTSD disturbances and support the notion that sleep disturbances may be exacerbating symptoms of PTSD.

CBT-I Combined with PTSD Treatment

Few studies have examined treatment approaches that combine sleep interventions with broader PTSD treatments. Because nightmares and problems falling and staying asleep are symptoms of PTSD, it is thought that these symptoms will remit along with the treatment of the constellation of re-experiencing, avoidance, and hyperarousal symptoms. As discussed further below, this approach has been the topic of some debate.

In one case series, five patients with residual insomnia after successful treatment of CBT for PTSD were treated with five sessions of CBT-I [74] (see Table 24.1). The authors found that in four of these cases, improvements were observed on self-reported sleep questionnaires and daily monitoring of sleep. This suggests that sleep difficulties that do not remit with treatment of PTSD may be responsive to interventions that directly target sleep.

Another theory is that improving sleep prior to initiating treatment for PSTD will result in improved treatment outcomes. A case study conducted by Baddeley and Gros [75] used six sessions of CBT-I followed by seven sessions of trauma-specific exposure therapy with a veteran suffering from comorbid PTSD and insomnia. After treatment, the patient exhibited a significant reduction in both insomnia and PTSD symptoms. This case study supports the use of insomnia treatment before PTSD treatment to both promote a smooth entry to exposure therapy and increase the efficacy of the treatment.

Other Sleep Treatments Combined with PTSD Treatment

A recent randomized controlled trial examined the effectiveness of sleep-directed hypnosis as a complement to CPT [76]. Participants completed either 3 weeks of hypnosis ($n = 52$) or a symptom monitoring control condition ($n = 56$) before beginning standard CPT in order to determine if improvements in sleep due to hypnosis would result in enhanced improvement in PTSD and depression symptoms during CPT. The hypnosis condition did result in significantly greater improvements in sleep and depression, but not PTSD, prior to initiating CPT. After CPT, both conditions showed significant improvement in sleep and PTSD; however, the hypnosis condition demonstrated greater improvement in depressive symptoms. Results suggest that hypnosis was effective in improving sleep impairment, but that those improvements did not enhance PTSD recovery during CPT.

Nightmare Rescription Combined with PTSD Treatment

To date, two case studies and an open trial have examined nightmare treatments subsequent to CBT for PTSD. One case study examined treatment of nightmares in an adolescent female rape victim who successfully completed Multiple Channel Exposure Therapy for PTSD and comorbid panic disorder [77] but had remaining nightmares at posttreatment [4]. Imagery rehearsal (with an emphasis on exposure) was implemented along with sleep hygiene modification and relaxation training. At follow-up 1 month and 3 months later, the client reported a reduction in nightmare frequency and disturbance. In a second case study, ERRT was implemented following successful CPT for PTSD in a male active-duty service member who was raped during a deployment [78]. Although the service member experienced significant reductions in PTSD symptoms over the course of CPT, he continued to experience trauma-related nightmares every night. After four sessions of ERRT, his nightmares substantially decreased, and he experienced further reductions in insomnia, PTSD, and depression. Forbes and colleagues [45] implemented six sessions of IRT delivered in group format to treat 12 Vietnam veterans who continued to have nightmares and PTSD at least 6 months after a comprehensive inpatient program for PTSD. At the 3-month follow-up, the nightmare targeted in treatment ceased for 7 of the 12 participants, and 11 of the 12 participants reported improvements in nightmare frequency and/or intensity. These gains were found to be largely maintained 12 months later [54].

Other Integrative Treatments

One example of an integrative treatment approach that is being developed to treat PTSD with co-occurring depression and sleep problems is cognitive behavioral social rhythm therapy (CBSRT) [79]. The approach is based on a social rhythm model of mood disruption [80] and integrates components of efficacious treatments including cognitive behavioral therapy for depression [81] and insomnia [82], interpersonal and social rhythm therapy (IPSRT) for bipolar disorder [83], and IRT for nightmares in PTSD [43]. Preliminary data from an open trial suggest the treatment is a promising approach [79] and further research is needed.

Should Sleep Interventions Be Considered in Combination with Other Treatment Interventions?

Nightmares and insomnia are often conceptualized as secondary problems that will abate with treatment of the primary PTSD diagnoses rather than as a primary diagnosis that requires clinical attention [84]. However, nightmares and insomnia may be resistant to treatments targeting PTSD, while treatments for trauma-related nightmares have been shown to alleviate symptoms of depression and PTSD and also improve sleep quality [43, 48, 50, 72] and physiological reactivity to nightmare content [49]. Given the distress associated with nightmares and sleep loss, and the availability of treatment approaches for nightmares and insomnia, some have argued that conceptualizing sleep disturbances as co-occurring primary conditions (requiring clinical attention), as opposed to secondary conditions, may be useful in treating individuals with posttraumatic stress [41, 84–88]. This approach is consistent with new guidelines included in the DSM-5 [9], which indicates that sleep disorders should be diagnosed even if they are comorbid with another mental disorder. See Fig. 24.1 for a depiction of models of disturbed sleep in PTSD.

Impact of PTSD Treatments on Nightmares and Insomnia

Efficacious psychological treatments for PTSD such as CPT and PE exist [13], and several studies have examined the impact of these treatments specifically on nightmares and insomnia [6, 7, 87, 89]. However, many of these studies of PTSD treatments report total PTSD scores rather than changes in specific PTSD symptoms, and standardized sleep measures are usually not included [87]. Overall, studies tend to indicate that while PTSD treatment results in improved sleep, insomnia and, to a lesser extent, nightmares remain in the clinically significant range [6–8, 90–92].

One study examining the impact of PTSD treatment on sleep outcomes has been conducted in a sample of 108 active-duty service members with combat-related PTSD. Pruiksma et al. [7] examined the impact of group CPT and group present-centered therapy on self-reported insomnia and nightmare items on the PTSD Checklist Stressor-Specific Version [93]. They found that insomnia was reported by 92% at baseline and by 74–80% at follow-up. Nightmares were reported by 69% at baseline and by 49–55% at follow-up. Among participants who no longer met criteria for PTSD following treatment, 57% continued to report insomnia, but only 13% continued to report nightmares.

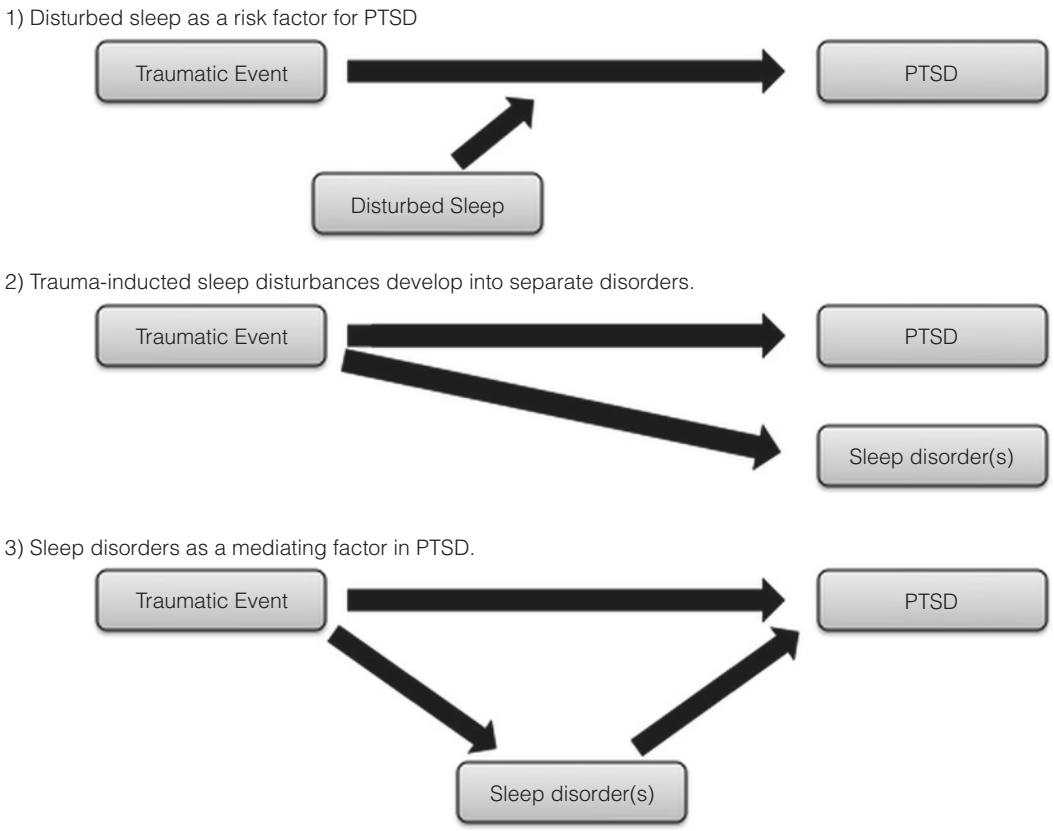

Fig. 24.1 Alternative models of sleep in PTSD (Reprinted from Spoormaker and Montgomery [87], with permission from Elsevier)

Nightmares were relatively more positively responsive to treatment. Among veterans presenting at a treatment facility for PTSD, Forbes, Creamer, and Biddle [5] report that 88% of experienced nightmares before treatment, and 77% continued to do so after completing treatment.

Several studies have also been conducted in civilian samples. One small study [92] examined sleep outcomes following EMDR in a sample of seven civilian victims of assault. Results found an increase in sleep efficiency and sleep quality as a result of treatment, providing some evidence that a treatment targeting PTSD symptomatology may be effective for improving sleep outcomes. Another study examined the effect of PTSD treatments on sleep disturbances [6] in 171 female rape victims receiving CPT or PE. Although CPT and PE resulted in significant decreases in insomnia and nightmare severity ratings on the Clinician-Administered PTSD Scale, there was not a complete remission in sleep symptoms. Galovski et al. [91] found that, although two 12-session CBT protocols for PTSD (PE and CPT) resulted in statistically significant improvements in self-reported sleep quality on the PSQI, sleep functioning at the end of treatment remained in the abnormal range. Nightmares were not examined in this study. Similarly, another study [90] found that, although there were significant improvements in sleep after 16–24 sessions of CBT for PTSD, 70% of individuals who reported sleep difficulties at baseline continued to report problems with sleep. With regard to nightmares, participants reported a significant decrease in "difficulties sleeping due to memories and nightmares of traumatic experiences"[90] (p. 321). However, as both memories and nightmares were included in this item, the impact of treatment specifically on nightmares is unclear. Zayfert and Deviva [8] found that among 27 civilians who no longer met criteria for PTSD after 16 sessions of CBT for PTSD, 48% reported residual insomnia. Only anger was endorsed more frequently at posttreatment (see Fig. 24.2). An effectiveness study [94] conducted in England in 246 civilians found that cognitive therapy for PTSD improved sleep and PTSD symptoms simultaneously but was moderated by depression. Sleep problems reduced the speed of recovery among those with comorbid depression. However, this study was limited by use of a very brief non-validated measure of sleep. Overall, it seems that for some trauma-exposed individuals, nightmares and problems

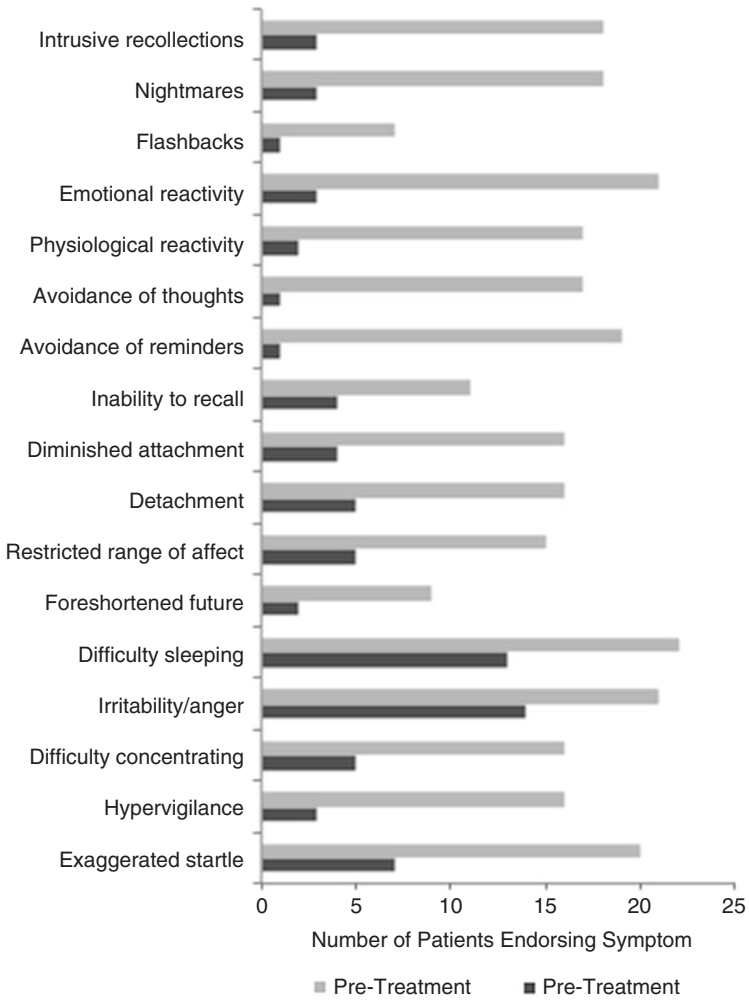

Fig. 24.2 Proportion of active-duty service members endorsing insomnia and nightmares on the PTSD Checklist – Stressor-Specific Version (PCL-S) prior to and following group cognitive processing therapy for PTSD and group present-centered therapy for PTSD

initiating and maintaining sleep continue to be a significant source of distress. A possible explanation for why sleep disturbances may be resistant to PTSD treatments is that the factors that perpetuate sleep difficulties are not addressed. Spielman's [95] behavioral model for the development and maintenance of insomnia purports that those individuals who are predisposed to developing insomnia (due to age, gender, genetics, personality characteristics, etc.) experience acute insomnia during some type of precipitating event that causes short-term sleep disturbances. These events could range from a number of life experiences (e.g., divorce, deployment, or traumatic experience). Certain behaviors that one develops during the precipitating event to obtain better sleep in the short term serve to perpetuate insomnia over the long term, even after the precipitating event has resolved. Perpetuating factors may include irregular sleep schedules and associating the bed and bedroom with a variety of activities (e.g., reading, watching television, paying bills, tossing and turning in bed, etc.) or avoiding the bedroom entirely. Whereas treatments for PTSD may address certain perpetuating factors (such as fear of sleep/vulnerability, feeling unsafe, hypervigilance), other behavioral components are not directly addressed and the sleep difficulties remain. The findings regarding comorbid depression and sleep are also worth pursuing.

The ordering of PTSD and sleep treatments is an empirical question, because there are several possible approaches. At least two randomized clinical trials examining this question are currently under way (NCT02773693, NCT02236390). Although few studies examining psychological treatments for PTSD contained validated measures of sleep outcomes, those that did found more pronounced improvements in PTSD symptom severity than in sleep disturbances, suggesting that PTSD treatment alone likely is not sufficient to resolve trauma-related sleep concerns including insomnia and nightmares [87]. This suggests that disturbed sleep is more than a "secondary symptom" of PTSD, because it often is not resolved after the primary disorder is treated. In contrast, some research purports that empirically supported treatments aimed at sleep disturbances (such as IRT for nightmares) may also reduce PTSD symptom severity. This suggests that disturbed sleep may be a mediating symptom that exacerbates PTSD [87] (see Fig. 24.1). The existing evidence does support the notion that sleep treatment incorporated into PTSD treatment may be successful in treating trauma-related sleep difficulties and that disturbed sleep in PTSD should be a frontline treatment [87]. In clinical practice, validated sleep questionnaires assessing factors such as sleep quality, insomnia, and nightmares should be included during intake. Then, since evidence-based, sleep-focused interventions have been shown to improve both sleep and PTSD symptoms, the inclusion of sleep-focused interventions should improve outcomes in response to standard PTSD treatment.

Spoormaker and Montgomery [87] and others [69, 96] suggest that sleep-focused treatment, including sleep hygiene, stimulus control, and IRT for nightmares, should be employed early in the course of PTSD treatment. Similarly, Nappi and colleagues [89] note that sleep impairment may be a motivating factor to seek treatment for PTSD. Effective treatment of sleep disturbances early in treatment may lead to subsequent engagement in evidence-based, trauma-focused treatments. Military personnel may in fact be more likely to seek treatment for sleep difficulties than for PTSD. However, others propose that treatments for sleep disturbance should only be employed if insomnia or nightmares persist after treatment for PTSD [8], because sleep-related difficulties may be alleviated by engagement in therapy for PTSD alone.

Alternatively, because cognitive behavioral therapies for nightmares and insomnia are brief, cost-effective interventions, they are amenable to integration into broader PTSD treatments. For example, treatment of insomnia could be addressed before or after treatment of PTSD in settings with clinic availability and in which therapists are trained in both treatments. After principles of sleep restriction and stimulus control are implemented, the therapist could potentially monitor and adjust the sleep schedule and adherence to these approaches for addressing sleep in 5–10 min in addition to the content of sessions for PTSD. Also, for those individuals with PTSD who experience significant sleep difficulties, unhelpful thoughts and behaviors related to sleep can be addressed in the context of PTSD treatment. For example, patients may avoid sleep or may repeatedly check the locks and the perimeter of the home for fear of something bad happening at night. These unhelpful thoughts can be addressed along with broader unhelpful thoughts about safety. In behavioral treatments, this may take the form of the response prevention of checking behaviors at night or in vivo exposure exercises to dark, safe locations.

Because there are limited data to guide the decision of what order to employ PTSD treatments or interventions targeting sleep disturbances, more integrated and crossover studies are needed to examine sequential or combined treatments for sleep and PTSD symptomatology [89]. At the writing of this chapter, at least two such studies are underway. Existing research is limited by a dearth of standardized protocols across studies and a lack of appropriate controls that consider the potential nonspecific effects of therapy. Furthermore, few PTSD treatment studies used validated measures of sleep outcomes. A first important step is to include standardized assessments of sleep symptoms in PTSD treatment studies and standardized assessment of PTSD symptoms in sleep/nightmare studies to more thoroughly understand the impact of each treatment on both symptom types. Specifically, prospective sleep measurements, such as nightmare and sleep diaries, should be included to assess changes in sleep over time as a result of treatment. Objective measures such as actigraphy may also be included to assess

sleep disturbance in patients with PTSD. Additionally, there is not enough existing evidence to ascertain the mechanism of the relationship between sleep disturbance and PTSD. Future research dismantling treatment protocols are needed to examine mechanisms of action for existing sleep and PTSD treatments in order to identify which aspects of the treatments contribute to significant effects.

Another important area for future research is to determine for which types of patients each treatment is effective. For example, few studies have examined military populations. Because some research [36] suggests that the efficacy of treatments such as IRT may be limited in veteran samples, more research is needed to determine factors specific to this group that may impact responsiveness to treatment. Additionally, as some research has shown that treatment nonresponders may share factors that impacted their treatment outcome [51], studies examining potential predictors of response to each type of treatment is important. Another limitation in existing research is a lack of data regarding treatment adherence and clinical outcomes. When analyzing adherence to IRT, one study [52] found that over half of the sample they reported never rehearsed imagery outside of session, and another study [70] reported that only half of their participants fully implemented the IRT protocol. Because this may have a significant impact on the effectiveness of treatment, future studies should systematically assess adherence to the therapy.

Consideration of Co-occurring Sleep Disorders

Another consideration for interventions for PTSD is co-occurring sleep disorders such as obstructive sleep apnea (OSA; see Brownlow et al. (2015) for a review of the literature [27]). OSA is characterized by repeated decreases and/or cessations of breathing during sleep and excessive daytime sleepiness (discussed further in Chap. 32 of this volume). Overnight polysomnography testing in a sleep laboratory is required to diagnose OSA. Untreated OSA affects an alarming number of important physiological and mental processes including cardiovascular disease [97, 98], cognitive impairment [99], psychiatric distress [100, 101], and overall mortality [102]. Symptoms associated with OSA may exacerbate PTSD symptoms such as concentration problems, irritability, sleep initiation and maintenance difficulties, and possibly nightmares. Indeed, a case study and a small uncontrolled retrospective study suggest adequate treatment of OSA with continuous positive airway pressure (CPAP) machines, the primary treatment for sleep apnea, improves PTSD symptoms [103–105]. However, adequate adherence to CPAP may be particularly difficult for individuals with PTSD [106]. Thus, sleep difficulties that may or may not be related to the hyperarousal symptoms included in the diagnostic criteria for PTSD may be present and may require specialized intervention in addition to treatment for PTSD.

Summary

In conclusion, there are a number of empirically supported treatments shown to improve PTSD or sleep symptoms. Several studies using limited sleep assessments indicate that PTSD treatments improve some sleep disturbances, such as insomnia and nightmares, but that these sleep disturbances remain in the clinically significant range for many individuals. Targeted treatment of sleep disturbances may be indicated and may also impact daytime symptoms of PTSD and depression. However, the optimal sequencing of sleep and treatments is an empirical question. Furthermore, there are no well-controlled trials examining combined treatments for sleep and PTSD symptoms. Future research clearly is needed in order to elucidate how best to treat the sleep symptoms so commonly associated with PTSD.

References

1. Glaubman H, Mikulincer M, Porat A, Wasserman O. Sleep of chronic post-traumatic patients. J Trauma Stress. 1990;3(2):255–63.
2. Inman DJ, Silver SM, Doghramji K. Sleep disturbance in post-traumatic stress disorder: a comparison with non-PTSD insomnia. J Trauma Stress. 1990;3(3):429–37.
3. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. Compr Psychiatry. 2000;41(6):469–78.
4. Davis JL, De Arellano M, Falsetti SA, Resnick HS. Treatment of nightmares related to post-traumatic stress disorder in an adolescent rape victim. Clin Case Stud. 2003;2(4):283–294.5.
5. Forbes D, Creamer M, Biddle D. The validity of the PTSD checklist as a measure of symptomatic change in combat-related PTSD. Behav Res Ther. 2001;39(8):977–86.
6. Gutner CA, Casement MD, Gilbert KS, Resick PA. Change in sleep symptoms across cognitive processing therapy and prolonged exposure: a longitudinal perspective. Behav Res Ther. 2013;51(12):817–22.
7. Pruiksma KE, Taylor DJ, Wachen JS, et al. Residual sleep disturbances following PTSD treatment in active duty military personnel. Psychol Trauma. 2016;8:697–701.
8. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. J Trauma Stress. 2004;17(1):69–73.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed., text rev. Washington, DC: American Psychiatric Association; 2013.
10. American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester: American Academy of Sleep Medicine; 2005.
11. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences: therapist guide. New York: Oxford University Press; 2007.
12. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: a review of randomized clinical trials. JAMA. 2015;314(5):489–500.
13. Cahill SP, Rothbaum BO, Resick PA, Follette VM. Cognitive-behavioral therapy for adults. In: Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Effective treatments for PTSD: practice guidelines from the international society for traumatic stress studies. 2nd ed. New York: Guilford; 2009.

14. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA. 2007;297(8):820–30.
15. Resick PA, Monson CM, Chard KM. Cognitive processing therapy for PTSD: a comprehensive manual. New York: Guilford; 2016.
16. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol. 2002;70(4):867–79.
17. Resick PA, Galovski TE, Uhlmansiek MOB, Scher CD, Clum GA, Young-Xu Y. A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. J Consult Clin Psychol. 2008;76(2):243–58.
18. Forbes D, Lloyd D, Nixon R, et al. A multisite randomized controlled trial of cognitive processing therapy for posttraumatic stress disorder in a naturalistic setting. J Anxiety Disord. 2012;26(3):442–52.
19. Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol. 2006;74(5):898–907.
20. Maieritsch KP, Smith TL, Hessinger JD, Ahearn EP, Eickhoff JC, Zhao Q. Randomized controlled equivalence trial comparing videoconference and in person delivery of cognitive processing therapy for PTSD. J Telemed Telecare. 2016;22(4):238–43.
21. Morland LA, Mackintosh MA, Greene CJ, Rosen C, Chard K, Resick P, Frueh BC. Cognitive processing therapy for posttraumatic stress disorder delivered to rural veterans via telemental health: a randomized noninferiority clinical trial. J Clin Psychiatry. 2014;75(5):470–6. doi:10.4088/JCP.13m08842.
22. Resick PA, Wachen JS, Mintz J, et al. A randomized clinical trial of group cognitive processing therapy compared with group present-centered therapy for PTSD among active duty military personnel. J Consult Clin Psychol. 2015;83(6):1058–68.
23. Shapiro F. Eye movement desensitization: a new treatment for post-traumatic stress disorder. J Behav Ther Exp Psychiatry. 1989;20(3):211–7.
24. Shapiro F, Maxfield L. Eye movement desensitization and reprocessing (EMDR): information processing in the treatment of trauma. J Clin Psychol. 2002;58(8):933–46.
25. Herbert JD, Mueser KT. Eye movement desensitization: a critique of the evidence. J Behav Ther Exp Psychiatry. 1992;23(3):169–74.
26. Spates CR, Koch E, Cusack K, Pagoto S, Waller S. Eye movement desensitization and reprocessing. In: Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Effective treatments for PTSD: practice guidelines from the international society for traumatic stress studies. 2nd ed. New York: Guilford Press; 2009. p. 279–305.
27. Brownlow JA, Harb GC, Ross RJ. Treatment of sleep disturbances in post-traumatic stress disorder: a review of the literature. Curr Psychiatry Rep. 2015;17(6):1–10.
28. Casement MD, Swanson LM. A meta-analysis of imagery rehearsal for post-trauma nightmares: effects on nightmare frequency, sleep quality, and posttraumatic stress. Clin Psychol Rev. 2012;32(6):566–74.
29. Hansen K, Höfling V, Kröner-Borowik T, Stangier U, Steil R. Efficacy of psychological interventions aiming to reduce chronic nightmares: a meta-analysis. Clin Psychol Rev. 2013;33(1):146–55.
30. Ho FYY, Chan CS, Tang KNS. Cognitive-behavioral therapy for sleep disturbances in treating posttraumatic stress disorder symptoms: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2016;43:90–102.
31. Koffel E, Khawaja IS, Germain A. Sleep disturbances in posttraumatic stress disorder: updated review and implications for treatment. Psychiatr Ann. 2016;46(3):173–6.
32. Taylor DJ, Pruiksma KE. Cognitive behavioral therapy for insomnia in psychiatric populations: a systematic review. Int rev Psychiatry. 2014;26:205–13. doi:10.3109/09540261.2014.902808.
33. Geer JH, Silverman I. Treatment of a recurrent nightmare by behavior modification procedures. J Abnorm Psychol. 1967;72(2):188–90.
34. Silverman I, Geer JH. The elimination of a recurrent nightmare by desensitization of a related phobia. Behav Res Ther. 1968;6(1):109–11.
35. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. Behav Res Ther. 2007;45(3):627–32.
36. Cook JM, Harb GC, Gehrman PR, et al. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. J Trauma Stress. 2010;23(5):553–63.
37. Aurora RN, Zak RS, Auerbach SH, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
38. Cranston CC, Davis JL, Rhudy JL, Favorite TK. Replication and expansion of "Best Practice Guide for the Treatment of Nightmare Disorder in Adults". J Clin Sleep Med. 2011;7(5):549–53.
39. Lancee J, Spoormaker VI, Krakow B, van den Bout J. A systematic review of cognitive-behavioral treatment for nightmares: toward a well-established treatment. J Clin Sleep Med. 2008;4(5):475–80.
40. Nappi CM, Drummond SPA, Thorp SR, McQuaid JR. Effectiveness of imagery rehearsal therapy for the treatment of combat-related nightmares in veterans. Behav Ther. 2010;41(2):237–44.
41. Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. Behav Sleep Med. 2006;4(1):45–70.
42. Kellner R, Neidhardt J, Krakow B, Pathak D. Changes in chronic nightmares after one session of desensitization or rehearsal instructions. Am J Psychiatry. 1992;149(5):659–63.
43. Krakow B, Hollifield M, Johnston L, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001;286(5):537–45.
44. Krakow B. Imagery rehearsal therapy for chronic posttraumatic nightmares: a mind's eye view. In: Rosner RI, Lyddon WJ, Freeman A, editors. Cognitive therapy and dreams. New York: Springer Publishing Co; 2004. p. 89–109.
45. Forbes D, Phelps A, McHugh T. Treatment of combat-related nightmares using imagery rehearsal: a pilot study. J Trauma Stress. 2001;14(2):433–42.
46. Thompson K, Hamilton M, West J. Group treatment for nightmares in veterans with combat-related PTSD. Natl Center PTSD Clin Q. 1995;5(4):13–7.
47. Buysse DJ, Reynolds CF, Monk TH, Berman SR. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
48. Davis JL, Wright DC. Randomized clinical trial for treatment of chronic nightmares in trauma-exposed adults. J Trauma Stress. 2007;20(2):123–33.
49. Rhudy JL, Davis JL, Williams AE, et al. Cognitive-behavioral treatment for chronic nightmares in trauma-exposed persons: assessing physiological reactions to nightmare-related fear. J Clin Psychol. 2010;66(4):365–82.
50. Davis JL, Rhudy JL, Pruiksma KE, et al. Physiological predictors of response to exposure, relaxation, and rescripting therapy for chronic nightmares in a randomized clinical trial. J Clin Sleep Med. 2011;7(6):622–31.
51. Harb GC, Cook JM, Gehrman PR, Gamble GM, Ross RJ. Posttraumatic stress disorder nightmares and sleep disturbance in Iraq war veterans: a feasible and promising treatment combination. J Aggress Maltreat Trauma. 2009;18(5):516–31.

52. Lu M, Wagner A, Van Male L, Whitehead A, Boehnlein J. Imagery rehearsal therapy for posttraumatic nightmares in U.S. veterans. J Trauma Stress. 2009;22(3):236–9.
53. Moore BA, Krakow B. Imagery rehearsal therapy for acute posttraumatic nightmares among combat soldiers in Iraq. Am J Psychiatry. 2007;164(4):683–4.
54. Forbes D, Phelps AJ, McHugh AF, Debenham P, Hopwood M, Creamer M. Imagery rehearsal in the treatment of posttraumatic nightmares in Australian veterans with chronic combat-related PTSD: 12-month follow-up data. J Trauma Stress. 2003;16(5):509–13.
55. Krakow B, Johnston L, Melendrez D, et al. An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. Am J Psychiatry. 2001;158(12):2043–7.
56. Krakow BJ, Melendrez DC, Johnston LG, et al. Sleep dynamic therapy for Cerro Grande fire evacuees with posttraumatic stress symptoms: a preliminary report. J Clin Psychiatry. 2002;63(8):673–84.
57. Krakow B, Sandoval D, Schrader R, et al. Treatment of chronic nightmares in adjudicated adolescent girls in a residential facility. J Adolesc Health. 2001;29(2):94–100.
58. Germain A, Nielsen T. Impact of imagery rehearsal treatment on distressing dreams, psychological distress, and sleep parameters in nightmare patients. Behav Sleep Med. 2003;1(3):140–54.
59. Rhudy JL, Davis JL, Williams AE, McCabe KM, Byrd PM. Physiological-emotional reactivity to nightmare-related imagery in trauma-exposed persons with chronic nightmares. Behav Sleep Med. 2008;6(3):158–77.
60. Balliett NE, Davis JL, Miller KE. Efficacy of a brief treatment for nightmares and sleep disturbances for veterans. Psychol Trauma Theory Res Pract Pol. 2015;7(6):507.
61. Long ME, Hammons ME, Davis JL, et al. Imagery rescripting and exposure group treatment of posttraumatic nightmares in veterans with PTSD. J Anxiety Disord. 2011;25(4):531–5.
62. Wanner J, Long ME, Teng EJ. Multi-component treatment for posttraumatic nightmares in Vietnam veterans: two case studies. J Psychiatr Pract. 2010;16(4):243–9.
63. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 1999;22(8):1134–56.
64. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). Sleep. 2006;29(11):1398–414.
65. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006;29(11):1415–9.
66. Gellis LA, Gehrman PR. Cognitive behavioral treatment for insomnia in veterans with long-standing posttraumatic stress disorder: a pilot study. J Aggress Maltreat Trauma. 2011;20(8):904–16.
67. Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, Perlis ML, Posner DA, Weiss B, Ruoff L, Varbel J. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. Sleep. 2014;37(2):327.
68. Berlin KL, Means MK, Edinger JD. Nightmare reduction in a Vietnam veteran using imagery rehearsal therapy. J Clin Sleep Med. 2010;6(5):487–8.
69. Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. J Clin Sleep Med. 2011;7(1):57–68.
70. Margolies SO, Rybarczyk B, Vrana SR, Leszczyszyn DJ, Lynch J. Efficacy of a cognitive-behavioral treatment for insomnia and nightmares in Afghanistan and Iraq veterans with PTSD. J Clin Psychol. 2013;69(10):1026–42.
71. Davis JL, Wright DC. Exposure, relaxation, and rescripting treatment for trauma-related nightmares. J Trauma Dissociation. 2006;7(1):5–18.
72. Davis JL. Treating post-trauma nightmares: a cognitive behavioral approach. New York: Springer Publishing Co; 2009.
73. Swanson LM, Favorite TK, Horin E, Arnedt JT. A combined group treatment for nightmares and insomnia in combat veterans: a pilot study. J Trauma Stress. 2009;22(6):639–42.
74. DeViva JC, Zayfert C, Pigeon WR, Mellman TA. Treatment of residual insomnia after CBT for PTSD: case studies. J Trauma Stress. 2005;18(2):155–9.
75. Baddeley JL, Gros DF. Cognitive behavioral therapy for insomnia as a preparatory treatment for exposure therapy for posttraumatic stress disorder. Am J Psychother. 2013;67(2):199–210.
76. Galovski TE, Harik JM, Blain LM, Elwood L, Gloth C, Fletcher TD. Augmenting cognitive processing therapy to improve sleep impairment in PTSD: a randomized controlled trial. J Consult Clin Psychol. 2016;84(2):167.
77. Falsetti SA, Resnick HS, Davis J. Multiple channel exposure therapy: combining cognitive-behavioral therapies for the treatment of posttraumatic stress disorder with panic attacks. Behav Modif. 2005;29(1):70–94.
78. Pruiksma KE, Taylor DJ, Peterson AL. Sleep disorders. In: Ainspan ND, Bryan CJ, Penk WE, editors. Handbook of psychosocial interventions for veterans: a guide for the non-military mental health clinician. New York: Oxford University Press; 2016.
79. Haynes PL, Kelly M, Scheller V, Quan SF, Bootzin RR. Stabilizing sleep and daily routine in veterans with comorbid PTSD and depression: follow-up outcomes for cognitive behavioral social rhythm therapy. Sleep. n.d.;(Abstract Supplement):A344.
80. Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms: a unified approach to understanding the etiology of depression. Arch Gen Psychiatry. 1988;45(10):948–52.
81. Beck AT, Rush AJ, Sahaw BF, Emery G. Cognitive therapy of depression. New York: Guilford Press; 1979.
82. Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press; 1993.
83. Frank E, Kupfer DJ, Ehlers CL, Monk TH. Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behavioral approaches. Behav Ther. 1994;17(7):143–8.
84. Spoormaker VI, Schredl M, van den Bout J. Nightmares: from anxiety symptom to sleep disorder. Sleep Med Rev. 2006;10(1):19–31.
85. Krakow B, Haynes PL, Warner TD, et al. Clinical sleep disorder profiles in a large sample of trauma survivors: an interdisciplinary view of posttraumatic sleep disturbance. Sleep Hypn. 2007;9(1):6–15.
86. Lancee J, Spoormaker VI, van den Bout J. Cognitive-behavioral self-help treatment for nightmares: a randomized controlled trial. Psychother Psychosom. 2010;79(6):371–7.
87. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12(3):169–84.
88. Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med. 2001;345(25):1825–32.
89. Nappi CM, Drummond SP, Hall JM. Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. Neuropharmacology. 2012;62(2):576–85.
90. Belleville G, Guay S, Marchand A. Persistence of sleep disturbances following cognitive-behavior therapy for posttraumatic stress disorder. J Psychosom Res. 2011;70(4):318–27.
91. Galovski TE, Monson C, Bruce SE, Resick PA. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? J Trauma Stress. 2009;22(3):197–204.
92. Raboni MR, Tufik S, Suchecki D. Treatment of PTSD by eye movement desensitization reprocessing (EMDR) improves sleep

quality, quality of life, and perception of stress. Ann N Y Acad Sci. 2006;1071:508–13.
93. Weathers F, Litz B, Herman D, Huska J, Keane T. The PTSD checklist (PCL): reliability, validity, and diagnostic utility. Paper presented at the annual meeting of the International Society for Traumatic Stress Studies, San Antonio; 1993.
94. Lommen MJ, Grey N, Clark DM, Wild J, Stott R, Ehlers A. Sleep and treatment outcome in posttraumatic stress disorder: results from an effectiveness study. Depress Anxiety. 2015;33:575–83.
95. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am. 1987;10(4):541–53.
96. Krakow B, Schrader R, Tandberg D, et al. Nightmare frequency in sexual assault survivors with PTSD. J Anxiety Disord. 2002;16(2):175–90.
97. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19–25.
98. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JPH, Calverley PMA. Cardiovascular and metabolic effects of CPAP in obese males with OSA. Eur Respir J. 2007;29(4):720–7.
99. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc. 2004;10(5):772–85.
100. Borak J, Cieślicki JK, Koziej M, Matuszewski A, Zieliński J. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. J Sleep Res. 1996;5(2):123–7.
101. Muñoz A, Mayoralas LR, Barbé F, Pericás J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J. 2000;15(4):676–81.
102. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009;6(8):e1000132–e1000132.
103. Krakow B, Lowry C, Germain A, et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. J Psychosom Res. 2000;49(5):291–8.
104. Tamanna S, Parker JD, Lyons J, Ullah MI. The effect of continuous positive air pressure (CPAP) on nightmares in patients with posttraumatic stress disorder (PTSD) and obstructive sleep apnea (OSA). J Clin Sleep Med. 2014;10(6):631–6.
105. Youakim JM, Doghramji K, Schutte SL. Posttraumatic stress disorder and obstructive sleep apnea syndrome. Psychosomatics. 1998;39(2):168–71.
106. El-Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. Sleep. 2010;33(11):6.

Cognitive Processing Therapy and Trauma-Related Sleep Disturbance

25

Ruth L. Varkovitzky, Sara E. Gilbert, and Kathleen M. Chard

Due to significant gains in research on post-traumatic stress disorder (PTSD), the scientific community has endorsed several therapies as "empirically supported," and many national organizations have created best practice guidelines [1]. One of the therapies that has received strong support is cognitive processing therapy (CPT) [2], a cognitive-behavioral treatment designed to specifically target PTSD and related symptoms. This chapter will provide an overview of the session content of CPT, the extant literature on CPT outcome studies, and a review of the impact CPT can have on PTSD-related sleep disturbance.

The Traditional Structure of CPT

CPT was created in 1988 as a manualized, predominantly cognitive treatment for PTSD and related symptoms in rape survivors [3]. Researchers have found that individuals with PTSD experience a wide array of emotions, intrusive memories, and conflicting schemas [4, 5] that are not fully accounted by the information processing theory of PTSD [6]. In order to address these trauma-related sequelae, CPT was designed to provide corrective information and to directly address maladaptive beliefs [1] to be utilized with a variety of clinical populations. CPT consists of 12 weekly sessions conducted in a manualized, serialized manner in either group, individual, or combined group and individual formats. The main goal of CPT is to reduce an individual's psychological distress caused by the symptoms of PTSD and related disorders. To facilitate this change, therapists and clients work together in a "collaborative empiricism" framework in which therapists teach clients the skills they need to achieve maximal improvement. CPT is divided into three phases including education, processing, and challenging (See Table 25.1). In the first phase (sessions 1–4), patients are educated regarding the theory behind CPT and are asked to explore the meaning of their trauma by writing an impact statement discussing why they believe the traumatic event occurred and how the event has shaped their beliefs about self, others, and the world, particularly in the areas related to safety, trust, power/control, esteem, and intimacy. Next, patients are taught the connection between events, thoughts, and feelings through using an A-B-C (Antecedents, Beliefs, Consequences) sheet, and together with the therapist, they begin to identify places where the patients have become "stuck" in their thinking. Specifically, they learn to identify "stuck points" which are thoughts related to (a) interpretations of their traumatic event, such as "It was my fault the trauma happened," or (b) thoughts of how they view themselves and the world based on their traumatic experiences, such as "I can't trust anyone" and "I am worthless." Finally, the patients write detailed trauma accounts of their most traumatic incident including sensory details, thoughts, and feelings (note: in the CPT cognitive-only version of this treatment, no trauma accounts are written). At the same time, the therapist uses Socratic dialogue to help the patients begin to analyze their stuck points and to view past, present, and future events with a more balanced interpretation.

In the second phase of the treatment (sessions 5–7), core cognitive therapy skills are taught, including use of the Challenging Questions Worksheet (CQW). The CQW consists of ten questions that help the veteran evaluate their stuck points in a variety of ways, including looking at the evidence for and against the belief, examining the context from which they believe was formed, and identifying how much the belief is based on feelings rather than facts. The

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Table 25.1 Session-by-session overview of CPT content

	CPT sessions	Practice assignments
1	Introduction and education	Write impact statement
2	Meaning of the event[a]	Complete one A-B-C sheet each day, including at least one on the worst trauma
3	Identification of thoughts and feelings	Reassign A-B-C worksheets; assign written trauma account
4	Remembering traumatic events	Rewrite trauma account; read full-written trauma account on a daily basis; complete A-B-C sheets daily
5	Identification of stuck points	Challenge one stuck point per day using the Challenging Questions Worksheet; continue work on trauma account if not finished; read trauma account daily
6	Challenging questions	Identify stuck points and complete Patterns of Problematic Thinking Worksheets for each. Look for patterns in thinking. Continue to read trauma account if still having strong emotions about it
7	Patterns of problematic thinking	Daily identification of stuck points, including one on safety using the Challenging Beliefs Worksheet; read safety module; continue to read trauma account if still have strong emotions about it
8	Safety issues	Read trust module and complete at least one Challenging Beliefs Worksheet on trust; continue to challenge stuck points on a daily basis using Challenging Beliefs Worksheets. Continue reading trauma account if still having strong emotions about it
9	Trust issues	Read power/control module and complete at least one Challenging Beliefs Worksheet on power/control issues. Continue to challenge stuck points on a daily basis using Challenging Beliefs Worksheets. Continue to read trauma account if still having strong emotions about it
10	Power/control issues	Read module and complete at least one Challenging Beliefs Worksheet on esteem, as well assignments regarding giving and receiving compliments and doing nice things for self. Continue to challenge stuck points on a daily basis using Challenging Beliefs Worksheets. Continue to read trauma account if still having strong emotions about it
11	Esteem issues	Continue giving and receiving compliments, read intimacy module and complete Challenging Beliefs Worksheets on stuck points regarding intimacy. Continue to read trauma account if still having emotions about it. Final assignment: write final impact statement
12	Intimacy issues and meaning of the event	Remind patient that she/he is taking over as therapist now and should continue to use the skills learned

[a]If applicable, a *traumatic bereavement session* can be conducted after session 2

Patterns of Problematic Thinking Worksheet is then introduced to allow patients to become familiar with common faulty thinking patterns that can interfere with recovery from PTSD. The veteran examines each stuck point to see which of the seven patterns are being activated by the stuck point, such as jumping to conclusions, exaggerating/minimizing, or emotional reasoning. Finally, the Challenging Beliefs Worksheet is introduced, which incorporates all of the prior worksheets and allows patients to look at their beliefs, challenge them, and provide alternative more realistic and balanced beliefs while also noting the change in their emotions.

In the third phase of CPT (sessions 8–12), the Challenging Beliefs Worksheets is used, which incorporates all of the previous skills gained in CPT, allowing patients to approach their beliefs, challenge them, and consider alternative, more realistic, and balanced beliefs while noting change in their emotions. When using CBWs, patients focus their stuck point examination in each of the five key areas including safety, trust, power/control, esteem, and intimacy.

In the final session, patients rewrite their impact statement and compare it to the initial version written at the beginning of the therapy. This allows the patients to clearly recognize the changes in their thoughts, feelings, and behaviors. The final impact statement may also be used to generate future areas for growth or additional treatment recommendations such as couples counseling, vocational rehabilitation, or relapse prevention. Finally, the therapist and patients look to the future and identify any areas that may continue to be problematic and discuss ways that they can be managed using the CPT principles.

Seminal Studies

Cognitive processing therapy (CPT) has been rigorously examined in randomized clinical trials, and it has been shown to be efficacious in reducing symptoms of PTSD and co-occurring symptoms for many different traumatic events [3]. The first study evaluating the effectiveness of CPT was in 1992 by Resick and Schnicke; this study compared sexual assault survivors who received CPT treatment, in group format, to a wait-list control group [1]. The wait-list control group consisted of individuals who met criteria for PTSD and were on the waiting list for CPT treatment for at least 12 weeks. CPT participants improved significantly from pre- to posttreatment on PTSD and depressive symptoms and maintained their improvement when reassessed after 6-month posttreatment. There was no change observed from pre- to posttreatment for the control group.

Resick and colleagues performed the first randomized controlled trial evaluating CPT in 2002 [7]. This study compared prolonged exposure (PE) [8], CPT, and a minimal attention (MA) waiting list in a sample of female rape victims intended to be treated in the study. The MA waiting list group consisted of participants on the waiting list for treatment for 6 weeks who were called every 2 weeks to ensure they did not need emergency services. Both PE and CPT reduced symptoms of PTSD and depression, as measured by the Clinician-Administered PTSD Scale for DSM-IV (CAPS) [9] and Beck Depression Inventory-II (BDI-II) [10]. CPT and PE were similarly effective in their ability to improve psychological functioning. Resick and her colleagues [7] conducted a follow-up assessment of those previously treated with either PE or CPT in their previous study [3]. The researchers contacted their previous participants with the length of time following completion of treatment ranging from 4.5 to 10 years, averaging 6.15 years (SD = 1.22). Both CPT and PE participants had similar maintenance of improvements in PTSD symptoms at follow-up. These results were not explained by additional psychotherapy posttreatment or medication usage. On the contrary, those who had sought further psychotherapy or had used medication demonstrated a pattern of worse outcomes. This study provides encouraging support for the sustained improvement in PTSD symptoms for those treated with CPT.

The effectiveness of CPT has also been evaluated in veterans by Monson and her colleagues [11]. Similar to results of other CPT studies, veterans who received CPT (compared to those in a wait-list control condition) were significantly less likely to meet diagnostic criteria for PTSD at posttreatment. In terms of a cluster-level symptom examination, results indicated that reexperiencing and numbing symptoms improved in the CPT condition but behavioral avoidance and hyperarousal symptoms did not change regardless of treatment group.

Dismantling and Modifications

Resick and her colleagues were interested in examining the components of CPT to assess if one individual component may be the most effective in treating PTSD [12]. One dismantling study examined CPT outcomes among female victims of sexual assault. The standard protocol was broken down into cognitive processing therapy-cognitive (CPT-C) and written accounts (WA), which were both compared to a standard CPT condition. The CPT-C condition consisted of 12 sessions over 6 weeks and included all of the modules of CPT without the written accounts of trauma narratives. The WA condition consisted of two one hour sessions in the first week and five two hours sessions once a week for the remaining 5 weeks. The WA condition included writing trauma narratives, reading them to the therapist, and engaging in an emotion-focused non-cognitive restructuring.

The results of this study indicate that all three conditions evidenced decreased PTSD symptoms. Similar to other studies of CPT, the decrease in PTSD symptoms was maintained through the follow-up assessments. The results indicated that the standard condition CPT was not significantly better at reducing PTSD symptoms than WA or CPT-C alone. The CPT-C group had significantly lower scores on the Posttraumatic Diagnostic Scale [13] than the WA group, while the CPT condition did not differ from either. These results indicate that the CPT-C protocol may have performed better than the WA condition, though the WA condition was still effective in reducing symptoms.

Modifications have been made to the original CPT format to adapt the protocol to various populations. CPT-C has been adapted in order to provide treatment through telehealth to rural populations [14]. Participants in this study were randomly assigned to either an in-person CPT-C group or a video teleconferencing CPT-C group. Both treatment groups received 12 90-min group sessions twice per week for 6 weeks. In the video teleconferencing group, there was the addition of an onsite observer with participants to facilitate faxing homework and to handle potential on-site emergent issues. Researchers found that there were no significant differences between the two treatment conditions and both conditions showed benefit from the treatment. While generalizability of this study may be limited by the small sample size, these results suggest that CPT-C can be effectively used over video teleconferencing.

CPT-C may be a preferable treatment option when participants are unwilling to complete a written trauma account, have limited memory of the traumatic event, or experience difficulty with writing. CPT-C has been examined among veterans with traumatic brain injuries (TBI) within a residential treatment setting and shown to significantly reduce PTSD symptoms [15]. A particularly noteworthy finding was that the reductions in PTSD symptoms were not only found for veterans with mild TBI but also found in veterans with a history of moderate-to-severe traumatic brain injury.

CPT has also been adapted to treat child abuse survivors (CPT-SA) [16]. CPT-SA was designed by integrating information processing, developmental, and self-trauma theories to appropriately address the fear processing, attachment, cognitions, and development associated with sexual abuse [17–20]. Changes from the original CPT protocol include focus on schema-congruent beliefs in addition to the inclusion of the schema-discrepant beliefs addressed in CPT.

Chard compared CPT-SA to a minimal attention wait-list control group [16]. The wait-list condition participants received a weekly phone call for the 17 weeks of the study, during which their emotional state was assessed. In the event they experienced a crisis, they were given supportive, nondi-

rective, brief counseling, and if their symptoms warranted immediate therapeutic intervention, their study participation was discontinued. Participants in the wait-list condition were offered the opportunity to receive the treatment after the completion of the study.

Individuals in the CPT-SA treatment condition were provided 17 weeks of treatment. CPT-SA utilizes a combination of group and individual sessions and consists of 17 90-min group therapy sessions and 60-min individual therapy sessions for the first 9 weeks of the protocol and the 17th week. The individual sessions provide the opportunity for participants to process their abuse experiences. There is also the addition of a developmental session 2, giving individuals the opportunity to discuss their family of origin. During sessions 10 through 16, participants receive only group treatment to increase their independence from their individual therapist and build support with fellow group members. The group format facilitates practice of appropriate social interactions and testing of skills learned in the therapy. Supplemental session modules on assertiveness/communication, sexual intimacy, and social support were created for CPT-SA.

The results of the study were encouraging and suggest this modification is effective for treating survivors of sexual abuse. Participants in the CPT-SA treatment condition showed significant decreases on measures of PTSD, depression, and dissociation, and these improvements were maintained at one year following the completion of treatment. Further analyses of the data showed large effect sizes for change in the treatment group as compared to the minimal attention group.

CPT has also been adapted to meet needs of refugees, which is a unique population because many refugees have experienced multiple traumas. Schulz and her colleagues studied a sample of foreign-born refugees resettled in the United States in a naturalistic, community setting [21]. Participants were assigned either to receive CPT with the aid of an interpreter or to receive CPT with a therapist that spoke their native language. Both of the treatment conditions showed significant reduction in PTSD scores, while the group with a native language-speaking therapist had a greater decrease in scores. Treatment effects were robust to the effects of age, gender, and education level. In both treatment conditions, CPT was demonstrated to be a highly effective treatment for PTSD in refugee populations.

Considering Comorbid Symptoms

Although CPT is a treatment for PTSD, it targets underlying maladaptive cognitions, which are central to both PTSD and depression. There are very high rates of comorbid diagnoses of depression and PTSD. Orsillo and colleagues found that 55% of those who met criteria for PTSD also met criteria for depression [22]. Further support for this finding was found in the National Comorbidity Study that found that 47.9% of men and 48.5% of women had a PTSD diagnosis and a comorbid major depression diagnosis [23]. Taking into account this high rate of comorbidity, researchers of CPT have examined the impact of CPT on depression.

Resick and her colleagues found that in their study comparing CPT, PE, and a minimal attention wait list in a sample of female rape victims, both CPT and PE showed a significant decrease in participant's self-reported depression at posttreatment and this improvement was maintained at follow-up [7]. In long-term follow-up data, Resick and her colleagues found that the impact of CPT and PE on depression was maintained up to 10 years after the completion of treatment [24]. Monson and her colleagues completed a study in which CPT was compared to a wait-list group and replicated the finding that CPT improves symptoms of depression [11]. Rizvi and her colleagues demonstrated that participants who had higher depression scores at the baseline had greater relative change in their PTSD severity over the course of treatment, suggesting that CPT is highly effective at treating depression [25]. CPT-C has also been shown to be effective in reducing depression in veterans with comorbid PTSD and traumatic brain injuries [15].

Researchers have examined the impact of CPT on several trauma-related symptoms, including guilt, affect dysregulation, anxiety, social problems, and physical health complaints [26–29]. In the Resick and colleagues [7] randomized controlled trial comparing CPT, PE, and minimal attention wait-list conditions, participants showed a differential response to the treatments on the subscales of the Trauma-Related Guilt Inventory [30], which include global guilt, hindsight bias, lack of justification, and wrongdoing. The aforementioned subscales are commonly challenged cognitive distortions and maladaptive thought patterns in CPT. While both CPT and PE groups showed decreases on all four subscales of the Trauma-Related Guilt Inventory, those in the CPT condition showed significantly lower scores on the hindsight bias and lack of justification subscales as compared to the PE and minimal attention (MA) groups, and at the 9-month follow-up assessment, this pattern was maintained. For the intent-to-treat sample, CPT showed a large effect size for guilt cognitions, as compared to the medium effect size for PE. In the sample of those who completed treatment, CPT showed moderate-to-large effect sizes compared to PE at posttreatment and 9-month follow-up assessment. These findings suggest that CPT was more successful at reducing hindsight bias and lack of justification than PE.

The data from Resick and colleagues [7] was reexamined by Nishith, Nixon, and Resick to further understand the relationship between trauma-related guilt and depression [31]. Researchers found that data showed that CPT was effective at treating guilt in those with PTSD and PTSD and comorbid depression. They also found support for CPT being more effective in reducing certain kinds of guilt than PE.

Sobel and colleagues examined the impact of CPT on problematic cognitions [32]. Resick and Schnicke proposed that after a traumatic event, some individuals overaccommodate the new experience from the trauma and overgeneralize the experience [33]. Others assimilate, defined as incorporating new, unchanged information into a preexisting worldview or schema. In CPT, the goal is to cultivate accommodated or balanced views of the traumatic event. Sobel and colleagues found that when comparing statements describing the impact of the trauma on an individual pre- to posttreatment, there were significant decreases in the number and percentage of overaccommodated and assimilated statements [32]. They also found there was an increase in accommodated clauses, supporting the hypothesis that CPT is effective in reducing maladaptive thinking and developing more adaptive thinking.

In a veteran sample, Monson and her colleagues found that at posttreatment, individuals receiving CPT showed improvement on several measures of co-occurring symptoms [11]. Monson and her colleagues utilized the Spielberger State-Trait Anxiety Inventory [34] to measure general anxiety and assessed guilt distress with the Trauma-Related Guilt Inventory [30]. Researchers evaluated affect functioning with the Affect Control Scale [35], and the Toronto Alexithymia Scale-20 [36] was used to measure the ability to distinguish emotions from bodily sensation, ability to describe emotions, and having an externally oriented style of thinking. They also employed the Social Adjustment Scale [37] to assess functioning in several domains. Their findings were similar to those reported by Resick and her colleagues showing a decrease on the Trauma-Related Guilt Inventory at posttreatment for CPT group [7]. Monson and colleagues also observed significant improvements in general anxiety, affect functioning, and social adjustment at posttreatment for those receiving CPT.

In a residential PTSD treatment program for veterans, Owens, Chard, and Cox studied the change in maladaptive cognitions, anger expression, PTSD, and depression over the course of treatment [38]. They utilized the Cognitive Distortion Scale [39], Trauma-Related Guilt Inventory [30], Beck Depression Inventory-II [10], State-Trait Anger Expression Inventory [40], and the PTSD Checklist for DSM-IV-Military Version [41]. The Cognitive Distortion Scale was designed to measure cognitions of those in mental health treatment, and it includes five subscales: self-criticism, self-blame, helplessness, hopelessness, and preoccupation with danger [39]. It was found that maladaptive cognitions, anger expression, PTSD symptoms, and depression were all significantly lower at posttreatment. While these results are limited in generalizability because participants were in a residential program receiving additional interventions (e.g., psychoeducation groups), these results provide further support for previous findings that CPT is effective in reducing maladaptive cognitions.

Chronic health problems and generally poorer perception of physical health have also been associated with PTSD [42–45]. Galovski and her colleagues compared participants receiving CPT and PE on measures of health-related concerns [46]. Researchers used the Pennebaker Inventory of Limbic Languidness [47] to measure the frequency of occurrence of 54 physical symptoms and sensations, such as coughing, back pains, headaches, and nausea. It was found that those who completed CPT showed a significant improvement in reported physical health symptoms beyond those who completed PE. While none of the studies above measured sleep disturbance directly, research demonstrates that PTSD, depression, and other health conditions often negatively impact sleep and, by treating these disorders, sleep commonly improves as evidenced in the studies below.

Cognitive Processing Therapy and Trauma-Related Sleep Disturbance

As many as 70% of individuals diagnosed with posttraumatic stress disorder (PTSD) report sleep disturbances, including insomnia and nightmares [48]. Though some have speculated that evidence-based PTSD treatments and pharmacological interventions may not improve trauma-related sleep disturbances [49, 50], four studies have found that receiving cognitive processing therapy (CPT) was associated with improved sleep outcomes [46, 51–53].

In a direct comparison of CPT and prolonged exposure (PE) [46], Galovski and her colleagues (2009) assessed sleep and health impairment in 108 female victims of adult sexual assault. Sleep problems were measured with the Pittsburgh Sleep Quality Index (PSQI) [54], a self-report measure that captures seven domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. Health issues were measured with the Pennebaker Inventory of Limbic Languidness [47]. Results indicated that while women in both treatment groups evidenced similar levels of sleep improvements, those in the CPT condition reported fewer perceived health problems compared to those in the PE condition (see Table 25.2) [46]. The authors hypothesized that the perception of health problems may be associated with a latent cognitive process that also functions as risk factor for development of PTSD, and therefore, a cognitive restructuring intervention such as CPT may better address perceptions of health problems compared to an exposure-based intervention like PE [46].

A preliminary study examined sleep symptoms among female victims of interpersonal violence who were receiving CPT [52]. Prior to receiving CPT, some women were assigned to receive hypnosis as a supplementary relaxation

Table 25.2 Hierarchical linear modeling results for sleep and physical health outcomes for prolonged exposure and cognitive processing therapy

	Global sleep		Sleep quality		Sleep latency		Sleep duration		Habitual sleep efficiency		Sleep disturbance		Daytime dysfunction		Total PILL	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Baseline																
Intercept	9.1***	0.5	1.6***	0.1	.7***	0.2	1.6***	0.2	0.8***	0.2	1.7***	0.1	1.8***	0.1	129.8***	4.5
Condition[a]	0.0	0.7	−0.1	0.2	−0.1	0.2	0.1	0.2	0.3	0.2	−0.1	−0.1	0.1	0.2	−3.9	6.2
Sleep medication changes																
Intercept	1.8***	0.2	0.1*	0.1	0.2**	0.1	0.1	0.1	0.3***	0.1	0.1*	0.0	0.1	0.1	5.6***	1.7
Condition[a]	0.5	0.4	0.2	0.1	0.1	0.1	0.1	0.1	−0.1	0.1	0.1	0.1	0.1	0.1	1.5	2.5
Change over time by condition																
Intercept	−3.6***	0.5	−0.8***	0.1	−0.7***	0.1	−0.6***	0.2	−0.5*	0.2	−0.4***	0.1	−0.8***	0.1	−13.3***	2.9
Condition[a]	0.3	0.7	0.0	0.2	0.1	0.2	0.1	0.2	−0.1	0.2	0.0	0.1	0.1	0.2	−11.6**	4.1

Galovski et al. [46]

PILL Pennebaker's Inventory of Limbic Languidness

* $p < .05$. ** $p < .01$. *** $p < .001$

[a]Prolonged exposure was the reference condition

treatment, while others were assigned to simply monitor their sleep symptoms. Hypnosis treatment was selected to supplement CPT as previous research has indicated that it can be helpful for improving sleep for individuals with PTSD [55, 56]. Sleep quality was assessed with the PSQI [54]. PTSD symptoms were assessed with the Clinician-Administered PTSD Survey for DSM-IV (CAPS) [9]. The Beck Depression Inventory, Second Edition, (BDI-II) [10] was used to assess depressive symptoms. Participants were assessed pretreatment, post-supplementary treatment (i.e., either hypnosis or symptom monitoring), post-CPT treatment, and then 3 months following treatment. For those who received hypnosis treatment, they reported improved sleep quality compared to those who were assigned to symptom monitoring at the assessment immediately following receiving the supplementary treatment but prior to receiving CPT. At follow-up assessments, when comparing those who received CPT with sleep symptom monitoring to those who received CPT supplemented by the hypnosis relaxation intervention, there were no significant differences between groups in terms of sleep quality, PTSD symptoms, or depressive symptoms. Based on these initial findings, it is possible that individuals completing CPT may not need supplementary treatment to address their sleep difficulties.

A recent randomized clinical trial expanded on this preliminary study and further examined the effect of supplementing CPT with self-directed hypnosis compared to CPT supplemented by sleep monitoring [53]. Women who experienced interpersonal violence were recruited for the study. Treatment was delivered in two phases: first sleep-related treatment was delivered, and CPT was delivered in a second phase. Results indicated that after the first phase of sleep-related treatment, those in the hypnosis condition showed greater improvement of sleep and depression than those in the monitoring condition but did not differ in terms of PTSD symptoms. After the second phase of treatment (CPT), both conditions demonstrated improvement in sleep and PTSD, but those from the hypnosis condition had greater improvement in depressive symptoms. As sleep improved, so too did PTSD and depressive symptoms, with the relationship between PTSD and sleep being particularly salient.

Although all participants of these studies reported significant improvements in trauma-related sleep impairments, individuals did not achieve normal sleep functioning after completing CPT [46, 53]. This finding is consistent with a previous study examining cognitive behavioral therapy (CBT) for PTSD-related insomnia, in which measures of sleep quality did not drop below clinically significant cutoffs at posttreatment [57]. It is evident that PTSD-related sleep disturbance is particularly challenging to treat, and additional research is needed to continually improve available treatment options.

Pharmacological Intervention in Conjunction with Psychotherapy

In addition to psychotherapeutic treatment for PTSD, there are numerous psychopharmacological agents available to aid sleep in PTSD patients, such as quetiapine [58, 59], olanzapine [60–62], risperidone [63–65], and prazosin [66–68]. Among these drugs, prazosin is unique in its mechanism of action and reported effect on nightmares. Prazosin is a centrally active α-1 adrenergic antagonist that has demonstrated effective reduction of trauma-related nightmares and overall PTSD symptoms in military and civilian populations [69–75]. It is thought that by reducing excessive sympathetic tone centrally, prazosin lowers blood pressure and further can diminish symptoms associated with PTSD [76].

Considering the substantial empirical support for use of CPT and PE for treating PTSD [11, 12, 16, 77, 78], and increasing use of prazosin for reducing trauma-related sleep disturbance [79], it is likely that CPT and prazosin are already being used concurrently in clinical settings. A recent retrospective chart review in a sample of veterans receiving CPT in a residential treatment program found that both prazosin and non-prazosin groups evidenced significant improvements in self-reported trauma-related sleep disturbance from admission to discharge [51]. Interpretation of this study is limited by the nature of retrospective chart review and lack of prazosin dose control. Additionally, sleep disturbance was captured by summing two items from a self-report measure of PTSD (the PTSD Checklist) [41], rather than using a validated measure of sleep quality. However, these results suggest that residential trauma programs with a focus on CPT may reduce trauma-related sleep disturbance without the additional use of prazosin.

Conclusion

The current literature suggests that CPT is an effective treatment for PTSD, related psychological disorders such as depression, and associated health problems. Research also suggests that CPT may not effectively remit all sleep problems for all patients. Thus further research with more refined measures of sleep needs to be conducted with individuals receiving CPT in order to determine which individuals find their sleep improved after CPT and which do not. In addition, research could focus on modifications or additions that could be made to CPT for those individuals whose sleep does not improve with CPT alone. For example, clinically some patients have been found to respond well to a cognitive behavioral treatment for insomnia after receiving CPT, while others react well to the use of medications. Future, large-scale studies of this sort could help to determine which treatment formula would be best indicated for the specific individual's PTSD and sleep problems.

References

1. Institute of Medicine. Treatment of posttraumatic stress disorder: an assessment of the evidence. Washington, DC: National Acadamies Press; 2008.
2. Chard KM, Resick PA, Monson CM, et al. Cognitive processing therapy therapist group manual: veteran/military version. Washington, DC: Department of Veterans' Affairs; 2008.
3. Resick PA, Schnicke MK. Cognitive processing therapy for sexual assault victims. J Consult Clin Psychol. 1992;60:748–56.
4. Veronen LJ, Kilpatrick DG, Resick PA. Treating fear and anxiety in rape victims: implications for the criminal justice system. In: Parsonage WH, editor. Perspectives on victimology. Beverly Hills: Sage; 1979. p. 148–59.
5. Pitman RK, Orr SP, Forgue DF, Altman B, de Jong JB, Hertz LR. Psychophysiologic responses to combat imagery of Vietnam veterans with posttraumatic stress disorder versus other anxiety disorders. J Abnorm Psychol. 1990;99:49–54.
6. Foa EB, Steketee BD, Olasov-Rothbaum B. Behavioral/cognitive conceptualizations of post-traumatic stress disorder. Behav Ther. 1984;20:155–76.
7. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive processing therapy with prolonged exposure therapy and a waiting list condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol. 2002;70:867–79.
8. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences: therapist guide. Oxford: Oxford University Press; 2007.
9. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8:75–90.
10. Beck AT, Steer RA, Brown GK. Manual for the Beck depression inventory-II. San Antonio: Psychological Corporation; 1996.
11. Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol. 2006;74:898–907.
12. Resick PA, Galovski TE, Uhlmansiek MO, Scher CD, Clum GA, Young-Xu Y. A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. J Consult Clin Psychol. 2008;76:243–58.
13. Foa EB. Posttraumatic stress diagnostic scale (manual). Minneapolis: National Computer Systems; 1995.
14. Morland LA, Hynes AK, Mackintosh MA, Resick PA, Chard KM. Group cognitive processing therapy delivered to veterans via telehealth: a pilot cohort. J Trauma Stress. 2011;24:465–9.
15. Chard KM, Schumm JA, McIlvain SM, Bailey GW, Parkinson RB. Exploring the efficacy of a residential treatment program incorporating cognitive processing therapy-cognitive for veterans with PTSD and traumatic brain injury. J Trauma Stress. 2011;24(3):347–51.
16. Chard KM. An evaluation of cognitive processing therapy for the treatment of posttraumatic stress disorder related to childhood sexual abuse. J Consult Clin Psychol. 2005;73:965–71.
17. Lang PJ. An information processing analysis of fear. Behav Ther. 1977;8:862–86.
18. Cole PM, Putnam FW. Effect of incest on self and social functioning: a developmental psychopathology perspective. J Consult Clin Psychol. 1992;60:174–84.
19. Finkelhor D. The trauma of child sexual abuse. J Interpers Violence. 1988;2:348–66.
20. Briere J. Treating adult survivors of severe childhood abuse and neglect: further development of an integrative model. In: Meyers J, Berlinger L, Briere J, Hendrix CT, Reid T, Jenny C, editors. The APSAC handbook on child maltreatment. 2nd ed. Newbury Park: Sage; 2002. p. 175–204.
21. Schulz PM, Resick PA, Huber LC, Griffin MG. The effectiveness of cognitive processing therapy for PTSD with refugees in a community setting. Cogn Behav Pract. 2006;13:322–31.
22. Orsillo SM, Weathers FW, Litz BT, Steinberg HR, Huska JA, Keane TM. Current and lifetime psychiatric disorders among veterans with war zone-related posttraumatic stress disorder. J Nerv Ment Dis. 1996;184(5):307–13.
23. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048–60.
24. Resick PA, Williams LF, Suvak MK, Monson CM, Gradus JL. Long-term outcomes of cognitive–behavioral treatments for posttraumatic stress disorder among female rape survivors. J Consult Clin Psychol. 2011;80:201–10.
25. Rizvi SL, Vogt DS, Resick PA. Cognitive and affective predictors of treatment outcome in cognitive processing therapy and prolonged exposure for posttraumatic stress disorder. Behav Res Ther. 2009;47(9):737–43.
26. Foa EB, Ehlers A, Clark DM, Tolin DF, Orsillo SM. The posttraumatic cognitions inventory (PTCI): development and validation. Psychol Assess. 1999;11:303–14.
27. Frazier P, Schauben L. Causal attributions and recovery from rape and other stressful life events. J Soc Clin Psychol. 1994;13:1–14.
28. Janoff-Bulman R, Wortman CB. Attributions of blame and coping in the "real world": severe accident victims react to their lot. J Pers Soc Psychol. 1997;35:351–63.
29. Kubany ES. A cognitive model of guilt typology in combat-related PTSD. J Trauma Stress. 1994;7:3–19.
30. Kubany ES, Haynes SN, Aubeg FR, Manke FP, Brennan JM, Stahura C. Development and validation of the trauma related guilt inventory (TRGI). Psychol Assess. 1996;8:428–44.
31. Nishith P, Nixon RDV, Resick PA. Resolution of trauma-related guilt following treatment of PTSD in female rape victims: a result of cognitive processing therapy targeting comorbid depression? J Affect Disord. 2005;86:259–65.
32. Sobel A, Resick P, Rabalais A. The effect of cognitive processing therapy on cognitions: impact statement coding. J Trauma Stress. 2009;22(3):205–11.
33. Resick PA, Schnicke MK. Cognitive processing therapy for rape victims: a treatment manual. Newbury Park: Sage; 1993.
34. Spielberger CD. Manual for the state-trait anxiety inventory (Form Y). [self-evaluation questionnaire]. Palo Alto: Consulting Psychologist Press; 1983.
35. Williams KE, Chambless DL, Ahrens AH. Are emotions frightening? An extension of the fear concept. Behav Res Ther. 1997;35:239–48.
36. Bagby RM, Taylor GJ, Parker JDA. Construct validity of the Toronto alexithymia scale. Psychother Psychosom. 1988;8:77–100.
37. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry. 1976;33:1111–5.
38. Owens GP, Chard KM, Cox TA. The relationship between maladaptive cognitions, anger expression, and posttraumatic stress disorder among veterans in residential treatment. J Aggress Maltreat Trauma. 2008;17(4):439–52.
39. Briere J. Cognitive distortion scales manual. Odessa: Psychological Assessment Resources; 2000.
40. Spielberger CD. Manual for the state-trait anger expression inventory (STAXI). Odessa: Psychol Assess Resources; 1988.
41. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist: reliability, validity, and diagnostic utility. Paper presented at the Annual Meeting of the International Society for Traumatic Stress Studies. San Antonio; Oct 1993.
42. Barrett DH, Doebbeling CC, Schwartz DA, Voelker MD, Falter KH, Woolson RF, Doebbling BN. Posttraumatic stress disorder

and self-reported physical health status among US military personnel serving during the Gulf war period: a population-based study. Psychosomatics. 2002;43:195–205.
43. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS, Grady DA. Trauma and the Vietnam war generation: report of the findings from the National Vietnam Veterans Readjustment Study. New York: Brunner/Mazel; 1990.
44. Schnurr P, Ford J, Friedman M, Green B, Dain B, Sengupta A. Predictors and outcomes of posttraumatic stress disorder in World War II veterans exposed to mustard gas. J Consult Clin Psychol. 2000;68:258–68.
45. Schnurr P, Jankowski M. Physical health and post-traumatic stress disorder: review and synthesis. Semin Clin Neuropsychiatry. 1999;4:295–304.
46. Galovski TE, Monson CM, Bruce SE, Resick PA. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? J Trauma Stress. 2009;55:197–204.
47. Pennebaker JW. The psychology of physical symptoms. New York: Springer-Verlag; 1982.
48. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. Compr Psychiatry. 2000;41(6):469–78.
49. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12(3):169–84.
50. Zayfert C, DeVira J. Residual insomnia following cognitive behavioral therapy for PTSD. J Trauma Stress. 2004;17(1):69–73.
51. Varkovitzky RL, Chard KM, Forrester JJ. Does prazosin reduce trauma-related sleep difficulties in veterans completing a residential cognitive processing therapy program for posttraumatic stress disorder? Unpublished manuscript, PTSD and Anxiety Disorders Division, Cincinnati Veterans Affairs Medical Center, Cincinnati; 2011.
52. Elwood L, Mott J, Galvoski T. Additive benefits of a brief sleep treatment prior to cognitive processing therapy in interpersonal violence survivors with PTSD. In: International Society for Traumatic Stress Studies Annual Conference. Baltimore; 2–5 Nov 2012.
53. Galovski TE, Harik JM, Blain LM, Elwood L, Gloth C, Fletcher TD. Augmenting cognitive processing therapy to improve sleep impairment in PTSD: a randomized controlled trial. J Consult Clin Psychol. 2016;84:167–77.
54. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice. Psychiatry Res. 1989;28:193–213.
55. Moore M. Hypnosis and post-traumatic stress disorder. Aus J Cli Exp Hypn. 2001;29(2):93–106.
56. Carter C. The use of hypnosis in the treatment of PTSD. Aus J Clin Exp Hypn. 2005;33(1):82–92.
57. DeViva JC, Zayfert C, Pigeon WR, Mellman TA. Treatment of residual insomnia after CBT for PTSD: case studies. J Trauma Stress. 2005;18(2):155–9.
58. Ahearn EP, Krohn A, Connor KM, Davidson JR. Pharmacologic treatment of posttraumatic stress disorder: a focus on antipsychotic use. Ann Clin Psychiatry. 2006;15(3/4):193–201.
59. Hamner MB, Dietsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP. Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. J Clin Psychopharmacol. 2003;23(1):15–20.
60. Butterfield M, Becker ME, Connor KM, Sutherland S, Churchill LE, Davidson JRT. Olanzapine in the treatment of posttraumatic stress disorder: a pilot study. Int Clin Psychopharmacol. 2001;16(4):197–203.
61. Petty F, Brannan S, Casada J, et al. Olanzapine treatment for posttraumatic stress disorder: an open-label study. Int Clin Psychopharmacol. 2001;16(6):331–7.
62. Stein MB, Klein NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry. 2002;159(10):1777–9.
63. Eidelman I, Seedat S, Stein DJ. Risperidone in the treatment of acute stress disorder. Depress Anxiety. 2005;11(4):187–8.
64. Krashin D, Oates EW. Risperidone as an adjunct therapy for posttraumatic stress disorder. Mil Med. 1999;164(8):605–6.
65. Lebya CM. Risperidone in PTSD. Psychiatr Serv. 1998;49(2):245–6.
66. Raskind MA, Thompson C, Petrie EC, Dobie DJ, Rein RJ, Hoff DJ, McFall ME, Peskind ER. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry. 2002;63(8):565–8.
67. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall ME. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.
68. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Fross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61(8):928–34.
69. Boynton L, Bentley J, Strachan E, Barbato A, Raskind M. Preliminary findings concerning the use of prazosin for the treatment of posttraumatic nightmares in a refugee population. J Psychiatr Pract. 2009;15(6):454–9.
70. Brkanac Z, Pastor JF, Storck M. Prazosin in PTSD. J Am Acad Child Adolesc Psychiatry. 2003;42(4):384–5.
71. Daly CM, Doyle ME, Raskind M, Raskind E, Daniels C. Clinical case series: the use of prazosin for combat-related recurrent nightmares among operation Iraqi freedom combat veterans. Mil Med. 2005;170(6):513–5.
72. Griffith LJ. Case report: use of prazosin for treatment of posttraumatic stress disorder. Am Fam Physician. 2005;72(5):758–61.
73. Peskind ER, Bonner LT, Hoff DJ, Raskind MA. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. J Geriatr Psychiatry Neurol. 2003;16(3):165–71.
74. Raskind MA, Dobie DJ, Kanter ED, Petrie EC, Thompson CE, Peskind ER. The alpha-1 adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2000;61(2):129–33.
75. Taylor F, Raskind MA. The alpha-1 adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. J Clin Psychopharmacol. 2002;22(1):82–5.
76. Geracioti TD, Baker DG, Edhator NN, et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158(8):1227–30.
77. Resick PA, Williams LF, Suvak MK, Monson CM, Gradus JL. Long-term outcomes of cognitive–behavioral treatments for posttraumatic stress disorder among female rape survivors. J Consult Clin Psychol. 2011;80:201–10.
78. Schnurr PP, Friedman MJ, Engel CC, Foa EB, Shea MT, Chow BK, Resick PA, Thurston V, Orsillo SM, Haug R, Turner C, Bernardy N. Cognitive-behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA. 2007;297(8):820–30.
79. Harpaz-Rotem I, Rosenheck RA. Tracing the flow of knowledge: geographic variability in the diffusion of prazosin use for the treatment of posttraumatic stress disorder nationally in the Department of Veterans Affairs. Arch Gen Psychiatry. 2009;66(4):417–21.

Imagery Rehearsal Therapy for PTSD-Related Nightmares

26

Amanda J. Countryman and Melanie K. Leggett

Introduction

Nightmares are a common, persistent, and distressing sleep complaint among individuals with post-traumatic stress disorder (PTSD), representing a classic reexperiencing symptom of the disorder. Frequent nightmares, estimated to affect 4–10% of the general population, occur at a much higher rate in PTSD; as many as 70% of individuals with PTSD report nightmares [1, 2]. The prevalence rates of nightmares in combat-exposed military veterans with PTSD range from 52% to 88% compared to <5% prevalence in veterans without PTSD [3–6].

Nightmares have characteristics unique to PTSD and combat-related trauma in particular. Common nightmare themes in PTSD include threat, anxiety, and aggression, with nightmare content often replicating the trauma memory [2, 7]. Veterans with combat-related PTSD are more likely to report nightmares with direct reference to combat experience or centering on an actual event when compared to nightmare sufferers without PTSD [8]. Furthermore, combat exposure in Vietnam veterans is highly correlated with the frequency of nightmares [5]. Even though PTSD is associated with disturbed sleep, trauma nightmares in combat-related PTSD may have specific sleep-disruptive effects beyond non-trauma nightmares such as increased wake time during the night [9]. Factors endemic to the combat experience (e.g., deployment stress, circadian misalignment, sleep deprivation, volitional efforts to maintain vigilance, substance use, post-deployment reintegration) likely increase susceptibility to insomnia and nightmares, which may persist well into post-deployment life [10, 11].

Given that the content of dreams often centers on trauma-related memories, theoretical underpinnings have been proposed to account for the function of memory recall during rapid eye movement (REM) sleep. Evidence from experimental and observational studies suggests that dreams may in part influence emotional adaptation to stress [7]. Though the exact neurobiological mechanisms remain unknown, REM sleep may function in the adaptive processing of memories. Individuals who develop enduring post-traumatic stress reactions exhibit some compromised adaptive memory-processing functions with respect to dream consolidation [7]. A neurobiological model of the interactions between sleep and PTSD has been proposed [12], with preliminary support proffered by a neuroimaging study that showed hypermetabolism in neural regions associated with arousal and fear during REM sleep and wakefulness in combat veterans with PTSD compared to veterans without PTSD [13]. In addition to neurological changes observed in PTSD, when trauma memories continue to predominate in the form of recurring nightmares, reinforcement of the trauma memory with accompanying emotional distress may occur [7]. Therapies that target trauma scenarios in dreaming may help the nightmare sufferer develop new cognitive networks of association and successfully process emotionally salient memories, so as to reduce the frequency of nightmare symptoms [7].

Several pharmacologic and cognitive-behavioral therapies for PTSD have proven effective in the treatment of more global symptomatology; however, clinical and experimental evidence suggests that disturbed sleep, including nightmares, often persists after frontline PTSD interventions [3, 7, 14, 15]. Chronic nightmares also may contribute to the

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maintenance of insomnia, resulting in additional impairments in sleep and daytime functioning. Taken together, these findings highlight the importance of effective nightmare treatment.

Imagery Rehearsal Therapy (IRT)

History of IRT

Imagery Rehearsal Therapy (IRT) is a cognitive-behavioral intervention, the primary components of which involve the patient rewriting or altering the story line of a nightmare in any way he or she chooses and mentally practicing the new story via imagery rehearsal techniques. In the1970s and 1980s, common psychological interventions for nightmares included relaxation, desensitization, and rehearsal techniques. IRT emerged out of this milieu and has been developed, tested, and refined over the past 25 years. Early proponents of IRT included a team of researchers at the University of New Mexico School of Medicine [16, 17]. Initial studies from this group tested samples of chronic nightmare sufferers recruited from the community, but subsequent IRT protocols have been applied to trauma survivors, including PTSD sufferers and victims of combat exposure [2, 17–23]. Over the past decade, research on IRT has flourished, and in 2010, the Standards of Practice Committee of the American Academy of Sleep Medicine recommended IRT as a top-level treatment for nightmare disorder [24].

Treatment Rationale

IRT conceptualizes chronic nightmares as a learned behavior, symptomatic of a malfunctioning imagery system [25]. The following assumptions are made about nightmares: (1) they are caused by trauma but sustained over time by habit; (2) they serve an important purpose in processing emotions related to the trauma but, over time, may no longer be beneficial and instead disturb sleep; and (3) they are a form of negative mental imagery [26]. Although the therapeutic mechanism of IRT is unknown, it is assumed that nightmare symptoms can be altered through relearning that occurs by accessing the mental imagery system during wakefulness. IRT provides the patient a means of coping with nightmares that often have been distressing and unrelenting for many years. Out of this history of helplessness, the patient develops a sense of control and self-efficacy. Mastery over intrusive images is suggested to be a core feature of therapeutic effectiveness [25, 27]. Although it is not an exposure therapy (in fact, IRT deemphasizes exposure components), some exposure and anxiety reduction may occur as a consequence of focus on the original nightmare.

Treatment Components

Detailed descriptions of IRT and its clinical implementation have been published elsewhere [17, 25, 28]. The intervention typically begins with an educational component about nightmares as a learned behavior amenable to change, as well as a discussion of the relationship between nightmares and disturbed sleep. Presenting the treatment rationale and instilling hope that nightmares can improve may be critical elements in engaging patients in the treatment process. Imagery techniques are introduced, often with a guided imagery practice done in session. The nightmare rescripting instructions are provided as described in Table 26.1. Patients initially are encouraged to rewrite their less distressing dreams until they become more practiced with the intervention before moving on to their worst nightmares.

Similar to other cognitive-behavioral interventions, homework and behavioral self-monitoring are critical components of the IRT protocol. Patients are encouraged to practice the imagery rehearsal of the rewritten dream daily. A nightmare log, such as that developed in our clinic (see Fig. 26.1), may be assigned to quantify the frequency and intensity of nightmares and to measure treatment response throughout the course of treatment. Clinicians have the flexibility to add other relevant behaviors for the patient to record on the nightmare log, such as home imagery practice, nightmare triggers, sleep variables, sleep medication or alcohol use, etc.

Indications and Contraindications

IRT is indicated for the treatment of chronic nightmares, including trauma-related nightmares. In individuals with PTSD, IRT is typically considered an adjunctive intervention targeting nightmare symptoms once psychotherapeutic and/or pharmacologic treatments for PTSD have been optimized. Because imagery techniques can trigger flashbacks, use of IRT may be contraindicated in individuals with severe PTSD symptoms [29]. Other contraindications include individuals with cognitive deficits (e.g., brain injury, inability to access

Table 26.1 Patient instructions for imagery rehearsal therapy

1.	Select a disturbing dream, preferably one of lesser intensity and not a reenactment of a trauma
2.	Change this nightmare in any way you wish
3.	Rehearse this new dream a few minutes each day at a time of your choosing
4.	Continue these instructions every day and consider working with another nightmare to change it into a new dream every 3–7 days, such that you only rehearse one or two new dreams each week

From: Krakow and Zadra [28]

Nightmare Log

Example

Day of the week (that you woke up)	**Monday**								
Calendar date	**3/25/12**								
I had ____ total nightmares last night.	**4**								
Please rate the intensity of each nightmare on the following 10 point scale: 1 = not at all disturbing ----------5 = Moderately disturbing----------10 = extremely disturbing									
Nightmare 1	**2**								
Nightmare 2	**5**								
Nightmare 3	**1**								
Nightmare 4	**8**								
Nightmare 5									
Nightmare 6									
I was awakened from sleep by nightmares ____ times.	**2**								
My awakenings due to nightmares lasted ____ minutes (list each awakening separately).	**20 min.** **45 min.**								
I would rate the quality of last night's sleep as: 1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent	**2**								

Fig. 26.1 Nightmare log

the visual imagery system), severe mental illness, and high levels of anxiety, stress, or avoidance [15, 17].

Treatment Obstacles

Certain challenges in implementing IRT can be anticipated. Because avoidance is a common response to anxiety-provoking nightmares, engaging the patient in the treatment process may be difficult. Indeed, investigators have reported dropout rates exceeding 40% in some samples, with many individuals dropping out before or very early in treatment [2, 30–33]. Patients may be skeptical about their ability to change nightmares or reluctant to engage in a psychological intervention. They may attend return visits having not revised their nightmare or practiced the imagery technique. Some individuals are resistant to changing the nightmare, particularly if it is replicative of a trauma memory, because such a change does not represent the reality of the event. We have found that such patients often respond positively to our "movie mogul" analogy wherein they are encouraged to pretend they are a movie director, producer, screenwriter, and starring actor of their new story line. This perspective may enhance the creative flexibility to create a new story. Overall, these challenges bespeak the importance of the therapeutic relationship for developing rapport and fostering treatment credibility.

Adverse effects related to IRT have been described [20, 24]. Patients engaging in imagery rehearsal may experience negative, distracting, or intrusive images. Teaching skills to help patients normalize and manage such experiences typically are incorporated into the IRT protocol [28]. Additionally, IRT may exacerbate PTSD symptoms in some cases [2, 24]. Clinically, we sometimes experience this phenomenon with patients who do not adhere to treatment recommendations and instead focus on their distressing nightmare while failing to complete the rescripting and rehearsal steps.

Treatment Modifications

Various treatment modifications have emerged as IRT has grown. These variations include elements of the technique itself, the application of IRT to special populations, and alterations in treatment duration, delivery, and format. IRT has also been combined with other therapies in attempts to maximize therapeutic success.

Treatment Protocol Variants

Original IRT protocols included the patient instruction to write down the relevant nightmare before rewriting the story line. Some clinicians have removed this component in order to reduce the chance that the patient will focus on the original nightmare [28]. Although the only rescripting guidance involves instructing the patient to change the

nightmare in any way he or she desires, many clinicians encourage the use of pleasant imagery and/or nonviolence in the new version. Some clinicians may suggest story line changes or, in a group therapy context, encourage group discussion on nightmare alterations [19]. However, Krakow and colleagues [22, 29] caution against suggesting dream changes to patients, as it may impede the development of self-efficacy or limit treatment acceptance by the patient. Harb et al. [34] evaluated the revised dream scripts in 40 US veterans with combat-related PTSD (Vietnam era) enrolled in an IRT research study. A poorer treatment response to IRT was associated with violent references in the rescripted story, supporting the clinical inclination to encourage nonviolent themes. Interestingly, patients whose rescripted stories addressed or "resolved" the theme of their target nightmare reported less sleep disturbance.

Although historically IRT has been implemented in adult nightmare sufferers and trauma survivors, recent variants have emerged for use in other populations. For example, IRT has been adapted for use with both children and adolescents [29, 35, 36]. An IRT protocol also has been developed for use in deployed military personnel and includes education specific to combat-related PTSD [22].

Treatment Delivery, Duration, and Format

IRT can be delivered effectively in group or individual therapy formats [23, 30, 37]. The course of treatment typically is completed in less than 3 months. Protocols for group therapy recommend four sessions, with a total therapy investment time of 10 h or less [17, 22, 28]. However, treatment gains also have been documented after single-session group interventions [38–40]. A recent meta-analysis by Hansen et al. [33] failed to detect an association between IRT treatment dosage and outcomes, suggesting that an effective treatment response can be obtained with a low treatment dosage such as a single session.

Inexpensive and cost-effective formats of IRT that can be widely disseminated through the use of patient-guided or technology-based interventions are being developed. Lancee et al. [41, 42] tested a 6-week self-help IRT workbook intervention, which was effective in reducing nightmare frequency. However, there is some indication from meta-analytic studies that the individual therapy format for IRT is more effective than self-help formats [30, 37]. Moore and Krakow [22] highlight the portability and flexibility of IRT, making it easily adaptable to military veterans and deployed personnel. Recently, the US Department of Defense launched a free mobile app, "Dream EZ," designed to support military service personnel receiving IRT treatment under the guidance of a trained healthcare provider [43]. The effectiveness of the emerging technology formats has yet to be established.

Combination Treatment

The combination of IRT with other sleep or trauma-focused techniques is an increasing trend. Efforts to target PTSD symptoms, such as anxiety and insomnia, in addition to nightmares, have led to treatments that combine IRT with elements of exposure therapy for PTSD, relaxation, mindfulness, and/or cognitive-behavioral therapy for insomnia (CBTI; e.g., sleep hygiene, stimulus control, sleep restriction, cognitive therapy) [44–51]. Although comparatively fewer studies have investigated the effectiveness of these combinations, two such approaches, Exposure, Relaxation, and Rescripting Therapy (ERRT) [52] and Sleep Dynamic Therapy [53], both of which contain an IRT component, have enough evidence to be considered for treatment of PTSD-related nightmares [24]. ERRT has been successfully adapted for use in a veteran population [44, 49].

Combination treatments appear to be equally effective in reducing nightmare frequency compared to IRT alone [37]. Studies combining IRT with CBTI have shown a greater therapeutic impact on sleep quality [31, 37] compared to IRT alone as well as a greater reduction in post-traumatic stress symptoms [37]. These findings are mirrored in studies of US military veterans receiving various IRT combination treatments [44, 45, 47, 49–51]. Two uncontrolled studies testing different IRT combination treatments in veterans with combat-related PTSD also reported significant posttreatment improvements in nightmares and sleep, with equivocal findings for amelioration of PTSD symptoms [47, 50].

Empirical Support

Among psychotherapy interventions for nightmares, IRT has received the most empirical support and has the highest recommendations for nightmare treatment based on substantial clinical data and strength of clinical consensus [24, 54]. Several meta-analytic reviews of IRT over the past few years have substantiated these clinical recommendations for samples that have included civilian and veteran populations [31, 33, 37]. IRT reduces nightmare frequency, improves sleep quality, and alleviates PTSD symptoms and other measures of psychological distress, with treatment effect sizes in the moderate to large range [30, 31, 33, 37, 55]. Furthermore, the therapeutic benefits of IRT are maintained long term [2, 31, 56–58, 59], with one study of civilian nightmare sufferers showing sustained treatment gains at 2.5 years follow-up [57]. Whether individuals with a PTSD diagnosis benefit

from IRT equally to those without a PTSD diagnosis is difficult to discern due to variations in sample reporting [30], although one small uncontrolled study suggests that individuals with PTSD may have a muted response to IRT treatment [60]. However, a recent randomized controlled study compared IRT to treatment as usual in an outpatient psychiatric population with nightmares and a diverse array of psychiatric disorders (including PTSD) [55]. The patients receiving IRT showed a significant reduction in nightmare symptoms, suggesting that individuals with psychopathology and comorbid nightmares can benefit from IRT.

Given the high rates of PTSD and sleep disturbances in military service members, there is growing interest in the application of IRT to military populations. Meta-analytic reviews suggest that military/veteran populations benefit as much as civilian populations in their posttreatment reductions in nightmare frequency and PTSD symptoms [31, 37]. Sleep quality outcomes are less clear, with one meta-analytic review reporting that civilian participants showed greater improvement in sleep quality compared to veteran participants [31], a finding that was not replicated in a second review [37]. Several investigators have recognized a potential benefit of trauma-focused PTSD treatment in preparing veterans for a successful therapeutic engagement in IRT [21, 23, 56, 61], although conditions determining the optimal sequencing of treatments remain to be elucidated. Difficulties with IRT treatment engagement and adherence in veterans have been observed [21, 23, 61] and will be an important focus of future research.

Future Directions

IRT is an effective short-term intervention that is both inexpensive and flexible. It is an attractive alternative for individuals who may be seeking non-pharmacologic approaches for treating nightmares. Pharmacologic treatments such as prazosin provide symptomatic relief of nightmares in combat veterans, the benefits of which may be lost after medication withdrawal [62]. In contrast, IRT provides therapeutic benefit long after the treatment is concluded, in a manner that is empowering to the patient.

Clearly, additional randomized controlled trials with larger veteran samples are needed to further clarify the benefits of IRT. The literature to date is limited not only by a paucity of randomized controlled study designs but also by variations in IRT treatment approaches and the use of different outcome measures to assess nightmares, insomnia, and PTSD. Developing a standardized treatment approach along with measures of treatment integrity and fidelity is needed to advance understanding [33]. In addition to measuring primary outcomes, investigators should explore secondary outcomes such as depression and anxiety. Dismantling studies are needed to reveal the therapeutic mechanisms or active ingredients of IRT. Further, the optimal dose of IRT (e.g., number and length of sessions) remains to be determined, along with the relative benefits of group versus individual formats. Combining IRT with other treatments for PTSD and/or insomnia shows much promise, although more information is needed on how to best apply these approaches. The optimal sequencing of IRT relative to trauma-focused therapy for PTSD as well as any additive benefit from prior trauma processing is unclear.

Additionally, studies are needed to clarify patient variables that influence IRT success in veterans. Such variables include comorbid psychiatric or medical disorders, nightmare content or type (e.g., recurrent, trauma related, replicative), PTSD severity, and era of military service. As others have noted, younger veterans returning from current conflicts and reassimilating into civilian life experience unique stressors (e.g., traumatic brain injury, threat of redeployment) and life situations (e.g., inflexible work or school schedules) that may impact their ability to engage in treatment [47, 51]. IRT may need to be tailored to suit the needs of these individuals. An important question with veterans newly exposed to trauma is whether early intervention with IRT could prevent or mitigate future PTSD symptoms.

Given that avoidance behaviors are characteristic of PTSD and that prior IRT studies have shown high dropout rates, factors related to treatment acceptance, adherence, and retention are of particular importance. The use of alternative treatment delivery formats such as self-help books or internet-based applications may reach a wider audience of veterans, but their relative success remains unexplored.

Summary

Although there have been few studies directly examining the efficacy of IRT for veterans exclusively with combat-related PTSD, data from initial meta-analytic reviews corroborate the effectiveness of IRT in nightmare and PTSD symptom reduction. IRT has demonstrated good success across multiple settings and diverse populations and holds much promise for ameliorating nightmares and related distress in combat veterans.

References

1. Levin R, Nielsen TA. Disturbed dreaming, posttraumatic stress disorder, and affect distress: a review and neurocognitive model. Psychol Bull. 2007;133(3):482–528.
2. Wittmann L, Schredl M, Kramer M. Dreaming in posttraumatic stress disorder: a critical review of phenomenology, psychophysiology and treatment. Psychother Psychosom. 2007;76:25–39.

3. Forbes D, Creamer M, Biddle D. The validity of the PTSD checklist as a measure of symptomatic change in combat-related PTSD. Behav Res Ther. 2001;39:977–86.
4. Holowka DW, Marx BP, Kaloupek DG, Keane TM. PTSD symptoms among male Vietnam veterans: prevalence and associations with diagnostic status. Psychol Trauma. 2011; doi:10.1037/a0023267.
5. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
6. Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75:546–50.
7. Mellman TA, Pigeon WR. Dreams and nightmares in posttraumatic stress disorder. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th ed. New York: Elsevier; 2011. p. 613–9.
8. van der Kolk B, Blitz R, Burr W, Sherry S, Hartmann E. Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry. 1984;141(2):187–90.
9. Woodward SH, Arsenault NJ, Murray C, Bliwise DL. Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry. 2000;48:1081–7.
10. Bramoweth AD, Germain A. Deployment-related insomnia in military personnel and veterans. Curr Psychiatry Rep. 2013;15(10):401. doi:10.1007/s11920-013-0401-4.
11. Mysliwiec V, Gill J, Lee H, et al. Sleep disorders in US military personnel: a high rate of comorbid insomnia and obstructive sleep apnea. Chest. 2013;144(2):549–57.
12. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95.
13. Germain A, James J, Insana S, et al. A window into the invisible wound of war: functional neuroimaging of REM sleep in returning combat veterans with PTSD. Psychiatry Res. 2013;211(2):176–9.
14. Pruiksma KE, Taylor DJ, Wachen JS, et al. (For the STRONG STAR Consortium). Residual sleep disturbances following PTSD treatment in active duty military personnel. Psychol Trauma. 2016.; http://dx.doi.org/10.1037/tra0000150.
15. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12:169–84.
16. Kellner R, Singh G, Irigoyen-Rascon F. Rehearsal in the treatment of recurring nightmares in posttraumatic stress disorders and panic disorder: case histories. Ann Clin Psychiatry. 1991;3:67–71.
17. Krakow B. Imagery rehearsal therapy for chronic posttraumatic nightmares: a mind's eye view. In: Rosner RI, Lyddon WJ, Freeman A, editors. Cognitive therapy and dreams. New York: Springer Publishing Co; 2003. p. 89–109.
18. Cook JM, Harb GC, Gehrman PR, et al. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. J Trauma Stress. 2010;23(5):553–63.
19. Forbes D, Phelps A, McHugh T. Treatment of combat-related nightmares using imagery rehearsal: a pilot study. J Trauma Stress. 2001;14(2):433–42.
20. Krakow B, Hollifield M, Johnston L, et al. Imagery rehearsal for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001;286(5):537–45.
21. Lu M, Wagner A, Van Male L, Whitehead A, Boehnlein J. Imagery rehearsal therapy for posttraumatic nightmares in U.S. veterans. J Trauma Stress. 2009;22(3):236–9.
22. Moore BA, Krakow B. Imagery rehearsal therapy: an emerging treatment for posttraumatic nightmares in veterans. Psychol Trauma. 2010;2(3):232–8.
23. Nappi CM, Drummond SPA, Thorp SR, McQuaid JR. Effectiveness of imagery rehearsal therapy for the treatment of combat-related nightmares in veterans. Behav Ther. 2010;41:237–44.
24. Aurora RN, Zak RS, Auerbach SH, et al. Standards of practice committee, American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
25. Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. Behav Sleep Med. 2006;4(1):45–70.
26. Krakow B, Hollifield M, Schrader R, et al. A controlled study of imagery rehearsal for chronic nightmares in sexual assault survivors with PTSD: a preliminary report. J Trauma Stress. 2000;13(4):589–609.
27. Germain A, Krakow B, Faucher B, et al. Increased mastery elements associated with imagery rehearsal treatment for nightmares in sexual assault survivors with PTSD. Dreaming. 2004;14(4):195–206.
28. Krakow B, Zadra A. Imagery rehearsal therapy: principles and practice. Sleep Med Clin. 2010;5(2):289–98.
29. Krakow B. Imagery rehearsal therapy for adolescents. In: Perlis M, Aloia M, Kuhn B, editors. Behavioral treatments for sleep disorders. Burlington: Elsevier; 2011. p. 333–42.
30. Augedal A, Hansen KS, Kronhaug CR, Harvey AG, Pallesen S. Randomized controlled trials of psychological and pharmacological treatments for nightmares: a meta-analysis. Sleep Med Rev. 2013;17(2):143–52.
31. Casement MD, Swanson LM. A meta-analysis of imagery rehearsal for post-trauma nightmares: effects on nightmare frequency, sleep quality, and posttraumatic stress. Clin Psychol Rev. 2012;32(6):566–74.
32. Harb GC, Phelps AJ, Forbes D, Ross RJ, Gehrman PR, Cook JM. A critical review of the evidence base of imagery rehearsal for posttraumatic nightmares: pointing the way for future research. J Trauma Stress. 2013;26(5):570–9.
33. Hansen K, Höfling V, Kröner-Borowik T, Stangier U, Steil R. Efficacy of psychological interventions aiming to reduce chronic nightmares: a meta-analysis. Clin Psychol Rev. 2013;33(1):146–55.
34. Harb GC, Thompson R, Ross RJ, Cook JM. Combat-related PTSD nightmares and imagery rehearsal: nightmare characteristics and relation to treatment outcome. J Trauma Stress. 2012;25(5):511–8.
35. Simard V, Nielsen T. Adaptation of imagery rehearsal therapy for nightmares in children: a brief report. Psychotherapy. 2009;46(4):492–7.
36. St-Onge M, Mercier P, De Koninck J. Imagery rehearsal therapy for frequent nightmares in children. Behav Sleep Med. 2009;7(2):81–98.
37. Seda G, Sanchez-Ortuno MM, Welsh CH, Halbower AC, Edinger JD. Comparative meta-analysis of prazosin and imagery rehearsal therapy for nightmare frequency, sleep quality, and posttraumatic stress. J Clin Sleep Med. 2015;11(1):11–22.
38. Germain A, Nielsen T. Impact of imagery rehearsal treatment on distressing dreams, psychological distress, and sleep parameters in nightmare patients. Behav Sleep Med. 2003;1(3):140–54.
39. Kellner R, Neidhardt J, Krakow B, Pathak D. Changes in chronic nightmares after one session of desensitization or rehearsal instructions. Am J Psychiatry. 1992;149(5):659–63.
40. Neidhardt E, Krakow B, Kellner R, Pathak D. The beneficial effects of one treatment session and recording of nightmares on chronic nightmare sufferers. Sleep. 1992;15(5):470–3.
41. Lancee J, Spoormaker VI, van den Bout J. Cognitive-behavioral self-help treatment for nightmares: a randomized controlled trial. Psychother Psychosom. 2010;79(6):371–7.
42. Lancee J, Spoormaker V, van den Bout J. Long-term effectiveness of cognitive–behavioural self-help intervention for nightmares. J Sleep Res. 2011;20(3):454–9.
43. National Center for Telehealth & Technology (T2). http://t2health.dcoe.mil/about.html.

44. Balliett NE, Davis JL, Miller KE. Efficacy of a brief treatment for nightmares and sleep disturbances for veterans. Psychol Trauma. 2015;7(6):507–15.
45. Germain A, Richardson R, Moul DE, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in U.S. military veterans. J Psychosom Res. 2012;72:89–96.
46. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. Behav Res Ther. 2007;45(3):627–32.
47. Harb GC, Cook JM, Gehrman PR, Gamble GM, Ross RJ. Posttraumatic stress disorder nightmares and sleep disturbance in Iraq war veterans: a feasible and promising treatment combination. J Aggress Maltreat Trauma. 2009;18(5):516–31.
48. Krakow B, Johnston L, Melendrez D, et al. An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. Am J Psychiatry. 2001;158(12):2043–7.
49. Long ME, Hammons ME, Davis JL, et al. Imagery rescripting and exposure group treatment of posttraumatic nightmares in veterans with PTSD. J Anxiety Disord. 2011;25:531–5.
50. Swanson LM, Favorite TK, Horin E, Arnedt JT. A combined group treatment for nightmares and insomnia in combat veterans: a pilot study. J Trauma Stress. 2009;22(6):639–42.
51. Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. J Clin Sleep Med. 2011;7(1):57–68.
52. Davis JL, Wright DC. Case series utilizing exposure, relaxation, and rescripting therapy: impact on nightmares, sleep quality, and psychological distress. Behav Sleep Med. 2005;3(3):151–7.
53. Krakow BJ, Melendrez DC, Johnston LG, et al. Sleep dynamic therapy for Cerro Grande fire evacuees with posttraumatic stress symptoms: a preliminary report. J Clin Psychiatry. 2002;63(8):673–84.
54. Lancee J, Spoormaker VI, Krakow B, van den Bout J. A systematic review of cognitive-behavioral treatment for nightmares: toward a well-establish treatment. J Clin Sleep Med. 2008;4(5):475–80.
55. van Schagen AM, Lancee J, de Groot IW, Spoormaker VI, van den Bout J. Imagery rehearsal therapy in addition to treatment as usual for patients with diverse psychiatric diagnoses suffering from nightmares: a randomized controlled trial. J Clin Psychia. 2015;76(9):1105–13.
56. Forbes D, Phelps AJ, McHugh AF, Debenham P, Hopwood M, Creamer M. Imagery rehearsal in the treatment of posttraumatic nightmares in Australian veterans with chronic combat-related PTSD: 12-month follow-up data. J Trauma Stress. 2003;16(5):509–13.
57. Krakow B, Kellner R, Neidhardt J, Pathak D, Lambert L. Imagery rehearsal treatment of chronic nightmares: with a thirty month follow-up. J Behav Ther Exp Psychiatry. 1993;24(4):325–30.
58. Krakow B, Kellner R, Pathak D, Lambert L. Long term reduction of nightmares with imagery rehearsal treatment. Behav Cogn Psychother. 1996;24(2):135–48.
59. van Schagen AM, Lancee J, Spoormaker VI, van den Bout J. Long-term treatment effects of imagery rehearsal therapy for nightmares in a population with diverse psychiatric disorders. Inter J Dream Res. 2016;9(1):67–70.
60. Thünker J, Pietrowsky R. Effectiveness of a manualized imagery rehearsal therapy for patients suffering from nightmare disorders with and without a comorbidity of depression or PTSD. Behav Res Ther. 2012;50(9):558–64.
61. Cook J, Thompson R, Harb GC, Ross RJ. Cognitive−behavioral treatment for posttraumatic nightmares: an investigation of predictors of dropout and outcome. Psychol Trauma. 2013;5(6):545–53.
62. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.

Nightmare Deconstruction and Reprocessing for PTSD Nightmares

27

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The increased prevalence of post-traumatic stress disorder (PTSD) among military personnel and veterans in the OEF/OIF/OND era has highlighted the challenges of treating PTSD and nightmares and other sleep disturbances which are among the most common refractory symptoms. This chapter introduces a psychotherapy called Nightmare Deconstruction and Reprocessing (NDR), a novel approach that combines deconstruction of and exposure to nightmare images, meaning making and reprocessing, and dream reconstruction.

Nightmares are a signature symptom of PTSD, occurring in up to 71% of PTSD patients [18]. Their occurrence predicts reactivation of PTSD symptoms [25] and correlates with comorbid anxiety, depression, and suicidality [3, 27]. In spite of significant effort given to developing PTSD treatments over the past decade, and despite evidence that nightmares and sleep disturbance play a major role in PTSD etiology and chronicity, most evidence-based psychotherapies do not target nightmares directly, and these symptoms often remain refractory following treatment [30]. 0. [21], one of the most widely used evidence-based treatments (EBTs), is based on fear memory extinction [23] and emotional processing [7] theories but does not target nightmares directly. Nor does cognitive processing therapy (CPT; [22]), a treatment based on information processing theory [17]. Imagery rehearsal therapy (IRT; [16]) does target trauma-related nightmares and has shown to be an effective treatment [4], but it does not utilize exposure or processing techniques. IRT focuses on psychoeducation and rescripting the nightmare while avoiding processing content because it is believed to reinforce the patient's nightmare habit. Avoiding nightmare content, however, misses the opportunity for exposure and processing which would facilitate fear memory extinction and reconsolidation.

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Growing evidence indicates that new experiences are consolidated into memory during REM and NREM sleep ([5, 20]), that newly learned material is reflected in dream content [32], and that dreams may play a role in new learning [33]. For established memories to be reconsolidated, they must be reactivated with sufficient emotional arousal to make them malleable [8, 26]. Thus, if nightmares play a role in trauma memory consolidation and if fear memory extinction and reconsolidation require exposure and reactivation of nightmare content, it makes sense to develop treatments for nightmares that use exposure and processing techniques.

NDR Origins and Preliminary Findings

Nightmare Deconstruction and Reprocessing integrates exposure through deconstruction of nightmare images, meaning making and reprocessing of maladaptive thoughts related to the nightmare and trauma, and reconstruction and rehearsal of a new dream into a three-stage approach to treating PTSD nightmares. NDR was adapted from the cognitive-experiential dream model (CEDM; [11, 12]). Like CEDM, NDR is a staged approach to working with dreams, with modifications tailored to working with trauma-related nightmares.

NDR integrates multiple theoretical approaches across the three stages. The initial stage, deconstruction and exposure, aligns with the extinction [23] and emotional processing [7] theories of exposure treatments through the detailed description and reexperiencing of nightmare images. The second stage, meaning making and reprocessing, is informed by psychodynamic and Gestalt dream theories [1, 6, 15, 24] in the focus on understanding the meaning of the dream, particularly gaining insight into the self and unconscious thoughts and emotions, and the impact of early experience on dream content. When working with combat veterans, an understanding of how moral injury [19] can intrude upon dream cognition is helpful, and the therapist can focus reprocessing on the patient's guilt, shame, and self-condemnation. Also underlying this stage is Beck's [2] belief that a function of dreams is

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to allow automatic, unrealistic thought patterns to enter awareness. With this knowledge, therapist and patient move beyond reliance on insight alone through the addition of emotional processing [7] and cognitive processing [22] techniques to challenge and reprocess maladaptive cognitions and emotions occurring in nightmares. The reconstruction and rehearsal completed in the third stage are based on memory reconsolidation [8, 26], which is accomplished by reconstructing the dream so that it is consistent with the meaning made and cognitive and emotional reprocessing done in the second stage and by guiding the patient to engage emotionally with the reconstructed dream through repeated rehearsals.

Preliminary findings from a randomized trial of an earlier CEDM adaptation for nightmares [10] indicated a small to moderate effect size for decreases in nightmare frequency and intensity and improved psychosocial functioning and significant increase in insight into nightmares across sessions in 29 civilians with frequent nightmares. Individual case examples ([28]; Personal communication, A. Hummel, LT MSC USN, 12/12/12) in veterans of recent wars show a decrease in PTSD symptoms and a decrease in severity of distressing dreams.

NDR Structure

NDR is a brief therapy of six to eight 60–90-min sessions. The three stages of NDR include: (1) deconstruction and exposure, (2) meaning making and reprocessing, and (3) reconstruction and rehearsal.

The first session comprises psychoeducation on PTSD, nightmares, and sleep, assessment of the patient's trauma history and pattern of nightmares and sleep disturbance, an overview of NDR, assessment of patient motivation for NDR, and practice of stress-reduction and grounding techniques for use in session and for returning to sleep after waking from a nightmare. It also includes an assessment of nightmare history, specifically the presence of nightmares with intolerable distress levels, which would lead to selecting a less disturbing dream to initiate NDR. The provider also introduces the Subjective Units of Distress Scale (SUDS; [34]), linking the importance of emotional arousal to the memory reconsolidation process. The session concludes with introduction and practice of relaxation and grounding techniques to help the patient modulate his or her distress level.

Stage 1: Deconstruction

Subsequent sessions introduce NDR's three-stage structure. Stage 1, deconstruction and exposure, lasts 30–45 min and is focused on detailed description and reexperiencing of nightmare images. Inherent in image deconstruction is exposure to nightmare content. The patient begins by retelling the nightmare in the first person, present tense, to facilitate reexperiencing. Patient and provider collaborate in choosing three to five key images. Each image is deconstructed using the four DRAW steps adapted from CEDM [12], illustrated in Table 27.1.

Table 27.1 DRAW steps

Describe the image in detail, including color, size, smells, and sounds. Encourage more detail: "Say I'm from another planet and have no knowledge of IEDs, how would you describe one to me?"
Reexperience emotions that were experienced with this specific image. Encourage the patient to identify present feelings: "How do you feel about it as we talk about it now?"
Associate the specific image to past experiences. Encourage associations from childhood, adult life, or earlier trauma: "Does this image remind you of any experiences you've had before?"
Waking life triggers that occurred at the time of the dream. Encourage associations with current life events: "What's going on in your life right now that might have triggered the dream?"

The reexperiencing step is likely to generate high distress levels. Optimal arousal level is important; reconsolidation requires that memory of the nightmare be reactivated in order to make it labile and subject to reconsolidation. Arousal level must not be so high as to overwhelm the patient and thereby reinforce the nightmare memory. The use of the SUDS with each image along with grounding techniques allows the patient to stay emotionally engaged but not overwhelmed. The patient may resist associating with past or present life experiences, particularly if their reexperiencing was very distressing. Again, grounding techniques can reduce arousal to a level that allows association. The patient repeats the *DRAW* steps for each image, with the images deconstructed in the order in which they occurred in the nightmare. When all images have been deconstructed, the patient summarizes the images, and the provider adds any essential elements the patient omits.

Stage 2: Meaning Making/Reprocessing

After deconstruction, many patients have a much more detailed understanding of nightmare content. Meaning making and reprocessing provide the tools and opportunity to gain deeper understanding, process grief and loss, discuss unresolved existential crises, evaluate fear and anxiety, and challenge negative self-image related to guilt or moral injury. This stage has two main steps: (1) find meaning in the nightmare through understanding the sources of distress and (2) reprocess thoughts and feelings with the goal of decreasing the distress level triggered by the nightmare images.

To engage the patient in making meaning, the provider asks the patient about the overall meaning of the nightmare. How this question is framed depends on the nightmare con-

tent, whether the patient has asked for a meaning or whether she or he already has come up with a meaning. For example, the provider might ask:

- "What do you think the dream means?"
- "I'll tell you what I think, but before I do, because this is your dream, it's important that we examine what it means to *you*."
- "What do you think it means about you as a [soldier, man, woman, father, mother, etc.]?

Once the patient gives an initial impression, the provider asks if anything in the nightmare was particularly distressing or puzzling. This image is the emotional core of the dream and provides guidance on an appropriate level of meaning making. During reprocessing, it also forms a basis for understanding and challenging perceptions about the nightmare or trauma. As a defense against overwhelming reexperiencing, patients may be inclined toward shallower levels of meaning such as, "Well, I watched 'American Sniper' last night, so that's probably why I had this nightmare again." It is important to respect the patient's experience of the trauma; a shallower level of meaning may be what is tolerable initially. However, it is important to encourage the patient gain as full an understanding as possible. If the patient has difficulty coming up with an initial meaning, the provider can offer a meaning, following up by asking the patient how the meaning seems to fit. Possible levels of meaning include:

- *The dream itself as an experience*: This level can be useful for bereavement dreams in which a deceased person is alive again or if the nightmare is an exact reexperience of traumatic events. For bereavement dreams, the provider can ask, "Imagine that the dream was an experience that you *actually had*. What would this mean about you and your relationship to _____? What was it like for you to talk with him? Is there anything you didn't say in the dream that you wish you had said to him?" If it is a direct reexperiencing of the trauma, focus on the central, most intense image.
- *Waking life events:* This level can be useful if the patient has experienced a subsequent trauma since the index event or met with an unexpected trigger. The provider might ask, "Has anything happened recently that might have caused you to start having these nightmares again?"
- *Inner personality dynamics*: This is a frequent level of meaning making for trauma-related nightmares because traumas challenge the patient's sense of self and the world, but it may also be the most complex and distressing. Within this level are several approaches:
  - Parts of self: The provider tells the patient, "It may be that each image in this dream represents a *part of you.* What part of you is like a ____?" For example, in Dorothy's dream in *The Wizard of Oz*, the "brainless" Scarecrow, "heartless" Tin Man, and "cowardly" Lion represented parts of Dorothy's conflicted self, as when the Scarecrow (brain) scolds the Tin Man (heart) for crying and potentially rusting himself rather than thinking of a way out of their dilemma of being stuck in the poison poppy field.
  - Conflicts originating in childhood: With this approach, the dream represents early childhood conflict or attachment difficulties. Many patients with PTSD have a history of childhood trauma. However, this approach should be used with caution; it may be off-putting to some patients, who might insist, "This is about seeing my buddy get killed. It is *not* about my childhood."
  - Spiritual/existential: Spiritual or existential approaches can have the greatest potential for meaning making, as trauma often challenges the survivor's view of self or the world. The patient can begin a search for meaning by examining questions such as, "What does this dream mean about who I am as a person? Am I now a killer, victim, survivor? Why did God allow this to happen?"

In discussing meaning found in the nightmare, the provider can begin to reprocess grief, loss, fear, guilt, shame, or moral injury and challenge maladaptive thinking contributing to the patient's distress. It is important to evaluate negative thoughts or emotions before challenging them in order to get a clear understanding of stuck points and how grounded in reality the thoughts and feelings are. For example, a patient's guilt about not saving a unit member may or may not be proportionate to his actual responsibility for that member. If the patient had only a tangential relationship with the deceased unit member, the guilt is likely disproportionate, which could be the focus of the challenge. If the individual did in fact bear responsibility for the member's death, then reprocessing may be focused more on the moral injury of failing in his duty.

Stage 3: Reconstruction/Rehearsal

In the final stage, reconstruction and rehearsal, provider and patient collaborate to reconstruct the nightmare with new images. The goal is to construct and incubate a potential dream that incorporates new insights into the nightmare and trauma that will facilitate fear extinction and memory reconsolidation. To begin reconstruction, the provider asks, "Based on how you now understand the nightmare, how would you change it?" Reconstructed images should derive from the patient's new understanding of the nightmare/trauma and should include a detailed description (similar to the "D" of the DRAW steps) and emotional engagement with

the new images. For example, a patient might describe in detail how he would like his lost buddy to appear in the reconstructed dream, including what the buddy is wearing, his facial expressions, and his speech and reactions to what the patient has to say. The provider then guides the patient to engage emotionally with the new image (similar to the "R" of the DRAW steps). For example, the provider might ask the patient to focus on his emotions on seeing his lost buddy and to anticipate how it will feel to see him in the reconstructed dream as they joke around or talk as they used to. The goal is to stimulate emotional arousal sufficient to facilitate reconsolidation of the images into a more tolerable memory, help alleviate distress, and engender a sense of mastery. Therapist and patient then rehearse the dream in session by acting out events, or role play, or other techniques. The patient then rehearses the reconstructed dream just before going to sleep and keeps a dream journal.

In subsequent sessions, any new dream images or themes are deconstructed using the DRAW steps. During meaning making and reprocessing, the focus is on the new images and what the patient believes these changes might mean. Subsequent dream reconstruction is based on the patient's understanding of the changed images. If the patient reports little or no change in the nightmares, deconstruction and exposure may not have been sufficiently activating or, conversely, may have been too intense. The therapist can cycle back to the DRAW steps and work on engaging the patient more intensely with the images if there was a lack of intensity or may utilize grounding techniques to modulate reexperiencing if the SUDS level was too high. It may also be that meaning making and reprocessing were not correctly targeted. Again, the image with the greatest emotional arousal level is usually an appropriate focus for reprocessing. Additionally, the reconstruction may not be appropriate or may require further rehearsal. Follow up with the patient regarding the appropriateness of the reconstructed dream, work to ensure the patient is emotionally engaged with the reconstructed images, and emphasize that the new dream should be rehearsed just prior to sleep.

Once the patient has gained some mastery over the nightmares, which may take several sessions, a third component is added to Stage 3 – making changes to the patient's waking life. These changes should be based on the meaning making, reprocessing, and reconstruction accomplished in previous sessions. Waking life changes might include specific behaviors, such as more interaction with a spouse or activities that help the individual feel less marginalized; conducting a ritual to honor the dream, such as listening to a lost buddy's favorite song; and continuing to work on the dream through journaling or talking with others.

In the final session, provider and patient focus on three tasks: (1) a review of the patient's progress in understanding and mastering nightmares and distressing dreams, (2) a review of waking life changes, and (3) a relapse prevention. To begin the progress review, the provider asks the patient what he learned about himself as well as about PTSD, nightmares, and trauma memory. The provider also asks what was most difficult and why and what the most valuable lessons were. The next task is to review waking life changes that were based on the dream work, specifically, what changes worked best and why, what did not work and why not, and what new changes the patient would like to make. Finally, to facilitate relapse prevention, the provider reviews and reinforces the importance of the patient practicing the newly learned skills of deconstruction, reprocessing, and reconstruction and how to make changes to waking life thoughts, feelings, and behaviors based on what is learned through the NDR process. The provider also encourages the continued use of the dream journal and bringing dream material to regular therapy sessions.

NDR Case Example

RG was a 25-year-old Hispanic male undergraduate at a large mid-Atlantic university. He was a US Army infantry veteran who served two combat tours, during which he had extensive combat exposure. Since separating from the military, RG experienced periods of depression during which his nightmares and insomnia worsened. He lost interest in his usual activities; was irritable with family, friends, and fellow students; and felt isolated. He was otherwise high functioning, doing well academically, and expected to graduate within a year. Treatment consisted of six 75- to 100-min sessions over 3 weeks.

The first session included psychoeducation about nightmares and sleep disturbance in PTSD and an overview of NDR. Nightmare history revealed multiple distressing dreams with military themes and content. He was asked to come to the next session prepared to discuss a specific nightmare. RG seemed highly motivated, explaining that he wanted help with his disturbing dreams.

In the second session, he deconstructed a distressing dream using the three stages. RG described the following nightmare (edited for brevity and confidentiality):

> I'm a police officer in civilian clothes. There are three others with us…. One is a woman…. We search a building [for] children being held in a gymnasium. The rest of the hallway is dark and looks like a hospital…We find bathtubs full of dead bodies and body parts....SWAT comes in, but it's a trap. I get into a firefight… I need a better weapon.

RG picked five key images: civilian clothes, his female partner, dead bodies, the SWAT team, and his weapon. Using the DRAW steps, he deconstructed each image, the SWAT team being the most intense. RG described the SWAT team as heavily armed, dressed in all black, and moving stealthily

through the building. His reexperienced emotions to the SWAT team image were surprise and extreme discomfort tied to vulnerability. Past associations included several combat experiences during which his unit was surprised. He reported no specific waking life triggers but had a pervasive vigilance and dislike of being surprised or startled – not unusual in a PTSD patient. RG was sufficiently emotionally activated to deconstruct the images without needing stress-reduction techniques.

RG's summary of the deconstructed images focused on how his civilian clothes felt inappropriate and his anxiety about his female partner; he felt he had to protect her rather than focus on the mission. The image of the bodies and body parts was distressing but not horrifying and was a reflection of actual combat events. The SWAT team was the most disturbing image and reminded him of his high distress when surprised in combat situations. The inadequate weapon contributed to his vulnerability and discomfort.

RG's understanding of the nightmare at the start of Stage 2 was that it reflected his extreme discomfort with being surprised and the need to be more vigilant, a feeling that was heightened when his unit was caught off guard during deployment. The female partner symbolized someone he had difficulty relying on and who needed protection. This related both to his combat unit being all male and to childhood trauma in which he witnessed a female relative being assaulted and felt powerless to stop it. The SWAT team represented a challenge to his self-image as vigilant and physically superior. Reprocessing focused on his sense of helplessness and vulnerability and on examining events in his life that could challenge those feelings. This led RG to a fuller meaning of the dream and deeper understanding of himself. He was conflicted about his roles as both protector and warrior; he reported that during deployment, he felt like both a sheepdog (protector) and a wolf (aggressor) and was uncertain about how those roles would transfer to his life as a civilian.

Based on this new understanding, RG reconstructed the dream so that his partner was a man, a change he believed would help him feel both less protective and less vulnerable. He also armed himself with a more appropriate weapon and changed the outcome so that his team found the children being held hostage.

Over the remaining sessions, RG presented nightmares with different themes, including distress at being surprised and vulnerable, the presence of family or other civilians in military situations, and isolation from family and friends. Dream content gradually changed so that RG felt less isolated. He also made changes to his waking life that reflected the dream reconstruction, including dating and more interaction with family and friends. His PTSD symptoms improved to a subclinical level, with the greatest changes in avoidance and hypervigilance. He developed a positive attitude toward dreams, and his sleep quality and duration remained good. These results suggest NDR can be useful for PTSD nightmares and sleep disturbance as well as addressing waking life symptoms. Further study is ongoing.

NDR for Combat-Related PTSD

Several aspects of NDR make it a promising treatment for combat-related PTSD. As described above, most current treatments for PTSD improve nightmares indirectly. One challenge to exposure-based therapies is their reliance on vivid retelling of actual trauma experiences. Exposure-based therapies may be poorly tolerated in military populations and associated with high dropout and low response rates [31]. A potential advantage of NDR is that by working with inherently imaginary content, it may therefore be less threatening than vivid retelling. Even though nightmares may be graphic and emotionally distressing, a cognitively intact patient cannot mistake the nightmares as real, even though the trauma informing the nightmare was real. Such a reality buffer may enable the patient to tolerate more vivid imagery, allowing access to distressing autobiographical material within a safe envelope of dream content. Another aspect of NDR that is promising for combat-related PTSD is its emphasis on sleep and dreaming. Sleep disruption is a common and troubling symptom of PTSD reported by veterans [30]. Current exposure-based therapies offer improvement in sleep quality, but only 40% of patients achieve remission of their sleep complaints [9]. Specifically targeting nightmares as a source of sleep disruption and poor sleep quality has the potential to further ameliorate this PTSD symptom.

Conclusion

Given the evidence supporting exposure for fear memory extinction and memory activation for reconsolidation and the roles that sleep and dreaming have in memory consolidation and PTSD chronicity, it makes sense to develop treatment approaches that apply exposure and processing techniques to PTSD nightmares such as NDR. Preliminary results provide evidence of NDR's tolerability and efficacy in reducing nightmare severity [10, 28]. NDR's precursor, CEDM, has been investigated in 25 studies to date, and one of the most consistent findings is that participants rate sessions highly, engage in treatment quickly, and appreciate the insight gained [13, 14, 29]. In addition, NDR's structured stages readily enable adherence checks, study replication, and component dismantling for research purposes and facilitate training and clinical use.

Disclaimer This chapter reflects the views of the authors alone and is not an endorsement of specific interventions or a statement of policy of the Uniformed Services University or the US Department of Defense.

References

1. Adler A. On the interpretation of dreams. Int J Individ Psychol. 1936;2:3–16.
2. Beck A. Cognitive patterns in dreams and daydreams. In: Rosner RI, Lyddon WJ, Freeman A, editors. Cognitive therapy and dreams. New York: Springer Publishing Company; 2004. p. 27–32. (Reprinted from Dream dynamics, pp. 2–7, by J. H. Masserman, Ed., 1971, New York: Grune & Stratton).
3. Bernert RA, Joiner TE, Cukrowicz KC, Schmidt NB, Krakow B. Suicidality and sleep disturbances. Sleep. 2005;28:1135–41.
4. Casement MD, Swansen LM. Meta-analysis of imagery rehearsal for post-trauma nightmares. Clin Psychol Rev. 2012;32:566–74.
5. Dudai Y, Kami A, Born J. The consolidation and transformation of memory. Neuron. 2015;88:20–32.
6. Freud S. The interpretation of dreams. New York: Avon; 1966. (Original work published 1900).
7. Foa E, Huppert J, Cahill S. Emotional processing theory: an update. Pathological anxiety: emotional processing in etiology and treatment. NY: Guilford Press; 2006. p. 3–24.
8. Gisquet-Verrier P, Riccio DC. Memory reactivation effects independent of reconsolidation. Learn Mem. 2012;19:401–9.
9. Gutner CA, Casement MD, Gilbert KS, Resick PA. Change in sleep symptoms across cognitive processing therapy and prolonged exposure: a longitudinal perspective. Behav Res Ther. 2013;51:817–22.
10. Heaton K. An investigation of nightmare-focused treatment using the Hill cognitive-experiential method of dream work. Unpublished doctoral dissertation. College Park: University of Maryland; 2002.
11. Hill CE. Working with dreams in psychotherapy. New York: Guilford Press; 1996.
12. Hill CE, editor. Dream work in therapy: facilitating exploration, insight, and action. Washington, DC: American Psychological Association; 2004.
13. Hill CE, Goates MK. Research on the Hill cognitive-experiential dream model. In: Hill CE, editor. Dream work in therapy: facilitating exploration, insight, and action. Washington, DC: American Psychological Association; 2004. p. 245–88.
14. Hill CE, Knox S. The use of dreams in modern psychotherapy. In: Clow A, McNamara P, editors. International review of neurobiology, vol. 92. New York: Academic Press; 2010. p. 291–317.
15. Jung CG. Dreams (Hull RFC, Trans.). Princeton: Princeton University Press; 1974.
16. Krakow B, Zadra A. Imagery rehearsal therapy: principles and practice. Sleep Med Clin. 2010;5:289–98.
17. Lang PJ. Imagery in therapy: an information analysis of fear. Behav Ther. 1977;8:862–86.
18. Leskin GA, Woodward SH, Young HE, Shiekh JI. Effects of comorbid diagnoses on sleep disturbance in PTSD. J Psychiatr Res. 2002;36:449–52.
19. Litz BT, Stein N, Delaney E, Lebowitz L, Nash WP, Silva C, Maguen S. Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. Clin Psychol Rev. 2009;29:695–706.
20. Llewellyn S, Hobson JA. REM sleep creates and NREM Stage 2 instantiates landmark junctions in cortical memory networks. Neurobiol Learn Mem. 2015;122:69–87.
21. McLean CP, Foa EB. Prolonged exposure therapy for post-traumatic stress disorder: a review of evidence and dissemination. Expert Rev Neurother. 2011;11:1151–63.
22. Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol. 2005;74:898–907.
23. Mowrer OH. On the dual nature of learning – a reinterpretation of conditioning and problem solving. Harv Educ Rev. 1947;17:102–48.
24. Perls F. Gestalt therapy verbatim. New York: Bantam; 1969.
25. Picchioni D, Cabrera OA, McGurk D, Thomas JL, Castro CA, Balkin TJ, Bliese PD, Hoge CW. Sleep symptoms as a partial mediator between combat stressor and other mental health symptoms in Iraq war veterans. Mil Psychol. 2010;22:340–55.
26. Schiller D, Monfils MJ, Raio CM, Johnson DC, LeDoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature. 2010;463(7277):49–53.
27. Sjostrom N, Hetta J, Waern M. Persistent nightmares are associated with repeat suicide attempt: a prospective study. Psychiatry Res. 2009;170:208–11.
28. Spangler PT. Nightmare deconstruction and reprocessing for trauma-related nightmares: an integrative approach. Psychother Bull. 2014;49:31–5.
29. Spangler PT, Hill CE. The cognitive-experiential dream model: a structured, integrative approach to working with dreams in therapy. In: Kramer M, editor. Dream research: contributions to clinical practice. New York: Routledge; 2015.
30. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: a secondary symptom or core feature? Sleep Med Rev. 2008;12:169–84.
31. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: a review of randomized clinical trials. J Am Med Assoc. 2015;314:489–500.
32. van Rijn E, Eichenlaub JB, Lewis PA, Walker MP, Gaskell MG, Malinowski JE, Blagrove M. The dream-lag effect: selective processing of personally significant event during rapid eye movement sleep, not during slow wave sleep. Neurobiol Learn Mem. 2015;122:98–109.
33. Wamsley EJ, Tucker M, Payne JD, Benavides J, Stickgold R. Dreaming of a learning task is associated with enhanced sleep-dependent memory consolidation. Curr Biol. 2010;20:850–5.
34. Wolpe J. The practice of behavior therapy. New York: Pergamon Press; 1969.

Hypnotic Interventions for Sleep in PTSD

28

Eva Szigethy and Eric Vermetten

Introduction

"And now you will be sound asleep." This can be heard often in popular media when hypnosis is demonstrated by lay hypnotists. It has given its name to a procedure and a phenomenology that has little to nothing to do with the nature of hypnosis or sleep. Perhaps because of the popularization in a variety of channels, the application and use of hypnosis in medicine, psychology, and psychiatry has varied considerably over time. There were periods when hypnosis was overvalued, and other times when it was undervalued or ignored, despite empirical evidence for its usefulness with different mental health problems and disorders.

Sleep disturbance is quite common in patients with posttraumatic stress disorder (PTSD), as a symptom of the underlying disorder; as a part of comorbid anxiety, depression, or chronic pain disorder; or as an independent sleep disorder diagnosis [1]. Chronic sleep disturbance from any cause is associated with poorer daytime functioning as well as medical comorbidities and thus critical to address [2]. Insomnia, the most common sleep symptom, is a state of hyperarousal linked to central changes in metabolism and electroencephalographic activity and peripheral mechanisms such as autonomic activation [3, 4]. This physiological state when combined with inadvertent behavioral conditioning (e.g., checking the bedside clock) can become a chronic condition. In patients with PTSD, insomnia can be even more severely chronic given how the associated heightened hypervigilance and nightmares further disrupt sleep [4]. Abnormalities in the brain's default mode network (DMN) have been implicated in both PTSD, combat trauma (even without PTSD), childhood trauma, and insomnia [5–9]. The DMN is a network of interconnected brain regions which is most active during low-demand tasks such as daydreaming and self-absorbed thinking and when not attending to outside stimuli. One of the under-recognized treatment modalities for insomnia in patients with PTSD is hypnosis. This chapter will review the empirical evidence on the effectiveness of hypnosis for insomnia and PTSD and summarize the neurobiological substrates underlying the hypnotic state, including changes in the DMN [9, 10].

Definition of Hypnosis

Hypnosis is a state of inner absorption or focused attention which leads to greater suggestibility [11]. Hypnosis is also both a procedure and a phenomenon or outcome of that procedure. Three key factors, or components, with accompanying changes in neural network activity of this state have been identified [12–14]:

- Absorption: a tendency to become deeply or intensely involved in a perceptual, imaginative, or ideational experience, with less vigilance about alternative foci of attention
- Suggestibility: responsiveness to social cues, leading to an enhanced tendency to comply with hypnotic instructions, representing a suspension of critical judgment, with an ability to engage in tasks with reduced anxiety about possible alternatives
- Dissociation: mental separation of components of experience that would ordinarily be integrated and is associated with mind wandering and self-reflection and reduced self-awareness

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There are different theories about how hypnosis works [15]. State theories propose that hypnosis is an altered state of consciousness and that state is associated with a dissociation from higher brain control centers leading to cognitive distortions and increased suggestibility [16]. This latter phenomenon is called trance logic, a voluntary state of acceptance of suggestions without critical judgment or evaluation. Non-state theories propose that the increased suggestibility is a product of a person's attitudes, expectancies, and motivation and that suggestibility is enhanced by an empathic connection with the hypnotherapist [17]. Regardless of the theoretical underpinnings, hypnosis is a trance state which is associated with different mental and physical processes that are present during a normal alert state [18]. Different depths of trance can be achieved, each associated with different brain wave patterns [19]. Lighter trance states are adequate for relaxation, limb and eyelid catalepsy, and more vivid mental imagery, while deeper trances are associated with catalepsy of all skeletal muscles, ideomotor phenomena (such as automatic writing), age regression, hallucinations, and post-hypnotic effects with amnesia for the event.

The depth of a trance state and individual can achieve is called hypnotizability [20, 21]. Hypnotizability, or hypnotic susceptibility, can best be viewed as a disposition, only manifested under certain conditions, in the same way that water vaporizes when heated and wood is flammable when it is dry and close to a fire. The hypnotic ability may become manifest not only during formal hypnotic induction procedures but also in the context of environmental challenges such as psychological trauma. Although hypnotizability is considered to be variable across individuals, it is stable *within* individuals, with a test-retest correlation of 60 over periods of 10–25 years, despite training and previous exposure effects [21, 22]. Those who are low on hypnotizability are typically unable to enter a hypnotic state, while those who are high in this trait do so very easily [23]. Hypnotizability appears to peak between the ages of 6 and 10 and then begins a gradual decline as age increases [24]. Approximately 10–15% of the population are highly susceptible to hypnosis, 10–15% are unresponsive, and the remaining 70–80% are moderately susceptible [25]. As a rule of thumb, low hypnotizables often prefer various introspective, analytically oriented psychotherapies. Those who are in the midrange group in hypnotizability respond better to consoltatioin and confrontation from the therapist. Highly hypnotizable individuals benefit most from firm guidelines to enhance their capacity to generate their own decisions and directions.

There is compelling evidence that robust psychological and physiological phenomena underlie hypnosis [26–30]. Changes in neural activity underlie the focused attention, enhanced somatic and emotional control, and lack of self-consciousness that characterizes hypnosis. Changes in relaxation, focus, and absorption, induced by standard hypnotic procedures, are associated with changes in brain activity within different brain areas. There is now growing evidence of the involvement of areas modulating self-related and external sensory input brain networks [29]. One network involves midline brain structures such as the precuneus and the rostral ACC [31], often referred to as the "default mode network" or DMN (which is thought to involve self-referential processing) [32]. A second network involves lateral frontoparietal regions, associated with attention-demanding tasks and the cognitive processing of sensory input. There are changes in the electrical activity of the brain as evaluated by electroencephalographic (EEG) studies which correlate with trance depth [33]. These EEG changes as well as patterns of eye movement are different than those observed during sleep, suggesting they are different states [34].

In addition to changes in the brain, there are measurable physiological changes in the periphery observed during hypnotic trance states including changes in autonomic (heart rate, respiration, skin conductance), metabolic, and endocrine (glucose and basal metabolism) systems [35, 36]. While these biological processes have been linked to therapeutically induced hypnotic states, they also occur in "spontaneous" hypnotic states such as religious rituals, physical exercise, or getting "lost" in music, a good book, or a mesmerizing movie. Hypnosis used as a therapeutic tool can be referred to as hypnotherapy, though in the literature, the two terms are often used interchangeably.

Hypnosis for Insomnia

The use of hypnosis in treating insomnia and sleep disturbances (e.g., night terror) has been described in numerous clinical reports. A meta-analysis by Lam (2015) of randomized controlled trials (RCTs) or quasi-RCTs where hypnosis was the intervention and insomnia the target [37], a total of 502 subjects were included with 6 using hypnotherapy and 7 using hypnotic techniques such as autogenic training or guided imagery. In a meta-analysis across all the studies, hypnosis was associated with significant reduction in sleep latency compared to wait-list control but no difference compared to a heterogeneous mix of conditions including psychotherapy, pharmacological treatment, back massage, and sham (placebo). Nonrandomized studies demonstrated that hypnosis can reduce sleep latency in patients with chronic insomnia [38] and increase slow wave sleep [39] and internet-based self-hypnosis and hypnosis audiotapes [40] can improve sleep over time. A meta-analysis of 59 outcome studies showed short- and longer-term advantages of hypnosis and relaxation training are comparable and, in some studies, greater than drug therapy effects [41].

Prior to using hypnosis, it is advisable to familiarize the patient with "hypnotic-like" experiences, to reinforce

debunking of myths about hypnosis, and to ameliorate potential underlying fears about the modality (e.g., loss of control), which will also help build rapport and trust. Quite contrary to giving up control, gaining expertise in self-hypnosis is an opportunity to enhance their control over both mental and physical states and also in gaining control over sleeping problems. In hypnotizability testing there is an element of surprise which is also important. It is this very occasion that can be turned around to demonstrate to the patient how easily he can enhance and expand his own sense of control of himself and his body. These brief quasi informal clinical tests are very useful in evaluating patients for possible hypnotherapy [42]. They not only serve to screen and evaluate, but their very administration can establish a positive psychological set and make later inductions of hypnosis easier. For these reasons, hypnosis may be of greatest benefit in psychotherapy when it is used as a means of teaching skills that empower the patient.

The beneficial effects of hypnosis for insomnia have been most linked to therapeutic targeting of mood (mainly anxiety), thoughts (mainly ruminative worries), and body sensations (physiological arousal). The most common techniques in published literature are relaxation, thought slowing and redirection, and access to preconscious cognitions and emotions [43, 44]. There are specific skills that someone suffering insomnia can learn that will make a positive difference. While relaxation using breathing, muscle relaxation, and guided imagery is the most common skill, targeting the cognitive symptom of rumination or repetitive thinking can also be a powerful tool for insomniacs.

Rumination (repetitive thinking) is the cognitive process of spinning around the same thoughts over and over again. It is considered an enduring style of coping with ongoing problems and stress [45]. Coping responses may distinguish between strategies oriented toward confronting the problem and strategies oriented toward reducing tension by avoiding dealing with the problem directly. Rumination can be thought of as a pattern of avoidance that actually increases anxiety and agitation. Ruminative responses include repeatedly expressing to others how badly one feels, thinking to excess why one feels bad, and catastrophizing the negative effects of feeling bad. By ruminating, the person avoids having to take decisive and timely action, further compounding a personal sense of inadequacy. Rumination leads to more negative interpretations of life events, greater recall of negative autobiographical memories and events, impaired problem-solving, and a reduced willingness to participate in pleasant activities. Various studies provide evidence that ruminative behavior is not only highly associated with depression but serves to increase both the severity and duration of episodes of depression [46]. Thus, rumination is an especially high-priority target at which to aim interventions, hypnotic or otherwise. Rumination generates both somatic and cognitive arousal, both of which can increase insomnia, but the evidence suggests cognitive arousal is the greater problem. Minimal cognitive processing and special effort toward sleep are key hypnotic treatment goals.

Hypnosis for Insomnia with PTSD

In one small parallel arm study included where the 32 participants were combat veterans with PTSD, group hypnosis twice a week for 2 weeks significantly improved symptoms of PTSD as well as insomnia immediately posttreatment and at 1 month follow-up compared to those randomized to zolpidem (10 mg) [47]. Age regression techniques were used to access memories from a time in life when the patient had no sleep disturbances. The past experiences were enhanced and then associated with present feelings using a technique called a cognitive-affective bridge. Ego-strengthening (building sense of self-efficacy and confidence) techniques were also used. For the larger meta-analysis, methodological weaknesses across the studies and a relatively small sample size were cited as limitations. A recent study examined the effectiveness of sleep-directed hypnosis as a complement to cognitive processing therapy (CPT) [48]. When 3-week hypnosis training preceded CPT, significantly greater improvement than the control condition was seen in sleep and depression, but not in PTSD. Hypnosis was effective in improving sleep impairment, but those improvements did not augment gains in PTSD recovery during the trauma-focused intervention. Nightmares are a hallmark symptom of PTSD and a frequently endorsed cause of poor sleep. The use of various behavioral techniques to help patients with nightmares has been discussed in previous chapters. While there is a relative absence of empirical evidence for the efficacy of hypnosis for nightmares, there are several ways that the hypnotic trance can be used to understand the etiology of these re-traumatizing dreams. For example, the content of the nightmares can be more vividly accessed, and related negative emotions can be more readily processed [49]. There is support that dissociation in hypnosis is similar to that which occurs spontaneously during dreams [50]. With the ability of the hypnotist to suggest amnesia for the material that might be re-traumatizing during an alert waking state, hypnosis provides a powerful medium by which to have patient rework traumatic origins of repetitive dream through revivification or dream substitution. There are several case studies supporting the use of hypnosis to improve repetitive nightmares both unrelated to [51] and related to PTSD [52]. These techniques demonstrate that patients can have control first of their hypnotic dreams and then dreams at night. Dream substitution is different from hypnotic abreaction or interpretation of dreams [53].

Hypnosis for PTSD

One way to help PTSD-related insomnia is to treat the PTSD directly. Hypnotic techniques were already used to treat combat neurosis during World War II [54]. There is evidence for the positive effects of hypnosis for both acute and chronic PTSD but few randomized controlled trials [55–58]. In the military, hypnosis has been found to be particularly useful in helping soldiers work through combat traumas [59, 60]. Patients with PTSD, including combat veterans, are more susceptible to dissociation than the general population [61, 62]. Hypnosis in this population can be thought of as controlled dissociation and dissociation in turn as a form of spontaneous self-hypnosis [63]. These patients need to learn to control their flashbacks and learn to regulate their capacity to dissociate. Hypnosis can help with anxiety, reverse traumatic dissociation, facilitate the process of working through traumatic memories, increase ego strength, and promote a sense of competency.

The arousal symptoms of PTSD (flashbacks, dissociative states) can be triggered by olfactory as well as other environmental cues. In a study using hypnosis to associate a particular environmental stimulus with a desired emotional response in a patient with combat-related PTSD, mood and anxiety disorders, and chronic insomnia, there was a nonspecific improvement in all of these disorders [64, 65]. The main hypnotic technique used was an "olfactory bridge" by which age regression leads the patient to access pleasant memories associated with a sense of control while experiencing a pleasant scent. During repetitive review of the traumatic event during hypnosis, the therapist offers a reframing of the traumatic olfactory memory, replacing it with the pleasant scent. The pleasant scent can be used as an anchor for patients to practice self-hypnosis in the face of anxiety. Other hypnotic techniques to treat trauma as part of PTSD, which are beyond the scope of this chapter, include cognitive restructuring of prior traumatic events [55], ego-part techniques [66], abreactive ego-state therapy [67], "hidden observer" technique to bring closure to the target event [68], and "split screen technique" by which patients project images of trauma memories on the left side and something they did to protect themselves or their safe place on the right side [69–71]. It remains to be seen what the best strategy is for the dissociative subtype for PTSD as this group of patients frequently engages in self-hypnosis in order to defend against traumatic and stressful experiences and memories [72].

Hypnosis as an Adjunct to Other Behavioral Approaches

With an understanding of hypnotic principles and techniques, hypnosis can be used to augment the effects of other therapeutic interventions covered in this book (e.g., imagery reversal therapy (IRT), exposure relaxation and reinterpreting (ERRT), nightmare deconstruction and reprocessing (NDR), cognitive processing therapy (CPT), and cognitive behavioral therapy (CBT)) using a multicomponent approach. For example, in classic CBT for insomnia which consists of modifying cognitions interfering with sleep (cognitive restructuring) and behavioral skills (sleep hygiene behaviors, stimulus control, and sleep restriction techniques), hypnosis can enhance the acceptance and internalization of suggestions in these other domains [73]. Because hypnosis can facilitate relaxation, facilitate imagery rehearsal, and help patients access to preconscious cognitions and emotions, it can be a helpful adjunct [74].

Cognitive hypnotherapy is a treatment where hypnosis combined with CBT is a useful intervention for PTSD [56, 75]. In a study comparing CBT plus hypnosis to CBT alone or supportive therapy, the cognitive hypnotherapy condition was associated with the greatest improvement in reexperiencing symptoms posttreatment but not at 3-year follow-up [76]. The hypothesized mechanism of action for the hypnotic augmentation of CBT in the acute phase of the study was the promotion of self-soothing skills to counter hyperarousal, fortification of positive expectations of the future, and cue-controlled relaxation where an image or verbal cue is paired with a conditioned response to relaxation or some other positive experiences. Even if hypnosis is not used as a therapeutic technique, training and certification to become a medical hypnotist are valuable as it can provide therapeutic value in understanding the language of change and patient receptivity to suggestion. The use of permissive language and techniques such as pacing and leading can all enhance treatment recommendations [77].

Hypnotic Techniques to Improve Sleep

Formal hypnosis involves a series of sequential steps: induction, deepening, hypnotic suggestions, re-orienting (arousal, awakening), and debriefing (processing and reflecting) when the patient is fully alert. An example of an induction is as follows:

1. Roll the eyes up.
2. Slowly close the lids (tense fists and arms and lift shoulders), take a deep breath, and hold.
3. Relax the eyes down, release the breath, and imagine yourself floating downward…and as this sensation of floating becomes clearer to you…you will feel your body naturally settle to a deeper comfort….

Traditional induction is often done with the eyes closed using suggestions of drowsiness or relaxation. One technique that has shown positive effects for veterans with PTSD is using an alert induction technique [78], where eyes are open and suggestion is for activity and alertness instead of relaxation. "You are becoming increasingly more alert and

attentive" (while the patient is doing something active such as moving arms or hands rigorously and with open eyes staring at a stationary spot). Examples of deepening techniques include:

- Walking down a secure and comfortable set of stair to a special/safe room of your own
- Generate a sense of soothing or comfort…a floating sensation…seem to drift in time and space
- Imagining a relaxing scene with all the senses
- Body scan or breathing focus
- Counting back or upward
- Repeating phrases
- Pauses

An example of deepening using a breathing focus:

> ….And as the body relaxes, deeper and deeper, notice the welcomed sense of release that occurs with each exhale….The body releasing more and more stress and tension with each exhale. Now, as the body breaths by itself, silently and slowly repeat in the mind the words "Relaxed" with each exhale and "Calm" with each inhale. Notice how the body responds to these words as it relaxes deeper and deeper each time they float through the mind….Breath in confidence and sense of safety and security, breath out tension….

Induction and deepening techniques get the patient the right level of trance depth for hypnotic suggestions to have the most powerful effects. The suggestion phase is called trancework. There are many different types of suggestions – direct, indirect, contingent, truisms, and metaphors as examples. To cover all these types of suggestion is beyond the scope of this chapter, but it is recommended that clinicians get formal training in hypnosis to learn a wealth of different techniques to use with patients. Hypnosis certification can be achieved through the American Society of Clinical Hypnosis, the Society of Clinical and Experimental Hypnosis, or the International Society of Hypnosis, constituted by over 30 countries in the world. There is no evidence for superiority of either direct or indirect suggestions or one type of indirect suggestion over another. It useful to learn and practice different types of suggestions and to match your choice of suggestion to your style, the therapeutic situation, and the patient's expectations.

As noted above, rumination can significantly impair sleep. Hypnosis can teach the ability to direct one's own thoughts rather than merely react to them. This is a well-established dynamic and a principal reason for employing hypnosis in any context. Reducing the stressful wanderings of an agitated mind and also relaxing the body while simultaneously helping people create and follow a line of pleasant thoughts and images that can soothe and calm the person are valuable goals in the service of enhancing sleep.

To achieve these aims, there are six important components to include in one's treatment plan. While only the sixth one focuses on hypnosis directly, the first five lay an important cognitive behavioral foundation:

1. Teaching the patient how to efficiently distinguish between useful analysis and useless ruminations. The distinction features variations in factors such how much information to gather and how long to contemplate what to do. The single most important distinguishing characteristic is the conversion from analysis to action.
2. Enhancing skills in "time organization" (compartmentalization) in order to better separate bedtime from problem-solving time with the well-defined goal in place of keeping them separate.
3. Establishing better coping skills that involve more direct and effective problem-solving strategies. The patient that avoids making decisions and implementing them out of the fear of making the wrong one, such as perfectionistic individuals, who are also at higher risk for depression as a result of their perfectionism, will need additional help learning to make sensible and effective, and sometimes imperfect, problem-solving decisions.
4. Helping the patient develop effective strategies for choosing among a range of alternatives. There is evidence that having more options, an oft-stated goal for clinicians, actually increases the anxiety and depression of those who don't have a good strategy for choosing among many alternatives.
5. Addressing issues of sleep hygiene and attitudes toward sleep in order to make sure the person's behavior and attitudes are consistent with good sleep.
6. Teaching "mind-clearing" or "mind-focusing" strategies, especially self-hypnosis strategies, which help the person direct their thinking in utterly harmless directions.

Each of the first five components listed above supports the potential value of the sixth, the actual hypnosis strategy one employs to help calm the person to sleep. In fact, regardless of the hypnotic target, providing patients with a therapy "game plan" is critical so that the hypnosis component can have a more enduring contribution to enhancing sleep and the patient can place hypnosis in the context of the larger therapy plan.

Hypnosis also can be used as a vehicle for teaching the patient effective ways to make distinctions between useful analysis and useless ruminations, organize time (compartmentalize) in various aspects of experience, develop better coping skills, develop more effective decision-making strategies, and develop good behavioral and thought habits regarding sleep. Such hypnosis sessions are quite different in their structure than is a session designed specifically for the purpose of enhancing the ability to fall and stay asleep.

The primary difference between a sleep session and a regular therapy session employing hypnosis is that hypnosis for

sleep enhancement is designed to actually lead the patient to fall asleep. In standard therapy sessions involving hypnosis, the opposite is true: the clinician takes active steps to prevent the patient from falling asleep during the session. It has been well established that hypnosis isn't a sleep state and that sleep learning is a myth. Thus, clinicians employing hypnosis encourage the patient to become focused and relaxed yet maintain a sufficient degree of alertness to be capable of participating in the session by listening and actively adapting the clinician's suggestions to his or her particular needs.

Another key difference between a hypnosis session for enhancing sleep and a standard therapy session is the role of the patient during the process. In therapy, the patient is defined as an active participant: actively involved in searching for relevance for the clinician's and the patient's own suggestions, actively involved in absorbing and integrating the suggestions, and actively finding ways to apply them in the service of self-help. Relaxation may or may not be a part of the therapy process. In fact, some suggestions a clinician offers during hypnosis might even be anxiety provoking or challenging to the patient's sense of comfort. After all, personal growth often means stepping outside one's "comfort zone." In the sleep session, however, cognitive and somatic arousal are to be minimized, and so challenges to the patient's beliefs (or expectations, role definition, or any other aspect a clinician might appropriately challenge) are precluded.

The content of the strategy (e.g., progressive relaxation, imagery from a favorite place, recollection of a happy memory, creation of fantasy stories, counting sheep, etc.) is a secondary consideration. Thus, what specific hypnotic approach one uses is relatively unimportant. The primary consideration is that whatever the patient focuses on, it needs to be something that reduces both physical (somatic) and cognitive arousal. Approaches can be direct or indirect according to what the patient finds easiest to respond to. Likewise, they can be content or process oriented, again depending on what the patient finds easiest to relate to. Since sleep isn't something that can be commanded, an authoritarian style is generally counterproductive. A permissive style is both gentler and more consistent with an attitude of allowing sleep to occur instead of trying to force it to occur.

The use of recorded hypnotic approaches (i.e., tape recordings or compact disc recordings) can be a useful means of helping the patient to develop the skills in focusing on calming suggestions. Generally, these should be considered a temporary help in the process so that the person is eventually able to fall and stay asleep independently using self-hypnosis. However, recordings pose no major or even minor hazards that warrant concern; they will be abused in some way, so there seems to be no good reason to push patients to stop using the recordings for as long as they find them helpful.

Here are a few examples of scripts showing trance work for insomnia:

> …As you prepare for sleep, you will see your bedroom free of tension and worry, and as you settle to lie down to a position that is most comfortable to you, allow the mind to let go of all from the outside that could distract from a deep restful sleep…releasing the lights and sounds from the television or phone…allowing a peaceful quiet to descend upon the room as you begin to dim the lights at your own pace…always in control of how you let go….Give yourself permission to release the clutter from inside the mind too as you give yourself permission to leave all worries and concerns outside the bedroom door…streaming out…leaving you comfortable and calm in just the right way… there is no need to bring these with you…your bed is safe and secure….As you settle the mind, focus on how much your body craves rest…with each breath bringing in calming energy to release tension from wherever in the body you feel it…letting go with each breath…notice you are feeling calmer, more peaceful as your limbs are growing heavier and heavier…the clock is unimportant because your body knows how to fall asleep…following its own internal clock…present from even before you were born…the deep effortless sleep of a newborn baby…just like you did…naturally, deeply as a small baby…safe and secure…(pause)…and for some it can be so helpful to allow the mind to settle to a soothing color or perhaps a comforting scene…it can be a place visited like a beautiful beach or garden…seeing, feeling, hearing with all the senses…a sense of being there, fully there…wonderful scents of the ocean breeze or flowers…wherever your mind takes you is the right place right now…your inner mind always taking the best care of you…there…further and further from here…and perhaps if you wish allowing a special image of a chest or box to appear where you are…with a lock on it…noticing the lock…what it is made of…walking up in and opening the vessel now…placing in this safe haven…all that would interfere with a deep sleep…safely tucked away…and only you control the key…when it is the right time…closing the vessel and locking securely and safely away… memories are just chemical imprints…they are safely out of sight and mind…as you are fading deeper into the beauty and calm of your beautiful safe place deep inside your mind…or it can be an even safer place imagined…perching on a fluffy cloud so soft yet safe and supportive, feeling it massage away tension as it engulfs your body…what a wonderful perspective on the world below…somewhere you can rest assure that your body knows how to fall into a deep sleep….wherever your mind takes you is the right place for you…and as you allow a beautiful sunset to appear in front of you…you find yourself surprised at how well you are able to fall deeply asleep….the muscles of the body becoming comfortably heavier and heavier…the sun begins to gradually set…and with each breath as the sun sets…the mind settles…becoming slower… and slower…letting go…and as the sun disappears on the horizon…the scene evolves into a safe soothing darkness…the mind lets go…coming to a pleasant halt…stillness…(pause)…entering a deep restful sleep with pleasant dreams, safe and secure and knowing that your mind will take the best care of you…confident in knowing your body is building strength and building its immune system and helping to heal wherever that energy released is most needed…you take all the time you need in all the time you have to sleep deeply and peacefully, always in charge…and you will be amazed to find when you awaken, how rested and refreshed you feel…for now…sailing off into a profound deep sleep…

It is important to facilitate the return from a trance to a state of full conscious awareness (re-alerting) and to process the experience with the patient. These steps are critical to make sure that the person has completely returned from the trance state but

also because reprocessing the parts that are consciously availably to the patient can further deepen their lasting effects. Finally, this discussion also informs the therapist if there has been amnesia for any part of the hypnotic work, so that this information can be used therapeutically to plan future sessions.

Contraindications or Adverse Events Using Hypnosis

There are no known contraindications to teaching patients with insomnia to focus and relax. Patients with PTSD may have trouble relaxing, or it may cause a paradoxical agitation or abreaction. Thus, it is critical that the clinician has appropriate training to work hypnotically with patients with PTSD. Severe psychopathology can be a relative contraindication such as psychosis or other extreme dissociative conditions (complex PTSD, borderline personality disorder, depression with severe suicidality). Hypnosis can be very helpful in these conditions but requires extra caution and training. Peer supervision can also be useful.

Resistance to hypnosis needs to be addressed. Common reasons for resistance include misconceptions about hypnosis, interfering anxiety, fear of loss of control, underlying psychopathology, and cultural and religious differences. Developing an empathic and trusting therapeutic alliance, root-cause analysis for reasons for anxiety and fear (e.g., learning patient was abused by authority figure in the past), and education about hypnosis and its underlying neurobiology are critical in reducing resistance.

Informed consent before initiating hypnosis is highly recommended. If patients are involved in litigation, it is important that they be informed that any material processed during hypnosis may be inadmissible in court due to concern for "false memory syndrome." Adverse events with hypnosis are rare, though with the caveat that they are often not studied or reported.

Conclusion

As this chapter has outlined, hypnosis can be well defined and structured. It can be used as a vehicle for teaching the patient effective ways to make distinctions between useful analysis and useless ruminations, organize time (compartmentalize) in various aspects of experience, develop better coping skills, develop more effective decision-making strategies, and develop good behavioral and thought habits regarding sleep. The use of hypnosis can be a valuable tool to psychotherapy. Clinicians employing hypnosis for improving insomnia or sleep-related problems in PTSD encourage the patient to become focused and relaxed yet maintain a sufficient degree of alertness to be capable of participating in the session by listening and actively adapting the clinician's suggestions to his or her particular needs. With a proper understanding of hypnotic principles and techniques, hypnosis can be used to augment the effects of other therapeutic interventions and is probably most effective in combination with them.

References

1. Association AP. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: APPI; 2013.
2. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol. 2015;66:143–72.
3. Harvey AG, Tang N. (Mis)perception of sleep in insomnia: a puzzle and a resolution. Psychol Bull. 2012;138:77–101.
4. Bonnet MH, Burton GG, Arand DL. Physiological and medical findings in insomnia: implications for diagnosis and care. Sleep Med Rev. 2014;18:111–22.
5. Suh S, Kim H, Dang-Vu TT, et al. Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. Sleep. 2016;39:161–71.
6. DiGangi JA, Tadayyon A, Fitzgerald DA, et al. Reduced default mode network connectivity following combat trauma. Neurosci Lett. 2016;615:37–43.
7. Reuveni I, Bonne O, Giesser R, et al. Anatomical and functional connectivity in the default mode network of post-traumatic stress disorder patients after civilian and military-related trauma. Hum Brain Mapp. 2016;37:589–99.
8. Zhang Y, Liu F, Chen H, et al. Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. J Affect Disord. 2015;187:114–21.
9. Bluhm RL, Williamson PC, Osuch EA, et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J Psychiatry Neurosci. 2009;34:187–94.
10. Deeley Q, Oakley DA, Toone B, et al. Modulating the default mode network using hypnosis. Int J Clin Exp Hypn. 2012;60:206–28.
11. Orne MT. The construct of hypnosis: implications of the definition for research and practice. Ann N Y Acad Sci. 1977;296:14–33.
12. Spiegel H, Greenleaf M. Commentary: defining hypnosis. Am J Clin Hypn. 2005;48:111–6.
13. Spiegel HS, Spiegel D. Trance and treatment: clinical uses of hypnosis. New York: Basic Books; 1978.
14. Jiang H, White MP, Greicius MD, et al. Brain activity and functional connectivity associated with hypnosis. Cereb Cortex 2016 July 28 [Epub ahead of print]
15. Kirsch I, Lynn SJ. Dissociation theories of hypnosis. Psychol Bull. 1998;123:100–15.
16. Hilgard ER. Altered states of awareness. J Nerv Ment Dis. 1969;149:68–79.
17. Spanos NP. Hypnotic behavior: a social-psychological interpretation of amnesia, analgesia, and "trance logic". Behav Brain Sci. 1986;9:499–502.
18. Jensen MP, Adachi T, Tomé-Pires C, et al. Mechanisms of hypnosis: toward the development of a biopsychosocial model. Int J Clin Exp Hypn. 2015;63:34–75.
19. Jensen MP, Adachi T, Hakimian S. Brain oscillations, hypnosis, and hypnotizability. Am J Clin Hypn. 2015;57:230–53.
20. Barber T. Hypnosis: a scientific approach. New York: Litton Educational Publishing; 1969.
21. Hilgard E. Hypnotic susceptibility. New York: Harcourt, Brace, and World; 1965.
22. Piccione C, Hilgard ER, Zimbardo PG. On the degree of stability of measured hypnotizability over a 25-year period. J Pers Soc Psychol. 1989;56:289–95.
23. HSD S. Trance and treatment: clinical uses of hypnosis. 2nd ed. Washington, DC: American Psychiatric Press; 2004.

24. Morgan AH, Johnson DL, Hilgard ER. The stability of hypnotic susceptibility: a longitudinal study. Int J Clin Exp Hypn. 1974;22:249–57.
25. Perru C, Nadon R, Button J. The measurement of hypnotic ability. In: E Fromm & M Nash (eds.) Contemporary Hypnosis research 1992:459–490, New York: Guilford.
26. Barber TX. A deeper understanding of hypnosis: its secrets, its nature, its essence. Am J Clin Hypn. 2000;42:208–72.
27. Landry M, Raz A. Hypnosis and imaging of the living human brain. Am J Clin Hypn. 2015;57:285–313.
28. Faymonville ME, Boly M, Laureys S. Functional neuroanatomy of the hypnotic state. J Physiol Paris. 2006;99:463–9.
29. Vanhaudenhuyse A, Laureys S, Faymonville ME. Neurophysiology of hypnosis. Neurophysiol Clin. 2014;44:343–53.
30. Rainville P, Price DD. Hypnosis phenomenology and the neurobiology of consciousness. Int J Clin Exp Hypn. 2003;51:105–29.
31. Hoeft F, Gabrieli JD, Whitfield-Gabrieli S, et al. Functional brain basis of hypnotizability. Arch Gen Psychiatry. 2012;69:1064–72.
32. McGeown WJ, Mazzoni G, Venneri A, et al. Hypnotic induction decreases anterior default mode activity. Conscious Cogn. 2009;18:848–55.
33. Gruzelier J. Frontal functions, connectivity and neural efficiency underpinning hypnosis and hypnotic susceptibility. Contemp Hypn. 2006;23:15–32.
34. Evans FJ. Hypnosis and sleep: the control of altered states of awareness. Sleep Hypn. 1999;1:232–7.
35. Levitt E, Chapman R. Hypnosis as a research method. New Brunswick: Aldine Transaction; 2009.
36. Gruzelier J. A working model of the neurophysiology of hypnosis: a review of evidence. Contemp Hypn. 1998;15:3–21.
37. Lam TH, Chung KF, Yeung WF, et al. Hypnotherapy for insomnia: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2015;23:719–32.
38. Stanton HE. Hypnotic relaxation and the reduction of sleep onset insomnia. Int J Psychosom. 1989;36:64–8.
39. Cordi MJ, Schlarb AA, Rasch B. Deepening sleep by hypnotic suggestion. Sleep. 2014;37:1143–52. 1152a–1152f
40. Scholtz O, Ott R. Effect and course of tape-based hypnotherapy in subjects suffering from insomnia. Aust J Clin Hypnother Hypn. 2000;21:96–114.
41. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994;151:1172–80.
42. Spiegel D. Dissociation and hypnosis in post-traumatic stress disorders. J Trauma Stress. 1988;1:17–33.
43. Hammond D. Handbook of hypnotic suggestions and metaphors. New York: Norton; 1990.
44. Fry A. Hypnosis in the treatment of insomnia. Med World. 1963;99:194–9.
45. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res. 2006;60:113–24.
46. Nolen-Hoeksema S. Responses to depression and their effects on the duration of depressive episodes. J Abnorm Psychol. 1991;100:569–82.
47. Abramowitz EG, Barak Y, Ben-Avi I, et al. Hypnotherapy in the treatment of chronic combat-related PTSD patients suffering from insomnia: a randomized, zolpidem-controlled clinical trial. Int J Clin Exp Hypn. 2008;56:270–80.
48. Galovski TE, Harik JM, Blain LM, et al. Augmenting cognitive processing therapy to improve sleep impairment in PTSD: a randomized controlled trial. J Consult Clin Psychol. 2016;84:167–77.
49. Gilligan S. Symptom phenomena as trance phenomena. New York: Brunner/Mazel; 1988.
50. Gabel S. Dreams and dissociation theory: speculations on beneficial aspects of their linkage. Dissociation. 1990;3:38–47.
51. Kingsbury SJ. Brief hypnotic treatment of repetitive nightmares. Am J Clin Hypn. 1993;35:161–9.
52. Eichelman B. Hypnotic change in combat dreams of two veterans with posttraumatic stress disorder. Am J Psychiatry. 1985;142:112–4.
53. Moss CS. Treatment of a recurrent nightmare by hypnosymbolism. Am J Clin Hypn. 1973;16:23–30.
54. Watkins JG. The psychodynamic treatment of combat neuroses (PTSD) with hypnosis during world war II. Int J Clin Exp Hypn. 2000;48:324–35. discussion 336–41
55. Lynn SJ, Cardena E. Hypnosis and the treatment of posttraumatic conditions: an evidence-based approach. Int J Clin Exp Hypn. 2007;55:167–88.
56. Lynn SJ, Malakataris A, Condon L, et al. Post-traumatic stress disorder: cognitive hypnotherapy, mindfulness, and acceptance-based treatment approaches. Am J Clin Hypn. 2012;54:311–30.
57. O'Toole SK, Solomon SL, Bergdahl SA. A meta-analysis of hypnotherapeutic techniques in the treatment of PTSD symptoms. J Trauma Stress. 2016;29:97–100.
58. Rotaru TS, Rusu A. A meta-analysis for the efficacy of hypnotherapy in alleviating PTSD symptoms. Int J Clin Exp Hypn. 2016;64:116–36.
59. Colosimo CP. Use of hypnosis in the military. Psychiatr Med. 1992;10:149–67.
60. Abramowitz EG, Bonne O. Use of hypnosis in the treatment of combat post traumatic stress disorder (PTSD). Harefuah. 2013;152:490–3. 497
61. Stutman RK, Bliss EL. Posttraumatic stress disorder, hypnotizability, and imagery. Am J Psychiatry. 1985;142:741–3.
62. Bryant RA, Guthrie RM, Moulds ML, et al. Hypnotizability and posttraumatic stress disorder: a prospective study. Int J Clin Exp Hypn. 2003;51:382–9.
63. Spiegel DVE. Physiological correlates of hypnosis and dissociation. Arlington: American Psychiatric Association; 1994.
64. Abramowitz EG, Lichtenberg P. A new hypnotic technique for treating combat-related posttraumatic stress disorder: a prospective open study. Int J Clin Exp Hypn. 2010;58:316–28.
65. Abramowitz EG, Lichtenberg P. Hypnotherapeutic olfactory conditioning (HOC): case studies of needle phobia, panic disorder, and combat-induced PTSD. Int J Clin Exp Hypn. 2009;57:184–97.
66. Phillips M, Frederick C. Healing the divided self: clinical and Ericksonian hypnotherapy for the treatment of post-traumatic and dissociative conditions. New York: W. W. Norton; 1995.
67. Barabasz A. Evidence based abreactive ego state therapy for PTSD. Am J Clin Hypn. 2013;56:54–65.
68. Gantt L, Tinnin L. Intensive trauma therapy of PTSD and dissociation: an outcome study. Arts Psychother. 2007;24:69–80.
69. Spiegel D. Vietnam grief work using hypnosis. Am J Clin Hypn. 1981;24:33–40.
70. Cardena E, Maldonado J, Van de Hart O, et al. Hypnosis. J Trauma Stress. 2007;24:33–40.
71. Poon MW. Hypnosis for complex trauma survivors: four case studies. Am J Clin Hypn. 2009;51:263–71.
72. Dutra SJ, Wolf E. Perspectives on the conceptualization of the dissociative subtype of PTSD and implications for treatment. Curr Opin Psychol. 2017;14:35–9.
73. Graci GM, Hardie JC. Evidenced-based hypnotherapy for the management of sleep disorders. Int J Clin Exp Hypn. 2007;55:288–302.
74. Becker PM. Hypnosis in the management of sleep disorders. Sleep Med Clin. 2015;10:85–92.
75. Alladin A, Amundson J. Cognitive hypnotherapy as a transdiagnostic protocol for emotional disorders. Int J Clin Exp Hypn. 2016;64:147–66.
76. Bryant RA, Moulds ML, Guthrie RM, et al. The additive benefit of hypnosis and cognitive-behavioral therapy in treating acute stress disorder. J Consult Clin Psychol. 2005;73:334–40.
77. Haley JE, MH. Uncommon therapy. New York: Norton; 1973.
78. Eads B, Wark DM. Alert hypnotic inductions: use in treating combat post-traumatic stress disorder. Am J Clin Hypn. 2015;58:159–70.

Medication for Sleep Problems in Posttraumatic Stress Disorder

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Joop de Jong and Eric Vermetten

Introduction

Several reviews on the treatment of posttraumatic stress disorder (PTSD) confirm that problems with sleep are the hallmark of this condition [53, 137, 154]. This is well known to patients and prescribing clinicians that there is pressure on the use of substances (e.g., alcohol, cannabis, benzodiazepines) to alleviate sleep deprivation, reduce nightmares, and overcome the "tossing and turning" or "fighting sleep loss." Patients with PTSD are seduced by the short-acting effect of alcohol and swindle down the negative effects related to their sleep disturbances and nightmares [117]. Without proper guidance and feedback, this can lead to serious problems. Similar to alcohol, benzodiazepines improve sleep problems only in the short term and can cause serious sleep problems when tapering [121, 125]. The benzodiazepine use is well reflected in the fact that 30% of veterans with PTSD received a benzodiazepine prescription for >90 days, even though this is not recommended in guidelines [2, 107], and as recent reviews and meta-analysis show, it is considered a status "relatively contraindicated" for this indication [57].

This chapter discusses the current state of research on medication for sleep disorders in PTSD. The focus of this clinically based chapter is on the effect of drugs on sleep in patients with PTSD, in patients with depressive disorders, and also in healthy persons. Finally, an algorithm is presented that is based on the extensive literature that is presented as well as clinical guidance.

The addition of effects on depressive disorders is important given that DSM-5 has added a new criterion called "negative alterations in cognitions and mood" that began or worsened after the traumatic event [6]. For PTSD patients, this new criterion will probably lead to more focus on symptoms that, in the DSM-IV period, would probably have been attributed to a comorbid depressive episode. Therefore, this chapter also focuses on the state-of-the-art literature related to depressive disorders, especially when comorbid with PTSD.

Medication for PTSD and Effect on Sleep

In their landmark review on the pharmacotherapy of PTSD, Ipser and Stein [73] highlight the inconsistency of the evidence regarding the efficacy of medication for PTSD. This inconsistency may (in part) be due to differences in study methodology, clinical characteristics of patient groups, and/or insufficient statistical power of the smaller studies. The authors found the largest amount of evidence on efficacy for the selective serotonin reuptake inhibitors (SSRIs) and promising results for venlafaxine and risperidone. According to these authors, other medications with an extra-serotonergic mechanism of action need more investigations to determine if and how they can be used in the treatment of PTSD, especially in the case of treatment of refractory cases and augmentation. In this chapter our focus is on the effect on sleep disorders within patients diagnosed with PTSD. This is a different way of looking at the effect of medication and has been chosen because of the heterogeneous phenotype of PTSD, which will probably not be cured by using just one kind of medication. Yet, targeting specific symptoms may lead to more success in treating our patients.

In the following sections, we describe medications that have been investigated for PTSD as well as those medications that are known to have a positive effect on sleep.

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The following classes of medications are discussed:

1. Selective serotonin reuptake inhibitors (SSRIs)
2. Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)
3. Tricyclic antidepressants (TCAs)
4. Monoamine oxidase inhibitors (MAOIs)
5. Other antidepressants (AD)
6. Antiepileptic drugs (AED), anticonvulsants, and mood stabilizers
7. Antipsychotics
8. Antiadrenergic drugs
9. Hypnotics/anxiolytics
10. Cyproheptadine
11. Cortisol and mifepristone
12. Cannabis and synthetic cannabinoids

Selective Serotonin Reuptake Inhibitors

There is general acceptance of the selective serotonin reuptake inhibitors (SSRIs) as first-line agents in PTSD. In some guidelines no distinction is made between the different SSRIs [52, 161] although the guidelines for PTSD published by Veterans Affairs (2010) recommend SSRIs and suggest that fluoxetine, paroxetine, or sertraline provide the best support; or they recommend selective serotonin and noradrenaline reuptake inhibitors (SNRIs) and found venlafaxine to provide the strongest support in this group (see below: SNRIs).

In general, SSRIs disturb sleep by diminishing the amount of rapid eye movement (REM) sleep (this is dose related) and delay entry into REM sleep. Further, changes include an increase of the times awake, increase of the total time awake, and increase of the amount (in time) of the lighter stages of the sleep; however, these effects tend to diminish over time. For fluoxetine, the effects last somewhat longer, probably due to the long half-life time of norfluoxetine (the active metabolite). In general, patients with depression experienced no change of subjective symptoms for sleep, and within 3–4 weeks, there was a better objective and subjective outcome of sleep, most probably due to improvement of the depression. Cessation of SSRIs can give a rebound of REM sleep [172]. According to Ohayon et al. [166], the use of SSRIs leads to more sleepwalking, but this might also be due to triggering in predisposed individuals. Nocturnal bruxism during sleep has been reported, also with the use of various SSRIs [51, 136]. This can be treated by reducing the dose or with the use of buspirone [127], clonidine [46], or gabapentin [21].

Paroxetine

Hicks et al. [69] conducted a randomized double-blind parallel study with 40 patients with depression, randomized to paroxetine 20–40 mg/day or to nefazodone 400–600 mg/day for 8 weeks. Paroxetine decreased total sleep time (TST), sleep efficiency (SE), and wake after sleep onset (WASO) early in treatment but with return to baseline at week 8; however, the number of awakenings and increase in stage 1 increased during therapy without decreasing later on. Paroxetine produced a marked suppression of REM sleep, especially in the first weeks, but decreased during the 8-week study period. In a pooled analysis of three 12-week placebo-controlled studies, Stein et al. [157] showed that paroxetine is effective in the treatment of PTSD, improving sleep disturbance and reducing all symptom clusters of PTSD with or without comorbid disorders, such as depression.

Sertraline

Paul et al. [123] conducted a placebo-controlled study in healthy volunteers who took sertraline up to 150 mg/day for 5 weeks and completed questionnaires and performed psychomotor tests. Sertraline use led to an increase of initial insomnia and increased awakenings, and middle insomnia. There was a transient effect of sleepiness and no impact on psychomotor tests. Around the same time Jindal et al. [76] performed a placebo-controlled randomized double-blind study including 47 patients with major depressive disorder (MDD). Sleep analysis was done after 12 weeks, and sertraline (mean dosage 142 mg/day) appeared to give an increase in delta wave sleep in the first sleep cycles and prolonged REM latency. Sertraline was not associated with worsening of measures of sleep continuity or subjective sleepiness, and both groups reported subjective improvement of the sleep.

Sertraline has been approved for its use in PTSD by the FDA [19, 41]. In the study of Brady et al. [19], 16.0% insomnia was reported as an adverse event in the sertraline group vs. 4.3% ($p = 0.01$) in the placebo group. Davidson et al. [41] studied 208 patients with PTSD who were randomized to 12 weeks of double-blind treatment with either sertraline (50–200 mg) or placebo. Insomnia was one of the adverse events that was mentioned more often in the sertraline group (35% vs. 22%). One of the secondary outcome parameters was sleep measured with the Pittsburgh Sleep Quality Index (PSQI), i.e., sertraline improved sleep but not significantly more when compared with placebo.

Fluoxetine

Gursky and Krahn [59] published a review on sleep disorders due to antidepressants and found that fluoxetine was the SSRI most extensively studied. Healthy volunteers showed increased waking after sleep onset, lengthened sleep latency, decreased REM time, and longer REM latency. However, in healthy volunteers, subjective sleep quality remained stable after 5 weeks [174]. Fluoxetine was found to have a clear and long-lasting negative effect on sleep in depressed patients [63] in whom most effects (except on stage 3–4) were still measurable 4 months after withdrawal. In a meta-analysis of fluoxetine

based on two studies with 356 patients, Ipser and Stein [73] found no efficacy for PTSD. This meta-analysis did not include the placebo-controlled study of Meltzer-Brody et al. [103] with 53 patients in whom fluoxetine provided a broad-spectrum effect in reducing all the symptom clusters of PTSD including self-reported improvement on sleep but had no significant effect on nightmares and no improvement on sleep when questioned by means of an interview.

Fluvoxamine

In a study including 12 healthy volunteers, the effects of a single nighttime dose of fluvoxamine 100 mg decreased total sleep time (TST), REM time, and sleep fragmentation [173]. Kupfer et al. [87] compared 4 weeks of fluvoxamine (200 mg/day) with desipramine in a group of 35 patients with major depression; they found that fluvoxamine provided an increase of sleep fragmentation and waking time and that S1 increased when 200 mg of fluvoxamine was given to these patients. In an open-ended study, de Boer et al. [47] gave 24 World War II resistance veterans with (partially) chronic PTSD and symptoms for decades fluvoxamine up to 300 mg/day for 12 weeks. There was only a moderate improvement in the whole group, and 13 patients dropped out of the study, one due to deterioration of sleep. Insomnia and nightmare symptoms showed no significant improvement in the whole group; however, 5 of the 11 completers reported a substantial improvement of their overall condition and showed markedly improved sleep quality (and continued to use fluvoxamine after the study ended).

Neylan et al. [113] studied the effect of fluvoxamine (modal dose of 150 mg) in a 10-week open-label trial with 21 veterans. In this study there was a global improvement for PTSD and a significant effect for dreams linked to traumatic experiences (effect size for this item 1.11) but not to generic unpleasant dreams; insomnia for staying asleep improved in contrast to falling asleep, but this was evaluated by subjective measurements only.

Citalopram and Escitalopram

In a randomized double-blind placebo-controlled study, Wilson et al. [175] gave 12 volunteers citalopram (20 mg), paroxetine (20 mg), or placebo and found that both SSRIs had an effect on REM (suppressed) and sleep fragmentation but with more effect with paroxetine than with citalopram at this dosage. As escitalopram is the active isomer of citalopram [110], it is expected to have the same effect on sleep as citalopram. The effect of citalopram on sleep in patients with a depressive disorder was earlier studied by van Bemmel et al. [12]. They performed a single-blind study with 16 patients who took citalopram 20 mg/day for 1 week and then 40 mg/day for 5 weeks, followed by 1 week of placebo. The effect appeared to be a significant decrease of REM and a significant lengthening of REM sleep latency; this was in the first and the last weeks of citalopram. The non-REM stage 2 was significantly increased, but there was no discontinuity in sleep. The change in subjective sleep quality was significantly better in patients who also scored better on self-rated depressed mood, but there were no differences between these groups with respect to the sleep polygraphy.

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Salin-Pascual et al. [140] followed eight healthy volunteers who used venlafaxine (75 mg on the first two nights, then 150 mg for two nights) which led to an increase in phase 1 and a reduction in phases 2 and 3; REM sleep was completely suppressed during the fourth night, and periodic limb movement syndrome (PLMS) began in six of the eight volunteers, of which two had PLMS 1 week after withdrawal. Around the same time Luthringer et al. [97] conducted a randomized double-blind placebo-controlled study with 24 inpatients with depressive disorder who received placebo or 75 mg up to 225 mg/day venlafaxine for 1 month. Influences on sleep were suppression of REM sleep, increase of REM latency, and decrease of sleep continuity (since after 1 month of treatment, there was an increase of total time awake after sleep onset).

Venlafaxine

Stein et al. [158] performed a pooled analysis on two placebo-controlled randomized studies with a total of 687 patients with PTSD and concluded that venlafaxine after 12-week use was effective on most of the PTSD symptoms (as measured with the CAPS), but there was no difference compared with placebo for the sleep items.

Duloxetine

Chalon et al. [31] compared duloxetine 80 mg (qd) with 60 mg (bid) and with desipramine (50 mg bid) in young, healthy male volunteers in a randomized placebo-controlled crossover study; with duloxetine, they found an increase in onset latency of REM sleep and a decrease in total REM. Sleep continuity showed a reduction with duloxetine 60 mg twice a day but some improvement with 80 mg once a day.

Kluge et al. [81] performed polysomnography in ten patients with major depression; after 7–14 days of treatment with duloxetine 60 mg/day, they found that stage 3 sleep significantly increased, REM latency increased, and REM sleep decreased. Villarreal et al. [166] performed a 12-week open-label trial with 20 veterans who took duloxetine (mean 81 mg/day). There were five dropouts, and nine veterans had a ≥20% improvement on PTSD, depression, and sleep measures. The mean Pittsburg Sleep Quality Index (PSQI) showed a

significant improvement ($n = 20$, $p < 0.001$). Walderhaug et al. [167] gave 21 combat veterans with comorbid MDD 60–120 mg/day duloxetine for 8 weeks and found significant improvement of PTSD and depression, with improved sleep and reduction of nightmares. However, they did not give specific numbers about the decrease of nightmares but did mention an increase in pleasant dream activity.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are reported to reduce REM sleep, increase REM latency, and worsen sleep continuity in the first month after treatment [172]. Concerning non-REM sleep, a division can be made into more or less sedating TCAs. Clomipramine, desipramine, and imipramine increase sleep latency and total waking time, decrease sleep efficiency, and are less sedating when compared with amitriptyline, doxepin, and trimipramine. In patients with depression, this difference disappears after some days of treatment with any TCA, except for trimipramine which, compared with other TCAs, is a weak monoamine reuptake inhibitor [172]. Also, trimipramine gives less REM sleep suppression and has more sleep-promoting effects which last for longer periods of time in patients and healthy volunteers. This outcome was found by Riemann et al. [129] in a double-blind placebo-controlled and lormetazepam-controlled study including 55 patients with primary insomnia; trimipramine was given at an average dose of 100 mg over 4 weeks which enhanced sleep efficiency, without rebound effects after stopping. Trimipramine is not available in all countries, and trials focused on PTSD are not yet available. Few studies are available for the use of TCAs for PTSD and sleep problems. One small study [131] included 25 pediatric burn patients of which 12 were on imipramine (1 mg/kg/day, with a maximum of 100 mg); of these, ten responded positively for symptoms of autism spectrum disorder, eight no longer had nightmares, and nine experienced less insomnia. Burstein and Burstein [25] published case reports on five patients who had night terrors after motor accidents occurring 2 weeks to 8 months before treatment with imipramine; regarding the night terrors, all improved within 5 days with a dose of 200–300 mg imipramine/day. Improvements lasted for at least 4 months and were confirmed by spouses or parents. In another study Burstein [24] gave 15 patients imipramine 50–350 mg/day (mean dose 260 mg/day) for 2–3 weeks. In this study there were five dropouts, four because of reasons not related to imipramine and one unknown. The ten patients who remained in the study had less insomnia and less dreams about trauma.

Kinzie and Leung [79] performed an open-label study with imipramine and clonidine (see section "Clonidine") with promising results. Their experience was that in refugees with chronic PTSD, imipramine was better than other drugs that were available in the 1980s [benzodiazepines, monoamine oxidase inhibitors (MAOIs)], and patients improved further with clonidine if they still had symptoms, compared with imipramine alone. The authors performed a prospective pilot study with 12 Cambodian refugees with chronic PTSD and depressive disorder; the patients started with imipramine, and clonidine was added if possible and if needed. With imipramine, there was one dropout and two improved considerably and stayed on imipramine alone. In the other nine patients some symptoms disappeared (e.g., in three of nine patients, sleep symptoms improved), whereas when clonidine was added there was much more improvement (e.g., six of nine had improvement in sleep problems, and seven of nine reported improvements in nightmares of which one reported to no longer have nightmares).

Monoamine Oxidase Inhibitors

In general, it is reported that MAOIs increase sleep latency, are able to disturb sleep continuity, and give a strong and persistent suppression of REM sleep [99, 172, 177].

Phenelzine and Tranylcypromine

Shen and Park [150] reported on two cases with "traumatic war neurosis" who improved with phenelzine, the first case with 75 mg a day. The second person (a Vietnam veteran) improved on phenelzine 105 mg; however, this patient developed sexual impotence which improved when tapering to 90 mg phenelzine a day, but the nightmares and flashbacks returned. After a switch to tranylcypromine 40 mg, the patient had no nightmares or flashbacks, but the sexual impotence reappeared at a dosage ≥30 mg/day. In the discussion following that report, it was postulated that the sexual side effects might occur many times, but not in this case at dosages above the dosage needed to decrease the nightmares and flashbacks.

Phenelzine

Hogben and Cornfield [72] presented case reports on five veterans who had suffered "traumatic war neurosis" for 5–30 years and still had many symptoms despite undergoing psychotherapy and trying various drugs (e.g., barbiturates, benzodiazepines, neuroleptics, and tricyclic antidepressants). Phenelzine (45–75 mg) led to less anxiety, less flashbacks, and no nightmares. At follow-up one veteran was lost, three discontinued phenelzine and maintained an improved condition for 18 months, and one continued to do well taking 30 mg of phenelzine sulfate. The nightmares stopped within 5 days–1 month.

The first true study on phenelzine was reported by Davidson et al. [39], who found improvement with phenelzine (45–60 mg) in a pilot study in 11 patients, 1 of whom dropped out after 2 weeks due to side effects. In general, the

authors found improvement for sleep disorders and other symptoms, although 4 of 11 patients experienced intensification of preexisting sleep problems of which 1 lowered the dosage and 3 stopped after 4 weeks. Lerer et al. [93] studied phenelzine (30–90 mg) used by 25 veterans with PTSD in an open prospective trial; they reported a statistically significant but clinically insignificant improvement, except for sleep disturbance. Sleep disturbance was reported to be the most severe symptom and was the symptom that most consistently improved; patients expressed considerable satisfaction with this improvement, and this contributed to the extended period of treatment with phenelzine, even in the absence of substantial improvement in the other symptoms. Three patients dropped out due to side effects. Shestatzky et al. [151] performed a randomized, placebo-controlled double-blind crossover study with 13 patients with PTSD who took phenelzine (45–75 mg/day) or placebo, for two times 4 weeks; they found no significant differences on general or specific measures focused on PTSD, depression, or sleep disturbance (items). Around that time Kosten et al. [82] compared phenelzine with imipramine and placebo in a randomized double-blind study with 60 Vietnam veterans (mean age 39 years); they found that more patients on phenelzine stayed in the study and made greater improvement on PTSD symptoms as measured by the impact of event scale (IES), and no change was found due to change in depression. The authors did not report separately on sleep disturbance or nightmares.

Landolt et al. [90] performed an open-label study and gave 11 patients with MDD 30–90 mg of phenelzine. Independent from the clinical response, REM sleep was dramatically suppressed and stage 2 increased. Slow-wave activity was not affected.

Moclobemide

Monti [109] reported on an open-label study with ten patients of which six had unipolar manic-depressive psychosis, three MDD, and one atypical depression. Stage 2 increased, stage 3 was minimal and increased, and stage 4 remained absent during the study period. Total and relative REM sleep increased during moclobemide use and withdrawal, whereas REM latency decreased during use and increased during the withdrawal phase. The last dose was taken at 18.00 h; the authors thought this might be an explanation (besides the short half-life time) for the different effect on REM compared with the other antidepressants or, alternatively, that the mild REM disturbance was counteracted by the increase in REM sleep which comes with recovery from the depressive period (most patients in this study recovered). Blois and Gaillard [17] asked ten healthy volunteers to sleep two times five nights, during which for two nights, they took 4 mg/kg or three nights 6.5 mg/kg moclobemide; they found dose-related changes such as an increase in stage 1 and 2 percentage, reduction of total sleep time, more transient awakenings, and reduction of REM sleep. The volunteers taking 4 mg/kg had only very moderate to no changes. Minot et al. [105] performed an open-label study with 12 patients with major depression who took moclobemide 450 mg/day for 4 weeks after 1 week placebo and, at the end, a withdrawal week. The sleep recordings showed a reduction in total sleep time; also, REM latency was much longer (especially during the first days of treatment) and duration and percentage were slightly reduced. The authors concluded that there was REM sleep habituation and a slight rebound effect early during withdrawal.

In patients with PTSD, Neal et al. [112] performed an open-label study lasting 12 weeks and found symptom reduction in 11 patients, as they no longer fulfilled the criteria for PTSD. Symptoms of nightmares and sleep disturbance diminished.

Önder et al. [119] performed a randomized open-label study among patients with PTSD after an earthquake in Turkey (in 1999). The patients took flexible doses of fluoxetine, moclobemide, or tianeptine. A total of 35 patients were assigned to moclobemide which led to a significant improvement in PTSD severity, as assessed with the CAPS, but separate measures for sleep were not published.

Other Antidepressants

Trazodone is a weak SSRI and is an antagonist on several receptors, e.g., 5-HT_{1A}, 5-HT_{1c}, 5-HT_2, and alpha-1 and alpha-2 adrenergic receptors. Yamadera et al. [178] performed a study with eight healthy men and compared placebo with trazodone and imipramine. They found an increase in slow-wave sleep (SWS), no REM suppression, and a decrease in percentage stage 1 and 2. Montgomery et al. [108] followed nine insomniacs who took trazodone 150 mg nightly for 3 weeks. The sleep improved subjectively, but rebound insomnia appeared after withdrawal. The arousals became half of the baseline amount, SWS increased, and stage 1 and REM reduced, but total sleep time, and time to fall asleep, did not change.

Mendelson [104] published a review on trazodone in insomnia and found inconsistent data, especially for non-depressed populations. It appeared to be the second most commonly prescribed medication for treatment of insomnia, whereas using this drug for depression has decreased.

Some studies have been performed with PTSD patients. For example, Hertzberg et al. [65] conducted an open-label study with six patients with chronic PTSD (and, in the past, MDD and alcohol dependence) who started with 50 mg/day and were titrated up to 400 mg/day; the authors found that sleep was the first symptom to improve. Sleep improved gradually within 2–3 months (sleep duration doubled) and the other PTSD symptoms within 4 months. Ashford and Miller [7] described a group of 57 veterans with PTSD symptoms (30 PTSD) who were rather therapy resistant and had combinations

of psychotherapy and medication. Half of them were still on medication. They were prescribed 50 mg trazodone daily and increased themselves the dosage after every three nights to reach a dosage with good sleep. If there was some sedation they returned to a lower dosage with a minimum of 25 mg. Most of them had less sleep disturbances.

Warner et al. [169] asked 74 PTSD patients (most of whom took other medications) to take trazodone (50–600 mg/day; mean 212 mg/day) as augmentation; 14 stopped because of adverse side effects. All remaining 60 patients reported that the treatment supported sleep: 72% of the patients with nightmares reported reduction in frequency, 92% reported better sleep onset, and 78% reported improvement in sleep maintenance.

Mirtazapine

In a double-blind, placebo-controlled crossover study with six healthy volunteers, Ruigt et al. [139] found that a single dose of mirtazapine 30 mg 2 h before bedtime created a shorter sleep latency, stage 1 reduction, increase of SWS and increase of REM sleep latency, and a lower frequency of awakenings after periods of movement.

Two promising pilot studies that have been performed [33, 42] did not report separate sleep measures. There is one report on mirtazapine for PTSD-related sleep disorders. Lewis [94] reported that he was impressed with the results after using mirtazapine for treatment of nightmares and other sleep problems, especially for refugees. He estimated that about 75% reported improvement based on a reduction of the frequency and intensity of nightmares. Lewis also reported that a substantial minority had a total absence of dreams related to the traumatic events. Winokur et al. [176] performed an open-label study including six patients with MDD who took 15–30 mg mirtazapine. Results showed that sleep latency decreased, TST and sleep efficiency increased, as did the total amount of SWS without change in REM sleep. Both clinical depression and sleep disturbance improved.

Concerning sleep, EEG recordings by Schmid et al. [143] led to the same conclusions; their study included ten patients with depression and insomnia who were studied for 28 days with EEG recordings and several other measures, such as cortisol and melatonin. Sleep continuity improved at day 2 with a persistent effect at day 28, when SWS was also increased. Recently Alderman et al. [5] reported on an open-label study with mirtazapine (15–45 mg/day and most used 30 mg/day) with 13 of 17 used mirtazapine for 18 months with a mean reduction of 22.2 (sd 23.7) points on the CAPS but no report on sleep items. Schneier et al. combined sertraline (200 mg/day) with mirtazapine (30–45 mg/day) for 24 weeks, and this appeared to be relatively well tolerated and resulted in greater remission rates and greater improvement in depressive symptoms over 24 weeks of treatment, but no more effect on sleep or less sexual dysfunction as compared to sertraline with placebo. There was a high number of dropouts (27 in total) and a relatively high dosage of mirtazapine in combination with sertraline.

Nefazodone

Nefazodone has been withdrawn from the market in many countries due to a publication by Spigset et al. [153] reporting a significant and unexpectedly high incidence of hepatic injury. However, nefazodone is still available in its generic form in some countries (e.g., the USA), but, e.g., in a European country like the Netherlands, it is not available. There are about eight studies on nefazodone with promising results concerning sleep; however, in view of the abovementioned adverse side effects, we will not discuss this drug (some details of the studies are presented in Table 29.1).

Agomelatine

Agomelatine was developed as a melatonergic receptor agonist and 5-HT2C antagonist antidepressant. Quera Salva et al. [126] performed an open study with 15 patients with MDD who received 25 mg agomelatine a day for 42 days; there was an increase in sleep efficiency, time awake after sleep onset, and the total amount of slow-wave sleep (SWS). The increase of SWS was predominant during the first sleep cycle. There was no change in REM latency, amount of REM, or REM density. No trials focusing on PTSD and use of agomelatine are available. The only publication is a case report by De Berardis et al. [46] describing one patient with PTSD who improved after 25 mg for 2 weeks, with improvement in sleep quality after only 1 week. After 2 weeks the patient started taking 50 mg/day and improved further until full remission, which still persisted after 7 months follow-up.

Vortioxetine

Vortioxetine has multiple effects that probably derive from the interaction with 5-HT-receptor-mediated feedback and appear to increase serotonergic, noradrenergic, dopaminergic, cholinergic, histaminergic, and glutamatergic neurotransmission in brain structures associated with MDD. The FDA and the European Medicines Agency have approved vortioxetine for the treatment of MDD. Concerning sleep, the effect can be better than with SSRI or SNRI as the sleep problems found as side effects are comparable with placebos, which are different than with the use of SSRIs or SNRIs.

There is some evidence that the HT7 receptor antagonism of vortioxetine might influence sleep fragmentation, but more research is needed concerning the effect on sleep [142] as PTSD is known to be related to sleep fragmentation.

Anticonvulsants

Anticonvulsants are thought to have anti-kindling effects, and several have been used to improve PTSD symptoms

Table 29.1 Comprehensive overview of three decades of studies focused on PTSD and sleep

Drug	Study	Type of study Duration and follow-up	*N*	Outcome sleep; insomnia (*p* value if given in publication)	Outcome sleep; nightmares (*p* value if given in publication)	Outcome sleep; objective parameters (*p* value if given in publication)
Paroxetine	Stein et al. (2003) [157]	Pooled analyses Placebo controlled 12 wks	1180	Less disturbed sleep	Not mentioned	Not mentioned
Sertraline	Davidson et al. (2001) [41]	Placebo controlled 12 wks	208	Impr PSQI, but placebo = sertraline		Not performed
Fluoxetine	Meltzer-Brody et al. (2000) [103]	Placebo controlled 5 wks	53	Self: Impr. Interview: NI	Self: trend Interview: NI	Not performed
Fluvoxamine	De Boer et al. (1992) [47]	Open label 12 wks	24 13 DO	Impr	Impr	Not performed
	Neylan et al. (2001) [113]	Open label 10 wks	21 (18 for sleep analysis)	Impr for staying asleep; NI for falling asleep	Impr	Not performed
Venlafaxine	Stein et al. (2009) [158]	Pooled analysis placebo controlled 12 wks	687 DO not reported (LOCF)	NI	NI (trend)	Not performed
Duloxetine	Walderhaug et al. (2010) [167]	Open label 8 wks	21 1 DO	Unknown	Impr (not specified)	Not performed
	Villareal et al. (2010) [166]	Open label 12 wks	20 5 DO	PSQI impr. Duration longer, but NI with Bonferroni correction		Not performed
Imipramine	Burstein and Burstein (1983) [25]	Case reports 4 months	5	"Deepening" of sleep		Not performed
	Burstein (1984) [24]	Open label 2–3 wks	$N = 15$; 5 DO	Less insomnia $p = 0.001$	Less dreams about trauma $P < 0.01$	Not performed
	Kinzie and Leung (1989) [79]	Open label	12	4 of 12 Impr; not specified	5 of 12 Impr; not specified	Not performed
Tranylcypromine	Shen and Park (1983) [150]	Case report	1	No information	Improved	Not performed
Phenelzine	Shen and Park (1983) [150]	Case reports	2	No information	Improved	Not performed
	Hogben and Cornfield (1981) [72]	Case reports	5	No information	Improved	Not performed
	Lerer et al. (1987) [93]	Open label 8–18 wks	25	Improved	Improved	Not performed
	Davidson et al. [39]	Open label 4–6 wks	11	Improved	Improved	Not performed
	Shestatzky et al. (1988) [151]	Randomized, crossover 4–5 wks	13 3 DO	NI	NI	Not performed
Moclobemide	Neal et al. (1997) [112]	Open label 12 wks	10	Impr $P = 0.001$	Impr $P = 0.014$	Not performed
Trazodon	Hertzberg et al. (1996) [65]	Open label 16 wks	6	Impr	Not specified	Not performed
	Warner et al. (2001) [169]	Open label 8 wks	74 14 DO	Impr	Impr	Not performed
	Ashford and Miller (1996) [7]	Open label Cases	57 patients (30 with PTSD)	Impr	Impr	Not performed

(continued)

Table 29.1 (continued)

Drug	Study	Type of study Duration and follow-up	*N*	Outcome sleep; insomnia (*p* value if given in publication)	Outcome sleep; nightmares (*p* value if given in publication)	Outcome sleep; objective parameters (*p* value if given in publication)
Mirtazapine	Lewis (2002) [94]	Open label report Period not reported	>300 ? DO	Impr	Impr	Not performed
	Schneier et al. (2015) [145]	Plac control RCT 24 wks	36 17 DO (1st 12 wks) 10 DO (2nd 12 week)	NI	NI	Not performed
Nefazodone	Davidson et al. (1998) [40]	Open label 12 wks	17	Impr	Impr	Not performed
	Hertzberg et al. (1998) [66]	Open label 16 wks	10	Impr	Not specified	Not performed
	Hidalgo et al. (1999) [70]	Pooled analysis of 6 open-label studies[a]	105	Impr	Impr	Not performed
	Mellman et al. [101]	Open label 12 wks	15 4DO	Impr	Impr	Less awakenings
	Zisook et al. (2000) [180]	Open label 12 wks	19	Impr	Impr	Not performed
	Gillin et al. (2001) [54]	Open label 12 wks	12	Impr	Impr	PSG didn't change
	Hertzberg et al. (2002) [68]	Open label 3–4 years	10	Impr	Not specified	Not performed
	Neylan et al. (2003) [114]	Open label 12 wks	10	Impr	Impr	Increase TST (0.001) Increase Sleep maintenance (0.016) Increase delta sleep (0.001)
	McRae et al. (2004) [100]	RCT (with sertraline)	26 for analysis 13 nefazodone	Impr (PSQI) but the same as sertraline		Not performed
Agomelatine	De Berardis et al. (2012) [46]	Case report 7 months	1	Impr	Impr	Not performed
Gabapentine	Hamner et al. (2001) [61]	Retrospective chart review 1–36 months	30	Impr	Impr	Not performed

(continued)

Table 29.1 (continued)

Drug	Study	Type of study Duration and follow-up	*N*	Outcome sleep; insomnia (*p* value if given in publication)	Outcome sleep; nightmares (*p* value if given in publication)	Outcome sleep; objective parameters (*p* value if given in publication)
Divalproex	Hamner et al. (2009) [62]	RCT 10 wks	29 (13 plc) DO 14 (7plc)	No difference with placebo		Not performed
Tiagabine	Taylor (2003) [160]	Case reports 1–4 months	7 DO 1	Impr	Impr	Not performed
	Connor (2006) [35]	2-phase study with first open label (OL) then plc-controlled phase	Open label: 29 DO 10 Plcc-part: 18 DO: 5 (1plc)	OL: Impr Plcc-part: tiagabine = plc	OL: Impr Plcc-part: tiagabine = plc	Not performed
	Davidson et al. (2007) [43]	Double-blind plcc RCT 12 wks	232 (116 each arm)	No difference with placebo		Not performed
	Krystal et al. [84]	Open-label 3 wks	20	Impr	Impr	Less WASO (0.03) Less NAW (0.01) More SWS (0.01) Less stage 1 (0.01)
Topiramate	Berlant (2001) [13]	Case reports 1–5 months	3	Impr	Impr	Not performed
	Berlant and Van Kammen (2002) [15]	Open label 1–119 wks Mean 33 wks	35 DO 5.	Not specified	Impr	Not performed
	Berlant (2004) [14]	Open label Duration unknown, study parameters at 4 wks	33 DO 12	Not specified	Impr	Not performed
	Alderman et al. (2009) [5]	Open label 8 wks	43	NI ($p = 0.08$)	Impr	Not performed
Pregabaline	Strawn et al. (2008) [159]	Case report At least 4 months	1	Impr	Impr	Not performed
	Paslakis et al. (2011) [122]	Case report Not reported	1	Impr	Impr	Not performed
Risperidone	Leyba and Wampler (1998) [95]	Case report	4	Impr	Impr	Not performed
	Stanovic et al. (2001) [155]	Retrospective chart review Unknown how long	10	Impr	Impr	Not performed
	David et al. (2006) [36]	Open label study At least 6 wks	17 completed at least 6 wks DO 1 (lost in follow-up)	Impr	Impr	Not performed
	Rothbaum et al. (2008) [138]	Plc controlled randomized augmentation study 8 wks	25 (14 risp and 11 plc) DO 5 (all risp)	Impr	NI (although trend $p = 0.09$)	Not performed
	Krystal et al. (2016)[86]; See as well Krystal et al. (2011) [85]	Plc controlled randomized augmentation study 24 wks	267 for secondary analysis	Impr ($p = 0.03$)	Impr ($p = 0.03$)	Not performed

(continued)

Table 29.1 (continued)

Drug	Study	Type of study Duration and follow-up	*N*	Outcome sleep; insomnia (*p* value if given in publication)	Outcome sleep; nightmares (*p* value if given in publication)	Outcome sleep; objective parameters (*p* value if given in publication)
Olanzapine	Labbate and Douglas (2000) [88]	Case report 4 months	1	Impr	Impr	Not performed
	Jakovljević et al. (2003) [75]	Case reports	5	Impr	Impr	Not performed
	Stein et al. (2002) [156]	Double-blind, placebo-controlled augmentation study	19	Impr		Not reported
Levomepromazine	Aukst-Margetić et al. (2004) [8]	Open-label study 4 wks	23 DO 2	Impr	Impr	Not performed
Thioridazine	Dillard et al. (1993) [50]	Case report 3 wks	1	Impr	Impr	Not performed
Aripiprazole	Lambert (2006) [89]	Case reports Not reported	5 DO 1	Impr	Impr	Not performed
	Villarreal et al. (2007) [165]	Open label study 12 wks	22 DO 8	Duration of sleep and PSQI improvements were not significant after Bonferroni		Not performed
Quetiapine	Robert et al. (2005) [132]	Open-label study 6 wks	20 DO 2	Impr	Impr	Not performed
	Byers et al. (2010) [26]	Retrospective chart review 0.5–6 years	324 (237 included) DO not clear	Impr	Impr	Not performed
Clonidine	Kinzie and Leung (1989) [79]	Open-label pilot Not reported	9	Impr	Impr	Not performed
	Kinzie et al. (1994) [80]	Case reports Not reported	4	Impr	Impr	Results not conclusive
Guanfacine	Neylan et al. (2006) [115]	Double-blind RCT 8 wks	63 DO 10	NI	NI	Not performed
	Davis et al. (2008) [44]	Double-blind RCT with open-label study 8 wks + 2 months	35 randomized DO 6 Open label extension period *N* = 24	NI	NI	Not performed
Clonazepam	Cates et al. (2004) [30]	Randomized, single-blind plc-controlled crossover study 2 wks	6 pts. with PTSD	Impr	NI	Not performed
Zolpidem	Dieperink and Drogemuller (1999) [49]	Case reports up to 20 months	32 DO 7	Impr	Impr	Not performed
	Abramowitz et al. (2008) [1]	Randomized study comparing zolpidem with hypnotherapy 2 wks	32; 15 received zolpidem of which DO 1	Hardly Impr and hypnoth was better		Not performed
Eszopiclone	Pollack et al. (2001) [124]	Double-blind plc-controlled Crossover RCT 3 wks each arm	24	Subjective improvement in sleep quality (PSQI), total sleep time, and sleep latency		Not performed

(continued)

Table 29.1 (continued)

Drug	Study	Type of study Duration and follow-up	*N*	Outcome sleep; insomnia (*p* value if given in publication)	Outcome sleep; nightmares (*p* value if given in publication)	Outcome sleep; objective parameters (*p* value if given in publication)
Buspirone	Wells et al. (1991) [170]	Case reports At least half to 1 year	3	Impr	Impr	Not performed
	Hamner et al. (1997) [60]	Open label case series Not reported	15 DO 2 (side effects)	Impr	Impr	Not performed
Cyproheptadine	Harsch (1986) [64]	Case reports Not clear	2	Not reported	Impr	Not performed
	Brophy (1991) [20]	Case reports Not reported	5 DO 2	Not reported	Improved	Not performed
	Rijnders et al. (2000) [130]	Case report Not reported	1	Impr	Impr	More deep sleep and less REM sleep
	Clark et al. (1999) [32]	Open label At least 1 week	36 baseline DO 9 16 for statistics of which another DO 3	Not impr 0,26 for number of awakenings	Not impr 0.07 for disturbance of dreams	Not performed
	Gupta et al. (1998) [58]	Case reports Not clearly reported	9	Impr	Impr	Not performed
	Jacobs-Rebhun et al. (2000) [74]	A double-blind, plc-controlled RCT	69 60 for analysis	NI PSQI worse in treatment group, but $p = 0.06$)	NI $p = 0.17$ (worse in treatment group)	Not performed

Impr improvement, *NI* no improvement, *DO* dropout, *Plc* placebo, *Plcc-part* placebo-controlled part of study, *wks* weeks

[16]. It is possible that they act via inhibition of glutamate neurotransmission. The effect on sleep and PTSD has been studied in a few small studies.

Legros and Bazil [92] performed a prospective study in patients with localization-related epilepsy by comparing sleep parameters of patients with and without antiepileptic drugs (AEDs). They found that gabapentin improved sleep by increasing SWS, valproic acid disrupted sleep by increasing stage 1 sleep, and lamotrigine had no significant effects. Vigo and Baldessarini [164] performed a review on AED for MDD. However, they found very few studies, and these differed in size and design and had uncontrolled use of antidepressants. The authors concluded that there was suggestive evidence of effects of carbamazepine, lamotrigine, and valproate for MDD and especially for long-term adjunctive use and for patients with recurring MDD with prominent irritability or agitation.

Gabapentin

Hamner et al. [61] retrospectively reviewed the files of 30 patients with PTSD (and 67% MDD) who received gabapentin as adjunctive medication. Gabapentin was mainly prescribed first to facilitate sleep; with a dose of 300–3600 mg/day, the majority (77%) showed moderate or greater improvement in the duration of sleep and a decrease in frequency of nightmares. The improvement appeared to be dose dependent; the group with moderate or marked improvement received 1344 ± 701 mg, and the group with mild or no improvement received 685 ± 227 mg.

Lamotrigine

There is some evidence that lamotrigine is helpful for PTSD; however, posttraumatic sleep disturbance or sleep difficulties caused by nightmares were not measured in studies such as that performed by Hertzberg et al. [67]. Their study included 15 patients with PTSD enrolled in a 12-week double-blind study of lamotrigine (start 25 mg and titration up to 500 mg if possible) and placebo. One patient dropped out, ten were on lamotrigine, and four on placebo; more patients on lamotrigine responded (50–25%), and patients on lamotrigine improved more on reexperiencing and avoidance/numbing symptoms.

Divalproex

Schneider et al. [144] studied the effect of di-n-propylacetic acid (DPA) (valproic acid) on sleep in 11 healthy volunteers. After short-term application (2 days), a shortening of the time to fall asleep and of the waking time was found, whereas under long-term administration (2 weeks), a decrease in deep synchronous sleep was observed. No marked influence on REM sleep was observed. Subjective sleep experiences did not change. Hamner et al. [62] performed a placebo-controlled study with divalproex in 29 chronic PTSD patients of whom most used other medication (antidepressants, anxiolytics); the authors found no difference compared with placebo concerning the sleep-related measures and even found a decrease in avoidance/numbing scores and improvement in the Clinical Global Impression Scale favoring placebo.

Tiagabine

Tiagabine is a GABAergic anticonvulsant. Mathias et al. [98] conducted a double-blind, placebo-controlled study of a single oral dose of 5 mg tiagabine on nocturnal sleep in ten healthy elderly volunteers (mean age 68 years) and found tiagabine to increase sleep efficiency, tendentially decreased wakefulness, and prominently increased both SWS and low-frequency activity in the EEG within non-REM sleep. Except for self-rated sleep intensity, there was no significant change in subjectively assessed sleep parameters nor perceived state upon awakening. Taylor [160] did a case series on seven patients with PTSD and reported positive findings on sleep disturbance, especially nightmares; the mean dose was 8 mg tiagabine. Connor et al. [34] performed an open-label tiagabine for 12 weeks with tiagabine (initiated at 2 mg bid and up to 16 mg daily max, mean dose 10.8 mg) in 29 outpatients with PTSD; those who showed significant improvement ($n = 19$) continued with placebo or tiagabine, and there was a greater trend toward a likelihood of further remission but no significant differences. Distressing dreams, nightmares, and PSQI improved significantly during the open-label part, but, in the placebo-controlled phase, the improvements stayed the same in both the placebo and tiagabine group. Walsh et al. [168], in a placebo-controlled, randomized, double-blind, parallel-group study in insomnia patients ($n = 232$) with different dosages of tiagabine, found a significant dose-dependent increase of slow-wave sleep and a decrease in stage 1 sleep but no change in WASO, sleep latency, or total sleep compared to placebo.

Davidson et al. [43] performed a 12-week, double-blind, randomized, multicenter study and included 232 patients with PTSD (tiagabine and placebo; both $n = 116$). There was no difference in change by tiagabine (mean dosage 11.2 mg/day) and placebo concerning PTSD symptoms (CAPS) ($p = 0.85$) baseline vs. final visit. There were no differences in sleep ratings between the tiagabine and placebo groups. Krystal et al. [83] performed an open-label 3-week study on 20 adults with PTSD who took 2–12 mg tiagabine daily (two times) with polysomnography measures. Contrary to the findings of Davidson et al. [58], there appeared to be an improvement in different sleep parameters such as the WASO (effect size 0.49; p0.033) and nightmares (e.g., PSQI item 5 h gave an effect size of 0.44; $p = 0.008$).

They also concluded that the first treatment night predicted PTSD response at 3 weeks. A decrease in self-reported and objective time awake after onset of sleep and an increase of SWS accounted for 94% of the week 3 PTSD score. More important, they found positive and significant correlations between changes in sleep parameters and total PTSD scores, such as WASO with PSG ($r = 0.6$; $p < 0.001$) or self-reported ($r = 0.82$; $p < 0.001$). This means that improvements in sleep can lead to improvements in PTSD symptoms.

Topiramate

In several case and open-label studies on topiramate [13–15], some effect of topiramate on PTSD was found, especially on sleep problems. The study of Berlant [14] was an open-label study with topiramate as monotherapy or augmentation (median dosage 50 mg/day); this led to a decline of PTSD symptoms in median 9 days, and 94% of the patients with nightmares reported full cessation after 4 weeks. Tucker et al. [162] conducted a double-blind, placebo-controlled study on topiramate monotherapy (median final dose 150 mg/day) in 38 patients with PTSD; the authors found no significant reduction in the CAPS score, but there was a significant decrease in reexperiencing symptoms and the treatment outcome PTSD scale. No separate sleep measures were reported.

Alderman et al. [5] performed an 8-week open-label pilot study of topiramate in 43 patients with PTSD; they found reductions in several scales and a significant reduction of PTSD symptoms (CAPS). The Stanford sleepiness scale tendentially improved ($p = 0.08$). There was a significant reduction in nightmares and a reduction in the number of patients who were anxious to fall asleep and the number of patients with high-risk drinking patterns.

Levetiracetam

Kinrys et al. [78] performed a retrospective chart review on 40 patients who have taken 9.3 weeks (sd 5.1) adjunctive levetiracetam. There was improvement, but change of severity was measured by use of clinical global inventory (CGI) only, and no information about sleep or nightmares was given.

Pregabalin

Hindmarch et al. [71] performed a randomized, double-blind, placebo- and active-controlled, 3-way crossover study with 24 volunteers (23 completers) who took pregabalin 150 mg t.i.d., alprazolam 1 mg t.i.d., and placebo t.i.d. for

3 days. Pregabalin increased slow-wave sleep and reduced sleep latency. REM sleep was reduced, but REM sleep latency appeared to be equal to placebo. Pregabalin reduced the number of awakenings. Subjective sleep improved, but ratings of behavior after awakening showed impairments.

Strawn et al. [159] wrote a case report about a patient with PTSD who took 75 mg b.i.d. in addition to her other medication; her nightmares stopped and insomnia improved within 2 weeks. Pae et al. [120] conducted an open-label study with nine patients with PTSD who were on stable doses of antidepressants. They were treated with flexibly dosed pregabalin [mean dose 200 mg/day (range 150–300 mg/day)] for 6 weeks and improved on PTSD complaints; however, but no sleep measures were made. Paslakis et al. [122] published a case report about a patient with PTSD who previously used different kinds of medication but improved on pregabalin with later addition of quetiapine because of an additional bipolar disorder. The patient reported improvement in sleep and nightmares within the first week.

Antipsychotics

Giménez et al. [55] compared effects on (subjective) sleep activity due to typical and atypical antipsychotic drugs; they performed a randomized, double-blind, placebo-controlled, four-period crossover clinical trial on 20 healthy young volunteers who took a single oral morning dose of olanzapine 5 mg, risperidone 1 mg, haloperidol 3 mg, or placebo. The drugs resulted in different changes in sleep patterns. Olanzapine led to an increase in TST, sleep efficiency, SWS, and REM sleep with a decrease in wake time and also resulted in a significant improvement in subjective sleep quality compared with risperidone and haloperidol and a tendency compared with placebo. Risperidone resulted in a decrease in wake time and REM sleep, whereas stage 2 increased. Haloperidol tended to increase sleep efficiency and stage 2, with a decrease of wake time. Neither haloperidol nor risperidone improved subjective sleep quality.

Risperidone

Risperidone was used in a study which consisted of two parts [148]. The first was a placebo-controlled, double-blind, crossover study on eight volunteers who took risperidone 1 mg for one night; this resulted in a significantly decreased REM sleep. The second part was an open-label study on eight patients with MDD who did not respond to a therapeutic dose of antidepressants and received 2 weeks of risperidone 0.5–1 mg (final mean 0.7 mg) daily. The depressed patients had significantly less wake and REM sleep as well as a significant decline in depressive symptoms.

There are a few case reports about the positive outcome when using risperidone for PTSD, e.g., the study of Leyba and Wampler [95]. Stanovic et al. [155] performed a retrospective chart study in acutely burned hospitalized patients with distressing acute stress symptoms that probably would not respond to brief psychotherapeutic interventions. Patients received 0.5–2 mg risperidone (mean 1 mg) at bedtime and had less sleep disturbances, nightmares/flashbacks, and hyperarousal. David et al. [36] conducted an open-label study of flexible dose adjunctive risperidone (1–3 mg) in patients who partially responded to medication (different use of AD, AED, and anxiolytics). A total of 17 Vietnam veterans completed at least 6 weeks and showed improvement of sleep disturbance measured by self-report sleep measures. Less awakenings and reduction in trauma-related dreams (CAPS item) were found, but improvement was especially found in sleep log data and not in retrospective scales, such as the PSQI.

Rothbaum et al. [138] performed a randomized augmentation study with risperidone and sertraline. The patients who did not remit during 8 weeks treatment with open-label sertraline received risperidone or placebo for 16 weeks. Of the 45 patients that started, 34 completed the sertraline part and 25 went on to the second part, of whom 20 completed. All patients improved, with no group differences. Post hoc analyses showed that the group that received risperidone improved more on the sleep item of the Davidson Trauma Scale ($p = 0.03$) and the sleep item of the CAPS Scale (trend $p = 0.09$). Krystal et al. [85] conducted a 6-month, randomized, double-blind, placebo-controlled multicenter trial with 367 screened patients, of which 296 were diagnosed with military-related PTSD and ongoing symptoms after at least two SRI treatments. Risperidone (up to 4 mg) or placebo was given to 247, and there was no significant change in total CAPS score. Post hoc analyses [86] showed a significant but small reduction in reexperiencing and hyperarousal symptoms, perhaps clinically not detectable. Risperidone use resulted in more adverse events than placebo, such as weight gain, fatigue, and somnolence. Sleep was measured by means of the PSQI, and risperidone provided some improvement ($p = 0.034$) as well as less severe nightmares (measured by means of CAPS item and $p = 0.033$). The improvements in sleep correlated with PTSD symptom reductions as a whole (measured by the CAPS; r-0.28, $p = 0.001$) and improvement in general mental health measured by means of the SF-36 V subscale ($r = 0.26$, $p = 0.003$). The scores became significantly different from placebo in week 24; before that time, the differences were not significant, and the positive effect was not seen in measures for global clinical status and general measures of quality of life. This gave the authors reason to conclude that the results have some, but limited, clinical significance.

Olanzapine

Sharpley et al. [149] studied olanzapine and its effects on sleep when used as augmentation to ineffective treatment with SSRIs in depression. In an open trial, 12 patients with SSRI-resistant depressive disorder took 2.5–10 mg olanzapine (mean 4.8 mg) for 3 weeks; the depressive symptoms decreased, while sleep efficiency increased, as did the subjective sleep quality and SWS. In general, the improvements occurred after the first week.

Labbate and Douglas [88] and Jakovljević et al. [75] reported on patients with PTSD given olanzapine 5–20 mg as augmentation; they described improvements in symptoms (e.g., nightmares and sleep disturbance) starting after 1–4 days. Stein et al. [156] performed a double-blind, placebo-controlled study with augmentation of olanzapine (15 mg/day) or placebo in 19 patients with PTSD who hardly responded to an SSRI; the authors found a significant clinical improvement of PTSD and depressive and sleep measures. The enhanced sleep accounted for much of the reported improvement. They concluded that the overall clinical magnitude of effects was modest for most of the patients but clinically meaningful for some. Carey et al. [28] performed a randomized 8-week placebo-controlled study with olanzapine (flexible dosage; ending at mean 9.3 mg/day) as monotherapy in 34 patients with PTSD (ten dropped out, and four of them were included in the analysis) and found more improvement on the CAPS compared with placebo. There were no special measurements on insomnia or nightmares.

Levomepromazine

Aukst-Margetić et al. [8] conducted an open-label study on levomepromazine (47.05 mg/day ± 27.78) for 4 weeks including 23 patients with PTSD; the authors found that nightmares (CAPS item recurrent nightmares) and the number of arousals decreased, total sleep increased, and sleep latency decreased. Two patients dropped out, and two had no improvement on the CAPS, but all showed prolongation of sleep.

Thioridazine

A case report by Dillard et al. [50] described a Vietnam veteran who improved 2 days after start of thioridazine 10 mg, four times daily; the insomnia, nightmares, and mood improved within 3 weeks.

Aripiprazole

Lambert [89] reported on five patients with PTSD who improved with aripiprazole 15–30 mg as monotherapy, or together with SSRI or psychotherapy, and found the medication well tolerable (although one patient stopped because of side effects) and effective for nightmares and sleep disturbances. Villarreal et al. [165] performed a study with 22 PTSD patients. There was among others an increase in sleep duration and an improvement in the PTSD component of the PSQI, but these improvements were not significant anymore when a "conservative" Bonferroni correction was made.

Additional studies on aripiprazole include those by Richardson et al. [128] and Youssef et al. [179] with some promising results; however, none mention data focused on sleep.

Quetiapine

Robert et al. [132] analyzed sleep data from a previously published study of quetiapine in PTSD. In this 6-week open-label trial, combat veterans meeting DSM-IV criteria for PTSD ($n = 20$) were treated with quetiapine starting at 25 mg at bedtime with subsequent titration based on clinical response and tolerability. The use of a mean of 100 (sd 70) mg/day resulted in a significant, albeit modest, improvement of various sleep disturbances. Byers et al. [26] performed a historical prospective cohort study using retrospective chart reviews to compare quetiapine with prazosin for treating nighttime symptoms in a large group of 324 veteran PTSD patients. In the 237 included patients, short-term effectiveness was similar, but patients prescribed with prazosin were significantly more likely to continue compared with quetiapine, thus achieving long-term effectiveness. Alternatively, patients in the quetiapine group were more likely to discontinue therapy because of adverse effects (sedation and metabolic effects) compared with the prazosin group. Initial quetiapine daily dose was 41 mg (mean) and was increased to 135 mg (range 2–600 mg/day) by the study end date.

Clozapine

There are some case reports of clozapine and PTSD, but although it is expected that sleep will improve, no known studies on sleep parameters are available.

Antiadrenergic Agents: Alpha-Blockers, Clonidine, Beta-Blockers, and Guanfacine

Intrusive experiences and hyperarousal are associated with increased noradrenergic activity; therefore, medication that has an effect on this system can be important in case of insomnia and nightmares. Among these agents, prazosin has been studied the most and is discussed in a separate chapter. Other α_1-adrenergic receptor inhibitors investigated are doxazosin [48, 133, 135, 146] and terazosin [116, 141].

Clonidine

Clonidine and guanfacine are centrally acting α2-adrenergic agonists and were originally used as antihypertensive drugs. Studies by Spiegel and De Vos [152] in healthy volunteers has shown that clonidine produces a significant increase in stage

2 as well as reduced deep and REM sleep duration. These results seem to be dose dependent: Spiegel and De Vos [152] found a dose-dependent decrease in REM 2 h after clonidine (0.15 and 0.30 mg), while guanfacine 1 mg had no effect and 2 mg had some effect after 5 h (but less than clonidine). Also, Miyazaki et al. [106] found that, after a low (25 μg) or medium (150 μg) dose of clonidine, low-dose clonidine significantly increased the amount of REM sleep and decreased the amount of non-REM (NREM) sleep during the second one-third of the drug nights, and medium-dose clonidine significantly decreased REM and increased NREM on drug nights compared to baseline nights.

Kinzie and Leung [79] performed a study with 12 traumatized Cambodian refugee patients who suffered from chronic PTSD and major depression who took imipramine (up to 150 mg/day); if they did not improve, they received a combination of clonidine (0.1 mg/day and max 0.6 mg/day) and continuation of imipramine. Imipramine alone was good for two patients, one dropped out, and nine patients used this combination in a prospective study lasting 12–19 months; this resulted in improved symptoms of depression in six patients, PTSD global symptoms improved in six patients but only in two to the point that DSM-III-R diagnoses were no longer met, there was no further sleep disorder in five patients, and the frequency of nightmares lessened in seven patients.

Kinzie et al. [80] reported on the use of clonidine (first 0.1 mg bid; then 0.1 in the morning and 0.2 at bedtime) in four patients with PTSD and MDD; all reported a subjective increase in sleep and less nightmares. However, the sample was small, the PSG data were not conclusive, and too few comparisons were made for statistical analyses.

Guanfacine

Neylan et al. [115] conducted an 8-week, double-blind, randomized controlled trial of guanfacine (mean dose 2.4 mg/day) including 63 patients with PTSD. The authors found no effect on PTSD symptoms, subjective sleep quality, or general mood disturbances. Guanfacine was associated with some side effects, like dry mouth and light-headedness. Davis et al. [45] performed a randomized double-blind, placebo-controlled study of guanfacine followed by a 2-month open-label extension phase and found no differences in the groups for PTSD, sleep, mood, or general clinical situation.

Hypnotics/Anxiolytics

Benzodiazepines and other hypnotics are widely used for insomnia. In healthy persons, Parrino and Terzano [121] described the effect of hypnotics as measured by polysomnography and other measures; these were a reduction in SWS and REM sleep and an increase of sleep continuity. Guidelines for patients with depressive disorder [37, 118] advise sparse use of benzodiazepines. These agents play a role if the patient has catatonic depression, acutely suicidal depression, or depression with symptoms of anxiety, agitation, or insomnia and are used for a short period only. On the longer term, adaptation and rebound will occur; therefore, for pharmacotherapy it is advised to use antidepressants as monotherapy or other forms of augmentation. Mellman et al. [102] conducted a placebo-controlled trial immediately after a trauma and found that temazepam improved subjective sleep; however, this effect stopped after withdrawal, and temazepam use for acute stress did not prevent later development of PTSD. A little later Cates et al. [30] performed a randomized, single-blind, placebo-controlled, crossover study including six patients with PTSD who took 1 mg clonazepam for 1 week at bedtime and then 2 mg for 1 week, followed by washout and then alternate treatment. The authors found no significant differences between clonazepam and placebo concerning sleep disturbance or nightmares. Clonazepam led to some improvements in difficulty in falling or staying asleep.

Non-benzodiazepine GABAergic Hypnotics

Hypnotics are often used in case of insomnia. Dieperink and Drogemuller [49] described some cases they successfully treated for insomnia. The authors describe how they gave zolpidem to at least 50 veterans with PTSD. Of the first 32 veterans with PTSD-associated insomnia, 25 remained on zolpidem and reported an improvement in insomnia with no side effects; some took zolpidem for as long as 20 months. Seven patients discontinued zolpidem due to lack of efficacy but none due to adverse effects. Krystal et al. [83] conducted a multicenter, 25-week, randomized, double-blind, placebo-controlled, and parallel-group study in a large group of 1018 insomniacs who took zolpidem extended-release 12.5 mg (n = 669) or placebo (n = 349) from a minimum of three nights/week to a maximum of seven nights/week. After 12 weeks, the zolpidem users ranked the medication more favorable than did the placebo users ($p < 0.0001$). Moreover, zolpidem scored better on scales concerning general functioning, sleep, morning sleepiness, and ability to concentrate. Adverse events were headache, anxiety, and somnolence; no rebound effect was seen. Abramowitz et al. [1] performed a randomized controlled trial in 32 patients with chronic PTSD who continued SSRI and supportive psychotherapy; they received adjunctive zolpidem 10 mg nightly for 14 nights (n = 15) or symptom-oriented hypnotherapy twice-a-week 1.5-h sessions for 2 weeks (n = 17). Hypnotherapy treatment had a better effect on PTSD symptoms and sleep variables (diaries), such as total sleep. There was no placebo-controlled group. Alderman and Gilbert [4] conducted a 6-month follow-up cohort study of zopiclone usage including 26 combat veterans with PTSD. A total of 24 subjects reported poor sleep quality at baseline, and actigraphy showed a mean

sleep efficiency score of 71.2 ± 13.7% at baseline. Thirteen men were followed up, and, because only minor differences were found, it was concluded that the efficacy of long-term use of zopiclone for PTSD-related sleep disturbance is low.

Pollack et al. [124] conducted a prospective, randomized, double-blind, placebo-controlled study including 24 patients with PTSD who took eszopiclone 3 mg at bedtime. The authors found more improvement on PTSD and sleep symptoms in the eszopiclone group. Compared with placebo, there was a subjective improvement in sleep quality (PSQI), total sleep time, and sleep latency. Roehrs et al. [134] studied a randomized group of 33 primary insomniacs, without psychiatric disorders, who took zolpidem 10 mg ($n = 17$) or placebo ($n = 16$) nightly for 12 months, while at 1, 4, and 12 months, placebo was given to all. There was some rebound, but there was no difference between the groups. Clinically significant withdrawal symptoms were not found.

Buspirone

Wells et al. [170] reported on three patients with PTSD who were treated with buspirone (35–60 mg/day). Symptoms that improved included anxiety, insomnia, nightmares, flashbacks, and depressed mood; they experienced hardly any side effects.

Hamner et al. [60] performed an open-label study with buspirone addition with 15 patients with PTSD. They found a relatively good response (11 of 15 patients), and, according to the separate case descriptions, three reported improvement of sleep and two a decrease of nightmares of which one both sleep and nightmares.

Cyproheptadine

Cyproheptadine is a 5-HT_2 receptor antagonist; it is used as an antihistamine and (like many anti-allergics) is also used for sleep disturbance. Sharpley et al. [147] reported an increase in SWS sleep and total sleep in 12 healthy volunteers, but not in patients with a history of major depression who still were on TCA; in both groups there was a similar decrease in REM sleep. Some case studies on cyproheptadine reported that cyproheptadine worked well for nightmares [20, 64, 130]. Gupta et al. [58] performed a retrospective chart review of nine patients with PTSD who received 4–12 mg cyproheptadine at bedtime for nightmares. The outcome ranged from complete remission to a decrease in intensity and frequency of nightmares. All patients reported an improvement in sleep quality and an initial reduction in nightmares within some days of starting cyproheptadine. The overall effect of complete remission or significant reduction in nightmares occurred within 3–4 weeks at the effective dosage. Clark et al. [32] performed an open-label study in which 36 patients with PTSD completed baseline sleep diaries and started cyproheptadine 4–8 mg at bedtime. Of these, 16 completed at least 1 week of cyproheptadine and continued to bring diaries. Cyproheptadine did not decrease nightmares or improve sleep quality. There was no significant change in the sleep diary items, and 6 of the 25 patients returning to the clinic found the drug to be effective. However, cyproheptadine was not well tolerated because 7 (28%) of the 25 patients discontinued the drug as a result of adverse side effects.

Jacobs-Rebhun et al. [74] conducted a double-blind, randomized, placebo-controlled trial of cyproheptadine in 69 patients with PTSD. There were data available of 60 patients, and the CAPS scores were worse in the cyproheptadine group than in the placebo group, as were the scores for nightmare severity and PSQI although the figures did not reach level of significance.

Cortisol and Mifepristone

Aerni et al. [3] gave three patients with PTSD 10 mg cortisol a day for 1 month in a double-blind, placebo-controlled study which lasted 3 months. The authors found significant treatment effect with reduction of traumatic memories, reductions of at least 38% (average rank) in one of the daily rated symptoms of traumatic memories (self-rating and the CAPS), and in one patient reduction of avoidance symptoms but not hyperarousal symptoms.

Mifepristone is a selective glucocorticoid receptor antagonist that induces an increase in cortisol and ACTH levels through blockade of cortisol's feedback inhibition of the hypothalamic-pituitary-adrenal axis. Wiedemann et al. [171] reported on the effect of 800 mg mifepristone given to a volunteer after a habituation day and a placebo day; this resulted in a disruption of sleep quality with a prolonged sleep onset, increased awakenings, and a reduction of SWS (80%) and REM sleep (>50%), especially in the first half of the sleep. Buckley et al. [23] conducted a pilot study on mifepristone by means of a placebo-controlled double-blinded prospective study for 30 days; they included ten patients with chronic insomnia who took 600 mg/day mifepristone for 5 days. Two weeks after this period, the Insomnia Severity Index decreased by four points, and the changes in sleep EEG were limited; however, this may partly be due to the design of the pilot study. Golier et al. [56] performed a randomized, double-blind trial of 1 week of treatment with mifepristone (600 mg/day) or placebo in eight patients with PTSD. After 1 month all four patients in the mifepristone group and one of the four in the placebo group achieved clinical response (≥12 points decrease on the CAPS); three of the four in the mifepristone group and one of the four in the placebo group remitted. Sleep measures were not mentioned separately.

Cannabis and Synthetic Cannabinoid

Cannabis is widely used in the USA and beyond, and people with PTSD appear to use it for PTSD and especially for sleep problems related to the disorder. Cameron et al. [27] did a retrospective chart study of 104 male patients with serious mental illness who stayed in a hybrid mental health center and correctional center and used nabilone (a synthetic cannabinoid). It appeared that in the group patients with insomnia, the mean total hours slept raised from 5.0 to 7.2 h ($p < 0.001$)($n = 101$), nightmares decreased in frequency from mean 5.2 to 0.9 per week ($p < 0.001$)($n = 90$), and total PTSD (measured with posttraumatic checklist-civilian version) ($p = 0.001$)(n-58) improved significantly. It is however not reported clearly how many patients with PTSD and nightmares or insomnia improved. Kevorkian et al. [77] showed that patients with lifetime PTSD had a significant association with cannabis use disorder ($OR = 1.22$). In a study of Bonn-Miller et al. [18] among 170 patients at a medical cannabis dispensary in California, it appeared that cannabis use was higher among people with higher PTSD scores, and (more important in the light of this chapter) it appeared that among the patients with high PTSD scores, the cannabis users who used it for sleep problems used it more frequently than patients who used it for other purposes. Belendiuk et al. [11] discovered that patients who used medical cannabis for sleep problems related to PTSD differentiated in the strain of the cannabis, depending on whether they used the cannabis for insomnia or for nightmares.

The possible use of cannabis and synthetic cannabinoids needs more prospective, randomized controlled studies; however, it seems promising, especially when people have chronic pain and/or also a cannabis dependency.

Conclusions and Discussion

Currently, many guidelines are available on PTSD. Among the most influential are those of the US Veterans Affairs (2004, 2010). Concerning insomnia in patients with PTSD, they advise to treat first patients with non-pharmacological treatments (like sleep hygiene and CBT). The next step will be a sleep agent, the choice for which will be affected by treatment decisions such as different other medications for PTSD, pain, or depression. Those guidelines recommend trazodone, hypnotics, and atypical antipsychotics, and, if nightmares remain severe, they suggest prazosin as adjunctive therapy. In their overview of pharmacotherapy for PTSD, they advise against the use of benzodiazepines, but studies conducted by Veterans Affairs show that these guidelines are difficult to implement; in 2009 it appeared that 37% of the veterans with PTSD who took medication were prescribed with benzodiazepines, 68.8% of this amount was attributable to mental healthcare providers, and most were prescribed for more than 90 days [2]. It is known from this and other guidelines/reviews that the non-pharmacological therapies for PTSD and sleep-related disorders in PTSD are preferable as a first step. Therefore, it is quite optimistic that in 2008 67% of the 442,359 patients with PTSD (in- or outpatients) started at least one outpatient psychotherapy episode. Less good is that, of these, 62% attended only one or two visits. Almost half (48%) of those who started one outpatient psychotherapy episode had at least one additional episode start in the same year. Veterans with PTSD have, on average, longer periods of PTSD and are therefore more difficult to treat [73]. The above data show that veterans with PTSD are eager to find support, but there seems to be considerable pressure to prescribe and use medication that is not in guidelines but nevertheless helps (among other problems) their sleep problems. The use of alcohol is probably based on the same background [29, 117].

Van Liempt [163] reported that PTSD leads to sleep disorders and that disturbed sleep is a precipitating and perpetuating factor in PTSD symptomatology, possibly creating a perpetual circle. This means that PTSD treatment also needs to include treatment of sleep disorders and vice versa. Germain [53] published an overview of this subject and critically reported that the efficacy of first-line treatments may be affected by chronic sleep disruption. The reason for this is that those treatments, and especially cognitive-behavioral approaches, rely on habituation or on cognitive processing, both of which are affected by sleep loss. Germain discussed the clinical implications of the above-cited findings and advised to develop guidelines, or reach consensus, on the inclusion of evidence-based sleep treatment strategies in the context of trauma and PTSD management, as well as in the context of comorbid conditions like depression, suicidality, and addictive disorders. Because so many variables still exist when the DSM or ICD classifications are used, it is important to define different steps or nodes using total and subscores of different validated scales, such as the CAPS, ISI, and PSQI where most people can agree on. In this new algorithm, psychotherapy steps are also required [10, 53]; this will allow to analyze different steps in the treatment. When this has been formalized, the various steps can be adapted as required for research purposes; this will enable an effective step forward in the treatment of these patients. The same observation stems from the work of Krystal et al. [86] who conclude in their article about risperidone that it is worthwhile to identify safe and effective strategies for treating sleep disturbances as they concluded that even this modest improvement in sleep leads to clinical improvement and also carries over some improvement in quality of life.

To overcome this complicated clinical challenge, much credit can be given to the integrated approach Bajor et al. [9] executed by producing an algorithm for pharmacotherapy for PTSD and related sleep problems. Sleep problems play a

very prominent role in this algorithm. The first step is to examine whether PTSD is present, and the second step is to establish whether there is sleep disturbance. If PTSD is present, but there is no sleep disturbance, an SSRI is advised, and, depending on the response, the subsequent steps are recommended based on the clinical information. There is a need for further elaboration of such a wise algorithm that is both theoretically grounded but is also based on clinical reality because of the complexity of PTSD and human behavior. It is important that there is a possibility of adjustment to local situations and state of affairs where needed. For example, in the Netherlands, prazosin is hardly available; it can be ordered but only via international pharmacies. Although this drug can then be imported, insurance companies will not cover payment, and patients have to pay themselves. Even though the empirical literature is not strong yet, the next best choice is made for doxazosin.

Based on Bajor's algorithm [10], clinical practice combined with the accumulated knowledge in this chapter leads to the novel algorithm that we present for use as an aid in treatment but also for discussion (Fig. 29.1). Based on conclusions of this book, we think it is preferable to focus if possible first on sleep improvement only and see if this gives enough improvement to apply psychotherapy as well. Non-pharmacological treatment has a place in this algorithm as well. In this algorithm the conclusion of Lee et al. [91] that study findings support the use of TFPs over nontrauma-focused psychotherapy or medication as first-line interventions has been integrated. It is important to keep in mind that psychotherapy is favorable but many times not possible due to lack of resources or patient-related factors. Therefore, we favor the start of psychotherapy early after onset of the disorder; if this cannot be performed this is a reason to start with medication. Focus is in line with this chapter on sleep. Other targeted-symptoms can be added to this algorithm in a later phase. There is a combination of some non-pharmacological interventions as well as pharmacotherapy and psychotherapy. It is very important to use the algorithm not only once for a patient but due to changes in clinical symptoms because of therapy, situational circumstances, and time; a change in therapy can be desirable as well. As there is so much evidence for efficacy of SSRIs, there is always a line in the algorithm toward the addition of SSRI or SNRI.

Based on the studies mentioned in this chapter, we can conclude that SSRIs are currently good first-line agents in PTSD but have hardly or no characteristics that make them specific agents for sleep disorders. In healthy volunteers SSRIs often have a negative impact on sleep; however, in patients with depression and PTSD, this is usually only for a few weeks (as measured with objective and subjective outcomes), and, after this initial period, sleep generally improves.

The pooled analysis of Stein et al. resulted in a reported reduction of sleep disturbance with help of paroxetine. Therefore, it can be concluded that many patients will derive some benefit for their PTSD complaints but may still have sleep problems. To deal with this problem, the addition of another drug may prove to be a successful strategy. An example is the study of Stein et al. [156], in which olanzapine (15 mg) was added to paroxetine, and this led to improvements in sleep and PTSD. Other examples include risperidone augmentation to therapy-resistant patients taking sertraline [138]. As pointed out by Bajor et al. [9], trazodone can also be a first-line medication because of its hypnotic qualities. Mirtazapine or trazodone can be used as augmentation to SSRIs, or as monotherapy in patients with prevailing sleep problems, or in the waiting period when starting SSRI.

The evidence for using anticonvulsants for PTSD-related sleep disorders is relatively low, although some patients improved and there were some positive tendencies. Additional and larger randomized controlled trials are required on the use of antipsychotics for PTSD. Most of the studies, as well as the evidence for the treatment of PTSD-related sleep disorders, have been performed with risperidone, and there is some good evidence that risperidone has a positive effect on sleep (Krystal et al. [86].

Prazosin is the most frequently investigated drug that is currently applicable for augmentation in PTSD-related problems. Prazosin has a short half-life and needs time to be titrated up, while doxazosin has a longer half-life and can be given without titration. There is only a very small place for hypnotics in the treatment of PTSD, e.g., as a short-term intervention in the presence of agitation, severe anxiety, or severe insomnia in the waiting period in the beginning phase of SSRI use. There appears to be some advantage for non-benzodiazepine hypnotics above non-benzodiazepines if used for insomnia, but more studies on this topic are required.

It is not known if following this or another algorithm is the best strategy, and various studies on the pharmacotherapy for sleep disorders in PTSD have mentioned the incomplete state of knowledge with regard to the treatment of sleeping problems in PTSD; some suggested more randomized placebo-controlled trials and the use of validated measures on sleep PTSD (e.g., [96, 111]). These comments are still valid; additional studies are needed on new drugs and on medications, for example, based on the orexin system [22]. However, we also need to further investigate the older, vintage drugs and set up more (symptom-based) research on

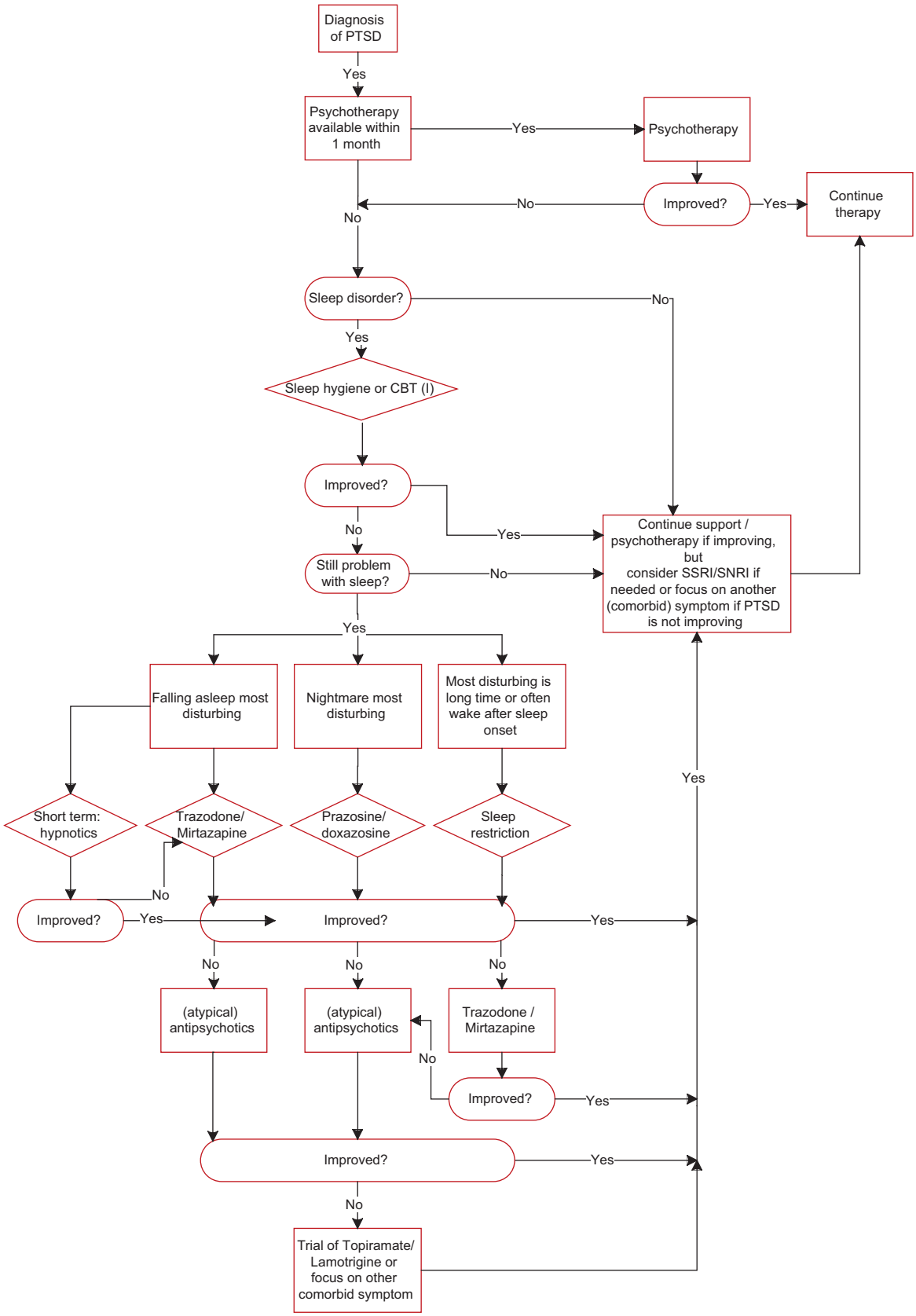

Fig. 29.1 Algorithm for treatment of sleep problems in relation to PTSD, based on current guidelines, review of current literature, as well as clinical guidance.

their efficacy, as also mentioned by Mohamed and Rosenheck [107] and Davidson [38]. In the meantime use and possible research based on this algorithm can be of help to guide patients and caregivers in choosing appropriate therapy.

References

1. Abramowitz EG, Barak Y, Ben-Avi I, Knobler HY. Hypnotherapy in the treatment of chronic combat-related PTSD patients suffering from insomnia: a randomized, zolpidem-controlled clinical trial. Int J Clin Exp Hypn. 2008;56(3):270–80.
2. Abrams TE, Lund BC, Bernardy NC, Friedman MJ. Aligning clinical practice to PTSD treatment guidelines: medication prescribing by provider type. Psychiatr Serv. 2013 Feb 1. 2013;64(2):142–8.
3. Aerni A, Traber R, Hock C, Roozendaal B, Schelling G, Papassotiropoulos A, Nitsch RM, Schnyder U, de Quervain DJ. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiatry. 2004;161(8):1488–90.
4. Alderman CP, Gilbert AL. A qualitative investigation of long-term zopiclone use and sleep quality among Vietnam war veterans with PTSD. Ann Pharmacother. 2009;43(10):1576–82.
5. Alderman CP, McCarthy LC, Condon JT, Marwood AC, Fuller JR. Topiramate in combat-related posttraumatic stress disorder. Ann Pharmacother. 2009;43(4):635–41.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
7. Ashford JW, Miller TW. Effects of trazodone on sleep in patients diagnosed with post-traumatic stress disorder (PTSD). J Contemp Psychother. 1996;26:221–33.
8. Aukst-Margetić B, Margetić B, Tosić G, Bilić-Prcić A. Levomepromazine helps to reduce sleep problems in patients with PTSD. Eur Psychiatry. 2004;19(4):235–6.
9. Bajor LA, Ticlea AN, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on posttraumatic stress disorder. Harv Rev Psychiatry. 2011a;19(5):240–58.
10. Bajor LA, Ticlea AN, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on posttraumatic stress disorder. Harv Rev Psychiatry. 2011b;19(5):240–58. https://doi.org/10.3109/10673229.2011.614483.
11. Belendiuk KA, Babson KA, Vandrey R, Bonn-Miller MO. Cannabis species and cannabinoid concentration preference among sleep-disturbed medicinal cannabis users. Addict Behav. 2015;50:178–81. https://doi.org/10.1016/j.addbeh.2015.06.032.
12. van Bemmel A, van den Hoofdakker RH, Beersma DGM, et al. Changes in sleep polygraphic variables and clinical state in depressed patients during treatment with citalopram. Psychopharmacology. 1993;113:225–30.
13. Berlant JL. Topiramate in posttraumatic stress disorder: preliminary clinical observations. J Clin Psychiatry. 2001;62(Suppl 17):60–3.
14. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonallucinatory posttraumatic stress disorder. BMC Psychiatry. 2004;4:24.
15. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. J Clin Psychiatry. 2002;63(1):15–20.
16. Berlin HA. Antiepileptic drugs for the treatment of post-traumatic stress disorder. Curr Psychiatry Rep. 2007;9(4):291–300.
17. Blois R, Gaillard JM. Effects of moclobemide on sleep in healthy human subjects. Acta Psychiatr Scand Suppl. 1990;360:73–5.
18. Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend. 2014;136:162–5. https://doi.org/10.1016/j.drugalcdep.2013.12.008.
19. Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farfel GM. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA. 2000;283(14):1837–44.
20. Brophy MH. Cyproheptadine for combat nightmares in posttraumatic stress disorder and dream anxiety disorder. Mil Med. 1991;156(2):100–1.
21. Brown ES, Hong SC. Antidepressant-induced bruxism successfully treated with gabapentin. J Am Dent Assoc. 1999;130(10):1467–9.
22. Brown RM, Khoo SY, Lawrence AJ. Central orexin (hypocretin) 2 receptor antagonism reduces ethanol self-administration, but not cue-conditioned ethanol-seeking, in ethanol-preferring rats. Int J Neuropsychopharmacol. 2013;16(9):2067–79. https://doi.org/10.1017/S1461145713000333.
23. Buckley T, Duggal V, Schatzberg AF. The acute and post-discontinuation effects of a glucocorticoid receptor (GR) antagonist probe on sleep and the HPA axis in chronic insomnia: a pilot study. J Clin Sleep Med. 2008;4(3):235–41.
24. Burstein A. Treatment of post-traumatic stress disorder with imipramine. Psychosomatics. 1984;25(9):681–3. 686–687
25. Burstein A, Burstein A. Treatment of night terrors with imipramine. J Clin Psychiatry. 1983;44(2):82.
26. Byers MG, Allison KM, Wendel CS, Lee JK. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. J Clin Psychopharmacol. 2010;30(3):225–9.
27. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. J Clin Psychopharmacol. 2014;34(5):559–64. https://doi.org/10.1097/JCP.0000000000000180.
28. Carey P, Suliman S, Ganesan K, Seedat S, Stein DJ. Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. Hum Psychopharmacol. 2012;27(4):386–91.
29. Carter AC, Capone C, Short EE. Co-occurring posttraumatic stress disorder and alcohol use disorders in veteran populations. J Dual Diagn. 2011;7(4):285–99.
30. Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395–9.
31. Chalon S, Pereira A, Lainey E, et al. Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. Psychopharmacology. 2005;177:1–10.
32. Clark RD, Canive JM, Calais LA, Qualls C, Brugger RD, Vosburgh TB. Cyproheptadine treatment of nightmares associated with posttraumatic stress disorder. J Clin Psychopharmacol. 1999;19(5):486–7.
33. Connor KM, Davidson JR, Weisler RH, Ahearn E. A pilot study of mirtazapine in post-traumatic stress disorder. Int Clin Psychopharmacol. 1999;14(1):29–31.
34. Connor KM, Davidson JR, Weisler RH, Zhang W, Abraham K. Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. Psychopharmacology (Berl). 2006a;184(1):21–5.
35. Connor KM, Davidson JR, Weisler RH, Zhang W, Abraham K. Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. Psychopharmacology (Berl). 2006b;184(1):21–5.

36. David D, De Faria L, Mellman TA. Adjunctive risperidone treatment and sleep symptoms in combat veterans with chronic PTSD. Depress Anxiety. 2006;23(8):489–91.
37. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry. 2010;71(Suppl E1):e04.
38. Davidson J. Vintage treatments for PTSD: a reconsideration of tricyclic drugs. J Psychopharmacol. 2015;29(3):264–9. https://doi.org/10.1177/0269881114565143.
39. Davidson J, Walker JI, Kilts C. A pilot study of phenelzine in the treatment of post-traumatic stress disorder. Br J Psychiatry. 1987;150:252–5.
40. Davidson JR, Weisler RH, Malik ML, Connor KM. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol. 1998;13(3):111–3.
41. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry. 2001;58(5):485–92.
42. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, van Meter S. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry. 2003;53(2):188–91.
43. Davidson JR, Brady K, Mellman TA, Stein MB, Pollack MH. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. J Clin Psychopharmacol. 2007;27(1):85–8.
44. Davis LL, Davidson JR, Ward LC, Bartolucci A, Bowden CL, Petty F. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. J Clin Psychopharmacol. 2008a;28(1):84–8.
45. Davis LL, Ward C, Rasmusson A, Newell JM, Frazier E, Southwick SM. A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. Psychopharmacol Bull. 2008b;41(1):8–18.
46. De Berardis D, Serroni N, Marini S, Moschetta FS, Martinotti G, Di Giannantonio M. Agomelatine for the treatment of posttraumatic stress disorder: a case report. Ann Clin Psychiatry. 2012;24(3):241–2.
47. De Boer M, Op den Velde W, Falger PJ, Hovens JE, De Groen JH, Van Duijn H. Fluvoxamine treatment for chronic PTSD: a pilot study. Psychother Psychosom. 1992;57(4):158–63.
48. De Jong J, Wauben P, Huijbrechts I, Oolders H, Haffmans J. Doxazosin treatment for posttraumatic stress disorder. J Clin Psychopharmacol. 2010;30(1):84–5.
49. Dieperink ME, Drogemuller L. Zolpidem for insomnia related to PTSD. Psychiatr Serv. 1999;50(3):421.
50. Dillard ML, Bendfeldt F, Jernigan P. Use of thioridazine in posttraumatic stress disorder. South Med J. 1993;86(11):1276–8.
51. Ellison JM, Stanziani P. SSRI-associated nocturnal bruxism in four patients. J Clin Psychiatry. 1993;54:432–4.
52. Forbes D, Creamer M, Bisson JI, Cohen JA, Crow BE, Foa EB, ..., Ursano RJ. A guide to guidelines for the treatment of PTSD and related conditions. FOCUS. 2013;11(3):414–27.
53. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170(4):372–82.
54. Gillin JC, Smith-Vaniz A, Schnierow BJ, et al. An open-label, 12-week clinical and sleep EEG study of nefazodone in chronic combat-related posttraumatic stress disorder. J Clin Psychiatry. 2001;62:789–96.
55. Giménez S, Clos S, Romero S, Grasa E, Morte A, Barbanoj MJ. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. Psychopharmacology. 2007;190(4):507–16.
56. Golier JA, Caramanica K, Demaria R, Yehuda R. A pilot study of mifepristone in combat-related PTSD. Depress Res Treat. 2012;2012:393251.
57. Guina J, Rossetter SR, DeRHODES BJ, Nahhas RW, Welton RS. Benzodiazepines for PTSD: a systematic review and meta-analysis. J Psychiatr Pract. 2015;21(4):281–303.
58. Gupta S, Popli A, Bathurst E, Hennig L, Droney T, Keller P. Efficacy of cyproheptadine for nightmares associated with posttraumatic stress disorder. Compr Psychiatry. 1998;39(3):160–4.
59. Gursky JT, Krahn LE. The effects of antidepressants on sleep: a review. Harvard Rev Psychiat. 2000;8:298–306. Review
60. Hamner M, Ulmer H, Horne D. Buspirone potentiation of antidepressants in the treatment of PTSD. Depress Anxiety. 1997;5(3):137–9.
61. Hamner MB, Brodrick PS, Labbate LA. Gabapentin in PTSD: a retrospective, clinical series of adjunctive therapy. Ann Clin Psychiatry. 2001;13(3):141–6.
62. Hamner MB, Faldowski RA, Robert S, Ulmer HG, Horner MD, Lorberbaum JP. A preliminary controlled trial of divalproex in posttraumatic stress disorder. Ann Clin Psychiatry. 2009;21(2):89–94.
63. Haro R, Drucker-Colín R. Effects of long-term administration of nicotine and fluoxetine on sleep in depressed patients. Arch Med Res. 2004;35:499–506.
64. Harsch HH. Cyproheptadine for recurrent nightmares. Am J Psychiatry. 1986;143(11):1491–2.
65. Hertzberg MA, Feldman ME, Beckham JC, Davidson JR. Trial of trazodone for posttraumatic stress disorder using a multiple baseline group design. J Clin Psychopharmacol. 1996;16(4):294–8.
66. Hertzberg MA, Feldman ME, Beckham JC, Moore SD, Davidson JR. Open trial of nefazodone for combat-related posttraumatic stress disorder. J Clin Psychiatry. 1998;59(9):460–4.
67. Hertzberg MA, Butterfield MI, Feldman ME, Beckham JC, Sutherland SM, Connor KM, Davidson JR. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biol Psychiatry. 1999;45(9):1226–9.
68. Hertzberg MA, Feldman ME, Beckham JC, Moore SD, Davidson JR. Three- to four-year follow-up to an open trial of nefazodone for combat-related posttraumatic stress disorder. Ann Clin Psychiatry. 2002;14(4):215–21.
69. Hicks JA, Argyropoulos SV, Rich AS, et al. Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression. Br J Psychiatry. 2002;180:528–35.
70. Hidalgo R, Hertzberg MA, Mellman T, Petty F, Tucker P, Weisler R, Zisook S, Chen S, Churchill E, Davidson J. Nefazodone in post-traumatic stress disorder: results from six open-label trials. Int Clin Psychopharmacol. 1999;14(2):61–8.
71. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep. 2005;28(2):187–93.
72. Hogben GL, Cornfield RB. Treatment of traumatic war neurosis with phenelzine. Arch Gen Psychiatry. 1981;38(4):440–5.
73. Ipser JC, Stein DJ. Evidence-based pharmacotherapy of posttraumatic stress disorder (PTSD). Int J Neuropsychopharmacol. 2012;15(6):825–40.
74. Jacobs-Rebhun S, Schnurr PP, Friedman MJ, Peck R, Brophy M, Fuller D. Posttraumatic stress disorder and sleep difficulty. Am J Psychiatry. 2000;157(9):1525–6.
75. Jakovljević M, Sagud M, Mihaljević-Peles A. Olanzapine in the treatment-resistant, combat-related PTSD – a series of case reports. Acta Psychiatr Scand. 2003;107(5):394–6.
76. Jindal RD, Friedman ES, Berman SR, et al. Effects of sertraline on sleep architecture in patients with depression. J Clin Psychopharmacol. 2003;23:540–8.
77. Kevorkian S, Bonn-Miller MO, Belendiuk K, Carney DM, Roberson-Nay R, Berenz EC. Associations among trauma, posttraumatic stress disorder, cannabis use, and cannabis use disorder in a nationally representative epidemiologic sample. Psychol Addict Behav. 2015;29(3):633–8. https://doi.org/10.1037/adb0000110.

78. Kinrys G, Worthington JJ, Wygant L, Nery F, Reese H, Pollack MH. Levetiracetam as adjunctive therapy for refractory anxiety disorders. J Clin Psychiatry. 2007;68(7):1010–3.
79. Kinzie JD, Leung P. Clonidine in Cambodian patients with posttraumatic stress disorder. J Nerv Ment Dis. 1989;177(9):546–50.
80. Kinzie JD, Sack RL, Riley CM. The polysomnographic effects of clonidine on sleep disorders in posttraumatic stress disorder: a pilot study with Cambodian patients. J Nerv Ment Dis. 1994;182(10):585–7.
81. Kluge M, Schüssler P, Steiger A. Duloxetine increased stage 3 sleep and suppresses rapid eye movement (REM) sleep in patients with major depression. Eur Neuropsychopharmacol. 2007;17:527–31.
82. Kosten TR, Frank JB, Dan E, McDougle CJ, Giller EL Jr. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis. 1991;179(6):366–70.
83. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and safety of doxepin 1mg and 3 mg in a 12 week sleep and outpatient trial of elderly subjects in chronic primary insomnia. Sleep. 2010;33:1553–61.
84. Krystal AD, Zhang W, Davidson JR, Connor KM. The sleep effects of tiagabine on the first night of treatment predict post-traumatic stress disorder response at three weeks. J Psychopharmacol. 2014;28(5):457–65. https://doi.org/10.1177/0269881113509903.
85. Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Horney RA, Huang GD, Stock C, Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA. 2011;306(5):493–502.
86. Krystal JH, Pietrzak RH, Rosenheck RA, Cramer JA, Vessicchio J, Jones KM, Huang GD, Vertrees JE, Collins J, Krystal AD, Veterans Affairs Cooperative Study #504 Group. Sleep disturbance in chronic military-related PTSD: clinical impact and response to adjunctive risperidone in the veterans affairs cooperative study #504. J Clin Psychiatry. 2016;77(4):483–91. https://doi.org/10.4088/JCP.14m09585.
87. Kupfer DJ, Perel JM, Pollock BG, et al. Fluvoxamine versus desipramine: comparative polysomnographic effects. Biol Psychiatry. 1991;29:23–40.
88. Labbate LA, Douglas S. Olanzapine for nightmares and sleep disturbance in posttraumatic stress disorder (PTSD). Can J Psychiatr. 2000;45(7):667–8.
89. Lambert MT. Aripiprazole in the management of post-traumatic stress disorder symptoms in returning global war on terrorism veterans. Int Clin Psychopharmacol. 2006;21(3):185–7.
90. Landolt HP, Raimo EB, Schnierow BJ, Kelsoe JR, Rapaport MH, Gillin JC. Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. Arch Gen Psychiatry. 2001;58(3):268–76.
91. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. Depress Anxiety. 2016. https://doi.org/10.1002/da.22511.
92. Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med. 2003;4(1):51–5.
93. Lerer B, Bleich A, Kotler M, Garb R, Hertzberg M, Levin B. Posttraumatic stress disorder in Israeli combat veterans. Effect of phenelzine treatment. Arch Gen Psychiatry. 1987;44(11):976–81.
94. Lewis JD. Mirtazapine for PTSD nightmares. Am J Psychiatry. 2002;159(11):1948–9.
95. Leyba CM, Wampler TP. Risperidone in PTSD. Psychiatr Serv. 1998;49(2):245–6.
96. van Liempt S, Vermetten E, Geuze E, Westenberg HG. Pharmacotherapy for disordered sleep in post-traumatic stress disorder: a systematic review. Int Clin Psychopharmacol. 2006;21(4):193–202.
97. Luthringer R, Toussaint M, Schaltenbrand N, et al. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression. Psychopharmacol Bull. 1996;32:637–46.
98. Mathias S, Wetter TC, Steiger A, Lancel M. The GABA uptake inhibitor tiagabine promotes slow wave sleep in normal elderly subjects. Neurobiol Aging. 2001;22(2):247–53.
99. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. Hum Psychopharmacol Clin Exp. 2005;20:533–59. Review
100. McRae AL, Brady KT, Mellman TA, Sonne SC, Killeen TK, Timmerman MA, Bayles-Dazet W. Comparison of nefazodone and sertraline for the treatment of posttraumatic stress disorder. Depress Anxiety. 2004;19(3):190–6.
101. Mellman TA, David D, Barza L. Nefazodone treatment and dream reports in chronic PTSD. Depress Anxiety. 1999;9(3):146–8.
102. Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. J Clin Psychiatry. 2002;63(12):1183–4.
103. Meltzer-Brody S, Connor KM, Churchill E, Davidson JR. Symptom-specific effects of fluoxetine in post-traumatic stress disorder. Int Clin Psychopharmacol. 2000;15(4):227–31.
104. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005;66:469–76. Review
105. Minot R, Luthringer R, Macher JP. Effect of moclobemide on the psychophysiology of sleep/wake cycles: a neuroelectrophysiological study of depressed patients administered with moclobemide. Int Clin Psychopharmacol. 1993;7(3–4):181–9.
106. Miyazaki S, Uchida S, Mukai J, Nishihara K. Clonidine effects on all-night human sleep: opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion. Psychiatry Clin Neurosci. 2004;58(2):138–44.
107. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. J Clin Psychiatry. 2008;69(6):959–65.
108. Montgomery I, Oswald I, Morgan K, et al. Trazodone enhances sleep in subjective quality but not in objective duration. Br J Clin Pharmacol. 1983;16:139–44.
109. Monti JM. Effect of reversible monoamine oxidase-a inhibitor (moclobemide) on sleep in depressed patients. Br J Psychiatry. 1989;6(Suppl):61–5.
110. Nadeem HS, Attenburrow MJ, Cowen PJ. Comparison of the effects of citalopram and escitalopram on 5-Ht-mediated neuroendocrine responses. Neuropsychopharmacology. 2004;29(9):1699–703.
111. Nappi CM, Drummond SP, Hall JM. Treating nightmares and insomnia in posttraumatic stress dis order: a review of current evidence. Neuropharmacology. 2012;62(2):576–85.
112. Neal LA, Shapland W, Fox C. An open trial of moclobemide in the treatment of post-traumatic stress disorder. Int Clin Psychopharmacol. 1997a;12(4):231–7.
113. Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, Lipsey TL, Marmar CR. Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress. 2001;14(3):461–7.
114. Neylan T, Lenoci M, Maglione M, et al. The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. J Clin Psychiatry. 2003;64:445–50.
115. Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Lindley SE, Otte C, Schoenfeld FB, Yesavage JA, Marmar CR. No improvement of posttraumatic stress dis-

order symptoms with guanfacine treatment. Am J Psychiatry. 2006;163(12):2186–8.
116. Nirmalani-Gandhy A, Sanchez D, Catalano G. Terazosin for the treatment of trauma-related nightmares: a report of 4 cases. Clin Neuropharmacol. 2015;38(3):109–11.
117. Nishith P, Resick PA, Mueser KT. Sleep difficulties and alcohol use motives in female rape victims with posttraumatic stress disorder. J Trauma Stress. 2001;14(3):469–79.
118. Nutt DJ. Rationale for, barriers to, and appropriate medication for the long-term treatment of depression. J Clin Psychiatry. 2010;71(Suppl E1):e02.
119. Önder E, Tural U, Aker T. A comparative study of fluoxetine, moclobemide, and tianeptine in the treatment of posttraumatic stress disorder following an earthquake. Eur Psychiatry. 2006;21(3):174–9.
120. Pae CU, Marks DM, Han C, Masand PS, Patkar AA. Pregabalin augmentation of antidepressants in patients with accident-related posttraumatic stress disorder: an open label pilot study. Int Clin Psychopharmacol. 2009;24(1):29–33.
121. Parrino L, Terzano MG. Polysomnographic effects of hypnotic drugs. A review. Psychopharmacology. 1996;126(1):1–16.
122. Paslakis G, Gilles M, Deuschle M. Pregabalin in the treatment of posttraumatic stress disorder: a case report. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35(4):1160–1.
123. Paul MA, Gray G, Lange M. The impact of sertraline on psychomotor performance. Aviat Space Envir Md. 2002;73:964–70.
124. Pollack MH, Hoge EA, Worthington JJ, Moshier SJ, Wechsler RS, Brandes M, Simon NM. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72(7):892–7.
125. Power KG, Jerrom DW, Simpson RJ, Mitchell M. Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. Br Med J (Clin Res Ed). 1985;290(6477):1246–8.
126. Quera Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, Lofaso F, Guilleminault C. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsychopharmacol. 2007;10(5):691–6.
127. Ranjan S, S Chandra P, Prabhu S. Antidepressant-induced bruxism: need for buspirone? Int J Neuropsychopharmacol. 2006;9(4):485–7.
128. Richardson JD, Fikretoglu D, Liu A, McIntosh D. Aripiprazole augmentation in the treatment of military-related PTSD with major depression: a retrospective chart review. BMC Psychiatry. 2011;11:86. https://doi.org/10.1186/1471-244X-11-86.
129. Riemann D, Voderholzer U, Cohrs S, Rodenbeck A, Hajak G, Rüther E, Wiegand MH, Laakmann G, Baghai T, Fischer W, Hoffmann M, Hohagen F, Mayer G, Berger M. Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. Pharmacopsychiatry. 2002;35(5):165–74.
130. Rijnders RJ, Laman DM. Van Diujn H Cyproheptadine for posttraumatic nightmares. Am J Psychiatry. 2000;157(9):1524–5.
131. Robert R, Blakeney PE, Villarreal C, Rosenberg L, Meyer WJ 3rd. Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study. J Am Acad Child Adolesc Psychiatry. 1999;38(7):873–82.
132. Robert S, Hamner MB, Kose S, Ulmer HG, Deitsch SE, Lorberbaum JP. Quetiapine improves sleep disturbances in combat veterans with PTSD: sleep data from a prospective, open-label study. J Clin Psychopharmacol. 2005;25(4):387–8.
133. Rodgman C, Verrico CD, Holst M, Thompson-Lake D, Haile CN, De La Garza R 2nd, Raskind MA, Newton TF. Doxazosin XL reduces symptoms of posttraumatic stress disorder in veterans with PTSD: a pilot clinical trial. J Clin Psychiatry. 2016;77(5):e561–5. https://doi.org/10.4088/JCP.14m09681.
134. Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. J Psychopharmacol. 2012;26(8):1088–95.
135. Roepke S, Danker-Hopfe H, Repantis D, Behnia B, Bernard F, Hansen ML, Otte C. Doxazosin, an α-1-adrenergic-receptor antagonist, for nightmares in patients with posttraumatic stress disorder and/or borderline personality disorder: a chart review. Pharmacopsychiatry. 2017;50(1):26–31. https://doi.org/10.1055/s-0042-107794.
136. Romanelli F, Adler DA, Bungay KM. Possible paroxetine-induced bruxism. Ann Pharmacother. 1996;30:1246–8.
137. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
138. Rothbaum BO, Killeen TK, Davidson JR, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. J Clin Psychiatry. 2008;69(4):520–5.
139. Ruigt GSF, Kemp B, Groenhout CM, et al. Effect of the antidepressant org 3770 on human sleep. Eur J Clin Pharmacol. 1990;38:551–4.
140. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry. 1997;58:348–50.
141. Salviati M, Pallagrosi M, Valeriani G, Carlone C, Todini L, Biondi M. On the role of noradrenergic system in PTSD and related sleep disturbances. The use of terazosin in PTSD related nightmares: a case report. Clin Ter. 2013;164(2):133–7.
142. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther. 2015 Jan. 2015;145:43–57.
143. Schmid DA, Wichniak A, Uhr M, et al. Changes in sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology. 2006;31:832–44.
144. Schneider E, Ziegler B, Maxion H. Gamma-aminobutyric acid (GABA) and sleep. The influence of di-n-propylacetic acid on sleep in man. Eur Neurol. 1977;15(3):146–52.
145. Schneier FR, Campeas R, Carcamo J, Glass A, Lewis-Fernandez R, Neria Y, Sanchez-Lacay A, Vermes D, Wall MM. Combined mirtazapine and ssri treatment of ptsd: a placebo-controlled trial. Depress Anxiety. 2015;32(8):570–9. https://doi.org/10.1002/da.22384.
146. Sethi R, Vasudeva S. Doxazosin for the treatment of nightmares: does it really work? A case report. Prim Care Companion CNS Disord. 2012;14(5). pii: PCC.12l01356. doi: https://doi.org/10.4088/PCC.12l01356.
147. Sharpley AL, Gregory CA, Solomon RA, Cowen PJ. Slow wave sleep and 5-HT2 receptor sensitivity during maintenance tricyclic antidepressant treatment. J Affect Disord. 1990;19(4):273–7.
148. Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijsman HJ, Cowen PJ. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. J Clin Psychiatry. 2003;64(2):192–6.
149. Sharpley AL, Attenburrow ME, Hafizi S, Cowen PJ. Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients. J Clin Psychiatry. 2005;66(4):450–4.
150. Shen WW, Park S. The use of monoamine oxidase inhibitors in the treatment of traumatic war neurosis: case report. Mil Med. 1983;148(5):430–1.

151. Shestatzky M, Greenberg D, Lerer B. A controlled trial of phenelzine in posttraumatic stress disorder. Psychiatry Res. 1988;24(2):149–55.
152. Spiegel R, DeVos JE. Central effects of guanfacine and clonidine during wakefulness and sleep in healthy subjects. Br J Clin Pharmacol. 1980;10(Suppl 1):165S–8S.
153. Spigset O, Hägg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. Int Clin Psychopharmacol. 2003;18(3):157–61.
154. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev. 2008;12(3):169–84.
155. Stanovic JK, James KA, Vandevere CA. The effectiveness of risperidone on acute stress symptoms in adult burn patients: a preliminary retrospective pilot study. J Burn Care Rehabil. 2001;22(3):210–3.
156. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry. 2002;159(10):1777–9.
157. Stein DJ, Davidson J, Seedat S, Beebe K. Paroxetine in the treatment of post-traumatic stress disorder: pooled analysis of placebo-controlled studies. Expert Opin Pharmacother. 2003;4(10):1829–38.
158. Stein DJ, Pedersen R, Rothbaum BO, Baldwin DS, Ahmed S, Musgnung J, Davidson J. Onset of activity and time to response on individual CAPS-SX17 items in patients treated for post-traumatic stress disorder with venlafaxine ER: a pooled analysis. Int J Neuropsychopharmacol. 2009;12(1):23–31.
159. Strawn JR, Dowling BP, Geracioti TD Jr. Pregabalin treatment of posttraumatic stress disorder. J Clin Psychopharmacol. 2008;28(5):596–7.
160. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. J Clin Psychiatry. 2003;64(12):1421–5.
161. Tol WA, Barbui C, Bisson J, Cohen J, Hijazi Z, Jones L, ..., Silove D. World Health Organization guidelines for management of acute stress, PTSD, and bereavement: key challenges on the road ahead. PLoS Med. 2014;11(12):e1001769.
162. Tucker P, Trautman RP, Wyatt DB, Thompson J, Wu SC, Capece JA, Rosenthal NR. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(2):201–6.
163. Van Liempt S. Sleep disturbances and PTSD: a perpetual circle? Eur J Psychotraumatol. 2012;3:19142.
164. Vigo DV, Baldessarini RJ. Anticonvulsants in the treatment of major depressive disorder: an overview. Harv Rev Psychiatry. 2009;17(4):231–41.
165. Villarreal G, Calais LA, Cañive JM, Lundy SL, Pickard J, Toney G. Prospective study to evaluate the efficacy of aripiprazole as a monotherapy in patients with severe chronic posttraumatic stress disorder: an open trial. Psychopharmacol Bull. 2007;40(2):6–18.
166. Villarreal G1, Cañive JM, Calais LA, Toney G, Smith AK. Duloxetine in military posttraumatic stress disorder. Psychopharmacol Bull. 2010;43(3):26–34.
167. Walderhaug E, Kasserman S, Aikins D, Vojvoda D, Nishimura C, Neumeister A. Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. Pharmacopsychiatry. 2010;43(2):45–9.
168. Walsh JK, Perlis M, Rosenthal M, Krystal A, Jiang J, Roth T. Tiagabine increases slow-wave sleep in a dose-dependent fashion without affecting traditional efficacy measures in adults with primary insomnia. J Clin Sleep Med. 2006;2(1):35–41.
169. Warner MD, Dorn MR, Peabody CA. Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. Pharmacopsychiatry. 2001;34(4):128–31.
170. Wells BG, Chu CC, Johnson R, Nasdahl C, Ayubi MA, Sewell E, Statham P. Buspirone in the treatment of posttraumatic stress disorder. Pharmacotherapy. 1991;11(4):340–3.
171. Wiedemann K, Lauer C, Loycke A, Pollmächer T, Durst P, Machér JP, Holsboer F. Antiglucocorticoid treatment disrupts endocrine cycle and nocturnal sleep pattern. Eur Arch Psychiatry Clin Neurosci. 1992;241(6):372–5.
172. Wilson S, Argyropoulos S. Antidepressants and sleep. A qualitative review of the literature. Drugs. 2005;65:927–47.
173. Wilson SJ, Bailey JE, Alford C, et al. Sleep and daytime sleepiness the next day following single night-time dose of fluvoxamine, dothiepin and placebo in normal volunteers. J Psychopharmacol. 2000;14:378–86.
174. Wilson SJ, Bailey JE, Alford C, et al. Effects of 5 weeks of administration of fluoxetine and dothiepin in normal volunteers on sleep, daytime sedation, psychomotor performance and mood. J Psychopharmacol. 2002;16:321–31.
175. Wilson SJ, Bailey JE, Rich AS, Adrover M, Potokar J, Nutt DJ. Using sleep to evaluate comparative serotonergic effects of paroxetine and citalopram. Eur Neuropsychopharmacol. 2004;14(5):367–72.
176. Winokur A, Sateia M, Hayes J, et al. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry. 2000;48:75–8.
177. Winokur A, Gary KA, Rodner S, et al. Depression, sleep physiology, and antidepressant drugs. Depress Anxiety. 2001;14:19–28.
178. Yamadera H, Nakamura S, Suzuki H, et al. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci. 1998;52:439–43.
179. Youssef NA, Marx CE, Bradford DW, Zinn S, Hertzberg MA, Kilts JD, Naylor JC, Butterfield MI, Strauss JL. An open-label pilot study of aripiprazole for male and female veterans with chronic post-traumatic stress disorder who respond suboptimally to antidepressants. Int Clin Psychopharmacol. 2012;27(4):191–6.
180. Zisook S, Chentsova-Dutton YE, Smith-Vaniz A, Kline NA, Ellenor GL, Kodsi AB, Gillin JC. Nefazodone in patients with treatment-refractory posttraumatic stress disorder. J Clin Psychiatry. 2000;61(3):203–8.

Pharmacology of Sleep and PTSD: Prazosin - An Alpha-1 Adrenoreceptor Antagonist Approach to Post-traumatic Stress Disorder Pharmacotherapy

30

Murray A. Raskind

Introduction

Development of a pharmacotherapy for a behavioral disorder is best guided by the pathophysiology underlying its clinical signs and symptoms. Human studies of central nervous system (CNS) noradrenergic activity in PTSD [1–6], laboratory data from an animal model of PTSD [7], and the phenomenology of major PTSD symptoms [8] support increased CNS noradrenergic activity contributing to PTSD pathophysiology. One approach to decreasing excessive CNS noradrenergic activity is to antagonize postsynaptic adrenoreceptors (ARs) in limbic and neocortical areas that are the targets of noradrenergic neurons originating from the locus ceruleus in the rostral pons [9].

Several lines of evidence from studies of sleep physiology, regulation of corticotrophin-releasing factor (CRF) secretion, and noradrenergic modulation of cognition suggest that the postsynaptic alpha-1 AR is a particularly relevant target for pharmacologic alleviation of PTSD symptoms [10–12]. Prazosin is a clinically available alpha-1 AR antagonist that crosses the blood-brain barrier and blocks brain responses to norepinephrine (NE) when administered peripherally [13]. Prazosin has been used safely for decades to treat hypertension and benign prostatic hypertrophy [14, 15]. Randomized clinical trials (RCTs) published over the past 10 years have demonstrated prazosin efficacy for PTSD nightmares, sleep disruption, daytime hyperarousal symptoms, and global clinical status in persons with PTSD from both military and civilian trauma [16–20].

This chapter will review how direct observations of PTSD clinical phenomenology in the context of patient care, together with data from earlier studies addressing CNS noradrenergic activity in PTSD, led to the initial use of prazosin for intractable combat trauma nightmares and sleep disruption in Vietnam combat Veterans; subsequent prazosin RCTs for military and civilian trauma PTSD; prazosin effects on PTSD-like symptoms in a rodent model of PTSD; and the use of prazosin in the treatment of disorders highly comorbid with military PTSD (alcohol use disorder, and persistent postconcussive headaches in military personnel with mild traumatic brain injuries). Finally, it will provide suggestions for optimizing therapeutic effects and minimizing adverse effects of prazosin in the treatment of PTSD and its comorbidities.

A Novel Pharmacologic Approach to Intractable Nighttime Symptoms in Combat PTSD

Sleep disturbance and recurrent trauma-content nightmares are major hyperarousal and reexperiencing symptoms of PTSD and are prominent among military Veterans [21]. Trauma-content nightmares are a hallmark feature of PTSD [22]. Distressed awakenings and inability to return to sleep with or without recalled trauma nightmares may be the most common symptom motivating combat Veterans to seek treatment for PTSD. In 1996, while providing ongoing clinical care to an African-American Vietnam War combat Veterans group therapy program [23], the author observed that sleep disruption and trauma nightmares were these Veterans' most troublesome and treatment refractory PTSD symptoms. Psychotropic medications including sedative hypnotics, SSRI antidepressants, and various types of psychotherapies including prolonged exposure [24] rarely had been helpful for these Veterans' nighttime PTSD symptoms.

Veterans' accounts of these nighttime PTSD symptoms revealed the following:

- The most salient feature of combat PTSD "sleep disturbance" was sleep disruption by distressed awakenings. These distressed awakenings usually (but not always)

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were coincident with trauma-content nightmares. Sleep initiation difficulty often was attributed to fear of entering a terrifying nightmare once sleep commenced.

- These combat trauma-content nightmares and distressed awakenings were accompanied by intense sweating, rapid heartbeat, shortness of breath, fearfulness, and hypervigilance. Veterans often described these symptoms as an "adrenaline storm." These autonomic arousal symptoms are consistent with inappropriately high nighttime CNS noradrenergic activity in combat PTSD. Such increased CNS noradrenergic activity during sleep has been demonstrated in combat PTSD and significantly correlates with sleep disturbance [3].
- Bed partners reported that Veterans' nightmares were accompanied by thrashing, striking out, and other large excursion movements of the extremities. Such movements are incompatible with the large muscle paralysis that accompanies rapid eye movement (REM) sleep stage normal dreaming [25].

A Postsynaptic Adrenoreceptor Antagonist Approach to PTSD Treatment

CNS-active drugs originally developed to lower blood pressure by reducing noradrenergic activity provide clinically available pharmacologic approaches to reducing excessive CNS noradrenergic activity in PTSD [26]. Using a postsynaptic adrenoreceptor (AR) antagonist rather than a drug that reduced presynaptic NE outflow as a therapeutic approach to intractable and debilitating PTSD trauma nightmares and sleep disruption was inferred from an innovative study performed by Southwick and colleagues in the early 1990s addressing CNS noradrenergic function and its relation to symptom expression in military PTSD [5].

Subject groups were Veterans with PTSD and non-Veteran healthy controls. CNS NE outflow was stimulated by the alpha-2 AR antagonist yohimbine, which eliminates alpha-2 AR autoreceptor inhibition of LC NE release [27]. They measured change in the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) to provide an estimate of CNS presynaptic noradrenergic outflow response, and measured PTSD symptom emergence or worsening to provide an estimate of postsynaptic AR response. Plasma MHPG increased following yohimbine in both PTSD and normal subjects with a somewhat greater increase in PTSD subjects. This modestly greater presynaptic response, however, was overshadowed by the markedly greater postsynaptic PTSD-like behavioral response in the Veterans group. Seventy percent of PTSD Veterans but no control subjects experienced panic attacks, and 40% of PTSD Veterans but no control subjects experienced flashbacks. Total score on a PTSD symptom scale and the individual symptoms emotional numbing, intrusive thoughts, and grief increased substantially in PTSD Veterans but not in controls. These results suggest a major role for increased postsynaptic AR responsiveness in the pathophysiology of PTSD.

There are two major postsynaptic ARs in the human brain, the alpha-1 AR and the beta AR [26]. CNS-active antagonists for both receptors were clinically available. Which postsynaptic AR antagonist should be evaluated for efficacy in PTSD first? The decision to prescribe the CNS-active beta AR antagonist propranolol initially was supported by its previous use in the treatment of other anxiety disorders [28], and case series in which Veterans and children reported PTSD symptom reduction following open-label propranolol treatment [29, 30]. In contrast, no reports of alpha-1 AR antagonist beneficial behavioral effects could be found in the clinical literature. Although the initial choice of a beta AR antagonist proved incorrect (see below), the effects of propranolol on PTSD nightmares paradoxically provided rationale for a trial of prazosin.

The first Vietnam Veteran was treated for intractable PTSD symptoms with a postsynaptic AR antagonist in 1996. He had fought through the bloody TET offensive in 1968 as an Army rifleman with the 1st Infantry Division. He suffered nightly severe trauma nightmares and sleep disruption accompanied by sweating, hypervigilance, and inability to resume sleep. In his graphically realistic nightmares, he repeatedly reexperienced horrific combat traumas. A particularly devastating nightmare "replayed" a terrifying firefight with Viet Cong forces during which a round from the Veteran's M16 assault rifle accidentally hit and killed his close friend. This recurrent nightmare worsened his intense remorse over this tragic killing, and he developed episodic suicidal ideation and alcohol dependence. Given that his trauma nightmares and sleep disruption had been unresponsive to multiple psychotropic medications and psychotherapies, the author prescribed the postsynaptic beta AR antagonist propranolol 20 mg twice daily (midmorning and before sleep). Two weeks later, the Veteran stated "Doc, we are going the wrong direction. My nightmares are even worse." That propranolol appeared to increase this combat Veteran's nightmare intensity was unexpected, but a review of the literature revealed that nightmares are indeed a reported occasional adverse effect of propranolol and other beta AR antagonists [31]. Although disappointing, this unexpected propranolol effect raised the possibility that the wrong postsynaptic AR had been targeted. In several neurobiologic systems, the alpha-1 AR can have opposite effects to those of the beta AR [32, 33]. If the CNS-active beta AR antagonist propranolol worsened this Veteran's trauma nightmares, would the CNS brain active alpha-1 AR antagonist reduce his trauma nightmares?

The Veteran's propranolol was discontinued and prazosin initiated at 1 mg at bedtime (drug labeling recommends low-dose initiation and gradual titration of an alpha-1 AR antagonist to avoid "first-dose" orthostatic hypotension) [34].

Prazosin was then titrated upward over 3 weeks to 8 mg at bedtime. At this dose, trauma nightmares ceased, sleep duration increased from 3 to 6 h, and the Veteran reported resumption of "normal" dreaming that had been absent since his Vietnam deployment. This response to prazosin was consistent with two other Veterans' spontaneous reports of markedly reduced PTSD trauma nightmare intensity and improved sleep following inhibition of prazosin for benign prostatic hypertrophy urinary outflow symptoms. His suicidal ideation also disappeared and he became able to abstain from alcohol. Although the Veteran's nighttime PTSD symptoms improved substantially, irritability and hypervigilance reemerged every afternoon. Addition of prazosin 5 mg midmorning and midafternoon greatly reduced these daytime hyperarousal symptoms. A modest tachycardia (100–110 beats/min) developed, which was likely a reflex tachycardia response to prazosin. Propranolol was reintroduced at 20 mg bid to treat the tachycardia. It was hoped that the presence of alpha-1 AR antagonism by prazosin would prevent the earlier adverse effect of propranolol to enhance trauma nightmares. Fortunately, trauma nightmares remained absent with combined prazosin and propranolol treatment. It is noteworthy that this Veteran has maintained abstinence from alcohol from 1996 to the present (2016) on a continuous regimen of prazosin and propranolol [35].

The second Vietnam Veteran treated with prazosin had endured 72 days of deadly artillery bombardment and repeated North Vietnamese infantry assaults while besieged with the 26th Marines at Khe Sahn in 1968. His severe and treatment-resistant trauma nightmares, sleep disruption, alcohol dependence, and suicidal ideation were of similar intensity and frequency to those of the first Veteran described above. This second Veteran's trauma nightmares, sleep disruption, and suicidal ideation also resolved on a regimen of prazosin 5 mg twice daily and 10 mg at bedtime. He too developed a mild reflex sinus tachycardia. Addition of propranolol to prazosin restored normal heart rate without reappearance of trauma nightmares. This second Veteran also has maintained abstinence from alcohol for the past 20 years on continuous maintenance prazosin and propranolol treatment [35].

The apparent beneficial effects of open-label prazosin effects on intractable PTSD symptoms in these and other Veterans under the author's care led to a search of the literature for studies suggesting alpha-1 AR regulation of neurobiologic systems relevant to PTSD pathophysiology. This search revealed alpha-1 AR modulation of rapid eye movement (REM) sleep, of release of the anxiogenic neuropeptide corticotrophin-releasing factor (CRF), of prefrontal cortex inhibition of primitive cognitive set, and of the acoustic startle response as described below.

PTSD trauma-content nightmares appear to emerge from disrupted REM sleep and from Stage 1 and Stage 2 light sleep [36]. Stimulation of CNS alpha-1 AR disrupts REM sleep, shortens REM sleep duration, and increases Stage 1 and Stage 2 light sleep, effects favoring emergence of trauma nightmares [37–40]. Prazosin reverses these effects [39]. If analogous prazosin effects on sleep physiology occur in humans (see below), they would be consistent with the reported decrease in trauma nightmares and resumption of normal dreaming frequently reported during prazosin treatment of PTSD (unpublished observations).

Studies in rodents and nonhuman primates implicate CRF effects in limbic and neocortical brain areas on the expression of anxiety, fear, and startle [41–44]. Paraventricular nucleus (PVN) CRF neurons are under alpha-1 stimulatory regulation [45, 46]. The increased CRF in cerebrospinal fluid in PTSD is consistent with increased activation of CNS alpha-1 ARs [47, 48]. The alpha-1 AR stimulatory regulation of CRF released from PVN into the portal system to the anterior pituitary is well established; it is likely that alpha-1 AR stimulation also stimulates CRF release from rostrally projecting PVN neurons.

In a series of elegant studies in nonhuman primates, Arnsten and colleagues demonstrated that stimulation of prefrontal cortex high-affinity postsynaptic alpha-2 AR[1] enhances logical thinking and stimulation of lower-affinity alpha-1 AR has the opposite effect [49, 50]. These alpha-2 AR are preferentially activated when NE concentrations are low. In contrast, lower-affinity prefrontal cortex alpha-1 AR are activated under the high NE concentration conditions present during stress. This prefrontal alpha-1 AR stimulation during stress disrupts logical cognitive processing and increases automatic and primitive responses to threats. These cognitive effects of prefrontal alpha-1 AR stimulation are consistent with the cognitive and emotional "fight or flight"-like symptoms of combat trauma PTSD.

The acoustic startle response is under alpha-1 AR stimulatory modulation [51]. Southwick et al. measured acoustic startle following yohimbine or placebo in combat Veterans with PTSD and a comparison group of combat Veterans without PTSD [6]. Only the Veterans with PTSD had an increased acoustic startle response following yohimbine stimulation of noradrenergic outflow. These results from a study with a very appropriate combat-exposed control group suggests that combat trauma PTSD, but not combat exposure per se, is associated with increased alpha-1 AR responsiveness to NE.

Randomized Controlled Clinical Trials of Prazosin for PTSD

The above open-label prazosin treatment observations in combat Veterans together with the alpha-1 AR modulation of neurobiologic systems relevant to PTSD provided rationale for prazosin RCTs for treatment-resistant nighttime PTSD symptoms. Six prazosin randomized controlled trials (RCTs) have

[1]Most CNS alpha-2 AR are presynaptic inhibitory autoreceptors; however, a modest expression of postsynaptic alpha-2 AR has been demonstrated in prefrontal cortex [49].

been completed and published. Four were performed by our research group at VA Puget Sound and the University of Washington. A fifth was performed at the University of Pittsburgh and VA Pittsburgh. A sixth was performed in Iran by an Iranian and Swiss collaborative group. These studies have demonstrated significant and substantial efficacy of prazosin for reducing nighttime PTSD symptoms reducing daytime hyperarousal symptoms and improving global clinical status.

The participants in the first two RCTs were Vietnam War combat Veterans with decades of treatment-resistant chronic PTSD. Drug was administered as a single evening dose specifically to target persistent and distressing trauma-related nightmares and sleep disruption as primary outcome measures. The Clinical Global Impression of Change (CGIC) [52] also was assessed to determine the impact of nightmare reduction and sleep improvement in global clinical status anchored to function at home and work. Because prazosin duration of action is approximately 6–10 h, the single evening dose regimen in these two studies was not optimally designed to test prazosin effects on daytime PTSD symptoms.

The first RCT was a double-blind placebo-controlled crossover study performed in ten Vietnam combat Veterans [18], all of whom had chronic PTSD with frequent and distressing trauma nightmares. Prazosin or placebo in random order were begun at an initial dose of 1 mg at bedtime and titrated upward for 3 weeks to a dose that eliminated trauma nightmares or to a maximum dose of 10 mg HS. The achieved maintenance dose was maintained for 6 weeks. Following a 1-week washout period, participants were crossed over to the other treatment condition, again for 3 weeks titration and 6 weeks maintenance. At a mean achieved maintenance prazosin dose of 9.6 mg, prazosin was significantly and substantially superior to placebo for reducing nightmares (Clinician-Administered PTSD Scale [CAPS] "recurrent distressing dreams of the event" item [53]) and sleep disturbance (CAPS "sleep difficulty" item) and improving global clinical status. All Cohen's d effect sizes for prazosin were large at >1.0. Change in total CAPS score and all three CAPS PTSD symptom clusters (reexperiencing, avoidance, and hyperarousal) also significantly favored prazosin.

The second RCT was a parallel group study. Forty Veterans with chronic PTSD and distressing trauma nightmares were randomized to prazosin or placebo [17]. Most had experienced combat trauma in the Vietnam War. A 4-week dose titration of prazosin or placebo was followed by 8 weeks of maintenance medication (maximum bedtime dose = 15 mg; mean maintenance bedtime prazosin dose = 13.3 mg). Prazosin was significantly and substantially superior to placebo for reducing nightmares and sleep disturbance and improving global clinical status. Effect sizes again were large (Cohen's d all >0.9). Consistent with the effect of prazosin to increase duration and continuity of REM sleep, dream characteristics of prazosin subjects demonstrated a change from those typical of trauma nightmares toward those typical of normal dreaming as assessed by the PTSD Dream Rating Scale [54]. Although there was a numerically greater reduction in total CAPS score with prazosin than placebo, these differences did not reach statistical significance. Prazosin was well tolerated.

The third RCT was a crossover study in participants with civilian trauma PTSD [20]. This RCT was a collaboration with Fletcher Taylor, MD, a Puget Sound area private practice psychiatrist who had independently observed prazosin beneficial effects on PTSD trauma nightmares in his practice. This study is unique in that it measured effects of both drug and placebo on an objective measure of sleep physiology. Thirteen civilian trauma PTSD participants with severe trauma nightmares and sleep disturbance were randomized to prazosin or placebo in a double-blind crossover trial. Prazosin or placebo was rapidly titrated to 3 mg in the evening during each 3-week treatment period. In the final three nights of each treatment condition, total sleep time, REM sleep time, and sleep latency were recorded at home with the two-lead portable REMView device, which distinguishes sleep from awake state and REM sleep from non-REM sleep [55]. Total sleep time was 94 min longer in the prazosin than in the placebo condition (374 ± 86 vs. 280 ± 105 min, $p < 0.01$). In contrast, sleep latency (time to fall asleep) was actually several minutes longer in the prazosin condition, consistent with the nonhypnotic nature of prazosin. Both REM time and mean REM period duration were significantly greater during prazosin, suggesting normalization of PTSD disrupted REM sleep. One interpretation of these data is that disruption of REM sleep by inappropriately elevated CNS noradrenergic activity may contribute to the pathogenesis of PTSD trauma nightmares and distressed awakenings. Disrupted REM sleep may also contribute to persistence of excessive emotional response to traumatic memories in PTSD [56]. Improvements in CAPS "recurrent distressing dreams of the event" item scores, PTSD Checklist-Civilian version total scores [57], and global clinical status were significantly greater with prazosin than placebo.

The fourth RCT was performed by Germain and colleagues at the University of Pittsburgh [16]. They randomized 50 Veterans with chronic sleep disturbances to one of three conditions: prazosin (mean dose = 9 mg at night); a behavioral sleep intervention (BSI) that included imagery rehearsal therapy, stimulus control, and sleep restriction; or placebo pill treatment. Both prazosin and BSI were significantly more effective than placebo for sleep improvement, reduction in daytime PTSD symptoms and improvement of global function. Pre- to posttreatment reductions of mean weekly nightmare scores were significantly greater for the BSI and prazosin groups than for the placebo group. Surprisingly, neither active treatment produced significant effects on standard polysomnographic parameters. The efficacy of both prazosin and BSI raises the possibility that a combination of prazosin and BSI, two mechanistically different treatments, may be

more effective for PTSD nighttime symptoms than either treatment alone in military Veterans.

The fifth RCT was performed in active duty American soldiers returned from combat deployments in Iraq and Afghanistan [19]. This study is the first prazosin RCT to have prescribed a midmorning prazosin dose in addition to a larger bedtime prazosin dose to increase likelihood of reducing daytime PTSD symptoms. Prescribing this two or three times daily regimen is consistent with prazosin use in general medicine to treat hypertension and benign prostatic hypertrophy. It is also supported by the ability of daytime prazosin to reduce the psychological distress response to trauma cues in PTSD [58]. Sixty seven soldiers in garrison at Joint Base Lewis McChord, Washington, were randomized to prazosin or placebo for 15 weeks. Participants met criteria for PTSD with frequent and severe combat trauma nightmares that had started subsequent to their traumatic combat event(s) in Iraq and Afghanistan. Prazosin was titrated upward over 6 weeks until trauma nightmares were absent or maximum doses of 5 mg midmorning and 20 mg bedtime for men ($n = 57$) and 2.0 mg midmorning and 10.0 mg bedtime for women ($n = 10$) were achieved. Maintenance prazosin doses were 4.0 ± 1.2 mg midmorning and 15.6 ± 6.0 mg bedtime for men; and 2.0 ± 0.0 mg midmorning and 7.0 ± 3.5 mg bedtime for women. Prazosin was significantly more effective than placebo for reducing CAPS "recurrent distressing dreams of the event" item scores; Pittsburgh Sleep Quality Index [59] scores; and total 17-item CAPS scores (reduction from baseline = 25.1 ± 3.4 prazosin group and 13.8 ± 3.3 placebo group [($p = 0.02$]). Total CAPS score decrease remained significantly greater in the prazosin group ($p = 0.04$) even after removing the nightmare item. The proportion of treatment "responders," defined as CGIC ratings "moderately improved" or "markedly improved" in ability to function at home and at work, was 64% for the prazosin group and 27% for the placebo group ($p < 0.001$). Even at the relatively high doses achieved, prazosin was well tolerated by these young soldiers. This study demonstrated that prazosin has clinically meaningful beneficial effects on both daytime and nighttime PTSD symptoms in active duty combat experienced soldiers when administered twice daily. Similar open-label prazosin beneficial effects with good tolerability have been reported in soldiers performing combat operations in the dehydrating Iraq desert warfare environment [60] and in elderly World War II Veterans and Holocaust survivors [61].

A sixth RCT was performed in 100 Iranian PTSD patients (28% women) equally divided between military Veterans and victims of civilian trauma [62]. Interestingly, subjects were randomized to one of three conditions: prazosin titrated to 15 mg at bedtime, the sedating antihistamine hydroxyzine titrated to 100 mg at bedtime, or placebo. Although sleep quality was the primary measure of interest, overall PTSD symptoms were assessed as well.

Improvement in Pittsburg Sleep Quality Index scores was significantly greater in both prazosin subjects (15.5 ± 2.2 to 10.2 ± 2.1) and hydroxyzine subjects (15.6 ± 2.2 to 12.2 ± 2.1) than placebo subjects (15.5 ± 2.0 to 15.0 ± 1.7). Both prazosin and hydroxyzine also were significantly superior to placebo for overall PTSD score and nightmare score, with prazosin significantly superior to hydroxyzine for overall PTSD and nightmares.

Finally, a small ($n = 8$) 16 day per treatment arm crossover study of the alpha-1 AR antagonist doxazosin for PTSD in military Veterans was recently reported [63]. Doxazosin has a substantially longer duration of action than prazosin, and an animal study suggests it penetrates into brain [64]. Doxazosin was not superior to placebo on the CAPS but did demonstrate a significant albeit modest superiority to placebo on the PTSD checklist.

Higher Pretreatment Blood Pressure Is a Potential Biomarker for Therapeutic Response to Prazosin

In the above described RCT of prazosin for PTSD in active duty soldiers [19], neither pretreatment PTSD symptom pattern nor severity distinguished between the 64% of soldiers who globally benefited from prazosin and the 36% who did not. The most direct potential biomarker for predicting prazosin efficacy would be the presence of elevated brain alpha-1 AR activity, the presumed therapeutic target of prazosin action. Although brain alpha-1 AR activity unfortunately is not currently measurable, brain and peripheral alpha-1 activity are co-regulated [65]. Standing systolic blood pressure (BP) is an easily measured and reliable function of alpha-1 AR activity on peripheral arterioles [66]. In a secondary analysis using linear mixed-effects models, we demonstrated a strong effect of standing systolic BP on PTSD outcome measures [67] in soldiers randomized to prazosin. Each 10 mmHg higher baseline systolic BP increment resulted in an additional 14-point reduction of CAPS total PTSD symptom score at endpoint ($p = 0.002$). For example, a higher standing systolic BP of 130 mmHg predicted a large 34-point CAPS score reduction, whereas a lower standing systolic BP of 110 mmHg predicted only a 7-point CAPS score reduction (numerically smaller than the mean placebo group response). All other combinations of BP parameters and PTSD outcome measures were similarly significant (although less robust than standing systolic BP) or demonstrated trends in the predicted direction. In the placebo group, there was no signal for a baseline BP effect on PTSD outcome measures. These findings suggest that a relatively high standing systolic BP for a person's demographic group is a potential biomarker that helps identify persons with PTSD more likely to respond to prazosin. They also are consistent with high alpha-1 AR activation contributing to the pathophysiology of PTSD in substantial subgroup patients.

Pharmacologic Reduction of Noradrenergic Activity in PTSD Animal Models

We assessed the effects of pharmacologic reduction of CNS noradrenergic activity on PTSD-like behaviors in a rodent model of PTSD [7]. Mice were exposed to foot shock followed by three weekly contextual reminders of the shock exposure. This modification of a rodent model of PTSD developed by Pynoos [68] produced a group of "susceptible" mice that developed increased acoustic startle response and aggression and decreased social interaction and a group of "resilient" mice that did not differ on these behavioral parameters from control mice. Both antagonism of NE effects at postsynaptic alpha-1 AR with prazosin and reduction of presynaptic NE outflow with the alpha-2 inhibitory autoreceptor agonist clonidine normalized acoustic startle response, aggression, social interaction, and other PTSD-like behaviors in susceptible mice. These data are consistent with both increased postsynaptic alpha-1 AR responsiveness and increased presynaptic NE outflow contributing to PTSD pathophysiology.

Although effects of a beta AR antagonist on established PTSD-like behaviors in an animal model (or in humans) have not been examined empirically, there is theoretical support for beta AR antagonism as a potential prophylactic intervention to reduce PTSD incidence when administered immediately following trauma [69]. Unfortunately, clinical studies addressing this hypothesis have overall been equivocal or negative [70, 71]. A recent PTSD propranolol prophylaxis study in rats is consistent with these disappointing clinical studies [72]. This study assessed the ability of a single post-trauma dose of propranolol to prevent expression of PTSD-like behaviors. An hour after exposure to well-soiled cat litter, rats were administered single bolus subcutaneous propranolol or normal saline. Propranolol effectively slowed heart rate and impaired memory on the object recognition task, indicating successful antagonism of both peripheral and CNS beta AR. However, 30 days following trauma exposure, there were no propranolol effects on PTSD-like behaviors.

Prazosin in Conditions Commonly Comorbid with PTSD

Postconcussive Headache

Persistent postconcussive symptoms following mild traumatic brain injury (mTBI) from improvised explosive devices (IEDs) are common in Veterans of the conflicts in Iraq and Afghanistan [73]. They usually resemble migraines phenomenologically [74], are highly comorbid with PTSD [75], and are often unresponsive to standard migraine prophylactic treatment [76]. Former Department of Veterans Affairs Director of Neurology Robert Ruff performed a large open-label prazosin observational study in 63 Iraq and Afghanistan wars combat Veterans who met criteria for mTBI with persistent postconcussive headaches [77]. The large majority of these Veterans with mTBI had comorbid PTSD nighttime symptoms with markedly disturbed sleep. Dr. Ruff asked whether treating disturbed sleep with prazosin would reduce postconcussive headache frequency and intensity in these Veterans with both mTBI and PTSD. They were treated with open-label prazosin and sleep hygiene counseling for 9 weeks. Prazosin was started at 1 mg at bedtime, titrated upward to 7 mg at bedtime by week 4, and continued at that dose for an additional 5 weeks. By week 9, percent of Veterans endorsing restorative sleep increased from 7% at baseline to 88%, headache pain (0–10 scale) decreased from 7.3 ± 0.3 at baseline to 4.1 ± 0.2. Headache frequency per month decreased from 12.4 ± 0.9 at baseline to 4.8 ± 0.3. Cognitive function as estimated by the Montreal Cognitive Assessment (MoCA) [78] improved from 24 at baseline to 28, and daytime sleepiness estimated by the Epworth Scale [79] (an indirect estimate of adequate nighttime sleep) decreased from 16 at baseline to 7. These changes all were highly statistically significant. The large majority of Veterans elected to continue maintenance prazosin. Improvements in sleep, headache severity and frequency, cognition, and daytime sleepiness were maintained at 6 months of prazosin treatment. An RCT to confirm these encouraging open-label prazosin results for postconcussive headache following blast mTBI in military Veterans has been initiated at our center.

Prazosin Preclinical Studies for Alcohol Use Disorder

The extended sobriety of the first two Veterans ever treated with prazosin for PTSD (see above) and increasing preclinical evidence supporting CNS noradrenergic involvement in mechanisms modulating arousal [9, 51], drug reinforcement effects [80], and stress responsivity [9] suggest a potential role for postsynaptic AR blockade in alcohol use disorder treatment. This hypothesis has been studied in animal models by Dennis Rasmussen in our laboratory at VA Puget Sound in collaboration with the Koob laboratory at Scripps Institute and the Froehlich laboratory at the University of Indiana. In rats made alcohol dependent, antagonism of the alpha-1 AR by prazosin blocked increases in responding for alcohol following a period of abstinence [81]. In genetically alcohol preferring (P) rats, prazosin substantially reduced alcohol drinking [82]. Doxazosin, a longer duration of action alpha-1 AR antagonist than prazosin, also reduced alcohol drinking in P rats [64]. The beta AR may also be involved in alcohol use disorders [44]. This possibility was tested by

measuring effects of the beta AR antagonist propranolol alone, prazosin alone, and propranolol in combination with prazosin on alcohol drinking in alcohol preferring (P) rats [83]. Although propranolol alone had no consistent effect on alcohol ingestion, adding propranolol to prazosin decreased alcohol ingestion significantly more than did prazosin alone. It is noteworthy that the two PTSD Veterans with 20 years sobriety described above were maintained on both prazosin and propranolol. Combined alpha-1 AR and beta AR blockade may prove to be a particularly effective regimen for alcohol use disorder.

Prazosin Clinical Studies for Alcohol Use Disorder With and Without Comorbid PTSD in Humans

Simpson et al. [84] evaluated prazosin in a pilot RCT in 20 community-residing men with alcohol dependence (but without PTSD) who were seeking to achieve abstinence. Participants were randomized to prazosin or placebo titrated over 2 weeks to a maximum dose of 4 mg AM, 4 mg PM, and 8 mg HS or highest tolerated dose. They were maintained at their achieved prazosin dose for an additional 4 weeks. During the maintenance dose period, prazosin subjects compared to placebo subjects reported significantly fewer drinking days per week (0.9 ± 0.5 days vs. 5.9 ± 1.9 days) and significantly fewer drinks per week (2.6 ± 1.3 drinks vs. 20.8 ± 6.5 drinks). Adverse effects were infrequent and comparable between treatment groups. These results suggest that prazosin reduces drinking in men with alcohol use disorder motivated to achieve abstinence. Consistent with these results, prazosin significantly reduced alcohol craving in alcohol-dependent persons studied in a laboratory environment [80]. Prazosin RCTs for alcohol use disorders with and without comorbid PTSD are underway in civilians, military Veterans, and active duty military service members.

In a second study, Simpson et al. [85] evaluated prazosin in 30 community-residing predominantly civilian patients (19 men, 11 women) with alcohol dependence and comorbid PTSD, which resulted from one or more civilian traumas in 80% of subjects. The prazosin titration and maximum dose were identical to their first study, but the post-titration phase was extended to 6 weeks. Consistent with their first study results, prazosin subjects compared to placebo subjects reported significantly decreased percent drinking days per week, percent heavy drinking days per week, and drinks per week (all $p < 0.01$). Although decreases in PTSD symptom scores were numerically greater in the prazosin group and the disturbing trauma dreams item reached a p-value of 0.09 favoring the prazosin group, PTSD between group differences did not reach the significance criteria of $p < 0.05$. These results suggest that beneficial effects of prazosin for alcohol dependence are direct rather than secondary to reduced need to "self-medicate" with alcohol for distressing PTSD symptoms. Petrakis and colleagues [86] reported a negative prazosin trial for alcohol use disorder in a military Veteran sample with a high proportion of participants meeting diagnostic criteria for PTSD. Veterans were recruited predominantly from residents of Department of Veterans Affairs domiciliary settings.

Differences between this negative study and the two positive studies described above may reflect differences in subject sample characteristics. Also, the extremely large placebo effect in the negative study would have made it difficult to detect an active drug effect.

A Chart Review Effectiveness Study of Prazosin vs. Quetiapine for Nighttime PTSD Symptoms in Military Veterans

Quetiapine is a sedating second-generation antipsychotic drug that has been widely prescribed for decades to treat nighttime PTSD symptoms in military Veterans. It has the highest "prazosin-like" affinity for the alpha-1 AR among commonly used antipsychotic drugs. Byers et al. used a retrospective chart review method to evaluate differential effectiveness between quetiapine and prazosin in Veterans treated with these drugs for nighttime PTSD symptoms at the Phoenix, Arizona VA Medical Center [87]. Two hundred thirty-seven Veterans (mean age = 54 years) were first prescribed prazosin (n = 62, initial mean nighttime dose = 1.4 mg) or quetiapine (n = 175, mean nighttime dose = 41 mg) between 2002 and 2006. Short-term benefit was estimated at 6 months after first prescription based on charting clinician's indication of symptom improvement. Long-term benefit and tolerability were estimated in 2008 (end study), by comparing percentage of patients remaining on their initially prescribed prazosin (end study mean dose = 6 mg) or initially prescribed quetiapine (end study mean dose = 135 mg). Tolerability was estimated by comparing adverse effects leading to drug discontinuation.

The two drugs produced equal rates of short-term improvement (prazosin = 61.3% vs. quetiapine 61.7%). However, prazosin was significantly superior to quetiapine on long-term effectiveness estimated by percentage remaining on original drug at end study (48% vs. 21%, $p < 0.001$). More Veterans discontinued quetiapine than prazosin for adverse effects (35% vs. 18%, $p < 0.01$) or for lack of efficacy (13% vs. 2%, $p = 0.03$). In contrast, discontinuation for symptom resolution (drug treatment no longer necessary) was significantly greater for prazosin than quetiapine (29% vs. 10%, $p = 0.02$). When specific adverse effects leading to discontinuation were examined, sedation (23% vs. 1%, $p < 0.001$) and metabolic effects (8% vs. 0%, $p = 0.01$) were

greater with quetiapine than prazosin. Hypotension and dizziness were infrequent and did not differ between groups. Substitution of one drug for the other also favored prazosin. Prazosin was substituted for quetiapine in 25% of patients initiated on quetiapine, whereas quetiapine was substituted for prazosin in only 8% of patients initiated on prazosin. These findings are consistent with increasing prazosin utilization for PTSD in the United States Veterans Health System every year since 2001. Although diffusion of prazosin treatment for PTSD in Veterans initially was related to facility geographic proximity to Seattle, Washington, prazosin recently has become more homogenously prescribed across United States Veterans Affairs Medical Centers [88].

Optimizing Therapeutic Effects and Minimizing Adverse Effects of Prazosin

Recommendations for the Prescriber

- Although prazosin must be initiated at a low dose (usually 1 mg at bedtime) to avoid "first-dose" hypotension, gradual titration to a high dose often is necessary to eliminate PTSD trauma nightmares and/or distressed awakenings. This appears particularly important in younger combat Veterans. Although some patients respond well to low doses (e.g., 2–4 mg HS), other patients require up to 40 mg at bedtime and 5 mg midmorning and midafternoon to achieve meaningful reduction or elimination of trauma nightmares, sleep disruption and daytime hyperarousal symptoms [89], and unpublished observations. In our experience, this broad effective dose range does not appear related to body mass.
- Prazosin is recommended for treatment of PTSD associated nightmares by the American Academy of Sleep Medicine [90]. In our experience, prazosin is most effective for frequent trauma nightmares with realistic content that are highly distressing and accompanied by intense autonomic arousal with large muscle group movements and vocalizations (REM sleep without atonia) [91]. It also appears effective for PTSD distressed awakenings in the absence of recalled trauma-content nightmares [92]. Higher pretreatment standing systolic BP, an indicator of elevated peripheral alpha-1 AR activity, is a potentially useful biomarker for identifying PTSD patients likely to respond to prazosin [67].
- Prazosin is not effective for "normal" unpleasant anxious dreams with bizarre content. In fact, normal anxiety dreams (and pleasant dreams) can become more frequent as prazosin presumably normalizes and lengthens REM sleep. Walker and colleagues have demonstrated that normal REM sleep dreaming is important for removing excessive emotional tone from memories [56]. Thus, normalization of REM sleep may contribute to prazosin mechanism of action in PTSD treatment.
- Although symptomatic orthostatic hypotension-induced dizziness or fainting is unusual, especially after the first few weeks of prazosin titration, several factors increase risk for this adverse effect. These include baseline orthostatic hypotension, erectile dysfunction medications, other maintenance antihypertensives, and inadequate hydration. Dizziness and syncope during early titration and in patients with hypotension risk factors are best avoided by instructing the patient to arise gradually from a supine to a sitting position, waiting 20 s without dizziness before standing, and an additional 30 s without dizziness before ambulating.
- If daytime hyperarousal and reexperiencing symptoms persist despite bedtime prazosin elimination of nighttime PTSD symptoms, addition of prazosin 1–5 mg midmorning (BID) or midmorning and midafternoon can reduce or eliminate persistent daytime PTSD symptoms.
- Prazosin is not a hypnotic and does not decrease sleep onset latency [20]. It can reduce difficulty falling asleep if directly related to fear of entering a distressing trauma-content nightmare once sleep has been achieved.
- Adverse effects include orthostatic hypotension, nasal congestion, and reflex tachycardia perceived as uncomfortable or frightening palpitations. The approach to orthostatic hypotension has been described above. Nasal congestion is usually self-limited or responds to spreading total daily dose across the day and night. Occasionally a nasal decongestant spray is helpful. Tachycardia and palpitations respond to low-dose propranolol. Although propranolol alone can exacerbate trauma nightmares (as in the first Veteran to receive prazosin described above), propranolol exacerbation of nightmares does not occur when prazosin is already prescribed. In fact, addition of propranolol to prazosin often appears to reduce residual daytime irritability and low anger threshold (unpublished observations).
- Although prazosin often needs to be titrated upward aggressively during early treatment, once an effective dose is achieved, that dose usually continues effective during long-term maintenance treatment. Why habituation to beneficial prazosin effects on PTSD is rare whereas habituation to prazosin hypotensive effects is common remains unclear.
- PTSD nighttime symptoms usually return within days to weeks of prazosin discontinuation in chronic PTSD. These symptoms may not return when prazosin is discontinued in persons with recent trauma (unpublished observations). Possible prazosin prophylaxis of PTSD if administered soon after trauma has not been evaluated empirically.

Summary

Prazosin is a useful tool in the management of PTSD trauma-content nightmares, sleep disruption and daytime hyperarousal symptoms, particularly when these symptoms are frequent, severe, distressing, and accompanied by high autonomic arousal. The effective dose range is highly variable, so titration upward guided by elimination of target symptoms without emergence of troublesome adverse effects is usually necessary. Prazosin is generally well tolerated with gradual dose titration and benefit usually continues for years once an effective dose is achieved. The positive results of prazosin RCTs suggest that increased responsiveness of alpha-1 AR to NE contributes to PTSD pathophysiology in a substantial proportion of persons suffering from this common disorder.

Reduction or elimination of these PTSD symptoms is associated with meaningful improvement of function at home and at work. Prazosin may also prove beneficial for alcohol use disorder and persistent postconcussive headaches, conditions commonly comorbid with PTSD and associated with sleep disturbance. Clinical effectiveness of prazosin is supported by increased utilization every year among Veterans with a PTSD diagnosis receiving care in the Veterans Health Care System since publication of the first case report series in 2000 [93].

References

1. Bremner JD, Innis RB, Ng CK, Staib LH, Salomon RM, Bronen RA, Duncan J, Southwick SM, Krystal JH, Rich D, Zubal G, Dey H, Soufer R, Charney DS. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54(3):246–54.
2. Geracioti TD Jr, Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, Schmidt D, Rounds-Kugler B, Yehuda R, Keck PE Jr, Kasckow JW. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158(8):1227–30.
3. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. Biol Psychiatry. 1995;38(3):174–9.
4. Pietrzak RH, Gallezot JD, Ding YS, Henry S, Potenza MN, Southwick SM, Krystal JH, Carson RE, Neumeister A. Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. JAMA Psychiat. 2013;70(11):1199–205.
5. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS. Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry. 1993;50(4):266–74.
6. Southwick SM, Morgan CA 3rd, Bremner AD, Grillon CG, Krystal JH, Nagy LM, Charney DS. Noradrenergic alterations in posttraumatic stress disorder. Ann N Y Acad Sci. 1997;821:125–41.
7. Olson VG, Rockett HR, Reh RK, Redila VA, Tran PM, Venkov HA, Defino MC, Hague C, Peskind ER, Szot P, Raskind MA. The role of norepinephrine in differential response to stress in an animal model of posttraumatic stress disorder. Biol Psychiatry. 2011;70(5):441–8.
8. Berridge C. The locus ceruleus-noradrenergic system and stress: implications for post-traumatic stress disorder. In: Shiromani P, Keane T, LeDoux J, editors. Post-traumatic stress disorder: basic science and clinical practice. New York: Humana Press; 2009. p. 213–30.
9. Valentino RJ, Van Bockstaele E. Convergent regulation of locus coeruleus activity as an adaptive response to stress. Eur J Pharmacol. 2008;583(2–3):194–203.
10. Arnsten AF, Mathew R, Ubriani R, Taylor JR, Li BM. Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol Psychiatry. 1999;45(1):26–31.
11. Day HE, Campeau S, Watson SJ Jr, Akil H. Expression of alpha(1b) adrenoceptor mRNA in corticotropin-releasing hormone-containing cells of the rat hypothalamus and its regulation by corticosterone. J Neurosci. 1999;19(22):10098–106.
12. Ross RJ, Gresch PJ, Ball WA, Sanford LD, Morrison AR. REM sleep inhibition by desipramine: evidence for an alpha-1 adrenergic mechanism. Brain Res. 1995;701(1–2):129–34.
13. Menkes DB, Baraban JM, Aghajanian GK. Prazosin selectively antagonizes neuronal responses mediated by alpha1-adrenoceptors in brain. Naunyn Schmiedeberg's Arch Pharmacol. 1981;317(3):273–5.
14. Hieble JP, Ruffolo RR Jr. The use of alpha-adrenoceptor antagonists in the pharmacological management of benign prostatic hypertrophy: an overview. Pharmacol Res. 1996;33(3):145–60.
15. Lund-Johansen P, Hjermann I, Iversen BM, Thaulow E. Selective alpha-1 inhibitors: first- or second-line antihypertensive agents? Cardiology. 1993;83(3):150–9.
16. Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, Rode N, Begley A, Nofzinger EA. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. J Psychosom Res. 2012;72(2):89–96.
17. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61(8):928–34.
18. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.
19. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O'Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Mayer CL, Freed MC, Engel C, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170(9):1003–10.
20. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63(6):629–32.
21. Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
22. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
23. Jones L, Brazel D, Peskind ER, Morelli T, Raskind MA. Group therapy program for African-American veterans with posttraumatic stress disorder. Psychiatr Serv. 2000;51(9):1177–9.
24. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. J Trauma Stress. 2004;17(1):69–73.

25. Mallick BN, Majumdar S, Faisal M, Yadav V, Madan V, Pal D. Role of norepinephrine in the regulation of rapid eye movement sleep. J Biosci. 2002;27(5):539–51.
26. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006. p. 237–95.
27. Peskind ER, Wingerson D, Murray S, Pascualy M, Dobie DJ, Le Corre P, Le Verge R, Veith RC, Raskind MA. Effects of Alzheimer's disease and normal aging on cerebrospinal fluid norepinephrine responses to yohimbine and clonidine. Arch Gen Psychiatry. 1995;52(9):774–82.
28. Ravaris CL, Friedman MJ, Hauri PJ, McHugo GJ. A controlled study of alprazolam and propranolol in panic-disordered and agoraphobic outpatients. J Clin Psychopharmacol. 1991;11(6):344–50.
29. Famularo R, Kinscherff R, Fenton T. Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. Am J Dis Child. 1988;142(11):1244–7.
30. Kolb L, Burns B, Griffiths S. Propranolol and clonidine in the treatment of the chronic posttraumatic stress disorders of war. In: van der Kolk B, editor. Post traumatic stress disorder: psychological and biological sequelae. Washington, DC: American Psychiatric Press; 1984. p. 97–107.
31. Yamada Y, Shibuya F, Hamada J, Sawada Y, Iga T. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. J Pharmacokinet Biopharm. 1995;23(2):131–45.
32. Werbel SS, Ober KP. Pheochromocytoma. Update on diagnosis, localization, and management. Med Clin N Am. 1995;79(1):131–53.
33. Day TA, Randle JC, Renaud LP. Opposing alpha- and beta-adrenergic mechanisms mediate dose-dependent actions of noradrenaline on supraoptic vasopressin neurones in vivo. Brain Res. 1985;358(1–2):171–9.
34. Medical Economics Company. Physicians desk reference, 62nd ed. Montvale. 2008.
35. Raskind M, Simpson TL. Effects of prazosin on drinking parameters in alcohol dependence. Alcohol Clin Exp Res. 2012;36(Suppl):318A.
36. Woodward SH, Arsenault NJ, Murray C, Bliwise DL. Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry. 2000;48(11):1081–7.
37. Cirelli C, Tononi G, Pompeiano M, Pompeiano O, Gennari A. Modulation of desynchronized sleep through microinjection of alpha 1-adrenergic agonists and antagonists in the dorsal pontine tegmentum of the cat. Pflugers Arch. 1992;422(3):273–9.
38. Hilakivi I, Leppavuori A. Effects of methoxamine, and alpha-1 adrenoceptor agonist, and prazosin, an alpha-1 antagonist, on the stages of the sleep-waking cycle in the cat. Acta Physiol Scand. 1984;120(3):363–72.
39. Pellejero T, Monti JM, Baglietto J, Jantos H, Pazos S, Cichevski V, Hawkins M. Effects of methoxamine and alpha-adrenoceptor antagonists, prazosin and yohimbine, on the sleep-wake cycle of the rat. Sleep. 1984;7(4):365–72.
40. Pickworth WB, Sharpe LG, Nozaki M, Martin WR. Sleep suppression induced by intravenous and intraventricular infusions of methoxamine in the dog. Exp Neurol. 1977;57(3):999–1011.
41. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol. 1999;160(1):1–12.
42. Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, Nemeroff CB. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci U S A. 1996;93(4):1619–23.
43. Kalin NH, Shelton SE, Davidson RJ. Cerebrospinal fluid corticotropin-releasing hormone levels are elevated in monkeys with patterns of brain activity associated with fearful temperament. Biol Psychiatry. 2000;47(7):579–85.
44. Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. Biol Psychiatry. 1999;46(9):1167–80.
45. Feldman S, Weidenfeld J. Involvement of amygdalar alpha adrenoceptors in hypothalamo-pituitary-adrenocortical responses. Neuroreport. 1996;7(18):3055–7.
46. Kiss A, Aguilera G. Participation of alpha 1-adrenergic receptors in the secretion of hypothalamic corticotropin-releasing hormone during stress. Neuroendocrinology. 1992;56(2):153–60.
47. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1999;156(4):585–8.
48. Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997;154(5):624–9.
49. Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharmacol. 1997;11(2):151–62.
50. Birnbaum S, Gobeske KT, Auerbach J, Taylor JR, Arnsten AF. A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex. Biol Psychiatry. 1999;46(9):1266–74.
51. Stevens DR, McCarley RW, Greene RW. The mechanism of noradrenergic alpha 1 excitatory modulation of pontine reticular formation neurons. J Neurosci. 1994;14(11 Pt 1):6481–7.
52. Guy W. ECDEU assessment manual for psychopharmacology. Rockville: US Department of Health, Education and Welfare; 1976. (ADM 76–338)
53. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8(1):75–90.
54. Esposito K, Benitez A, Barza L, Mellman T. Evaluation of dream content in combat-related PTSD. J Trauma Stress. 1999;12(4):681–7.
55. Ajilore O, Stickgold R, Rittenhouse CD, Hobson JA. Nightcap: laboratory and home-based evaluation of a portable sleep monitor. Psychophysiology. 1995;32(1):92–8.
56. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol. 2011;21(23):2029–32.
57. Weathers F, Litz B, Herman J, Huska J, Keane T. The PTSD checklist: reliability, validity, and diagnostic utility. Paper presented at Annual Meeting of the International Society for Traumatic Stress Studies, San Antonio. 1993.
58. Taylor FB, Lowe K, Thompson C, McFall MM, Peskind ER, Kanter ED, Allison N, Williams J, Martin P, Raskind MA. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. Biol Psychiatry. 2006;59(7):577–81.
59. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
60. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. J Trauma Stress. 2010;23(5):645–8.
61. Peskind ER, Bonner LT, Hoff DJ, Raskind MA. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. J Geriatr Psychiatry Neurol. 2003;16(3):165–71.
62. Ahmadpanah M, Sabzeiee P, Hosseini SM, Torabian S, Haghighi M, Jahangard L, Bajoghli H, Holsboer-Trachsler E, Brand S. Comparing the effect of prazosin and hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. Neuropsychobiology. 2014;69(4):235–42.

63. Rodgman C, Verrico CD, Holst M, Thompson-Lake D, Haile CN, De La Garza R 2nd, Raskind MA, Newton TF. Doxazosin XL reduces symptoms of posttraumatic stress disorder in veterans with PTSD: a pilot clinical trial. J Clin Psychiatry. 2016;77(5):e561–5.
64. O'Neil ML, Beckwith LE, Kincaid CL, Rasmussen DD. The alpha1-adrenergic receptor antagonist, doxazosin, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol Clin Exp Res. 2013;37(2):202–12.
65. Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. Curr Neuropharmacol. 2008;6(3):254–85.
66. Reid JL. Alpha-adrenergic receptors and blood pressure control. Am J Cardiol. 1986;57(9):6E–12E.
67. Raskind MA, Millard SP, Petrie EC, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Hill J, Daniels C, Hendrickson R, Peskind ER. Higher pretreatment blood pressure is associated with greater posttraumatic stress disorder symptom reduction in soldiers treated with prazosin. Biol Psychiatry. 2016;80(10):736–42.
68. Pynoos RS, Ritzmann RF, Steinberg AM, Goenjian A, Prisecaru I. A behavioral animal model of posttraumatic stress disorder featuring repeated exposure to situational reminders. Biol Psychiatry. 1996;39(2):129–34.
69. Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. Nature. 1994;371(6499):702–4.
70. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, Cahill L, Orr SP. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry. 2002;51(2):189–92.
71. Stein MB, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: results from a randomized controlled proof-of-concept trial in physically injured patients. J Trauma Stress. 2007;20(6):923–32.
72. Cohen H, Kaplan Z, Koresh O, Matar MA, Geva AB, Zohar J. Early post-stressor intervention with propranolol is ineffective in preventing posttraumatic stress responses in an animal model for PTSD. Eur Neuropsychopharmacol. 2011;21(3):230–40.
73. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. Headache. 2010;50(8):1262–72.
74. Theeler BJ, Erickson JC. Posttraumatic headache in military personnel and veterans of the iraq and afghanistan conflicts. Curr Treat Options Neurol. 2012;14(1):36–49.
75. Ruff RL, Ruff SS, Wang XF. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. J Rehabil Res Dev. 2009;46(9):1071–84.
76. Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: an observational study. Headache. 2011;51(6):932–44.
77. Ruff RL, Riechers RG 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. J Rehabil Res Dev. 2012;49(9):1305–20.
78. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9.
79. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5–11.
80. Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res. 2012;36(2):351–60.
81. Walker BM, Rasmussen DD, Raskind MA, Koob GF. alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol. 2008;42(2):91–7.
82. Rasmussen DD, Alexander LL, Raskind MA, Froehlich JC. The alpha1-adrenergic receptor antagonist, prazosin, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol Clin Exp Res. 2009;33(2):264–72.
83. Rasmussen DD, Beckwith LE, Kincaid CL, Froehlich JC. Combining the alpha1 -adrenergic receptor antagonist, prazosin, with the beta-adrenergic receptor antagonist, propranolol, reduces alcohol drinking more effectively than either drug alone. Alcohol Clin Exp Res. 2014;38(6):1532–9.
84. Simpson TL, Saxon AJ, Meredith CW, Malte CA, McBride B, Ferguson LC, Gross CA, Hart KL, Raskind M. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. 2009;33(2):255–63.
85. Simpson TL, Malte CA, Dietel B, Tell D, Pocock I, Lyons R, Varon D, Raskind M, Saxon AJ. A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 2015;39(5):808–17.
86. Petrakis IL, Desai N, Gueorguieva R, Arias A, O'Brien E, Jane JS, Sevarino K, Southwick S, Ralevski E. Prazosin for veterans with posttraumatic stress disorder and comorbid alcohol dependence: a clinical trial. Alcohol Clin Exp Res. 2016;40(1):178–86.
87. Byers MG, Allison KM, Wendel CS, Lee JK. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. J Clin Psychopharmacol. 2010;30(3):225–9.
88. Hermes E, Harpaz-Rotem I, Rosenheck R. Diffusion of prazosin treatment for PTSD. Am J Psychiatry. 2014;171(1):117.
89. Koola MM, Varghese SP, Fawcett JA. High-dose prazosin for the treatment of post-traumatic stress disorder. Ther Adv Psychopharmacol. 2014;4(1):43–7.
90. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, Maganti RK, Ramar K, Kristo DA, Bista SR, Lamm CI, Morgenthaler TI, Standards of Practice C, American Academy of Sleep M. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
91. Mysliwiec V, O'Reilly B, Polchinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia encompassing disruptive nocturnal behaviors, nightmares, and REM without atonia in trauma survivors. J Clin Sleep Med. 2014;10(10):1143–8.
92. Thompson CE, Taylor FB, McFall ME, Barnes RF, Raskind MA. Nonnightmare distressed awakenings in veterans with posttraumatic stress disorder: response to prazosin. J Trauma Stress. 2008;21(4):417–20.
93. Lund BC, Bernardy NC, Alexander B, Friedman MJ. Declining benzodiazepine use in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2012;73(3):292–6.

Part VI

Specific Populations

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Refugees, torture victims, or "ethnically cleansed" persons – both young and old – differ from military war survivors by their status as nonparticipants in military operations. Chapters in this section detail some of the important research about epidemiological and developmental aspects of and relationships between sleep and post-traumatic stress disorder (PTSD) in these populations. There is currently a remarkable lack of mapping of trauma exposure on pathological phenotypes or endophenotypes. So, are there "special" features about these groups that might inform the field to advance knowledge and interventions, and if so, what are they? Combatants and civilians both experience severe stress and traumatic events during war that are associated to some degree with distressing symptoms, illness, and impairments. Among these symptoms are poor sleep and bad dreams. Perhaps the answer to the question lies outside of what is usually measured. Culture-bound constructs, such as "PTSD," "mental health," and "physical symptoms," might limit what we can find. The British-Hungarian scientist-philosopher Michael Polanyi argued that positivism supplies a false sense of knowing, because epistemology always involves personal and cultural commitments. Polanyi aligned with Aristotle who believed that "the whole is greater than the sum of the parts," by concluding that "we believe more than we can prove" and "we know more than we can say." Empirical methods bring us great information and simultaneously are a lens through which facts are sometimes limited more than expanded, distorted more than clarified.

Refugees of war displaced to the USA are said to have experienced between 3 and 19 traumatic events when using standard instruments designed by expert consensus methods. These events have been described as psychological, physical, or sexual types. Yet, when a similar group of refugees are included in the research process using mixed methods, we find that there are over 250 traumatic events to which they as a group have been exposed, and each person on average experienced 150 events. Looking in more detail, this breadth and depth of experiences factored into 12 event types instead of 3, a few of which, such as forms of deprivation/discrimination, displacement, separation/isolation, and difficulties during migration, are not in the common quantitative literature about war survivors. It is no surprise that strength of association between events and any measure of health is larger when using a broader – rather than a narrower – range of events. These types of experiences also extend from early wartime, through migration and displacement, and into resettlement in a new "home." Displacement, for example, is a variable that has not found its way into a mainstream research, while key studies detail the pathogenic effects of it. Dimensions of place define the immediate environment outside of

the person. Place facilitates attachment, development and identity, and survival. Disruptions to place threaten biopsychosocial homeostasis by altering attachments, familiarity, and place identity and result in psychological problems of nostalgia, disorientation, and alienation. Place loss affects people's sense of identity and belonging and is an identified risk factor for poor health. One could hypothesize that displacement affects sleep, either directly or mediated through stress chronicity and/or resettlement factors that impair identity formation and meaning.

Likewise, common instruments that assess symptoms or health status in civilian war survivors have been developed by expert consensus methods, usually having between 9 and 30 items that most often assess single disorders that are either "physical" or "mental." When refugees are included in the research using mixed methods, 121 possible chronic symptoms were identified, with the average person experiencing 48 (SD 31, range 0–118) of them. Further evaluation found 12 symptom types, 9 of which are somatic and 2 psychological. Symptoms of depression and PTSD factor together, except for a factor termed "PTSD vulnerability," which consists of seven symptoms regarding a lack of emotional feelings for others and thinking that traumatic events are going to occur again. The overall correlation between war-trauma scores and symptoms was 0.47, which is nearly double the correlation using common instruments. Looking at individual symptom scales, six of the nine somatic scales correlated just as highly with trauma as did the anxiety and PTSD/depression scales (range 0.35–0.42). The fact is most war survivors experience a myriad of symptoms throughout the body, all of which are related to trauma due to profound effects on multiple biological systems. Cambodians displaced to the USA have a two- to threefold higher number of medical/psychiatric disorders decades after migration compared to the general US population. The narrower the health construct, the smaller the associations between health and trauma. And while war-related trauma is a significant predictor of symptoms, other prewar, migrational, and post-migrational experiences explain a large part of the variance of symptoms and disorders.

Perhaps special features of civilian war survivors are features of all war survivors: effects of war are deep and broad and defy easy categorization. Research regarding trauma and health outcomes lacks adequate assessment about constructs that matter, which allow us to find valid associations and make valid conclusions. The whole is greater than the sum of the parts. We believe more than we can prove. Exposure to the almost uncountable stressors during war, in the context of being an unwilling participant, has effects that are difficult to measure. Losses are profound. How do we measure the effect of world loss and soul loss on sleep? Is it abnormal to not sleep where one does not belong, where one was told by collective action that one should not exist? Perhaps we need to focus the lens differently in order to view more of the whole.

Posttraumatic Stress Disorder in Youth Exposed to War and Terror

31

Hilit Kletter and Victor G. Carrion

Introduction

For many populations around the world, the reality of war is a far too common experience. Modern warfare has resulted in increased involvement of civilians in conflict, a large proportion being children. During the last decade, it was estimated that 2 million youth were killed in wars, 4–5 million were disabled, 12 million were left homeless, more than 1 million were orphaned or separated, and 10 million were psychologically traumatized [1]. Children are especially vulnerable to the effects of war as they often experience repeated, uncontrollable, and unpredictable threats to their sense of safety, well-being, and bodily integrity [2]. They may be affected in multiple ways either as direct victims, through secondary exposure, or as perpetrators [3]. In their review of regions impacted by war, Murthy and Lakshminarayana found that children had higher rates of war-related psychological problems compared to other vulnerable populations [4]. A wide range of consequences have been reported for war-exposed youth including anxiety, depression, emotional and behavioral dysregulation, somatic complaints, attention problems, learning difficulties and poor academic achievement, sleep disturbances, nightmares, increased aggression, impaired social functioning, and insecure attachments [2, 3]. War deliberately instills fear, and the development and maintenance of posttraumatic stress disorder (PTSD) are driven by overactivation of the brain's fear circuits in response to traumatic experiences. Thus, the risk for PTSD is especially high for war-exposed youth. PTSD is prominent across cultures exposed to war. A large meta-analysis of 7,920 children from many different regions exposed to war found that approximately 50% had PTSD [5]. Prevalence rates as high as 93.8% have been reported [6].

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Definition of PTSD in Youth

The Diagnostic and Statistical Manual (DSM-V) defines a traumatic event as "exposure to actual or threatened death, serious injury or sexual violation" [7]. This exposure can be through direct traumatic experience, witnessing of traumatic events, hearing that a traumatic event occurred to a close family member or friend, or first-hand repeated or extreme exposure to aversive details of the traumatic event. Symptoms of PTSD are divided into four clusters: reexperiencing of the traumatic event (criterion B), which includes flashbacks, recurrent dreams related to the trauma, prolonged psychological distress, and intrusive recollections; avoidance of distressing memories, thoughts, emotions, or external reminders of the trauma (criterion C); negative cognitions and mood (criterion D), which include sense of blame of self or others, diminished interest in activities or estrangement from others, and inability to recall key aspects of the event; and arousal (criterion E) which is marked by aggressive or self-destructive behavior, sleep disturbances, and hypervigilance. Six symptoms are needed for a diagnosis of PTSD with at least one symptom from criterion B and C and at least two symptoms from criterion D and E. Symptoms must persist for more than a month (criterion F) and result in impairment in functioning (criterion G). There is a preschool subtype for children 6 years and younger that requires only three symptoms for diagnosis (one from B, one from C or D, and one from E). In addition, there are subtypes for dissociative symptoms and delayed expression.

Symptoms in War-Exposed Youth

Infants and Toddlers

Compared to older children, who present with the more typical symptoms of PTSD, younger children may respond with increased nonspecific behavior problems and symptoms of underlying anxiety [8]. Feldman and Vengrober found that

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common symptoms of PTSD in young children exposed to war included nonverbal representations of traumatic play, frequent crying, disrupted sleep, mood changes, social withdrawal, object focus, and increased behavioral avoidance [9]. Israeli infants and toddlers in sealed rooms during the Gulf War often experienced fear, aggression, and distress at seeing their parents wearing gas masks [10]. Furthermore, long-term changes occurred in their general behavior including shifts in eating and sleeping patterns, regression such as bedwetting and use of a bottle instead of solid food, prolonged crying episodes, severe stomachaches, and temper tantrums [11]. Similarly, Thabet et al. found that preschool children in Gaza had increased trouble falling asleep, irregular eating, overactivity, poor concentration, temper tantrums, worries, and fears [8]. War may also diminish caregivers' responsiveness to their children as they try to deal with their own reactions [2, 9]. This may impede development of trust in caregivers' abilities to support and protect their children leading to impaired attachments. The chaotic environment created by war and constant threats to safety results in younger children being especially preoccupied with separation and loss. Studies show that exposure to war in this age group results in increased sleep with parents, attention-seeking behaviors, dependency, clinging, and separation anxiety [8, 12, 13].

School-Age Children

School-age children are more likely to display the classic DSM symptoms of PTSD such as nightmares, preoccupation with the traumatic events, complex reenactment, appreciation of irreversibility, hyperarousal, hypervigilance, withdrawal, avoidance, and aggressive behaviors [2]. Other symptoms such as fear of loneliness, irritability, nocturnal enuresis, thumb sucking, and nail biting have been observed in this age group [14]. Frequent illnesses and somatic complaints including stomachaches, nausea, general aches and pains, dizziness, and loss of appetite are common [14, 15]. Furthermore, war disrupts academic functioning in a variety of ways. It has been associated with impaired attention and concentration, deficits in memory and language performance, poor achievement, school refusal, truancy, defiance, and dropout [2, 16–18].

Adolescents

Of all the different age groups, adolescents appear to be the most susceptible to the effects of war [4]. They are likely to have greater exposure, and their higher cognition makes them better able to understand the ramifications of war. Symptoms in war-affected adolescents include depression, anxiety, hopelessness, suspicion, heightened sensitivity, withdrawal, somatic complaints, interrupted thoughts, attention problems, and poor academic achievement [19–21]. War-exposed adolescents also engage in greater risk-taking behaviors, such as increased substance use [22, 23]. Other risk-taking behaviors as observed in Israeli adolescents exposed to recurrent terrorism include disobedience to authority, reckless driving, carrying weapons, stealing, running away, self-injury, and Russian roulette-type games [23].

Trauma and Sleep in Youth

Recent research has suggested that rather than being a secondary symptom of PTSD, sleep disturbances may actually serve as a biomarker for PTSD in traumatized youth [24]. However, compared to the adult literature, the research on sleep in youth with PTSD is minimal. There is higher reporting of sleep disturbances among traumatized youth than non-trauma-exposed populations [25]. Common symptoms include trouble falling or staying asleep, awakening from sleep, nightmares or night terrors, fear of sleeping, and sleep enuresis.

In a study of Kuwaiti preadolescents exposed to the Gulf War, 27% rated sleep quality in the past month as "fairly bad or very bad," 21% could not fall asleep within 30 min three times a week or more, 29% woke up in the middle of the night at least three times a week or more, and 46.7% experienced sleep disturbances that interfered with daily functioning at moderate to severe levels in the past month [26]. Similar results were found in a sample of 403 refugee youth with 20.3% reporting sleep disturbances "sometimes" and 31.6% reporting sleep disturbances "mostly, most of the time" [27]. Furthermore, among Middle Eastern refugee youth, parents reported that 20% had nightmares and difficulty falling or staying asleep [28]. In preschoolers exposed to the World Trade Center attacks, those exposed to high-intensity events (e.g., witnessing the towers collapse, injured people, dead bodies, or people jumping out of buildings) were five times more likely to have sleep problems 3 years later compared to those not exposed [29]. Furthermore, the greater the number of events youth were exposed to, the greater the risk for sleep problems.

Separation and Loss

Experiences such as separation from family or loved ones, death, loss of property, and displacement from one's home serve to exacerbate the traumatic responses of war-exposed youth. Taylor et al. found that separation and loss are equivalent to some other forms of trauma in terms of symptoms and functional impairment [30]. For war-exposed youth,

separation may be especially traumatic as it often results in loss of primary caregivers eliminating a critical protective factor against stress [31]. Indeed studies show that separation or loss leads to increased trauma symptoms and anxiety in war-exposed youth [31–33]. Furthermore, studies from World War II suggest that these symptoms may persist into adulthood, especially for children separated from their caregivers at a very young age [34]. Finnish adults separated in early childhood from both parents during World War II had elevated levels of the stress hormones cortisol and plasma adrenocorticotropin (ACTH) and greater salivary cortisol reactivity in response to a social stress test compared to non-separated adults [35]. These results suggest that early childhood separation may alter an individual's stress physiology later in life. Separation and loss also make children particularly vulnerable to falling prey to those who seek to exploit their youth, strength, and innocence [36]. It may lead to trafficking, rape, abduction, crime, social violence, and recruitment by armed forces [37, 38]. Children may have to assume adult roles and take on dangerous tasks [38]. Displacement may result in unstable living conditions with limited access to education and healthcare [38]. Children may have to relocate without their caregivers and are often at the mercy of external sources to meet their basic needs during resettlement [39]. Forced displacement means loss of homeland, family, friends, and material possessions. Loss of loved ones may be accompanied by few opportunities to stay in touch with family members across geographic and political boundaries [39]. This may result in cultural bereavement, a loss of touch with the attributes of the homeland, which may lead to survivor guilt, anger, and ambivalence [40].

The violent nature of death during war places youth at heightened risk for development of traumatic grief. Traumatic grief is a severe form of bereavement in which the sudden, shocking nature of the loss (i.e., homicide, witnessing murder, suicide) prevents children from accomplishing the normal grieving process [41]. Thoughts and reminders of the traumatic nature of the death, the actual loss, or changes resulting from the death may trigger reminders that inhibit pleasant or comforting memories of the loved one. Behaviors such as avoidance may be used to manage distress, which interfere with adjustment to the death [41]. Traumatic grief has been linked to PTSD in war-exposed youth. Persistent fighting and displacement in Southern Darfur disrupted the normal tasks of grieving for youth and resulted in significant symptoms due to multiple losses and the sudden, traumatic nature of deaths [31]. Pfefferbaum found that youth who lost a friend in the Oklahoma City bombing had greater PTSD symptoms than those who lost an acquaintance, and those that lost an immediate family member had the greatest symptoms [42]. Similarly, grieving children of uniformed service personnel who died during the World Trade Center attacks experienced greater PTSD, anxiety, and depression [43].

Acute Versus Chronic Exposure

Garbarino and Kostelny differentiated between two types of war experiences: acute and chronic [44]. They suggest that although acute exposure has the potential to cause significant harm, it generally has limited effects on children and may result in naturally adaptive reactions of fear and anxiety [45]. Acute exposure results in minimal disruption to normal development and often only requires situational adjustment by the child [46, 47]. Children exposed to an acute war trauma are usually able to assimilate this event into their existing worldview by rationalizing that the event was an aberration and accident and that "things are back to normal" [46]. Youth with acute war trauma may experience symptoms such as specific fears; regressive behavior; loss and grief reactions; changed attitudes about the self, others, or the future; and reexperiencing of perceptual, affective, ideational, or somatic components of the trauma [47]. Impairments in academic performance, social functioning, and at times in daily living activities may occur; however individuals are expected to recover fully [48].

Chronic war exposure is likely to have more severe and enduring effects with major changes in personality and behavior [44]. The deviation from the normal trajectory of development occurs earlier and the chronic nature of the trauma inhibits the trajectory from returning to its normal course [47]. Repeated exposure may result in anger, despair, psychic numbing, massive denial, and indifference to emotional pain (self-anesthesia) [45, 47]. Ongoing threat heightens the risk for persistent PTSD and may result in negative conclusions about self-worth, reliability of adults, and safe ways to approach the world [46]. Furthermore, children forced to cope with chronic threat may start to misinterpret normal situations as dangerous ones leading to dysfunctional reactions. An example of this would be a child who responds hyperagressively on the playground when not picked for a game, which could lead to future rejection. Certain behaviors such as emotional withdrawal may be adaptive in the short term but could become a threat to the next generation when the child becomes a parent [46].

Indirect Exposure

Research suggests that even greater numbers of children are indirectly affected by war [49]. Youth may be indirectly exposed to war in numerous ways through hearing others talk about it or witnessing their reactions, knowing someone who participated or was directly impacted, hearing nearby bombing or gunshots, being under threat of attack, or experiencing abrupt displacement. In addition, greater media coverage, especially via television and the Internet, has extended

the reach of violence through its impact on children geographically distant from the epicenter of war [50]. Uncensored images of victims, violent acts, or family members searching for relatives serve to traumatize youth and may lead to increased psychological problems [51].

Studies on children indirectly exposed to war are sparse. In a study of youth geographically distant from the Oklahoma City bombing, media coverage contributed to increased symptoms with 20% of youth reporting impaired functioning 2 years later [52]. Smith and Mayer-Guse found that among youth in Michigan, watching news coverage of the war in Iraq predicted increased safety concerns [53]. Younger children were frightened by concrete, visual dangers, while older children were more frightened by abstract, verbally communicated threats. Furthermore, viewing explicit images of mutilation on television influenced the severity of symptoms in Kuwaiti children following the Gulf War [54]. Similarly, Duarte et al. found that intensive media use was associated with PTSD in children without direct or familial exposure to war [55].

It has been suggested that war not only affects indirectly exposed children just as much as directly exposed ones, but that the impact might actually be worse in some instances. A study of Israeli adults residing in a suburb of Jerusalem frequently exposed to terror compared to adults residing in a suburb indirectly exposed found no differences between the two groups on PTSD symptoms [56]. Israeli children residing in a town subject to terrorist acts slept longer and had fewer bad dreams compared to children residing in a town in central Israel that had never experienced terror [57]. In another study of Israeli youth exposed to missile attacks during the Gulf War, individuals in near-proximity showed greater distress; however, they also utilized more coping mechanisms than did the far-proximity group [58]. One possible explanation for these results is that the mere experience of living in a country with chronic war could lead to much anxiety. Another possibility is that indirectly exposed youth may have more difficulty deciding how they should cope with a situation that remains ambiguous to them. A third possibility is that indirectly exposed youth face uncertainty about the potential for danger. "Indirect exposure" may not be the proper term because despite being physically distant from the war, indirectly exposed youth might still experience it through the permeation of war-related reminders into their everyday lives. For example in Israel, regardless of where one lives, soldiers carrying guns are a common sight on the streets. This is a constant reminder to youth that army service is a given part of their future and this knowledge is usually accompanied by worry about where they will end up serving. These days, it is hard to escape information about a war raging in some locale as it enters our homes, schools, and communities. This may cause indirectly exposed youth to develop a constant anticipation of threat and worry about the possibility that something similar may happen to them. Thus, the phenomenon they may be experiencing is one of "direct exposure to imminent threat" rather than "indirect exposure."

Psychosocial Treatments

Treatments for war-exposed youth cover many different modalities. Some are aimed at prevention while others are curative. This section will focus on summarizing individual, school-based, and family treatments. A review of all available treatment interventions is beyond the scope of this chapter; however comprehensive reviews of interventions specifically for war-exposed youth have been conducted by Jordans et al. and Peltonen and Punamaki [59, 60]. In addition, Foa et al. provide a best-practice reference for treatment of PTSD in both youth and adults [61].

Individual

One of the most widely used treatments for traumatized youth is Trauma-Focused Cognitive Behavioral Therapy (TF-CBT). Adaptations of TF-CBT have been utilized for different populations. They all share components summarized by the acronym PRACTICE: psychoeducation, relaxation and coping skills, affective expression and modulation, cognitive processing, trauma narrative, in vivo exposure to trauma reminders, conjoint child-parent sessions, and enhancing safety and future development [62]. The Child and Adolescent Trauma Treatment and Services Project (CATS) examined two forms of TF-CBT in youth exposed to the September 11 attacks. Children with moderate to severe PTSD received TF-CBT, children with mild to moderate PTSD received only the PRAC components, and children with very mild symptoms received treatment as usual [63]. Due to the low number of individuals in the latter group, these were combined with the PRAC group for analyses. Results showed significant improvement with no differences between groups suggesting that matching treatment according to initial symptom severity is a feasible method for allocating care following mass disasters [63]. However, improvement in the group that received full TF-CBT was greater over 6 months. Cognitive and behavioral components are also utilized in Trauma Systems Therapy (TST) which was designed for use with a wide range of traumas including war exposure. TST focuses on the child's emotional dysregulation and environmental factors [64]. It has five phases of treatment: surviving, stabilizing, enduring, understanding, and transcending. TST has been shown to improve PTSD symptoms, social-environmental stability, and child functioning in youth exposed to different trauma types including war [64, 65].

Following the positive results of Narrative Exposure Therapy (NET) in treatment of adults with chronic trauma exposed to war, terror, and organized violence, a variation of the intervention, KIDNET, was adapted for use with children and adolescents [66]. KIDNET is a short-term, manual-based treatment that emphasizes the construction of a

detailed life narrative while the therapist assists the child in recalling and processing emotions, thoughts, physiological reactions, and behaviors related to traumatic experiences. Studies examining KIDNET for treatment of war-exposed youth and HIV/AIDS orphans found that it is efficacious in reducing PTSD symptoms and traumatic grief, as well as improving overall functioning [67].

School-Based

The Classroom-Based Intervention (CBI) is a group treatment that has two core objectives: (1) reduction of psychosocial problems and risk of maladaptation and (2) facilitation of resilience and empowerment through enhanced coping, prosocial behavior, and hope [68]. In samples of war-exposed Nepalese and Indonesian youth, CBI improved general symptoms and maintenance of hope; however traumatic stress was not reduced [69, 70]. In addition, treatment resulted in a reduction of general psychological difficulties (hyperactivity, peer, emotional, and conduct problems) and aggression for boys and increased prosocial behavior for girls suggesting that the efficacy of components of this intervention may be gender specific [69]. ERASE-Stress is another classroom-based intervention that covers the following topics: psychoeducation about stress, strengthening personal coping style, being in your body, knowing your feelings, controlling emotions with your mind, dealing with anger and rage, dealing with fears, coping with grief and loss, turning a crisis into an opportunity, boosting self-esteem, building a support system, and seeking a better future [71]. Each of the teacher-administered sessions are comprised of homework review, warm-up introduction, experiential exercise, psychoeducation, learned skill, and closing exercise with a new homework assignment. ERASE-Stress resulted in decreased PTSD, depression, somatic complaints, and functional problems in terror exposed Israeli and Sri-Lankan youth [71, 72]. Overshadowing the Threat of Terrorism (OTT) is a universal treatment that builds upon CBT by adding art therapy, body-oriented strategies, and narrative approaches [73]. The treatment also includes homework assignments to enlist family participation. Israeli students exposed to terrorism receiving teacher-administered OTT reported significant improvement on all measures of PTSD symptoms, somatic complaints, and generalized separation anxiety compared to healthy controls [73]. Layne et al. found that a three tier intervention consisting of classroom-based psychoeducation and coping skills, a manual-based trauma and grief-focused group intervention, and referral of youth at risk of harm to community-based mental health services reduced PTSD symptoms in Bosnian children exposed to war [74]. More recently, Wolmer, Hamiel, and Laor examined a teacher-based resilience-focused intervention for Israeli children exposed to the Second Lebanon War [75]. The treatment consists of manualized didactic modules that cover working through positive and negative experiences, stress management and control of bodily tension, affective regulation and processing, attention control, identification and correction of negative thoughts, and use of humor as well as other coping and social-emotional competencies [76]. Compared to healthy controls, symptoms of PTSD were significantly reduced in war-exposed youth [76].

Family Therapy

Following a trauma, the availability of support is crucial to recovery; thus family involvement in therapy is essential [77]. Family functioning impacts the development and manifestation of PTSD in youth. Aims of family therapy include improving communication among family members, increasing understanding of the trauma and subsequent symptoms, and co-constructing healthy coping strategies. Studies on family therapy in war-exposed individuals have focused primarily on combat veterans. Only one study was found related to youth. Dybdahl examined a psychosocial intervention for Bosnian mothers and their young children [78]. The intervention consisted of group meetings and semi-structured discussions led by preschool teachers combined with home visits focused on psychoeducation about trauma reactions, strengthening of coping strategies, promotion of sensitive emotional-expressive communication, stimulating interaction, and reactivation of indigenous child-rearing practices. The intervention resulted in children's increased cognitive performance and reduction in psychological problems as well as in reduction of mothers' trauma symptoms and increases in life satisfaction and perceived social support [78].

Treatment of Sleep Disturbances in Traumatized Youth

While none of the abovementioned psychosocial treatments target sleep problems directly in youth with PTSD, it has traditionally been thought that treating the PTSD would also result in improvement in sleep problems. However, this may not be the case, and sleep-specific interventions may be necessary. Much research has been done on treatment of sleep disturbances in adults with PTSD, and a review of these interventions is provided by Schoenfeld et al. [79]. However, there have been very few adaptations of these interventions for youth. Image rehearsal therapy (IRT), successfully used in adults with PTSD to treat nightmares, has been modified for use with adolescents [80]. The treatment was conducted in a 6-h workshop involving three steps: (1) selection of a night-

mare, (2) "change the nightmare anyway you wish," and (3) rehearse the images of the changed dream 5–20 min each day. Participants in the intervention experienced 20 nightmares per month with a frequency of one nightmare every other night. Three months following the intervention, nightmare frequency reduced by 57% measured in nights per month and 71% measured in nightmares per month [80]. However, overall sleep complaints and PTSD symptoms did not improve. Cognitive-behavioral therapies have also been found to be effective in treatment of sleep disturbances in traumatized youth. Davis et al. piloted a modified exposure, relaxation, and rescripting therapy (ERRT) in an adolescent rape victim [81]. ERRT emphasizes exposure while adding relaxation strategies, sleep habit identification and modification, and reframing of cognitive distortions. Treatment resulted in reduction of trauma-related nightmares, sleep problems, anxiety, depression, and PTSD [81]. More recently two case studies of ERRT in youth found improvement in nightmare and sleep disturbance frequencies [82]. While typically psychosocial treatments are the first line of intervention for PTSD and associated symptoms, some research has found effectiveness for psychotropic medications including prazosin, clonidine, and guanfacine in individual cases of traumatized youth with moderate improvement in sleep, mainly reduction in nightmares, which was assessed subjectively [83, 84].

Treatment Challenges

Treatment of war-exposed youth presents many unique challenges. Interventions often take place in insecure settings that have limited access to resources and few trained mental health professionals to deliver services [68]. Most wars happen in low-income regions and require a variety of humanitarian aid beyond psychological interventions resulting in very low provision of mental health services despite overwhelming demand [85]. Given the economic constraints and lack of accessibility in war torn regions, there is a need for population-oriented outreach models for psychosocial rehabilitation and treatment that may be administered by local leaders lacking extensive mental health training [85, 86]. In this respect, schools may become ideal settings for treatment of war-exposed youth. Youth's routine attendance at school increases compliance rates and may address survivors' reluctance to seek help [87]. The familiar teacher-student relationship facilitates immediate feedback and follow-up [87]. The school-based studies described above demonstrate training feasibility for school personnel for effective treatment delivery. Furthermore, school interventions are more accessible, affordable, and non-stigmatizing, enabling populations of diverse socioeconomic and ethnic backgrounds to be reached that otherwise might not receive services [74].

Frequently, nonevidence-based interventions are employed for war-exposed youth as a quick fix given their pressing needs [70]. There is a scarcity of formulated therapeutic interventions and treatment efficacy research [88]. Thus, more rigorous treatment outcome studies are needed that consider both risk and resilience factors. Furthermore, the majority of war trauma is not a single event, but rather children are chronically forced to confront violence. As a result, there does not seem to be a "post"-trauma period, and instead trauma becomes a central condition and ongoing stressor in their lives [89]. This constant exposure necessitates interventions that enhance children's capacity for stress tolerance and help them cope with their everyday reality. Another challenge to treatment of war-affected youth is that existing services are not always adapted to the traditions of the native culture nor are they available in the native language [90]. Development of treatment interventions should strive to have proper cultural adaptations. Finally, traditional models of psychiatric services are insufficient as they target a narrow range of symptoms rather than encompassing all the areas of need that war-exposed youth may be experiencing [90]. War-exposed youth deal with a wide range of problems such as displacement and relocation, grief/loss reactions, unstable environment, disrupted community, change in family dynamics, financial struggle, physical injuries or health concerns, and educational difficulties. In view of the complex nature of the sequelae of war trauma, treatments that focus only on the individual seem too narrow and insufficient; hence new approaches that consider supporting systems may need to be added to an effective treatment plan. Therefore, effective approaches should incorporate comprehensive treatment models as the one discussed below.

Ecological Framework for Treatment

There is growing support for use of an ecological perspective in treatment of war-exposed youth [91–94]. War impacts children at multiple levels of individual and societal functioning with each level capturing a different element of the effects of exposure [95]. Child development is influenced by many interlocking systems comprised of individual, family, community, and cultural environments. In order to fully comprehend the effects of war on a child, one has to examine and target each of these systems.

Bronfenbrenner conceptualized an ecological framework toward a more comprehensive understanding of the effects of social environments on youth [96, 97]. This framework consists of several nested levels of differing degrees of proximity to the child's functioning. These levels influence child outcomes both independently and through interaction with each other and may serve as either

risk or protective factors. At the bottom of the model is the ontogenic level. This level considers individual characteristics such as age, gender, and temperament [98]. The next level is the microsystem representing the direct environmental experiences of the child. Within this level, the family is considered to be the primary context [91, 99]. Parenting styles may moderate and mediate the relationship between war exposure and child psychosocial outcomes [91]. Family stressors such as economic hardship, loss, parental mental health, and ability of the family to provide support have an important role in children's adjustment [98]. The third level is the exosystem which examines community influences on the child such as neighborhoods, peers, social support networks, and schools [96, 97]. Finally, the macrosystem represents societal beliefs and values including public policy, economies, modes of production, and government and political functioning [95, 100]. Elbedour suggested a fifth level for war-exposed youth consisting of the intensity, duration, and suddenness of conflict [94].

Several studies have applied the ecological model to war-exposed youth. Among former child soldiers in Nepal, individual factors that impacted PTSD development included exposure to torture and abduction as well as lack of education; at the microsystem level, living in extended families, lower caste status, and physical abuse in the household predicted poor outcomes; and at the exosystem level, living in a high caste community predicted lack of reintegration support [100]. Betancourt utilized an ecological framework to study the experience of displacement and implementation of an emergency education program for Chechen adolescents [98]. She found that the education program played an important role in the social ecology of the relocation settlements by offering the adolescents a place to go and engage in age-appropriate activities, enabling development of new friendships and social support, reducing idleness, and renewing a sense of hope [98]. In addition, Cummings et al. found support for a social-ecological model of the association between political violence in Northern Ireland and child outcomes [95, 101]. Sectarian community violence was related to increased marital conflict and children's reduced security about multiple aspects of their environment including the family, parent-child relations, and community [95, 101]. In addition, emotional security and adjustment problems were more negatively affected in single-parent families [101]. The results from these studies highlight the importance of employing a multi-tiered approach to treatment of war-exposed youth that not only assesses individual needs but also identifies needs and available support in family, community, and institutional systems and encourages these systems to collaborate together to foster the child's well-being.

Conclusion

Youth are most vulnerable to the physical and psychological effects of war. The outcomes of war depend on the child's developmental level, degree of exposure, and proximity to war-related events. War-exposed youth are at significantly greater risk for development of PTSD; however many challenges still remain in the assessment and treatment of this population. Experiences of separation and loss are common and ought to be incorporated into the assessment for PTSD as grief reactions may augment trauma symptoms. In addition, further research is needed to determine the impact of indirect exposure and to develop preventative methods for increasing the stress threshold and coping capabilities of children indirectly exposed to war. School-based group treatments are currently the most widely used interventions for war-exposed youth. Schools appear to be viable places for intervention because teachers and other nonmental health professionals can be trained to administer effective treatment, large populations of children can be reached, and the setting is familiar, thus normalizing the experience. However, future studies should focus on clarifying what types of interventions are most effective for whom, how to best deliver these interventions, and how they may be adapted to different cultures. PTSD affects and is affected by all the environments with which the child interacts. Therefore, targeting individual symptoms alone is not enough. Instead an ecological approach to treatment of PTSD for war-exposed youth should be adopted that addresses the needs of all the different systems influencing the child.

References

1. United Nations Children's Fund (UNICEF). The state of the world's children. www.unicef.org. Accessed 1 Dec 2011.
2. Alkhatib A, Regan J, Barrett D. The silent victims: effects of war and terrorism on child development. Psychiatr Ann. 2007;37:586–9.
3. Williams R. The psychosocial consequences for children of mass violence, terrorism, and disasters. Int Rev Psychiatr. 2007;19:263–77.
4. Murthy RS, Lakshminarayana R. Mental health consequences of war: a brief review of research findings. World Psychiatry: Off J World Psychiatr Assoc. 2006;5:25–30.
5. Attanayake V, McKay R, Joffres M, et al. Prevalence of mental disorders among children exposed to war: a systemic review of 7,920 children. Med Confl Surviv. 2009;25:4–19.
6. Goldstein RD, Wampler NS, Wise PH. War experiences and distress symptoms of Bosnian children. Pediatrics. 1997;100:873–8.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington/Washington DC: American Psychiatric Association; 2013.
8. Thabet AA, Karim K, Vostanis P. Trauma exposure in pre-school children in a war zone. Br J Psychiatry. 2006;188:154–8.

9. Feldman R, Vengrober A. Posttraumatic stress disorder in infants and young children exposed to war-related trauma. J Am Acad Child Adolesc Psychiatry. 2011;50:645–58.
10. Rosenthal MK, Levy-Shiff R. Threat of missile attacks in the Gulf War: mothers' perceptions of young children's reactions. Am J Orthop. 1993;63:241–54.
11. Levy-Shiff R, Hoffman MA, Rosenthal MK. Innocent bystanders: young children in war. Infant Ment Health J. 1993;14:116–30.
12. Murray JS. Helping children cope with separation during war. J Spec Pediatr Nurs. 2002;7:127–30.
13. Sadeh A, Hen-Gal S, Tikotzky L. Young children's reactions to war-related stress: a survey and assessment of an innovative intervention. Pediatrics. 2008;121:46–53.
14. Yurtbay T, Alyanak B, Abali O, Kaynak N, Durukan M. The psychological effects of forced emigration on Muslim Albanian children and adolescents. Community Ment Health J. 2003;39:203–12.
15. Llabre MM, Hadi F. Health-related aspects of the Gulf crisis experience of Kuwaiti boys and girls. Anxiety Stress Coping. 1994;7:217–28.
16. Elbert T, Schauer M, Schauer E, et al. Trauma-related impairment in children-a survey in Sri Lankan provinces affected by armed conflict. Child Abuse Negl. 2009;33:238–46.
17. Husain SA, Allwood MA, Bell DJ. The relationship between PTSD symptoms and attention problems in children exposed to the Bosnian war. J Emot Behav Disord. 2008;16:52–62.
18. Thabet AA, Vostanis P. Posttraumatic stress disorder reactions in children of war: a longitudinal study. Child Abuse Negl. 2000;24:291–8.
19. Amone-P'Olak K. Mental states of adolescents exposed to war in Uganda: finding appropriate methods of rehabilitation. Torture. 2006;16:93–107.
20. Hasanovic M, Haracic E, Ahmetspahic S, Kurtovic S, Haracic H. The psychological disturbances of war-traumatized adolescents in rural and urban areas of Bosnia and Herzegovina and correlation with poverty and hopelessness. Int J Child Adolesc Health. 2009;2:89–97.
21. Rostami R, Babapour-Kheiroddin J, Shalch B, Badinloo F, Hamzavi-Abedi F. Emotional and behavioral problems of Afghan refugees and war-zone adolescents. Iran J Psychiatry. 2009;4:36–40.
22. Chemtob CM, Nomura Y, Josephson L, Adams RE, Sederer L. Substance use and functional impairment among adolescents directly exposed to the 2001 World Trade Center attacks. Disasters. 2009;33:337–52.
23. Pat-Horenczyk R, Peled O, Miron T, et al. Risk-taking behaviors among Israeli adolescents exposed to recurrent terrorism: provoking danger under continuous threat? Am J Psychiatr. 2007;164:66–72.
24. Brown TH, Mellman TA, Alfano CA, Weems CF. Sleep fears, sleep disturbance, and PTSD symptoms in minority youth exposed to Hurricane Katrina. J Trauma Stress. 2011;24:575–80.
25. Kovachy B, O'Hara R, Hawkins N, et al. Sleep disturbance in pediatric PTSD: current findings and future directions. J Clin Sleep Med. 2013;9:501–10.
26. Llabre MM, Hadi F. War-related exposure and psychological distress as predictors of health and sleep: a longitudinal study of Kuwaiti children. Psychosom Med. 2009;71:776–83.
27. Thabet AA, Abed Y, Vostanis P. Comorbidity of PTSD and depression among refugee children during war conflict. J Child Psychol Psychiatry. 2004;45:533–42.
28. Montgomery E, Foldspang A. Traumatic experience and sleep disturbance in refugee children from the Middle East. Eur J Pub Health. 2001;11:18–22.
29. Chemtob CM, Nomura Y, Abramovitz RA. Impact of conjoined exposure to the world trade center attacks and to other traumatic events on the behavioral problems of preschool children. Arch Pediatr Adolesc Med. 2008;162:126–33.
30. Taylor LK, Weems CF, Costa NM, Carrion VG. Loss and the experience of emotional distress in childhood. J Loss Trauma. 2009;14:1–16.
31. Morgos D, Worden JW, Gupta L. Psychosocial effects of war experiences among displaced children in Southern Darfur. Omega (Westport). 2008;56:229–53.
32. Kuterovac-Jagodic G. Posttraumatic stress symptoms in Croatian children exposed to war: a prospective study. J Clin Psychol. 2003;59:9–25.
33. El Zein HL, Ammar DF. Assessing Lebanese children's reactions to war-related stress. J Loss Trauma. 2011;16:195–204.
34. Rusby JSM, Tasker F. Long-term effects of the British evacuation of children during World War 2 on their adult mental health. Aging Ment Health. 2009;13:391–404.
35. Pesonen AK, Raikkonen K, Feldt K, et al. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. Psychoneuroendocrinology. 2010;35:758–67.
36. Betancourt TS, Khan KT. The mental health of children affected by armed conflict: protective processes and pathways to resilience. Int Rev Psychiatry. 2008;20:317–28.
37. Mels C, Derluyn I, Broekaert E, Rosseel Y. The psychological impact of forced displacement and related risk factors on Eastern Congolese adolescents affected by war. J Child Psychol Psychiatry. 2010;51:1096–104.
38. United Nations Children's Fund (UNICEF) Office of Emergency Programmes. UNICEF and displacement: a guidance note. 2004;www.unicef.org. Retrieved 13 Dec 2011.
39. Papadopoulos RK. Refugee families: issues of systemic supervision. J Fam Therapy. 2001;23:405–22.
40. Eisenbruch M. From post-traumatic stress disorder to cultural bereavement: diagnosis of southeast Asian refugees. Soc Sci Med. 1991;33:673–80.
41. Cohen JA, Mannarino AP. Treatment of childhood traumatic grief. J Clin Child Adolesc Psychol. 2004;33:819–31.
42. Pfefferbaum B, Gurwitch RH, McDonald NB, et al. Posttraumatic stress among young children after the death of a friend or acquaintance in a terrorist bombing. Psychiatr Serv. 2000;51:386–8.
43. Brown EJ, Goodman RF. Childhood traumatic grief: an exploration of the construct in children bereaved on September 11. J Clin Child Adolesc Psychol. 2005;34:248–59.
44. Garbarino J, Kostelny K. The effects of political violence on Palestinian children's behavior problems: a risk accumulation model. Child Dev. 1996;67:33–45.
45. Garbarino J, Kostelny K. Children's response to war: what do we know? In: Leavitt LA, Fox NA, editors. The psychological effects of war and violence in children. Hillsdale: Lawrence Erlbaum Associates Inc; 1993. p. 23–39.
46. Garbarino J, Kostelny K, Dubrow N. What children can tell us about living in danger. Am Psychol. 1991;46:376–83.
47. Terr LC. Childhood traumas: an outline and overview. Am J Psychiatr. 1991;148:10–20.
48. McDermott BM. Child and youth emotional trauma: an explanatory model of adverse outcomes. Psychiatry Psychol Law. 2004;11:269–79.
49. Ladd GW, Cairns E. Children: ethnic and political violence. Child Dev. 1996;67:14–8.
50. Wexler ID, Branski D, Kerem E. War and children. JAMA. 2006;5:579–81.
51. Fremont WP, Pataki C, Beresin EV. The impact of terrorism on children and adolescents: terror in the skies, terror on television. Child Adolesc Psychiatr Clin N Am. 2005;14:429–51.
52. Pfefferbaum B, Seal TW. Posttraumatic stress two years after the Oklahoma City bombing in youths geographically distant from the explosion. Psychiatry: Interpersonal Biol Process. 2000;63:358–70.

53. Smith SL, Moyer-Guse E. Children and the war on Iraq: developmental differences in fear responses to television news coverage. Media Psychol. 2006;8:213–37.
54. Nader KO, Pynoos RS, Fairbanks LA, al-Ajeel M, al-Asfour A. A preliminary study of PTSD and grief among the children of Kuwait following the Gulf crisis. Br J Clin Psychol. 1993;32:407–16.
55. Duarte CS, Wu P, Cheung A, et al. Media use by children and adolescents from New York City 6 months after the WTC attack. J Trauma Stress. 2011;24:553–6.
56. Shalev AY, Tuval R, Frenkiel-Fishman S, Hadar H, Eth S. Psychological responses to continuous terror: a study of two communities in Israel. Am J Psychiatry. 2006;163:667–73.
57. Rofe Y, Lewin I. The effect of war environment on dreams and sleep habits. Clin Comm Psychol. 1982;8:67–79.
58. Bat-Zion N, Levy-Shiff R. Children in war: stress and coping reactions under the threat of scud missile attacks and the effect of proximity. In: Leavitt LA, Fox NA, editors. The psychological effects of war and violence in children. Hillsdale: Lawrence Erlbaum Associates; 1993. p. 143–61.
59. Jordans MJD, Tol WA, Komproe IH, de Jong JVTM. Systematic review of evidence and treatment approaches: psychosocial and mental health care for children in war. Child Adolesc Mental Health. 2009;14:2–14.
60. Peltonen K, Punamaki RL. Preventive interventions among children exposed to armed conflict: a literature review. Aggress Behav. 2010;36:95–116.
61. Foa EB, Keane TM, Friedman MJ, Cohen JA. Effective treatments for PTSD: practice guidelines from the international society for traumatic stress studies. New York: Guilford Publications; 2009.
62. Cohen JA, Mannarino AP. Trauma-focused cognitive behavioural therapy for children and parents. Child Adolesc Mental Health. 2008;13:158–62.
63. Hoagwood K, CATS Consortium. Implementing CBT for traumatized children and adolescents after September 11: lessons learned from the Child and Adolescent Trauma Treatment Services (CATS) Project. J Child Adolesc Clin Psychol. 2007;36:581–92.
64. Saxe GN, Ellis BH, Fogler J, Hansen S, Sorkin B. Comprehensive care for traumatized children. Psychiatr Ann. 2005;35:443–8.
65. Ellis BH, Fogler J, Hansen S, et al. Trauma systems therapy: 15-month outcomes and the importance of effecting environmental change. Psychol Trauma: Theory Res Pract Policy. 2011; advance publication.
66. Neuner F, Catani C, Ruf M, et al. Narrative exposure therapy for the treatment of traumatized children and adolescents (KidNET): from neurocognitive theory to field intervention. Child Adolesc Psychiatr Clin N Amer. 2008;17:641–64.
67. Robjant K, Fazel M. The emerging evidence for narrative exposure therapy: a review. Clin Psychol Rev. 2010;30:1030–9.
68. Macy RD, Macy DJ, Gross SI, Brighton P. Healing in familiar settings: support for children and youth in the classroom and community. New Dir Youth Dev. 2003;98:51–79.
69. Jordans MJD, Komproe IH, Tol WA, et al. Evaluation of a classroom-based psychosocial intervention in conflict-affected Nepal: a cluster randomized controlled trial. J Child Psychol Psychiatry. 2010;51:818–26.
70. Tol WA, Komproe IH, Susanty D, et al. School-based mental health intervention for children affected by political violence in Indonesia. JAMA. 2008;300:655–62.
71. Gelkopf M, Berger R. A school-based, teacher-mediated prevention program (ERASE-stress) for reducing terror-related traumatic reactions in Israeli youth: a quasi-randomized controlled trial. J Child Psychol Psychiatry. 2009;50:962–71.
72. Berger R, Gelkopf M. School-based intervention for the treatment of tsunami-related distress in children: a quasi-randomized controlled trial. Psychother Psychosom. 2009;78:364–71.
73. Berger R, Pat-Horenczyk R, Gelkopf M. School-based intervention for prevention and treatment of elementary-students' terror-related distress in Israel: a quasi-randomized controlled trial. J Trauma Stress. 2007;20:541–51.
74. Layne CM, Saltzman WR, Poppleton L, et al. Effectiveness of a school-based group psychotherapy program for war-exposed adolescents: a randomized controlled trial. J Amer Acad Child Adolesc Psychiatr. 2008;47:1048–62.
75. Wolmer L, Hamiel D, Laor N. Preventing children's posttraumatic stress after disaster with teacher-based intervention: a controlled study. J Amer Acad Child Adolesc Psychiatr. 2011;50:340–8.
76. Wolmer L, Hamiel D, Barchas JD, Slone M, Laor N. Teacher-delivered resilience-focused intervention in schools with traumatized children following the second Lebanon War. J Trauma Stress. 2011;24:309–16.
77. Bernardon S, Pernice-Duca F. A family systems perspective to recovery from posttraumatic stress in children. Fam J. 2010;18:349–57.
78. Dybdahl R. Children and mothers in war: an outcome study of a psychosocial intervention program. Child Dev. 2001;72:1214–30.
79. Schoenfeld FB, DeViva JC, Manber R. Treatment of sleep disturbances in posttraumatic stress disorder: a review. J Rehabil Res Dev. 2012;49:729–52.
80. Krakow B, Sandoval D, Schrader R. Treatment of chronic nightmares in adjudicated adolescent girls in a residential facility. J Adolesc Health. 2001;29:94–100.
81. Davis JL, de Arellano M, Falsetti SA, Resnick HS. Treatment of nightmares related to post-traumatic stress disorder in an adolescent rape victim. Clin Case Stud. 2003;4:283–94.
82. Fernandez S, De Marni CL, Borntrager C, et al. A case series: cognitive-behavioral treatment (exposures, relaxation, and rescripting therapy) of trauma-related nightmares experienced by children. Clin Case Stud. 2013;12:39–59.
83. Strawn JR, Keeshin BR. Successful treatment of posttraumatic stress disorder with prazosin in a young child. Ann Pharmacoter. 2011;45:1590–1.
84. Horrigan JP. Guanfacine for PTSD nightmares. J Amer Acad Child Adolesc Psychiatry. 1996;35:975–6.
85. Catani C, Jacob N, Schauer E, Kohila M, Neuner F. Family violence, war, and natural disasters: a study of the effect of extreme stress on children's mental health in Sri Lanka. BMC Psychiatr. 2008;8:1–10.
86. Kos AM, Derviskadic-Jovanovic S. What can we do to support children who have been through war? Forced Migr Rev. 1998;3:4–7.
87. Wolmer L, Laor N, Yazgan Y. School reactivation programs after disaster: could teachers serve as clinical mediators? Child Adolesc Psychiatr Clin N Amer. 2003;12:363–81.
88. Morris J, van Ommeren M, Belfer M, Saxena S, Saraceno B. Children and the sphere standard on mental and social aspects of health. Disasters. 2007;31:71–90.
89. Berman H. Children and war: current understandings and future directions. Public Health Nurs. 2001;18:243–52.
90. National Child Traumatic Stress Network Refugee Trauma Task Force. Mental health interventions for refugee children in resettlement: white paper II. www.NCTSNet.org. Accessed 5 Dec 2011.
91. Dubow EF, Huesmann LR, Boxer P. A social-cognitive-ecological framework for understanding the impact of exposure to persistent ethnic-political violence on children's psychosocial adjustment. Clin Child Fam Psychol Rev. 2009;12:113–26.
92. Boothby N. Political violence and development: an ecologic approach to children in war zones. Child Adolesc Psych Clin N Amer. 2008;17:497–514.
93. Joshi PT, O'Donnell DA. Consequences of child exposure to war and terrorism. Clin Child Fam Psychol Rev. 2003;6:275–92.
94. Elbedour S, ten Bensel R, Bastien DT. Ecological integrated model of children in war: individual and social psychology. Child Abuse Negl. 1993;17:805–19.

95. Cummings EM, Goeke-Morey MC, Schermerhorn AC, Merrilees CE, Cairns E. Children and political violence from a social ecological perspective: implications from research on children and families in Northern Ireland. Clin Child Fam Psychol Rev. 2009;12:16–38.
96. Bronfenbrenner U. The ecology of human development. Experiments by nature and design. Cambridge, MA: Harvard University Press; 1979.
97. Bronfenbrenner U. Ecology of the family as a context for human development: research perspectives. Dev Psychol. 1986;22:732–42.
98. Betancourt TS. Stressors, supports and the social ecology of displacement: psychosocial dimensions of an emergency education program for Chechen adolescents displaced in Ingushetia, Russia. Cult Med Psychiatry. 2005;29:309–40.
99. Belsky J. Child maltreatment. An ecological integration. Am Psychol. 1980;35:320–35.
100. Kohrt BA, Jordans MJD, Tol WA, et al. Social ecology of child soldiers: child, family, and community determinants of mental health, psychosocial well-being, and reintegration in Nepal. Transcult Psychiatry. 2010;47:727–53.
101. Cummings EM, Schermerhorn AC, Merrilees CE, et al. Political violence and child adjustment in Northern Ireland: testing pathways in a social-ecological model including single- and two-parent families. Dev Psychol. 2010;46:827–41.

Predicting Sleep Quality and Duration in Adulthood from War-Related Exposure and Posttraumatic Stress in Childhood

32

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Wars are potentially traumatic events for children, who may be exposed to numerous stressors during war, including witnessing and experiencing violence [1]. Exposure to war stressors has been linked to a variety of symptoms in children, such as posttraumatic stress (PTS) symptoms [2, 3], health problems [4], and somatic symptoms [5]. Sleep problems are among the most commonly reported symptoms of children exposed to war traumas. For example, in a study of refugee children (ages 9–15) living in the Gaza Strip during armed conflict, 52% of children reported sleep problems [6]. Another study of Israeli youth (ages 14–24) found that 58% reported sleep problems in the first week of the Gulf War [7]. Studies connecting exposure to war trauma and sleep problems have primarily focused on the time period during or immediately following war. Longer-term studies examining war exposure in childhood and sleep are needed in order to understand whether war exposure in childhood predicts longer-term sleep problems [1] or whether war exposure in childhood results in transient sleep problems that will resolve. This review, which includes a data-driven example, addresses this gap in the literature.

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Despite the dearth of long-term follow-up studies examining this question, childhood exposure to war trauma is likely to predict sleep problems in young adulthood. Exposure to other types of traumatic events (e.g., natural disasters, abuse) predicts later sleep difficulties. For example, in a study conducted 24 and 30 months after Hurricane Katrina, general sleep disturbance was reported by 46% and 50% of children (ages 8–15), respectively [8]. In addition, Glod and colleagues [9] reported that abuse that occurred an average of 3.3 years prior to the study was significantly related to difficulties falling and staying asleep among abused children (ages 6–12 years). Zhang, Zhu, Du, and Zhang also found evidence of trouble sleeping in a sample of Chinese children and adolescents both 3 and 6 months after surviving a 7.0-magnitude earthquake [10].

War trauma is also likely to predict sleep problems in young adulthood as long-term sleep difficulties after exposure to war trauma are well documented among *adults*. Among adults exposed to war trauma, documented sleep difficulties include insomnia, difficulty maintaining sleep, nightmares, and anxiety dreams [11, 12]. As an additional illustration, a study of service members and veterans deployed in either Operation Enduring Freedom or Operation Iraqi Freedom observed sleep disturbances as well as difficulty breathing, experiencing pain, and feeling too hot or too cold [13].

To our knowledge, only two research studies to date have focused on how exposure to traumatic events *in childhood* relates to adult sleep outcomes. In the first study, avalanche survivors in Iceland were more likely to suffer from sleep disturbances (i.e., clinically significant sleep problems, poor sleep quality, moderate/severe sleep disturbance, and sleep paralysis) compared to controls 10 years after exposure to the trauma. While this study was conducted on participants 18 years and older, the avalanches occurred 16 years prior to data collection, meaning a subsample of the participants were children or adolescents at the time of the avalanches. This subgroup was not analyzed separately to determine if the prevalence of sleep disturbances differed between

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survivors that experienced the avalanche during adolescence compared to adulthood [14]. In the second study, Swanson, Hamilton, and Muzik examined the relationship between sleep disturbances and PTS symptoms in a sample of postpartum women who had experienced a traumatic event (e.g., neglect, physical abuse, physical abuse with sexual abuse) during childhood. As adults, even after adjusting for symptoms of depression, difficulties staying asleep were significantly associated with PTS symptoms. Even women who had recovered from their PTS symptoms were much more likely to experience trouble falling and staying asleep compared to women who had never experienced PTS symptoms [15]. These results lend support for the hypothesis that experiencing a trauma in childhood may put young adults at increased risk of sleep disturbances.

Although emerging evidence indicates that childhood traumatic event exposure is linked with long-term sleep problems, it is not clear what mechanisms may drive this relationship. PTS symptoms may be one potential mechanism in this relationship. It is well documented that exposure to war trauma is significantly associated with PTS symptoms and PTSD in children [2, 16]. PTS symptoms are associated with sleep difficulties, which are a component feature of the PTSD diagnosis. In the DSM-5 criteria for PTSD, nightmares may be an indicator of the intrusion cluster, and trouble falling and staying asleep may be an indicator of the alterations in arousal and reactivity cluster [17].

To date, limited research has examined associations between PTS symptoms and sleep problems among children [18, 19]. However, initial evidence suggests that they may be linked. For example, in a sample of adolescent earthquake survivors, not only did PTSD symptom severity predict sleep disturbances, each PTSD symptom cluster significantly predicted sleep difficulties [20].

Significantly more research has been conducted to understand whether PTS symptoms and sleep are related in adult populations [21, 22]. For example, in a study of war veterans, veterans reported more repetitive nightmares and sleep disruption than patients in general [22]. Associations between PTS symptoms and sleep were also observed among veterans seeking treatment for PTSD. In comparison with primary insomnia patients without PTSD, veterans exhibited more insomnia symptoms, worse sleep efficiency, greater variability on subjective and objective sleep measures, and greater night-to-night variability in sleep time and sleep efficiency [23].

Clearly, there is a complex relationship between PTS symptoms and sleep disturbances. Longitudinal studies may help to clarify this relationship. For example, it is not clear whether PTSD symptoms predict sleep difficulties or whether sleep difficulties predict PTSD symptoms in children and adolescents. Some evidence indicates that PTSD symptoms may precede sleep difficulties. Wittmann et al. found sleep onset and maintenance problems 6 months after experiencing a road traffic accident were significantly predicted by PTS severity 2 months postaccident in children ranging in age from 7 to 16 years old [24]. In contrast, Brown et al. found sleep disturbances 24 months after Hurricane Katrina were a significant predictor of PTS symptom severity 30 months after Katrina [8]. Zhang et al. found a similar pattern. Endorsing sleep difficulties at 3 months post-earthquake significantly predicted PTSD symptoms 6 months post-earthquake [10].

Unlike the literature focusing on youth, there is more consistency in findings among studies of adults that examine the longitudinal relationship between PTSD symptoms and sleep disturbances. Chipman et al. found sleep disturbances significantly predicted PTSD-related impairment, even at subthreshold levels of PTSD [25]. Wright et al. studied the relationship between insomnia and psychological symptoms of PTSD and depression in a sample of combat veterans from both directions. They found insomnia was a much stronger predictor of later psychological symptoms than psychological symptoms were of insomnia [26].

It is important to better understand sleep problems among young adults exposed to war traumas in childhood because sleep is strongly linked to health and well-being. Sleep problems predict a variety of maladaptive outcomes, including alcohol use, physical symptoms, decreased immune functioning, and psychopathology [11, 27, 28]. Further, it may be particularly important to distinguish between difficulties with sleep quality and sleep quantity, as health and well-being outcomes have been found to relate more strongly to the quality of sleep than the quantity of sleep among young adults [29].

A Data-Driven Example

To illustrate some of these issues, this chapter includes a sample analysis of a study of Kuwaiti preadolescents (ages 9–12) exposed to the Gulf War in childhood. These preadolescents were followed into young adulthood (ages 19–23). As the Gulf War was limited in duration (1990–1991), preadolescent exposure to the war was time limited, and damage to Kuwaiti infrastructure was minimal. Thus, the Gulf War provides a unique opportunity to understand how a clearly defined period of war exposure relates to sleep problems without the confounding effects attributable to a prolonged recovery period. This study is one of the few long-term, longitudinal datasets following children exposed to war into adulthood. Examination of this data for this chapter had two main objectives: to examine exposure to war trauma in childhood as a predictor of sleep problems in young adulthood and to examine PTS symptoms as a mediator of this relationship. Findings have important implications for interventions

with youth exposed to war. Data reported here represent a subset of data previously used [1] to test a broader model of the effects of exposure to war trauma on health outcomes.

This data-driven example uses data from 151 Kuwaiti children (ages 9–12) who participated in a study examining exposure to war-related trauma and psychological distress resulting from the Iraqi occupation of Kuwait and the Gulf War. The initial assessment occurred in 1993, 2 years after the end of this conflict. Participants were recruited through government-sponsored organizations and the school system. There were four recruitment sources: the Martyr's Office (source 1), the National Committee for Missing and Prisoners of War (source 2), the Association for Defending War Victims (source 3), and local schools (source 4). These recruitment sources were used to identify children with varying exposure to war-related trauma, as a result of the experiences of their fathers. Each of these four sources provided a list of names, from which 20 boys and 20 girls were randomly sampled. Nine families did not participate. The final sample included 20 boys and 20 girls whose fathers had been killed (source 1), 19 boys and 20 girls whose fathers were missing at the time of the first assessment (source 2), 15 boys and 17 girls whose fathers had been arrested but later returned home (source 3), and 20 boys and 20 girls whose fathers and family members were neither killed, missing, nor arrested (source 4).

During the initial assessment, families were contacted by phone and informed about the study. Interested families provided informed consent to contact their children through their schools. Testing was done by a psychologist at the school. Measures assessing war-related exposure and PTS symptoms were administered in a fixed order by interview in Arabic. Full procedures are detailed in a previous paper [1].

Children's level of exposure to trauma and violence during the Gulf crisis was assessed with the crisis structured interview (CSI) [4], a 16-item (rated yes or no) measure that assesses children's own experiences, that of their parents, brothers or sisters, other relatives, and friends and acquaintances (e.g., "Was your father killed by the Iraqis?"). Participants also reported whether they witnessed violence in real life, on television, or through pictures. Responses were summed to yield a total score that included both witnessing and victimization; higher scores reflect high levels of exposure to war-related trauma.

Participants completed a translated version of the Posttraumatic Stress Disorder Symptom Scale (PTSDS), a measure adapted from the Davidson Self-Rating Post Traumatic Stress Disorder Scale [30]. The PTSDS is a 17-item measure assessing three major symptom categories (i.e., reexperiencing, avoidance, and increased general arousal) for the diagnosis of PTSD, developed based upon criteria from the DSM-III-R [31]. Participants were instructed to respond based upon events occurring during the Gulf crisis. Items were rated on a 5-point scale (0 = *none*, 1 = *once only*, 2 = *two to three times*, 3 = *four to six times*, and 4 = *everyday*) and were summed to create a total score. Internal consistency for the translated PTSDS was 0.80.

In 2003, the families of 120 of the original participants (who were then between the ages of 19 and 23) were contacted to participate in a follow-up assessment. The purpose of the follow-up assessment was to obtain parental permission and confirm contact information of participants. Participants who agreed were interviewed either in the office or at their home by the PI (FH) and completed measures assessing life events that had occurred since the original assessment and sleep quality and duration. Of the original sample, two had died, ten could not be located, nine were studying abroad, and ten did not wish to participate.

The Life Events Checklist (LEC) [32, 33] was adapted for this study to create an 11-item measure (rated yes or no) of nonwar-related stressful life events. Participants indicated whether they had experienced major life events between 1993 and 2003 related to personal loss (e.g., death of a family member), extended separations from family members (e.g., separation and divorce, serious illness), or other potentially stressful life events (e.g., breakup with friend/spouse). Items were summed to create a total score.

In addition to the LEC, participants completed the Pittsburgh Sleep Quality Index (PSQI) [34], a 19-item self-report measure assessing sleep quality and duration over a 1-month period. Response options vary, and they include customary bedtime and time getting up, ratings of quality of sleep, actual hours of sleep per night, usual amount of time to fall asleep, sleep disturbances, daytime dysfunction associated with sleep problems, and frequency of sleep medications taken. Items were combined to yield seven component scores: sleep quality, sleep duration, sleep latency, sleep efficiency, sleep disturbances, daytime dysfunction, and use of medications. A psychometric evaluation of this measure was conducted (see below).

Analyses were conducted with Mplus (version 6.11). Good fitting models met the following criteria [35]: nonsignificant χ^2 test, *CFI* close to 0.95, root-mean-square error of approximation (*RMSEA*) <0.06, and a standardized root mean square residual (*SRMR*) <0.08.

First, confirmatory factor analysis was used to assess a measurement model of sleep. Two models were tested. The first model included a single sleep factor with six indicators (i.e., six component scores from the PSQI). An alternate second model included two factors: *sleep duration* and *poor sleep quality*. The *sleep duration* factor was indicated by sleep duration and sleep efficiency. The *poor sleep quality factor* was indicated by poor sleep quality, time to fall asleep, sleep disturbances, and sleep daytime dysfunction. Use of sleep medications was not incorporated in the models, as most participants (95%) were not taking such medications. A

chi-square difference test was used to determine which of these two nested measurement models should be retained.

The first measurement model, a single sleep factor model, did not fit the data well [χ^2 (9) = 23.26, $p < 0.001$, *CFI* = 0.87, *RMSEA* = 0.12, and *SRMR* = 0.07]. In contrast, the alternate measurement model containing two sleep factors (*sleep duration* and *poor sleep quality*) had good fit to the data [$\chi^2(8)$ = 6.46, p = 0.60, *CFI* = 1.0, *RMSEA* = 0.0001, *SRMR* = 0.03]. Standardized loadings were all at 0.49 or higher. The two latent factors were moderately correlated at −0.36 ($p < 0.01$), indicating good discrimination between the factors. Factor variances indicated limited variability in *sleep duration* but significant individual differences in *poor sleep quality*.

A chi-square test comparing the two-factor sleep model to the one-factor sleep model was significant, χ^2 (1) = 16.80, $p < 0.001$; thus, the differences between the two measurement models were significant, and the two-factor model increased model fit. The two-factor model of sleep was retained as the best fitting model.

After determining the best fitting measurement model for sleep, a structural model was tested. In this model, shown in Fig. 32.1, it was hypothesized that exposure to war-related trauma predicts PTS symptoms, and both exposure and PTS symptoms prospectively predict sleep quality and duration, controlling for intermediary life events. Exposure was considered to have both direct and indirect effects on sleep. The indirect effect was viewed as mediated by PTS symptoms. The grouping variables resulting from the sampling plan were included in the model as a means of validating the measure of exposure (Table 32.1).

The mediation model (see Fig. 32.1), indicating exposure as a predictor of PTS and sleep quality and duration, and PTS together with intermediary life events as predictors of sleep quality and duration, fits the data well [χ^2 (45) = 38.40, p = 0.75, *CFI* = 1.0, *RMSEA* <0.001, *SRMR* = 0.06]. Table 32.2 displays unstandardized path coefficients, standard errors, and p-values. The model significantly predicted 19% of the variance in *poor sleep quality*. The model did not significantly predict *sleep duration*, explaining only 3% of the variance in *sleep duration*. The direct effect of war-related exposure on *poor sleep quality*, controlling for PTS symptoms and life events, was statistically significant ($p < 0.001$). War-related exposure was not significantly related to *sleep duration*, when controlling for PTS symptoms and life events (p = 0.32). PTS symptoms and life events were not significant predictors of either *poor sleep quality* or *sleep duration*. It is of note that the measurement analyses indicated limited variability in *sleep duration* in this sample, and this limits our ability to observe significant effects. Given that PTS symptoms did not significantly predict either sleep outcome, further tests of mediation were not conducted.

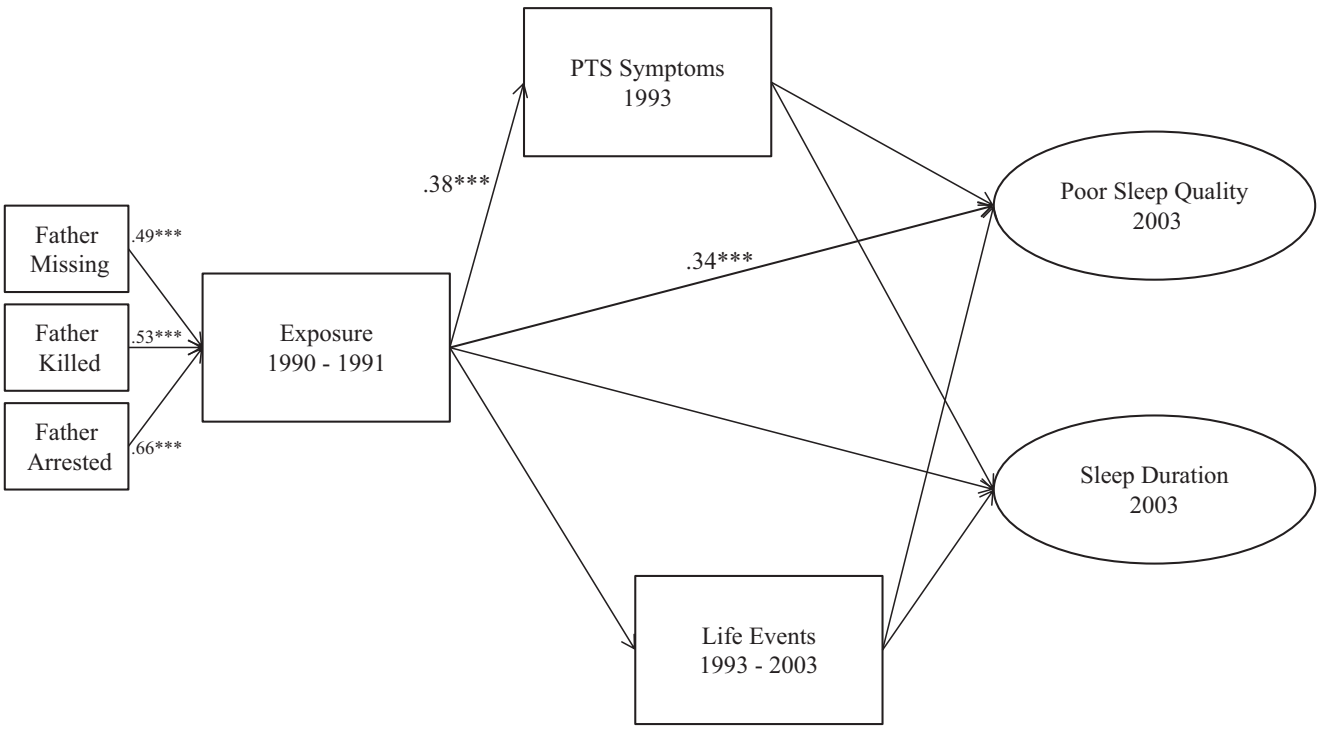

Fig. 32.1 Mediation model of exposure to war-related trauma predicting PTS symptoms, sleep quality, and sleep duration. Omitted from the figure are indicators for latent variables and error terms. Significant paths are shown with standardized coefficients. *** $p \leq 0.001$

Table 32.1 Means, standard deviations, and observed ranges for all measures

	Mean	Standard deviation	Range
Measures from 1993 (n = 151)			
Exposure	7.0	2.6	1–14
PTS symptoms	12.4	9.6	0–46
Measures from 2003 (n = 120)			
Number of stressful events	2.2	1.5	0–7
Sleep latency (minutes)	31.8	32.5	2–180
Sleep efficiency	0.9	0.2	0.14–1
Sleep duration (hours)	7.2	2.2	1–13
Sleep disturbances	18.7	5.0	10–34
Poor sleep quality	2.0	0.8	1–4
Daytime dysfunction	6.2	2.0	3–11

Table 32.2 Unstandardized path coefficients, standard errors, and *p*-values for direct and indirect effects

	Coefficient	SE	*p*-value
Direct paths			
Father missing to exposure	2.90	0.48	<0.001
Father killed to exposure	3.13	0.47	<0.001
Father arrested to exposure	4.21	0.50	<0.001
Exposure to PTS symptoms	1.40	0.28	<0.001
Exposure to life events	0.08	0.06	0.17
Exposure to poor sleep quality	0.04	0.01	<0.01
Exposure to sleep duration	0.07	0.08	0.36
PTS symptoms to poor sleep quality	0.002	0.003	0.45
PTS symptoms to sleep duration	0.01	0.02	0.74
Life events to poor sleep quality	0.03	0.02	0.13
Life events to sleep duration	0.03	0.12	0.81
Indirect paths			
Exposure to poor sleep quality via PTS symptoms	0.003	0.004	0.45
Exposure to poor sleep quality via life events	0.002	0.002	0.31
Exposure to sleep duration via PTS symptoms	0.01	0.02	0.74
Exposure to sleep duration via life events	0.002	0.01	0.82

Discussion

This chapter reviewed gaps in the literature on the effects of childhood trauma exposure on long-term sleep outcomes. PTS symptoms may be one potential mechanism linking trauma exposure to long-term sleep difficulties. However, the direction of this relationship is unclear. To address these issues, this chapter included a data-driven example that examined the long-term relationship between war exposure in childhood and sleep problems in young adulthood, among a sample of Kuwaiti youth exposed to the Gulf War of 1990. Overall, findings highlight that war exposure in childhood contributed to poor sleep quality in young adulthood. Importantly, this longitudinal relationship was not mediated by PTS symptoms in preadolescence. These findings are elaborated below.

Exposure to war trauma predicted sleep problems among young adults 10 years after youth's initial exposure. Sleep problems among adults are concerning because they are associated with numerous maladaptive outcomes, including hypertension [36], cardiovascular disease [37], and depression [37, 38]. In this example, exposure to war trauma significantly predicted *sleep quality* but not *sleep duration*. In fact, youth were homogenous in reporting an adequate amount of sleep, as indicated by the limited variability in sleep duration. This finding is important, because among adults receiving an adequate amount of sleep, as indicated by sleep duration, it has been found that poor *sleep quality* is related to a variety of problems, including tension, depression, anger, fatigue, and confusion [29]. Given the unfortunate increase in children's exposure to war trauma, our results indicate that we may expect more children and young adults to be at risk for sleep problems and, by extension, the health and psychological consequences of poor sleep.

Second, results were not consistent with the hypothesis that PTS symptoms are a mediator of the effects of war on sleep. While numerous studies implicate PTS symptoms in the development of health problems [39, 40], PTS symptoms did not link war exposure to sleep problems. Thus, it appears that other consequences of war exposure lead to sleep problems. This is a surprising finding, given that sleep difficulties are a potential feature of the PTSD diagnosis (i.e., intrusion cluster and the alterations in arousal and reactivity cluster) [17], and two sleep systems are impacted by PTSD: (a) the ability to modulate arousal (resulting in hyperarousal) and (b) memory consolidation in dreams [27]. It is possible that we did not observe that PTS symptoms mediated exposure and sleep problems because PTS symptoms were assessed 10 years before sleep problems. This protracted time difference may have been too long for observing relationships between PTS symptoms and sleep. Future studies assessing sleep problems closer in time to PTS symptoms may be needed in order to clarify the relationship between PTS symptoms and sleep after war exposure. Further, depressive symptoms may need to be considered when examining PTS symptoms, given that these symptoms are often comorbid after traumatic events [6]. This question was explored in the larger study from this dataset [1], which examined psychological distress (i.e., PTS symptoms as well as depressive symptoms) as a potential mechanism linking war exposure and sleep. When depressive symptoms were included in the model, the relationship between psychological distress and sleep quality trended toward significance ($p < 0.10$), but psychological distress did not mediate the relationship between war exposure and sleep quality.

Recommendations for Future Research

- Efficacy of sleep disturbance treatments used for adults should be researched in child and adolescent populations.
- Longitudinal research with assessments closer in time to trauma exposure may help clarify whether PTS precedes, follows, or develops concurrently with sleep problems.
- Adjunctive treatments for sleep should be considered in treatment research for psychological symptoms, especially with regard to PTS symptoms.
- Additional comorbid symptoms (e.g., anxiety, depression) should be considered when examining the relationship between PTS symptoms and sleep disturbances.

Clinical Recommendations

In conclusion, findings from the literature on child traumatic stress exposure and sleep have implications for public health practice. Clinicians, parents, and schools should identify children who experience high levels of exposure to war stressors, as these children may be most at risk for developing sleep problems in adulthood. It is also imperative that doctors and clinicians assess individuals who have been exposed to war trauma for sleep problems. Assessments performed by school counselors should be considered to identify at-risk children and adolescents who do not come into contact with doctors and clinicians. Sleep problems should be assessed not only among those who participated in war but also among civilians and especially among children. Further, clinicians and doctors should continue to assess for sleep problems long after individuals have been exposed to war, as our results indicate that war exposure may impact individuals as long as 10 years after initial exposure. Assessment may help prevent future complications associated with sleep problems: hypertension, depression, and cardiovascular disease.

Following assessment, at-risk youth should receive interventions specifically geared toward addressing both PTSD symptoms and sleep disturbances. Interventions for children and young adults exposed to war need to include components focusing on improving sleep. In particular, interventions should focus on sleep hygiene, as knowledge about sleep hygiene is positively related to sleep practices and overall sleep quality [41, 42]. Other potential nonpharmacological interventions, such as cognitive behavioral therapy, imagery rehearsal therapy, and stimulus control, are discussed in Table 32.3 [43]. More research is needed in order to determine the most effective interventions for treating comorbid sleep disturbances and psychological symptoms [13]. Ideally, nonpharmacological interventions should be considered as the first line of treatment, but in adults, pharmacological interventions (e.g., prazosin) have also been shown to improve sleep disturbances caused by nightmares. These may be considered when treating individuals with nightmares due to PTSD [8, 43]. Although these recommendations are presented alongside an example focusing on youth exposed specifically to the Gulf War crisis, their applicability extends to all youth exposed to war. Our findings demonstrate that the impact of wars may reach far beyond fatalities and destroying buildings, impacting sleep among those exposed to war.

Table 32.3 Nonpharmacological interventions for PTSD-related sleep disorders [43]

Type of intervention	Type of sleep disturbance treated	Description of intervention
Trauma-focused CBT for PTSD	Insomnia and nightmares	Direct engagement with memories and challenges to maladaptive beliefs. Generally associated with improvements in sleep. Some people still report residual sleep disturbances
Eye movement desensitization and reprocessing	Sleep efficiency and reduced wake time following sleep onset	Includes components of CBT (i.e., exposure, cognitive restructuring, and processing of emotional responses to trauma cues) but also incorporates saccadic eye movement tracking during exposure
Imagery rehearsal for nightmares in PTSD	Nightmares and sleep quality	Participants choose a distressing nightmare they have repeatedly had, change a detail in the nightmare, and rehearse the new version of the nightmare
CBT for insomnia	Insomnia	Combines stimulus control therapy, sleep restriction therapy, relaxation training, cognitive restructuring, and sleep hygiene instructions
Combined imagery rehearsal and CBT for insomnia	Varies based on combination method used – nightmares were the most common	Several different combinations of the two treatment methods exist. Most combinations include imagery rehearsal and stimulus control techniques

CBT cognitive behavioral therapy, *PTSD* posttraumatic stress disorder

References

1. Llabre MM, Hadi F. War-related exposure and psychological distress as predictors of health and sleep: a longitudinal study of Kuwaiti children. Psychosom Med. 2009;71(7):776–83. 778p
2. Thabet AAM, Vostanis P. Post-traumatic stress reactions in children of war. J Child Psychol Psychiatr Allied Discip. 1999;40(3):385.

3. Klingman A. Children under stress of war. In: La Greca AM, Silverman WK, Vernberg EM, et al., editors. Helping children cope with disasters and terrorism. Washington, DC: American Psychological Association; 2002. p. 359–80.
4. Llabre MM, Hadi F. Health-related aspects of the Gulf crisis experience of Kuwaiti boys and girls. Anxiety Stress Coping: Int J. 1994;7(3):217–28.
5. Llabre MM, Hadi F. Social support and psychological distress in Kuwaiti boys and girls exposed to the Gulf crisis. J Clin Child Psychol. 1997;26(3):247–55.
6. Thabet AAM, Abed Y, Vostanis P. Comorbidity of PTSD and depression among refugee children during war conflict. J Child Psychol Psychiatr. 03//. 2004;45(3):533–42.
7. Klingman A. Stress reaction of Israeli youth during the Gulf war: a quantitative study. Prof Psychol: Res Pract. 1992;23(6):521–7.
8. Brown TH, Mellman TA, Alfano CA, Weems CF. Sleep fears, sleep disturbance, and PTSD symptoms in minority youth exposed to Hurricane Katrina. J Trauma Stress. 10//. 2011;24(5):575.
9. Glod CA, Teicher MH, Hartman CR, Harakal T. Increased nocturnal activity and impaired sleep maintenance in abused children. J Am Acad Child Adolesc Psychiatr. 1997;36(9):1236–43.
10. Zhang J, Zhu S, Du C, Zhang Y. Posttraumatic stress disorder and somatic symptoms among child and adolescent survivors following the Lushan earthquake in China: a six-month longitudinal study. J Psychosom Res. 2015;79(2):100–6.
11. Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med. 2001;345(25):1825–32.
12. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep-what a nightmare! Sleep Med Rev. 2000;4(2):183–200.
13. Plumb TR, Peachey JT, Zelman DC. Sleep disturbance is common among service members and veterans of operations enduring Freedom and Iraqi Freedom. Psychol Serv. 2014;11(2):209–19.
14. Thordardottir EB, Valdimarsdottir UA, Hansdottir I, Resnick H, Shipherd JC, Gudmundsdottir B. Posttraumatic stress and other health consequences of catastrophic avalanches: a 16-year follow-up of survivors. J Anxiety Disord. 2015;32:103–11.
15. Swanson LM, Hamilton L, Muzik M. The role of childhood trauma and PTSD in postpartum sleep disturbance. J Trauma Stress. 2014;27(6):689–94.
16. Catani C, Schauer E, Elbert T, Missmahl I, Bette J-P, Neuner F. War trauma, child labor, and family violence: life adversities and PTSD in a sample of school children in Kabul. J Trauma Stress. 2009;22(3):163–71.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
18. Famularo R, Fenton T. Early developmental history and pediatric posttraumatic stress disorder. Arch Pediatr Adolesc Med. 1994;148(10):1032–8.
19. Noll JG, Trickett PK, Susman EJ, Putnam FW. Sleep disturbances and childhood sexual abuse. J Pediatr Psychol. 2006;31(5):469–80.
20. Zhou X, Wu X, An Y, Fu F. Longitudinal relationships between posttraumatic stress symptoms and sleep problems in adolescent survivors following the Wenchuan earthquake in China. PLoS One. 2014;9(8):1–7.
21. van Liempt S, Vermetten E, Lentjes E, Arends J, Westenberg H. Decreased nocturnal growth hormone secretion and sleep fragmentation in combat-related posttraumatic stress disorder; potential predictors of impaired memory consolidation. Psychoneuroendocrinology. 2011;36(9):1361–9.
22. Inman DJ, Silver SM, Doghramji K. Sleep disturbance in posttraumatic stress disorder: a comparison with non-PTSD insomnia. J Trauma Stress. 1990;3(3):429–37.
23. Straus LD, Drummond SPA, Nappi CM, Jenkins MM, Norman SB. Sleep variability in military-related PTSD: a comparison to primary insomnia and healthy controls. J Trauma Stress. 2015;28(1):8–16.
24. Wittmann L, Zehnder D, Jenni OG, Landolt MA. Predictors of children's sleep onset and maintenance problems after road traffic accidents. Eur J Psychotraumatol. 2012;3:1–9.
25. Chipman KJ, Palmieri PA, Canetti D, Johnson RJ, Hobfoll SE. Predictors of posttraumatic stress-related impairment in victims of terrorism and ongoing conflict in Israel. Anxiety, Stress Coping. 2011;24(3):255–71.
26. Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol. 12//. 2011;67(12):1240.
27. Caldwell BA, Redeker N. Sleep and trauma: an overview. Issues Ment Health Nurs. 2005;26(7):721–38. 718p
28. Gregory AM, O'Connor TG. Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. J Am Acad Child Adolesc Psychiatr. 2002;41(8):964–71.
29. Pilcher JJ, Ott ES. The relationships between sleep and measures of health and well-being in college students: a repeated measures approach. Behav Med. 1998. 1998;23(4):170–8.
30. Davidson J, Smith R, Kudler H. Validity and reliability of the DSM-III criteria for posttraumatic stress disorder. Experience with a structured interview. J Nerv Ment Dis. 1989;177(6):336–41.
31. Association AP. Diagnostic and statistical manual of mental disorder. 3rd revised ed. Washington, DC: American Psychiatric Association; 1987.
32. Johnson JH, McCutcheon SM. Assessing life stress in older children and adolescents: preliminary findings with the life events Checklist. Stress and Anxiety. 1980;7:111–25.
33. Johnson JH, Bradlyn AS. Assessing stressful life events in childhood and adolescence. In: Karoly P, Karoly P, editors. Handbook of child health assessment: biopsychosocial perspectives. Oxford: Wiley; 1988. p. 303–31.
34. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
35. Hu L-t, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model. 1999;6(1):1–55.
36. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the sleep heart health study. Sleep. 2006;29(8):1009–14.
37. Newman AB, Enright PL, Manolio TA, Haponik EF, Wahl PW. Sleep disturbance, psychosocial correlates, and cardiovascular disease in 5201 older adults: the cardiovascular health study. J Am Geriatr Soc. 1997;45(1):1–7.
38. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry. 1996;39(6):411–8.
39. Schnurr PP, Spiro A. Combat exposure, posttraumatic stress disorder symptoms, and health behaviors as predictors of self-reported physical health in older veterans. J Nerv Ment Dis. 1999;187(6):353–9.
40. Engel CC Jr, Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for Gulf War-related health concerns. Psychosom Med. 2000;62(6):739–45.
41. Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. Sleep Med Rev. 2003;7(3):215–25.
42. Brown FC, Buboltz WC, Jr., Soper B. Relationship of sleep hygiene awareness, sleep hygiene practices, and sleep quality in university students. Behav Med. 2002;28(1):33–38.
43. Schoenfeld FB, Deviva JC, Manber R. Treatment of sleep disturbances in posttraumatic stress disorder: a review. J Rehabil Res Dev. 2012;49(6):729–52.

Sleep Disorders Among Holocaust Survivors

33

Ido Lurie and Itzhak Levav

During the war, my sleep was very bad. That was because of the fear. One could go to sleep next to Moses, and the next morning, he would be gone, dead. I could not sleep because I was so afraid. I did not have fear that I would die, but rather that I would be killed. I would sleep with one eye open, because I was thinking of what could happen any minute. Ever since the war is over, those things come back to me when I dream. I used to wake up at night, screaming. Why would I burst out? Because I had this thought in my head that people are after me. I used to dream and shout. Falling asleep was not difficult, but to sleep without breaks... There were always interruptions—from the outside like a sudden noise would make me jump or from the inside if I remember something or a though... I could not get a straight night sleep. I sleep an hour or so, and I wake up. I do not want to force myself to sleep with pills; it is not natural. Why should I take pills to sleep? … I dream of things that happened. I dream about the past. It is like fog within a thought. But you know the reason for this memory; I cannot remember my dreams in details. In fact, I do not want to look for that and to remember. I do not want to make this effort.

KW is a Polish-born Holocaust survivor. He spent the war in a ghetto and later in the forests, as a partisan. The interview was held in a psychiatric clinic, Israel, December, 2011.

The Second World War (WWII) started in September 1939 and ended in May 1945. However, for an untold number of Jews, it began earlier in Germany and Austria with the election of Hitler and ended long after 1945, following the pogroms in Poland and the tortuous path toward resettlement in a number of continents.

During those years, Jews of many European and North African countries suffered assaults of varying nature, intensity, and duration. Those included:

Physical assaults (e.g., head traumas, overcrowding, sleep and food deprivation, exposure to extreme temperatures, lack of medical care, and infectious diseases)

Psychological assaults (e.g., murder of relatives and others, suppression of self-identity, witnessing cruelty, constant fear, threats of death)

Psychosocial assaults (e.g., loss of civil rights, social status, community support, livelihood, freedom)

Cultural-religious assaults (e.g., anti-Semitic campaigns, harassment, discrimination) [1, 2]

Holocaust Exposure and Psychopathology

During those years, about six million Jews lost their lives, among them about a million children [3], and the psychological toll was enormous. The survivors had to confront long-lasting psychopathological consequences following forced labor and extermination camps, living in ghettos, hiding or living in disguise, fighting with paramilitary groups (partisans), and death marches. Research has shown a dose effect of the traumatization, e.g., increasing levels of demoralization were associated with increasing severity of exposure [4]. In assessing the above impact, recall here that the survivors were at different stages of their life cycle when the Nazi terror befell them [5]. Age at the time of trauma was found to be negatively related with some symptoms of posttraumatic stress disorder (PTSD, i.e., psychogenic amnesia, hypervigilance, emotional detachment) and positively correlated with intrusive thoughts [6]. Also, some survivors were born to parents who lived under extreme circumstances; the effect of stress in utero has been researched [5].

To partially describe the psychopathologic impact of all those conditions, Krystal coined the term "massive psychic trauma" [7], while the protracted and intense events caused "maximum adversity" [1].

The effects of internment in concentration camps on the mental health of the prisoners were observed during the war [8–10]. Postwar observations of the effects of the traumatic

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experiences on the survivors were made soon after liberation [11, 12]. Through the years, the accumulating evidence originated in clinical observations [13], claim applications [14], community-based surveys [15], and biological laboratory research [16]. Recently, a meta-analysis was added to the available body of evidence [17].

As the data were beginning to accumulate, survivors, clinicians, and researchers faced a previously unknown condition that was termed "concentration camp syndrome" (CCS) [18]. This syndrome included, among other symptoms, *impairments of sleep and insomnia* and *fatigue* (Table 33.1). A clinical equivalent, the "survivor syndrome," included the typical "survivor triad": headaches, *persistent nightmares*, and chronic depression [13].

Studies conducted in many countries found Holocaust survivors (HS) to be at increased risk for psychiatric symptoms compared to suitable controls who had not been directly exposed to the Holocaust, regardless of the age of exposure and the experience of the traumatic events [19].

The aforementioned meta-analysis focused on the long-term health effects as expressed by psychiatric, psychosocial, and physical outcome measures [17]. The analysis included 71 clinical and nonclinical samples from Australia, Canada, Israel, and the USA (N = 12,746). In general, HS were found to be less well adjusted. In a set of 25 nonclinical samples (n = 8270), a significant difference was found in psychopathology between survivors and comparison participants. The combined effect size was a Cohen's d 0.33, $p < 0.01$, 95% CI [0.23, 0.44]. In 12 studies, survivors also showed substantially more posttraumatic stress symptoms than their counterparts (d = 0.72, $p < 0.01$, 95% CI [0.46, 0.98], n = 1763).

Table 33.1 Subjective complaints and inclusion (yes/no) in the "concentration camp syndrome" (N = 100)

Subjective complaints	*n*	In CCS
Increased fatigue	85 (85%)	Yes
Nervousness, irritability, restlessness	78 (78%)	Yes
Impairment of memory	78 (78%)	Yes
Dysphoria	72 (72%)	Yes
Emotional instability	70 (70%)	Yes
Impairment of sleep	61 (61%)	Yes
Anxiety	55 (55%)	No
Feeling of insufficiency	54 (54%)	Yes
Loss of initiative	54 (54%)	Yes
Headache	53 (53%)	Yes
Vegetative instability	48 (48%)	Yes
Vertigo	43 (43%)	Yes
Nightmares	36 (36%)	No
Depressions	36 (36%)	No
Tremor, other involuntary movements	21 (21%)	No
Alcohol abuse	19 (19%)	No
Reduced alcohol tolerance	14 (14%)	No

Adapted from Eitinger [25]

Holocaust Exposure and Sleep Disturbances

Often, psychopathology and sleep disturbances coexist. Sleep disorders constitute part of the DSM–IV and ICD–10 criteria of mood and anxiety disorders, including PTSD [20, 21]. Sleep disturbances, such as increased percentage of REM sleep and a reduction in REM sleep latency [22], have been described with regard to mood disorders. For some [23], but not for all, authors (e.g., [24]), sleep disturbances and nightmares are the hallmark of PTSD among the anxiety disorders.

Importantly, sleep disturbances may linger for decades after the initial exposure to the traumatic event(s). It is thus not surprising that HS, and especially those who carry emotional scars, complain of sleep disturbances that may have haunted them for decades.

This chapter reviews the sleep disturbances as identified in studies conducted in different contexts: clinical settings, pension claims, community surveys, and sleep laboratories. Laboratory studies focused specifically on sleep disturbances, e.g., nightmares and dreaming among survivors. In contrast, in most – but not in all – of the other types of studies, sleep disturbances were reported as part of another primary outcome (i.e., emotional distress, psychiatric disorders).

We reviewed publications in English that reported sleep disturbances, insomnia, and nightmares, even if those were not the primary outcome of the publication, preferably when studies had a comparison group, used standard methods of diagnosis, and relied on quantitative methods of analysis. The studies were mostly selected by period of publication: short term (until 10 years following WWII), middle term, and late term (since 2000, over 55 years from liberation). In each section, the selected studies are described mainly in order of publication (from early to late) (Table 33.2).

Observational Reports and Studies on Sleep Disorders in Clinical Settings

Niederland [13], who conducted clinical observations in about 800 survivors (no demographic or clinical details were provided), described the "survivor syndrome." He noted: "*sleep disorders* are extraordinarily frequent and include early morning awakening as well as the fear of falling asleep at night because of the dread of tormenting nocturnal experiences such as nightmares, awakening in terror, hallucinatory or semi-hallucinatory reliving of the past."

Table 33.2 Studies and findings addressing sleep disturbances among the Holocaust survivors

Author	Publication year	Country	*N*	Objective/s	Main findings
Observational reports and clinical studies					
Niederland [13]	1968	USA	800	Description of "survivor syndrome"	Chronic depression, anxiety, *insomnia*, *nightmares*, personality changes, somatization
Eitinger [25]	1961	Norway	100	Characterization of "concentration camp syndrome"	Increased fatigue (85%), *sleep impairment* (61%)
Nathan et al. [26]	1964	Israel	157	Psychiatric characteristic of hospitalized survivors	Presence of a clinical syndrome not amenable to the accepted psychiatric classification
					Most frequent symptom: *insomnia* (51.6%). *Nightmares* were rarely reported (5.1%)
Conn et al. [27]	2000	Canada	477	To retrospectively assess depressive symptoms in HS versus non-Holocaust survivors	HS group was significantly more likely to receive a diagnosis of DSM PTSD. No significant differences in early ($p = 0.672$), middle ($p = 0.46$), or late ($p = 0.12$) *insomnia*
Trappler et al. [30]	2007	USA	36	To examine early lifetime trauma in later life and the interplay of depression and PTSD	Depressed HS had worse psychological and social functioning than depressed controls ($p = 0.002$). Depressed HS had more PTSD symptoms than nondepressed survivors ($p = 0.001$). HS displayed an elevation in the arousal with elevation of anxiety and *worsening of sleep disturbance*
Reparation claim-based studies					
Winkler [31]	1959	Germany	32	To examine survivors' claims	Descriptive findings: *poor sleep* with *nightmares*
Chodoff [14]	1963	USA	23	To examine the effects of "concentration camp syndrome"	Anxiety and depressive symptoms. Anxiety symptoms were worse at night and accompanied by *insomnia and nightmares*
Kuch and Cox [32]	1992	Canada	124	To describe long-term effects of concentration camps	*Sleep disturbances*, 96%, recurrent *nightmares*, 83.1%, $p < 0.001$. Anxiety symptoms were invariably accompanied by *insomnia and nightmares*
Community-based studies					
Friedman [11]	1949	Cyprus	172	To describe clinical phenomena in displaced persons	*Sleepiness*

(continued)

Table 33.2 (continued)

Author	Publication year	Country	*N*	Objective/s	Main findings
Nadler et al. [33]	1989	Israel	68	To examine the presence of "survivor's syndrome"	HS reported *nightmares* and *problems of insomnia*
Rosen et al. [34]	1991	USA	133	To assess sleep quality and sleep problems in Holocaust survivors	HS had significantly greater *sleep impairment* than healthy comparison subjects, more *frequent awakenings* due to bad dreams when compared to depressed subjects. Sleep disturbances and frequency of nightmares were significantly and positively correlated with the duration of the internment in concentration camps (Pearson $r = 0.39$, df = 39, $p < 0.01$; Spearman rank-order correlation, $r_s = 44$, df = 37, $p < 0.005$)
Collins et al. [37]	2004	Israel	756	To compare sleep variables and other outcomes between HS and non-Holocaust survivors	Female HS went to bed *later and awoke later* than the comparison group ($p < 0.5$). No difference in total sleep duration, between HS and comparison groups in either sex
Carmil and Carel [38]	1986	Israel	3309	To compare emotional distress in working HS and control group	No differences were found regarding sleep disturbances
Yehuda et al. [6]	1997	USA	100	To compare PTSD symptoms in different traumatic exposure: concentration camp HS and HS who had been in hiding	Of the sample population, 75% *reported sleep disorders* in the PTSD-*DSM-III* symptom criteria, and 60% reported symptoms regarding dreams
Shemesh et al. [44]	2008	Israel	1227	To examine emotional distress and health dimensions, including sleep problems, among elderly HS	Sleep problems were found to be significantly more prevalent in HS group ($p < 0.0002$)
Stessman et al. [45]	2008	Israel	458	To describe mortality, medical, and social parameters in HS of old age, with the hypothesis that Holocaust exposure at younger ages had more adverse effects	At baseline, survivors more frequently reported poor self-rated health ($p = 0.04$), but the level of global sleep satisfaction was similar between the groups, as it was found during the subsequent wave, 7 years later

(continued)

Table 33.2 (continued)

Author	Publication year	Country	*N*	Objective/s	Main findings
Sharon et al. [15]	2009	Israel	257	To examine anxiety and depressive disorders, sleep disturbances, other health problems, and use of services among HS and comparison	The percentage of HS who reported at least one sleep disturbance (62%; $n = 90$) was twice that of the comparison group (33%; $n = 46$; OR = 3.4, 95% CI 2.0–5.6). The difference remained significant after adjusting for age, education, religious observance, and past-year presence of anxiety and depressive disorders (OR = 2.5, 95% CI 1.4–4.4)
Laboratory studies					
Hefez et al. [47]	1987	Israel	11, (HS, $n = 5$)	To examine sleep data of survivors of different traumatic events	Compared to controls, all participants who were exposed to trauma had *lower sleep efficiency indices*, with prolonged sleep latency ($p < 0.1$) and larger amounts of awake plus movement time within sleep periods ($p < 0.1$), shorter REM time ($p < 0.2$), and longer REM latencies ($p < 0.01$)
Kaminer and Lavie [49, 50]	1991	Israel	33 (HS $n = 23$)	To examine whether a decrease in dream recall that minimizes the probability of anxiety dreams and nightmares is a form of long-term adjustment to traumatic events among HS (with differentiation between well- versus less-adjusted individuals)	The less-adjusted HS had more prolonged sleep latency than the well-adjusted and the control groups and had lower sleep efficiency than did the control The well-adjusted group had a significantly lower dream recall rate than did the less-adjusted and control groups ($p < 0.002$) There were also significant between-group differences in dream structure and content, in the direction of less complex and less salient dreams in the well-adjusted HS ($p < 0.05$). Dream content of danger to existence was found significantly more often in the two HS groups; (81% poorly adjusted and 79% in well-adjusted)

Eitinger [25] described a sample of 100 non-Jewish Norwegians (men = 93) who were former concentration camp prisoners and who were referred for medical evaluation because of problems of adaptation to "normal life." These subjects were admitted to a hospital and underwent a thorough evaluation by a team that was purposely built for this task. Half were under the age of 30 at the time of arrest. Four were imprisoned in Japanese camps and the rest in German camps. Eitinger noticed two symptoms, increased fatigue in 85 and *sleep impairment* in 61 individuals. Those two symptoms were part of the "concentration camp syndrome" (Table 33.1).

Nathan et al. [26] described psychiatric symptoms in 157 concentration camp (CC) survivors admitted to a psychiatric hospital in Israel, years 1949–1959. They were compared to 120 hospitalized patients who were in Soviet Russia during WWII (detention camps in Siberia, displacement to Central Asia). The most frequent symptom was *insomnia*, 51.6% in both groups. *Nightmares* were rarely reported (5.1% and 5.0%, respectively). Judging by this study, sleep disturbances are common in people who had been traumatized.

Conn et al. [27] retrospectively assessed depressive symptoms in HS versus non-Holocaust survivors (nHS) treated in a psychiatric day hospital in Toronto, Canada, between 1986 and 1998. The sample included 477 subjects (HS, 24%; women, 69.8%; mean age, 75 years; Jewish, 90.6%; Europe-born, 61.4%; education, 20 completed high school). The nHS had a higher level of education than the HS ($p = 0.047$; the Bonferroni corrected p-value ≤ 0.004). The HS were significantly more likely to receive a diagnosis of *DSM–IV* PTSD (27% versus 1.1%, $p < 0.001$) and to receive a diagnosis of major depressive disorder (78.2% versus 67.8%, $p < 0.03$). However, there was no difference between groups in the severity of their depression (Hamilton Depression Rating Scale, HDRS [28], and the Geriatric Depression Scale, GDS [29]), both on admission and on discharge. The groups scored similarly on the Mini Mental State Examination (MMSE); however, the HS group scored significantly less on the Mattis Dementia Rating Scale, ($p < 0.001$), even after controlling for education. The HDRS subscale on insomnia on admission was available for 447 of the subjects that were day hospitalized. When HS were compared to nHS, there were no significant differences in early ($p = 0.672$), middle ($p = 0.465$), or late insomnia ($p = 0.126$).

Trappler et al. [30] examined the impact of early lifetime trauma in late life, in particular, the interplay of depression and PTSD in HS. They described three groups of patients in a primary healthcare practice in New York: (1) HS with depression (HD, $n = 20$; mean age: 79 years), (2) nondepressed HS (HSND, $n = 16$), and (3) older depressed non-Holocaust Jewish persons (NHSD, $n = 18$; mean age, 84). All HS had been in concentration camps. The comparison was based on the Impact of Events Scale, Hamilton Depression Scale (HAM-21), Beck Anxiety Inventory (BAI), and Brief Psychiatric Rating Scale (BPRS) for an overall score for 16 different categories of psychiatric disorders. Several of these instruments were also used as an indicator of guilt symptoms. A modified Clayton Inventory was used to measure the degree of social integration and functioning. The HD group was older and more likely to report PTSD and guilt symptoms, to have higher BAI and BPRS scores, and to have more impaired social functioning. There were no significant differences in gender, HAM-D scores, or suicidal ideation as measured on the HAM-D. The HSD and HSND differed significantly on six of nine variables. The authors mentioned in the discussion that the HS had elevation in the *arousal* domain with elevation of anxiety and *worsening of sleep disturbance* in the BDI and HAM-D and agitation in the BPRS, but no data were presented.

Studies Based on Reparation Claims

Winkler [31], in 1959, reported findings on 32 appraisal claims. The data are presented without figures or statistical analysis; however the description is illuminating: "The most characteristic symptom is *poor sleep with nightmares*. The content of the dream is almost universally the same. The horrors of the concentration camp are relived. Mothers dream of their last contact with their children, and still see the children who perished asking for help. Waking up in profuse perspiration is reported by the majority of patients. They relate that persons who sleep with them have told them later about screaming during sleep."

Chodoff [14], in the USA, performed neuropsychiatric evaluations of 23 persons between the years 1960 and 1963 that submitted claims to the German government for reparations. All subjects were Jews, except for two women who had married Jewish men. The age range was from 29 years to over 60. Nineteen claimants exhibited similar problems: anxiety, depression, and characterological changes. Anxiety symptoms "were worse at night and almost invariably accompanied *by insomnia and nightmares*- the latter either direct or only slightly disguised repetitions of their traumatic experiences …and still occurring, in a …large number of cases, 15 years after the war had ended. In addition to nightmares, many patients had other repetitive dreams, which were essentially loving, nostalgic, reminiscences involving their parents and siblings in an idyllic version of their lives before the Nazis."

Kuch et al. [32], in Toronto, Canada, published a study that described PTSD-related phenomena among concentration camp survivors. Their sample included 124 Jewish HS (58 males; 66 females; mean age, 62.0 years; SD = 9.4; range = 39–86), selected from German compensation boards. To focus on only symptoms of PTSD, subjects with

confirmed or suspected other psychiatric disorder were excluded. One subject was excluded from the analysis because the stay in Auschwitz lasted less than a month. The remaining 123 subjects were divided into three groups:

1. Concentration camp survivors (CC): persons who had been detained in various camps for at least 1 month ($n = 78$).
2. Extermination camp survivors: a subgroup of Auschwitz HS ($n = 20$).
3. Labor camps/ghettos/hiding ($n = 45$): these subjects represented a comparison group, with a more limited exposure to atrocities.

The groups did not differ significantly in age, gender, and date of assessment.

All 124 subjects were examined by a psychiatrist for an independent examination, as requested by the German compensation boards. The examination included a psychiatric interview of 1–2 h and a review of the compensation board files (containing documentation of the applicant's persecution and medical reports). The interview recorded current symptoms based on checklists that included *DSM-III-R* and PTSD symptoms with a mean time span between the initial interview of the assessment of 7.5 years (SD = 5.7, range = 0–17).

On average, 78% of the first-degree relatives of each subject had been killed. The mean subjects' age at the onset of persecution was 19.3 years (SD = 6.5, range = 3–51). The majority (80.6%) were married; others were widowed (11.3%) or divorced (4.8%) (incomplete data, four subjects). The majority had children (81.3%).

Subjects were predominantly blue-collar workers, with a mean percentage of work time of 61.9% (SD = 26.7%, range = 0–100%).

PTSD *DSM-III-R* diagnosis was made in 46.8% of the total sample, 51.3% of the concentration camps survivors, and 65.0% of the extermination camp survivors.

The latter had a significant higher number of PTSD symptoms compared with subjects who had not been in concentration camps (mean = 9.4, SD = 2.4, and mean = 6.7, SD = 2.4, respectively, $t = 4.16$, df = 63, $p < 0.001$). Among PTSD symptoms *sleep disturbances with recurrent nightmares* of Holocaust-related content were almost universal. *Sleep disturbances* were reported in 96.0% of the total sample, 98.7% of the CC survivors, and 100% of the extermination camp survivors. Recurrent *nightmares* were reported in 83.1% of the total sample, 87.2% of the CC survivors, and 90% of the extermination camp survivors.

Studies that were part of compensation claims are informative but, perhaps, contaminated by secondary gains, at least among some claimants. This bias was circumvented in community-based epidemiological studies, which are free from benefit seeking. However, they all noted sleep disturbances as salient complaints.

Community-Based Studies

In a pioneer paper published in 1949, the author described his observations (not truly a survey, as acknowledged by the author) on a group of 172 displaced persons, 88 adults and 84 children and adolescents (up to the age of 18), hosted in displaced persons' camps (DP) in Cyprus, year 1947 [11]. Among other symptoms, he noted a remarkable tendency toward *sleepiness*, "ranging from slight *narcoleptic* states to periods of prolonged sleep lasting for days."

Nadler et al. [33] examined the effects on personality and psychopathology of the survivor's syndrome in a community, more than 40 years after the WWII. The study sample included both survivors ($n = 34$) and comparison respondents ($n = 34$). Each group included half residents of a kibbutz (socialist community) and half residents of urban areas. Complete comparability between both groups' respondents could not be ascertained, but their similarity on key variables enabled comparison of their scores on relevant dimensions. Respondents were similar in age (60–66 years old), marital status (all married, except for three widowers), number of children (range of means = 2.3–2.8), origin (prewar Poland), and religiosity (over 80%, nonreligious). All respondents were drawn from various hometown organizations and did not include psychiatric units. The study had four strict criteria for choosing survivors: (a) internment in a concentration camp for at least 12 months, (b) no membership in an organization that actively fought the Nazis, (c) at least aged 12 when imprisoned, and (d) no older than 70 years when interviewed. Comparison respondents spent the years of WWII as free men and women. Most had immigrated in pre-State Israel before 1939, and a few had lived in other countries as free people (e.g., USSR).

The questionnaire included *The Clinical Analysis Questionnaire CAQ-A and CAQ-B* (a two-part theory-based personality test that assesses normal and pathological personality dimensions), *Tennessee Self-Concept Scale* (*TSC*- a 100-item self-esteem scale), *and Centrality of Family Scale*. Respondents were asked to take part in a follow-up clinical interview conducted about 2 weeks thereafter. Thirty survivors and twenty-seven comparison respondents agreed. Respondents were asked about psychosomatic complaints, insomnia, nightmares, fears, and depression and suicidal thoughts. The results indicated that the psychological effects were evident even 40 years after of the Holocaust. On almost all dimensions, survivors' scores were significantly worse than the comparison group. In the open interviews, 25 survivors (vs. only six comparison respondents) reported problems of *insomnia*. Almost all survivors reported frequent *nightmares*.

Rosen et al. [34] published the only community-based study that specifically aimed to assess sleep quality and sleep problems in HS, 45 years after WWII. Sleep quality and sleep problems were compared among survivors (n = 42), depressed (predominately hospitalized) patients (n = 37), and same-age healthy subjects (n = 54), all living in the community in the USA. Of the survivors, 34 had been in concentration camps (mean incarceration: 2.5 years, SD = 1.7), and eight had been in slave labor camps or in hiding. The Pittsburgh Sleep Quality Index (PSQI) [35] was used to check for sleep patterns. PSQI is a self-rating instrument that includes 19 questions tapping different aspects of sleep: quality, latency, duration, habitual sleep efficiency, disturbances of sleep (nightmares), use of sleeping medication, and daytime dysfunction. The PSQI is scored on a scale of 0–3, where higher scores indicate poorer sleep quality and greater impairment (up to a maximum score of 21). The PSQI was sent to 166 members of the Holocaust Center in the local city. The response rate reached 25.3%.

Sleep disturbances were found significantly higher among the HS, as follows: HS, 8.15, SD 5.28; healthy comparison subjects, 2.64, SD 1.79; and depressed patients, 11.8, SD 3.7. Neither age nor gender was correlated with the PSQI score. Survivors had significantly greater *sleep impairment* than the healthy comparison subjects but less impairment than the depressed patients except on the sleep disturbances and daytime dysfunction subscales. However, for specific items within these subscales, survivors had significantly more *frequent awakenings* due to bad dreams when compared to depressed subjects. Also, sleep disturbances and frequency of nightmares were significantly and positively correlated with the duration of the survivors' internment in concentration camps (Pearson r = 0.39, df = 39, $p < 0.01$; Spearman rank-order correlation, $r_s = 44$, df = 37, $p < 0.005$). Survivors who experienced awakenings due to bad dreams at least once a week (36%, n = 15) had been incarcerated for longer periods of time than the HS who had less frequent nightmares (2.4, SD = 17; 1.4, SD = 1.7, respectively, $t = -2.70$, df = 39, $p < 0.01$). This dose-effect relationship, which was elicited after 45 years, suggests that the duration of a stressor with the accompanied greater risk to suffer more severe and continuous traumas (e.g., torture, malnutrition) may have important implications for residual sleep disturbance.

This single study had some limitations: e.g., the survivors were members of a Holocaust organization, the response rate was low, the comparison depressed group included both hospitalized and nonhospitalized patients, there was no control for age, and in contrast with the depressed and healthy groups that were assessed with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L), the HS were only assessed with the PSQI (Table 33.3).

The Jerusalem Community Health Study

This project had three waves of publications, of which two are described below (the first publication [36] did not report on sleep disturbances).

Collins et al. [37], based on data collected in 1985–1987 that included Europe-born HS (men, n = 130; women, n = 158; mean ages, 68.0 years, SD = 9.0, 67.2 years, SD = 8.4, respectively) and Europe-born Jews not exposed to the Holocaust (men, n = 202; women, n = 284; mean ages 69.0 years, SD = 8.7, and 69.0 years, SD = 9.6, respectively). Participants answering positively to the question, "During WWII, were you in a concentration camp, labor camp, in hiding or living in a ghetto?" were defined as HS, and those who responded negatively were selected for the comparison group (36% had immigrated to Israel before WWII). Both

Table 33.3 Subscale and global scores on the Pittsburgh sleep quality index of HS, depressed patients, and healthy comparison subjects

Pittsburgh sleep quality index	Survivors (S) (N = 42)		Depressed patients (D) (N = 37)		Healthy comparison subjects (C) [53]		One-way analysis of variance		Significant post hoc pairwise comparisons
Subscale	Mean	SD	Mean	SD	Mean	SD	F	df	
Sleep quality	1.29	041.	2.03	0.86	220.	0.42	59.11	2,128	SD, SC, DC
Sleep latency	1.26	1.04	1.94	1.11	0.45	0.61	29.05	2,124	SD, SC, DC
Sleep duration	1.00	0.95	2.06	1.06	0.44	0.69	33.46	2,127	SD, SC, DC
Sleep efficiency	1.43	1.28	2.18	1.11	0.19	0.63	42.59	2,123	SD, SC, DC
Sleep disturbances	1.63	0.84	1.36	0.54	1.04	0.39	11.04	2,126	SC, DC
Daytime dysfunction	0.90	0.82	1.19	0.91	0.26	0.48	19.63	2,130	SC, DC
Global	8.15	5.28	11.84	3.72	2.64	1.79	61.69	2,117	SD, SC, DC

Taken from Rosen et al. [34]
[a]Higher score indicates greater impairment
[b]Every F ratio was significant at $p < 0.0001$
[c]Varying degrees of freedom reflect missing data on some items
[d]$p < 0.05$, Tukey's Honestly Significant Difference Test

groups were compared on psycho-behavioral factors, clinical variables, and mortality.

The structured survey questionnaire included [1] a physical examination, [2] blood chemistry variables, and [3] the demoralization scale of the Psychiatric Epidemiology Research Interview (PERI) that measures emotional distress. It consists of 27 questions arranged in subscales, measuring poor self-esteem, hopelessness, dread, sadness, anxiety, psychophysiological symptoms, and perceived physical health; [4] all-cause mortality; [5] an abbreviated eight-item scale from the Cornell Medical Index (CMI) that assesses symptoms of emotional health; and [6] sleep variables, as follows: duration (night and total sleep categorized for analysis as less than 6 h, 6–8 h, and more than 8 h), the time of going to sleep at night, and the time of morning awakening and daytime sleep (*siesta*). The study excluded assessment of sleep quality and other sleep disturbances.

Female but not men HS reported poorer emotional health both in PERI and CMI than the unexposed control group. These scales were correlated with one another in both genders (Spearman's, women, $r = 0.54$ $p < 0.001$; men, $r = 0.57$, $p < 0.001$). Male HS reported poorer self-appraised health than did unexposed men, whereas in women, there was no statistically significant difference between the groups. With regard to sleep variables, female HS, but not male HS, *went to bed later and awoke later* than the control group. Female HS woke up in the morning 30 min later on average than male survivors. There was no statistically significant difference, however, in night or total (day and night) sleep duration, between the Holocaust and control groups in either sex. There was a similar prevalence of *siesta* in the female Holocaust and comparison groups, which was lower than that reported by men in both groups (Table 33.4).

Carmil and Carel [38], in 1977–1982, investigated emotional distress among (nonclinical) Israeli working population, taken from a computerized database of subjects who undertook periodic health examinations. Both HS and comparison groups did not include mentally or physically impaired individuals. The HS (n = 1,150; 395 females) were under Nazi occupation at the ages of 15–40, by 1940. The comparison group (n = 2,159 subjects; 793 females) was not in the Holocaust. The mean age of the HS group was 59.8, SD = 5.7. The questionnaire was based on the CMI [39] and a question regarding sleep ("Do you suffer from sleep distur-

Table 33.4 Age-adjusted mean (SD) values of psycho-behavioral characteristics, sleep variables, and selected risk factors by Holocaust status and sex

	Men				Women			
	Holocaust survivors (n = 130)		Comparison group (n = 202)		Holocaust survivors (n = 158)		Comparison group (n = 284)	
Variable	M	SD	M	SD	M	SD	M	SD
Age	68.0	8.8	69.0	8.7	67.2	8.4	68.8	9.7
Demoralization scale	21.7	15.0	22.5	14.0	32.7*	16.1	28.8	14.8
Cornell Medical Index	1.2	1.7	1.1	1.6	2.0*	2.0	1.5	1.9
Self-assessed health status	2.4*	0.9	2.2	0.8	2.6	2.6	2.4	0.8
Self-appraised life status	7.2	1.9	7.0	2.0	6.8	2.1	6.5	2.1
Time going to sleep p.m. (h:min)	23:12	1:12	23:06	1:06	23:18*	1:18	23:00	1:12
Time waking up a.m. (h:min)	5:42	1:12	5:42	1:06	6:12*	1:12	5:45	1:12
Night sleep duration (min)	393.9	84.1	399.2	71.1	411.4	100.7	416.2	89.4
Total sleep duration (min)	434.0	106.9	432.7	81.5	442.1	113.1	441.2	97.6
Height (cm)	166.5	6.3	165.6	7.3	153.1	7.4	152.8	7.2
BMI (kg/m^2)	26.5	3.6	26.7	3.5	27.3	4.5	27.2	5.2
SBP (mmHg)	133.9	20.3	135.8	21.1	137.7	23.2	138.8	23.3
DBP (mmHg)	77.6	12.4	78.7	11.6	75.5*	11.2	77.8	11.6
Cholesterol (mg/dl)	215.4	45.7	219.6	45.3	255.4	45.8	248.7	45.0
HDL-cholesterol (mg/dl)	43.7	15.1	43.4	13.0	54.8	18.5	56.0	16.8
Creatinine (micromol/l)	101.7	21.6	104.2	26.2	85.4*	19.1	80.0	19.6
Glucose (mmol/dl)	5.8	2.3	6.0	2.8	5.7	2.1	5.9	2.4
Albumin (g/dl)	4.4	0.3	4.4	0.3	4.4	0.2	4.4	0.3

Taken from Collins et al. [37]
*$p < 0.05$

bances?"). The variable "psychosomatic complaints" included the question "Do you suffer lately from general fatigue?" HS had significantly more emotional distress than their counterparts, primarily due to the differences between women in both groups, but none regarding sleep disturbances in both genders.

Yehuda et al. [6] published in 1997 data comparing concentration camp (CC) HS (n = 70, 40% men) and survivors who had been in hiding (n = 30, 17% men). Participants were recruited primarily from a list of participants in an oral history of the Holocaust and volunteers who saw newspaper descriptions of the ongoing research efforts at the Mount Sinai Treatment Clinic for HS and their families in New York City. All subjects were community residents: women, 67%; mean age, 65.7, (SD = 5.7, range 50–79). Subjects were excluded from the study if they had severe concurrent medical illness or axis I disorder other than mood and anxiety disorders.

The following measures were used: the OARS medical checklist [40] to determine the existence of severe concurrent medical illness, structured clinical interview for the DSM-III-R [41] for axis I disorders other than PTSD, Antonovsky's Life Crises Scale [42] for the assessment of wartime and non-Holocaust experiences during the subject's life (a measure of cumulative lifetime stressful events), and the Clinician-Administered PTSD Scale (CAPS) [43] for the presence and severity of current PTSD symptoms. Survivors who were in hiding were consistently younger at the time of their trauma than survivors of CC (camp survivors: M = 20.72, SD = 4.9 years; in hiding, M = 12.8, SD = 6.3 years; t (98) = 6.72, $p < 0.0001$). Survivors in hiding (M = 8.2, SD = 4.1) reported a higher total trauma exposure than the camp survivors (M = 6.5, SD = 3.2), with t = 2.16; $p < 0.02$. After controlling for gender and age, this association was no longer significant.

Of the sample population, 75% *reported sleep disorders* in the PTSD-*DSM-III* symptom criteria (M = 3.9 symptoms, SD = 2.7), and 60% reported symptoms regarding dreams (M = 2.6, SD = 2.5).

Shemesh et al. [44] conducted a large community study that examined emotional distress and other health dimensions, including sleep problems among HS, 60 years and above, and a suitable comparison group. This study, nested in a comprehensive health and social survey, was conducted in Israel in 1997–1998. Respondents had been between 7 and 28 years of age by the end of WWII. The interview schedule included (a) sociodemographic information (including place of birth, year of immigration); (b) emotional distress, measured by a modified version of the 12-GHQ; (c) self-reported diagnosed chronic illnesses (e.g., myocardial infarction, stroke); (d) sleep problems, including difficulty in falling asleep, difficulty in staying asleep, and early-morning awakening; (e) visits to the family physician in the preceding 6 months; (f) social activities; and (g) life satisfaction. Exposure to the Holocaust was measured using a single item: "Did you live in a country under Nazi occupation?" If positive, the respondent was asked about the exposure (ghetto, hiding, work or extermination camp, or been in none of these situations; the more severe situation was coded). The survivors were compared with Europe- and North and South America-born elderly who did not live in Nazi-occupied countries. Sleep problems were analyzed either as no problems or at least one of them present. The survivors in the sample were 896. Statistically significant intergroup differences were found for marital status (HS included more divorced/separated/widowed persons than the comparison group) and for years of education (more HS were in the 0–8 years category than the comparison group). HS had a statistically significant higher emotional distress score (M = 2.7, SE = 0.1, than their counterparts = 2.1, SE .1, $p < 0.003$). This difference remained statistically significant across gender ($p < 0.004$), marital status ($p < 0.005$), age groups ($p < 0.002$), and chronic health conditions ($p < 0.02$) and marginal for education ($p < 0.06$). *Sleep problems* were found to be significantly more prevalent in the HS group ($p < 0.0002$). A multivariate analysis to control for confounding variables showed significant differences for sleep problems ($p < 0.001$).

Stessman et al. [45] studied mortality and medical and social parameters in HS of old age in the Jerusalem Longitudinal Study, a cohort sample born in 1920–1921. Subjects of European origin (N = 458) were evaluated at the age of 70 years at baseline and at age 77. Three groups were compared: CC survivors of extermination, concentration, or labor camps (n = 93), HS who avoided camp incarceration (n = 129), and a comparison group, Europe-born subjects or of European descent (n = 236). CC were more likely to be male (p = 0.015) and to have had less than 12 years of education (p = 0.001) but similar marital and economic status. At both phases of data collection, the information included sociodemographic, medical, and functional variables. Among the health status measures, participants were questioned about their global sleep satisfaction, with a positive answer being "always or generally satisfied" versus a negative answer, "occasionally or never satisfied with overall sleep." Depression was identified using the Brief Symptoms Inventory [46]. At baseline, survivors more frequently reported poor self-rated health (p = 0.04), but the level of global sleep satisfaction was similar between the groups, as it was found during the subsequent wave, 7 years later.

The Israel component of the World Mental Health Survey (WMHS) [15] included a HS population. In this study, HS living in the community (i.e., not institutionalized) were compared with a suitable group. Both groups were part of the overall survey sample (N = 4859). The survivors group comprised Europe-born Jews who fled from Nazi-controlled

countries before WWII started or immigrated to Israel following the war's end until 1950, when survivors ceased to arrive in large numbers. Of the HS group (n = 145), 55 had been in concentration camps, 36 in ghettos/hiding, and 54 fled their country while it was under a Nazi regime (14 before the war began). The comparison group comprised Europe-born Jewish Israelis who had arrived before 1939 and had not lived under a Nazi regime (n = 31) and Israel-born respondents whose fathers were born in Europe (n = 112). The interview included six parts:

1. A sociodemographic section.
2. The Composite International Diagnostic Interview (CIDI) which is a structured interview schedule that enables diagnosis of selected psychiatric disorders: anxiety disorders (panic disorder, generalized anxiety disorder, agoraphobia without panic disorder, PTSD) and depressive disorders (major depressive disorder, dysthymia) according to *ICD–10* and *DSM–IV* classification systems. Organic exclusion criteria were taken into account in determining *DSM–IV* diagnoses. Lifetime and 12-month prevalence rates were estimated when respondents' psychiatric disorders met DSM–IV diagnostic criteria for those periods.
3. The 12-item General Health Questionnaire (GHQ–12) was used to measure emotional distress and was referenced to the past 30 days.
4. Evaluation of sleep disturbances: to meet criteria, respondents had to report at least one difficulty in falling and/or staying asleep and/or waking up too early, which was present for 2 weeks or more almost nightly, at some time during the preceding 12 months.
5. Other health-related conditions: headaches, other pain localizations, problems related to the cardiocerebrovascular system, smoking, weight and height (BMI), and use of any type of mental health services, ever and in the preceding year.
6. Exposure to adverse events: respondents were asked about Holocaust-related and unrelated adverse events faced during both their lifetime and the 2 years preceding the interview. Those events were classified as fateful (e.g., terrorist attack) and non-fateful (e.g., divorce). The adjustments made for the possible effects of adverse events on outcome variables excluded those that were Holocaust related.

The percentage of the survivor group who reported at least one *sleep disturbance* (62%; n = 90) was twice that of the comparison group (33%; n = 46; OR = 3.4, 95% CI 2.0–5.6). The difference remained significant after adjusting for age, education, religious observance, and past-year presence of anxiety and depressive disorders (OR = 2.5, 95% CI 1.4–4.4).

Sleep Laboratory Studies

Sleep laboratory studies were conducted in Israel in the late 1980s and at the beginning of 1990s (after 40 years from liberation). These studies included objective (i.e., REM and non-REM sleep variables) and subjective (narrative of dreaming and nightmares) measures.

Hefez et al. [47] reported sleep data obtained on 11 participants who had survived different traumatic events and suffered from sleep disturbances. The heterogeneous survivor group included (1) Holocaust survivors (n = 5; age = 45–68 years), of whom two were diagnosed with depression; (2) combat veterans (n = 4; age = 33, 35 (two patients), 44 years), all of them were diagnosed with PTSD; and (3) sea disaster victims (n = 2; age = 20 and 25 years). The diagnostic criteria were not mentioned. HS were outpatients, while the other two groups were studied during their hospitalization. Objective sleep measures were recorded during two to five consecutive nights of polysomnography (with EEG, ECG, electrooculogram (EOG), electromyogram (EMG), respiration monitoring with respiratory belt and nostril thermistor, and accelerometer for leg movement monitoring). Each participant was awakened from REM and non-REM sleep for dream recall (see below).

Nine age-matched controls for the combat veterans and the sea disaster survivors were obtained from a different study. The HS group was compared to 12 controls from the general literature regarding EEG sleep studies but not to subjects that participated in this study [48] (Table 33.5).

Table 33.5 Sleep laboratory data of HS (n = 5) and of control group (n = 12)

	Patients		Control group[a]		Analysis	
Measure	Mean	SD	Mean	SD	t (df = 15)	p
Total sleep time (min)	296.7	32.4	389.8	49.5	3.64	<0.01
Sleep latency (min)	16.1	16.2	11.9	10.5	0.59	n.s.
REM latency (min)	102.3	28.3	84.8	19.4	1.38	n.s.
Sleep efficiency (%)	75.5	9.5	92.0	4.0	4.73	<0.01
"Awake" plus "movement" time (%)	15.9	7.9	4.3	2.3	4.36	<0.1
Stage 1 sleep (%)	5.2	2.3	7.6	3.9	1.21	n.s.
Stage 2 sleep (%)	55.2	7.8	61.7	10.3	1.19	n.s.
Stages 3 and 4 sleep (%)	14.7	3.4	4.9	7.7	2.57	<0.05
REM sleep (%)	14.9	4.0	21.5	4.0	2.9	<0.02

Control data from general literature regarding EEG [46]

Compared to controls, all trauma-exposed participants had prolonged sleep latency, increased movements during sleep, and more frequent awakenings. The participants had *lower sleep efficiency indices* (because of prolonged sleep latency and larger amounts of "awake" plus "movement" time within sleep periods), shorter REM time, and longer REM latencies than did control subjects.

Four of the eleven survivors (of whom one was a 45 year-old HS at the time of the study) had REM- and non-REM-related nightmares, which, in two sea disaster survivors, were associated with REM-related motor activity. The Holocaust survivor with the repeated REM and non-REM haunting nightmares was a child survivor. Upon awakening he reported the same anxiety dream, in which he was haunted by the Nazis at the age of six, with many elements of the actual trauma, which happened more than 39 years before the study took place. The rest of the seven survivors had unusually low dream recall in spite of high REM density. The few dreams that could be recalled were short and dealt with trivial nontraumatic daily events. The authors concluded that they could not learn about the adaptive value of these sleep alternations, as one of the more adapted patients was the Holocaust survivor with the repeated haunting dreams. This ignited further research into whether sleep changes and dreams were related to better adaptation.

This initial study was followed by a larger study.

Kaminer and Lavie [49, 50] examined the impact of surviving the Holocaust on sleep and dreams, with differentiation between well-adjusted versus less-adjusted persons. Participants were excluded for psychiatric diagnoses, including *DSM-III* diagnosis of PTSD. However, differentiation between groups was made through an interview by a clinical psychologist and based upon post-Holocaust level of adjustment that included problems at work, social and familial problems, somatic complaints, and general satisfaction with life. This division was later validated with Structured and Scaled Interview to Assess Maladjustment (SSIAM) [51] and SCL-90 [52]. The sample included 33 participants, of whom 23 were HS, and was divided into three groups: [1] well-adjusted HS ($n = 12$, mean age:62.7, SD 4.4), including six CC survivors (three males, three females) and six survivors of hideouts (two males, four females); [2] poorly adjusted HS ($n = 11$, mean age: 57.5, SD 5.7), including six CC survivors (three males, three females) and five survivors of hideouts (three males, two females); and [3] a control group of Israel-born, age-matched normal subjects ($n = 10$, five males and five females, mean age: 61.1, SD 5.4), who lived in pre-State Israel during WWII and were not exposed directly to WWII. The majority of the survivors immigrated to Israel soon after WWII (between the years 1947 and 1950) and were from the same socioeconomic middle-class group. All participants underwent four nights of polysomnography, with the same protocol monitoring as the former study (EEG, ECG, EOG, EMG, respiration, and movement). Participants were interviewed with psychiatric and psychological batteries (e.g., Horowitz Trauma Impact Event Scale). During the first, third, and fourth nights, participants were awakened from the REM periods for dream recall. After each awakening, subjects were asked to report their conscious thoughts immediately prior to the awakening, and then participants were asked specific questions regarding their dreams (i.e., did you recognize the people or places in the dream? Were they from the past or present?), as well as their feelings toward the dreams. The volunteers knew that they would be awakened and would be questioned about their dreams. Previously devised scales were used for dream structure [53] and dream content [54]. Dream structure analysis included the following elements: vividness, imagery, complexity, length, visual elements, emotional and conflict-ridden elements, and overall salience. Dream content was coded on anxiety, hostility-aggression, and personal-social alienation scales. Other categories used for the dream content coding included danger to existence, Holocaust, unfinished affairs, everyday life, close family, and sleep lab.

The researchers obtained a total of 121 whole-night polysomnographic recordings, with 256 REM awakenings for dream recall. Since there were no significant differences between concentration camp survivors and survivors who were in hideouts, they were grouped together. The SCL and the SSIAM showed significant differences between less-adjusted group and the other two groups.

Sleep data results indicated that poorly adjusted survivors experienced longer latency to sleep onset and lower sleep efficiency in comparison to well-adjusted survivors and controls. Poorly adjusted survivors had increased sleep latency (mean, 33; SD, 25.4) compared to well-adjusted (mean, 20; SD, 7.6) survivors and controls (mean, 12.3; SD, 6.8). There were no differences in REM latency and the percent of REM and sleep stages 2 and 3/4. Dream recall differed between the well- and poorly adjusted survivors. Well-adjusted survivors had the lowest mean rate of reported dream recall (33.7 ± 21.6%) compared to the poorly adjusted survivors (50.5 ± 30.4%) and controls (80 ± 47.5%) ($F = 7.61$, $p < 0.002$). Total number of dreams recalled in each group was 34/100, 38/76, and 63/80 in the well-adjusted, poorly adjusted, and controls. Upon awakening, most well-adjusted HS often were unable to recall dreaming at all.

Regarding specific content, dreams of danger to existence were found significantly more often in the two HS groups: 81% of the dreams in the poorly adjusted, 79% in the well-adjusted, and 36% in controls, $X^2 = 7.2$, $p < 0.03$. Contents related directly to the Holocaust appeared in 4% of dreams in the well-adjusted HS, 7.8% of dreams in the poorly adjusted, and in none of the controls. The authors speculated that the suppression of dream recall in the well-adjusted HS had served an adaptive protective function. Whether this was a

premorbid personality characteristic or a postwar defense mechanism remained an unknown issue.

Although this is a unique study worldwide, the study did not examine directly the association of sleep, the Holocaust experience, and PTSD. Specifically, PTSD was not examined in the poorly adjusted group. In addition, while emphasizing internal validity, the study results cannot be generalized to other samples or traumatic event types.

Conclusion

This chapter included a diversity of studies conducted in different countries, with different subgroups of HS, in different contexts, and with different methods of problem ascertainment. In general, most but not all of the selected studies found that sleep disturbances of different types characterize the sleep of HS. They seem to be present over the course of time, from the time of liberation to six decades after the end of WWII. The second finding is of no less interest; some studies found those disturbances even in the absence of clinical disorders but, probably, in the presence of subclinical problems. To paraphrase one report [15], sleep disturbances are the remaining witness of the traumatic events undergone by a subject, whether or not a satisfactory adjustment was achieved during the course of life. Recall in this regard that sleep disturbances are the last to disappear after a response to antidepressant medication [55].

Important as well is to note that although PTSD and depression are more frequent in women, both sexes reported sleep disturbances. Also the differences between the sexes seemed to be negligible.

Of the different contexts in which studies were conducted, the sleep laboratory provided the single direct source of information regarding sleep in HS, as opposed to other studies reviewed above. Although unique in design, including the use of careful methodology regarding sleep measurements, the relative small sample size of the studies makes it difficult to generalize to the larger and heterogeneous Holocaust survivor groups. Also, the studies excluded Holocaust survivors with a psychiatric diagnosis. Recruitment methods of participants (or patients) were not described. Nevertheless, the findings were interesting and valuable. Those included (a) long-standing changes in sleep architecture, including decreased REM sleep, and (b) different patterns of dreaming and recalling in better-adjusted survivors and poorly adjusted survivors. Duration of sleep was significantly shorter in the study described first [45] but with only a tendency that did not reach significance in the latter study [49, 50].

Survivors of mass trauma and their families and those who deliver services to those people should all be aware of the long-lasting emotional effects of traumatic exposure, as expressed in sleep problems, even without the existence of full-blown psychiatric diagnosis.

References

1. Levav I. Individuals under conditions of maximum adversity: the Holocaust. In: Dohrenwend BP, editor. Adversity, stress, and psychopathology. New York: Oxford University Press; 1998. p. xv, 567 p.
2. Bauer Y, Keren N. A history of the holocaust. Rev. ed. New York: Franklin Watts; 2001.
3. Laqueur W, Baumel-Schwartz JT. The Holocaust encyclopedia. New Haven: Yale University Press; 2001.
4. Fennig S, Levav I. Demoralization and social supports among Holocaust survivors. J Nerv Ment Dis. 1991;179(3):167–72.
5. Solomon Z Chaitin J., editor. Childhood in the Shadow of the Holocaust, Survived Children and Second Generation [in Hebrew]: Hakibbutz Hameuchad; 2007.
6. Yehuda R, Schmeidler J, Siever LJ, Binder-Brynes K, Elkin A. Individual differences in posttraumatic stress disorder symptom profiles in holocaust survivors in concentration camps or in hiding. J Trauma Stress. 1997;10(3):453–63.
7. Krystal H. Wayne State University. Massive psychic trauma. New York: International Universities Press; 1969.
8. Bondy C. Problems of internment camps. J Abnorm Soc Psychol. 1943;38(4):453–75.
9. Kral VA. Psychiatric observations under severe chronic stress. Am J Psychiatry. 1951;108(3):185–92.
10. Tas J. Psychical disorders among inmates of concentration camps and repatriates. Psychiatry Q. 1951;25:679–90.
11. Friedman P. Some aspects of concentration camp psychology. Am J Psychiatry. 1949;105(8):601–5.
12. Niremberski M. Psychological investigation of a group of internees at Belsen camp. J Ment Sci. 1946;92:60–74.
13. Niederland WG. Clinical observations on the "survivor syndrome". Int J Psychoanal. 1968;49(2):313–5.
14. Chodoff P. Late effects of the concentration camp syndrome. Arch Gen Psychiatry. 1963;8:323–33.
15. Sharon A, Levav I, Brodsky J, Shemesh AA, Kohn R. Psychiatric disorders and other health dimensions among Holocaust survivors 6 decades later. Br J Psychiatry. 2009;195(4):331–5.
16. Yehuda R, Bierer LM, Andrew R, Schmeidler J, Seckl JR. Enduring effects of severe developmental adversity, including nutritional deprivation, on cortisol metabolism in aging Holocaust survivors. J Psychiatr Res. 2009;43(9):877–83.
17. Barel E, Van Ijzendoorn MH, Sagi-Schwartz A, Bakermans-Kranenburg MJ. Surviving the holocaust: a meta-analysis of the long-term sequelae of a genocide. Psychol Bull. 2010;136(5):677–98.
18. Eitinger L. Concentration camp survivors in Norway and Israel. The Hague: Martinus Nijhoff; 1972.
19. Eaton WW, Sigal JJ, Weinfeld M. Impairment in Holocaust survivors after 33 years: data from an unbiased community sample. Am J Psychiatry. 1982;139(6):773–7.
20. American Psychiatric Association, American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2000.
21. World Health Organization. The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
22. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry. 1992;49(8):651–68. discussion 69–70
23. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
24. Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch gen Psychiatry. 2004;61(5):508–16.

25. Eitinger L. Pathology of the concentration camp syndrome. Preliminary report. Arch Gen Psychiatry. 1961;5:371–9.
26. Nathan TS, Eitinger L, Winnik HZ. A psychiatric study of survivors of the Nazi holocaust. A study in hospitalized patients. Isr Ann Psychiatr Relat Discip. 1964;2:47–80.
27. Conn DK, Clarke D, Van Reekum R. Depression in holocaust survivors: profile and treatment outcome in a geriatric day hospital program. Int J Geriatr Psychiatry. 2000;15(4):331–7.
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
29. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37–49.
30. Trappler B, Cohen CI, Tulloo R. Impact of early lifetime trauma in later life: depression among Holocaust survivors 60 years after the liberation of Auschwitz. Am J Geriatr Psychiatry. 2007;15(1):79–83.
31. Winkler G. Neuropsychiatric symptoms in survivors of concentration camps. J Soc Ther. 1959;5:281–90.
32. Kuch K, Cox BJ. Symptoms of PTSD in 124 survivors of the holocaust. Am J Psychiatry. 1992;149(3):337–40.
33. Nadler A, Ben-Shushan D. Forty years later: long-term consequences of massive traumatization as manifested by holocaust survivors from the city and the kibbutz. J Consult Clin Psychol. 1989;57(2):287–93.
34. Rosen J, Reynolds CF 3rd, Yeager AL, Houck PR, Hurwitz LF. Sleep disturbances in survivors of the Nazi holocaust. Am J Psychiatry. 1991;148(1):62–6.
35. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
36. Levav I, Abramson JH. Emotional distress among concentration camp survivors – a community study in Jerusalem. Psychol Med. 1984;14(1):215–8.
37. Collins C, Burazeri G, Gofin J, Kark JD. Health status and mortality in holocaust survivors living in Jerusalem 40–50 years later. J Trauma Stress. 2004;17(5):403–11.
38. Carmil D, Carel RS. Emotional distress and satisfaction in life among holocaust survivors – a community study of survivors and controls. Psychol Med. 1986;16(1):141–9.
39. Haessler HA, Holland T, Elshtain EL. Evolution of an automated database history. Arch Intern Med. 1974;134(3):586–91.
40. Blazer D. Durham survey: description and application, in multidimensional functional assessment OARS methodology: a manual. 2nd ed. Durham: Duke University Center for the Study of Aging and Human Development; 1978.
41. Spitzer RL. National institute of mental health (U.S.). User's guide for the structured clinical interview for DSM-III-R: SCID. Washington, DC: American Psychiatric Press; 1990.
42. Antonovsky A. Health, stress, and coping. 1st ed. San Francisco: Jossey-Bass Publishers; 1980.
43. Blake D. Clinician-administered PTSD Scale (CAPS-I). National Center for posttraumatic stress disorder. Boston: Mass. Behavioral Science Division; 1990.
44. Shemesh AA, Kohn R, Radomislensky I, Brodsky J, Levav I. Emotional distress and other health-related dimensions among elderly survivors of the Shoa living in the community. Isr J Psychiatry Relat Sci. 2008;45(4):230–8.
45. Stessman J, Cohen A, Hammerman-Rozenberg R, Bursztyn M, Azoulay D, Maaravi Y, et al. Holocaust survivors in old age: the Jerusalem longitudinal study. J am Geriatr Soc. 2008;56(3):470–7.
46. Derogatis LR, Melisaratos N. The Brief symptom Inventory: an introductory report. Psychol med. 1983;13(3):595–605.
47. Hefez A, Metz L, Lavie P. Long-term effects of extreme situational stress on sleep and dreaming. Am J Psychiatry. 1987;144(3):344–7.
48. Williams RL, Karacan I, Hursch CJ. Electroencephalography (EEG) of human sleep: clinical applications. New York: Wiley; 1974.
49. Kaminer H, Lavie P. Sleep and dreaming in holocaust survivors. Dramatic decrease in dream recall in well-adjusted survivors. J Nerv Ment dis. 1991;179(11):664–9.
50. Lavie P, Kaminer H. Dreams that poison sleep: dreaming in holocaust survivors. Dreaming. 1991;1(1):11–21.
51. Gurland BJ, Stone AR, Yorkston NJ, Frank JD, Fleiss JL. Structured and scaled interview to assess Maladjustment (Ssiam). 1. Description, rationale, and development. Arch Gen Psychiat. 1972;27(2):259. -&
52. Derogatis LR. SCL-90: administration, scoring & procedures manual for the (Revised) version and other instruments of the psychopathology rating scale series. s.l.: s.n.; 1977.
53. Winget CN, Kramer M. Dimensions of dreams. Gainesville: University of Florida Press; 1979.
54. Gottschalk LA, Winget CN, Gleser GC. Manual of instructions for using the Gottschalk-Gleser content analysis scales: anxiety, hostility, and social alienation--personal disorganization. Berkeley: University of California Press; 1969.
55. Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry. 2004;65(Suppl 16):27–32.

Sleep Studies in Serbian Victims of Torture: Analysis of Traumatic Dreams

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Introduction

A prominent characteristic of the clinical picture of posttraumatic stress disorder (PTSD) is "recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)" [1] (p. 271). Distressing dreams in PTSD are considered as one of the symptoms of which main characteristic is re-experiencing of traumatic events: "A common reexperiencing symptom is distressing dreams that replay the event itself or that are representative or thematically related to the major threats involved in the traumatic event (Criterion B2)" (ibid., p. 275). This is in line with the conception that traumatic dreams are specific and different from ordinary dreams in the sense that they represent memories of traumatic events as they happened. Sometimes the dreams are described as "exact replicas" [2] or "repetitive replicas of traumatic scenes" which means that they "incorporate clear elements or even contain exact replications of a traumatic event" [3]. A contrasting view claims, however, that psychic processes, including dream processes, after traumatization are more complex and could not be reduced to a "replay" of traumatizing scenes.

Dreaming has been identified as important for safeguarding sleep by creating space for fulfilling wishes [4], problem-solving and integrative functions and for affect regulation [5–11]. Dreaming is thus held to be vital for the mind's functioning in that present stress and conflicts may be modified by dream work. There is also evidence that mental processes during sleep help in shaping and securing attachment in infanthood and that the present attachment style is reflected in interactions and affective experiences within the dream [7]. Dreaming is also believed to secure internal bonds important for internal safety [12] or attachment security in adulthood [7]. One of the main functions of dreaming is, according to several authors, memory reorganization and integration, through which the enhancement of waking cognitive functions is achieved [13]. In that sense, it is not surprising to find that persons exposed to catastrophic life events would have dreams related to these events. But the claim that these dreams are qualitatively different (i.e. just repetition or replica and without dream work in the Freudian sense) from dreams of non-traumatized individuals, or the assertion that the dreams related to the traumatic event are qualitatively different than other dreams in the same individual, requires further investigation.

Repetitive posttraumatic nightmares that apparently accurately replay the traumatic event are more easily explained by current models of PTSD, but that is not the case with the nightmares that have symbolic content related to traumatic event [14], and furthermore, there seems to be little empirical

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support for the claim that posttraumatic dreams are replicas [15] (p. 229). Traumatic dreams can instead be seen as a consequence of a posttraumatic process characterized by a failure to achieve the aforementioned functions of dreaming. Traumatic dreams are hypothesized as attempts to overcome the helplessness of the traumatic experience [16] by restoring agency and security in the dreamer's mind [8]. Lansky and Bley, in an intensive study of the dreams and nightmares of Vietnam veterans, concluded that such dreams contain defence and screening (screen memories) and are subject to distortion, symbolic substitution and displacement, which make the dream work involved comparable to ordinary dreams [17].

To our knowledge, there are no systematic studies of traumatic dreams in order to answer the questions in what way the dream content relate to original traumatic events and to what degree, if any, traumatic dreams imply work to overcome helplessness of the traumatic experience as claimed by Freud [18] and other authors [5, 17]. We believe that a better understanding of the structures of these dreams can be helped by research guided by psychoanalytical theories and their utilization in a modern-day neurophysiologic research.

In order to answer some of these questions, a study of the traumatic dream as it appears in the traumatized person's mind and is told to another is needed. Aims of our study are the investigation of latent structures of reported narratives of dreams and how these structures are reflected in posttraumatic states, as changes in affect regulation, symbolization and attachment to others. Two different methods of qualitative analysis of dreams were used. In addition we would like to demonstrate how we developed and utilized psychoanalytical qualitative methods for investigating structures of the dreams which can elucidate more complex posttraumatic psychological mechanisms beyond apparent "replaying "of the trauma in the dream.

Historical Context

After the disruption of the Yugoslavia in 1991, a series of violent conflicts erupted and lasted almost permanently until the end of war in Kosovo in 1999. All these wars resulted in hundreds of thousands of deaths, huge number of individuals injured, physically disabled and, even more important to our immediate concern, unknown number of individuals suffering from chronic mental disorders resulting from exposure to war-related atrocities, torture and violence. Combat operations encompassed huge territories and included significant proportions of population, either as combatants or as civilian victims of war. Every sixth citizen of the former Yugoslavia experienced forced displacement [19] and every third citizen from the territories encompassed by combat operations (33.54% of the total population of Croatia, Bosnia and Herzegovina and Kosovo) [20].

There are several characteristics of wars in ex-Yugoslavia that should be mentioned here for the purpose of better understanding. Most important is that these were interethnic wars in multiethnic territories. Military operations in many cases were conducted in urban areas (e.g. in Vukovar or Sarajevo); civilians were intentionally targeted within the so-called ethnic cleansing, the "term [which] denotes a set of actions that the police, military and political authorities take in order to annihilate or significantly reduce an ethnic group in a particular territory" [20]. All of these resulted in "grisly and bloody street fighting, with a rather uncertain destiny of those ethnic groups that found themselves unorganized and unarmed [and] unselective destruction or eviction of whole villages" (ibid.). Mobilizations of men to combat units were carried out voluntarily or by force [21], and a majority of armed personnel of these units were civilians prior to war.

Consequences of these factors could be seen in traumatic destinies of survivors: one individual could be a refugee, a warrior or a torture victim, exposed to combat-related stressors for years or only surviving a single incident, living in a war zone on a distance from a combat line but still surviving horrible abuse from neighbours of other ethnicity, etc. These huge differences influenced the problem of assessment of war-related traumas as well.

Method

The research presented here was part of the larger, multicentre research project entitled "Psychobiology of posttraumatic stress disorder". Implemented from 2004 to 2008, the aim had been to better understand the correlations among biological and psychological variables of PTSD [22, 23].

Subjects

Subjects of this study are coming from a larger network of clients of the Centre for Rehabilitation of Torture Victims (CRTV), which operates within the civil society organization International Aid Network (IAN). CRTV developed, over the course of time, significant relationships with associations of victims of war (refugees, torture survivors, war veterans) and governmental healthcare institutions able to provide additional treatment for clients [24]. These networks were used for the recruiting of subjects in the current research. The group of subjects with current PTSD (n = 133), as diagnosed with the Clinician Administered PTSD Scale CAPS-DX [25], was assessed for the presence of nightmares in a 2-week period prior to assessment. Among these 133 subjects, we selected 25 subjects who reported having had three or more nightmares in a two-week period. A structured clinical interview for DSM-IV, SCID-CV [26], was used as a

diagnostic tool for co-morbid disorders which were enlisted as exclusion criteria, such as current psychotic disorder, except major depression. Other exclusion criteria were current organic mental disorder, alcohol or substance dependence or alcohol abuse within 6 months prior to the entry procedure and use of medications (benzodiazepines, antidepressants, antipsychotics) within at least 4 weeks prior to the entry procedure.

Selection of Torture Survivors

In this paper we focus on torture survivors. Torture is characterized by complex psychological and physical measures aiming at creating extreme anxiety and affect personality functions in deleterious ways. To identify torture survivors, the War-Stressors Assessment Questionnaire (WSAQ) [27], a measure for assessment of war-related stressors, was used, which is a self-reporting questionnaire designed specifically for individuals who survived combat operations in ex-Yugoslavia. WSAQ contains 67 items describing eight different clusters of war-related stressors: (a) "active combat", (b) "witnessing of death or wounding", (c) "loss of organizational/military structure", (d) "war-related deprivation", (e) "injury", (f) "life in hostile surrounding", (g) "imprisonment/torture" and (h) "combat exposure". Subscales of the questionnaire appear to have relatively good psychometric characteristics, e.g. Cronbach alpha coefficient ranging from 0.72 for subscale "life in hostile surrounding" to 0.93 for subscale "witnessing of death and wounding" [27]. Subjects were selected using the score on subscale "imprisonment/torture" of the WSAQ. This subscale consists of ten items of which nine are directly related to experiences related to imprisonment and one item is related to witnessing of torture of family members. Nine subjects in experimental group were identified as victims of torture, and they are included in this study. The average age of participants (years) was 46.11 (SD = 7.32), and average education (years) was 12.56 (SD = 3.36).

Ethical approval was obtained from the Ethical Review Board of the University Medical School, Belgrade, Serbia. Detailed oral explanations were given, and written consent was signed by all subjects included in the study.

Sleep Laboratory Procedure

Prior to entering the study, a psychologist explained the study protocol in detail to the potential subject, presenting also written informed consent that had to be signed upon agreeing to participate. Participants were informed that they should be willing to report their dreams to a technician during the night in the sleep laboratory and in the morning to a psychoanalytically trained researcher.

The participants were then scheduled for two nights in a sleep laboratory in Median Psychiatric Clinic in Belgrade for polysomnography (PSG) and dream narrative recordings. The participants were instructed how to use a sleep diary (2 weeks prior to assessment).

Each participant spent two consecutive nights in the sleep lab. A brief introductory interview with the neuropsychiatrist and preparation for recording with electrode placement was carried out between 21:00 and 22:00 h. The Oxford Medical EEG/PSG and videometry system P3 with 32 EEG and eight polygraphic channels (and auxiliary equipment) were used for polysomnographic measurements. The start of PSG recordings (lights off) was at 22:00 h. At 06:45 h, the following morning or after the last REM sleep episode, but not exceeding 07:00 h, subjects were awakened and PSG recordings were stopped. A maximum of three awakenings per night were performed. Ten minutes after onset of sleep phases REM-II, REM-III and REM-IV, the subjects were awakened and asked for any memories of what had been going on in their minds prior to awakening. In case of a dream memory, the participants were asked to report the dream spontaneously and uninterrupted. After the first spontaneous report, the interviewer asked specifying questions. Thus, material that was memorized during the interview could also be collected as a dream narrative. After finishing the interview, electrodes were controlled, and the participant was sent to sleep again.

In case of nightmares or night terrors, narratives of dreams were collected during the night, immediately upon awakening by a technician trained for performing dream interviews.

The dreamer was not interrupted while he was telling a dream. In the early morning, the participant was interviewed by one of two psychoanalytically trained researchers. All interviews were audiotaped, transcribed and translated into English. The recorded data allowed a reliable identification of sleep phases during the night and of systematic analysis of the recorded dream narratives.

Dream Analysis

The Zurich Dream Process Coding System of Moser and von Zeppelin

The dream coding method by Moser and von Zeppelin [28] is an evaluating system which helps to analyse the dream material based on a model of cognitive-affect regulation. Formal criteria are used in order to investigate manifest dream content and its changing structures. Moser and von Zeppelin describe the regulating processes of dream organization as based on positioning elements into the dream world. They assume a working memory, which is monitoring the dream activity. The memory system contains information of the different dream situations and of their possible consequences

(affective feedback) as well as regulating procedures responsible for changes that seem necessary in the dream process.

Formal criteria and structures of a dream are the number of situations contained in a dream; the type of places and social settings named in a dream (descriptions, attributes); objects appearing (and their descriptions, attributes); placements, movements, interactions of objects as well as the question of whether the dreamer himself was involved in interactions or if he remains a spectator; affective reactions; and finally the ending and beginning of a situation (how, when, interrupts). The dream coding system aims at making these structural aspects of dreaming transparent in order to better understand the affect regulation processes taking place.

Two principles of affect regulation are assumed: (1) a security principle and (2) an involvement principle. The former becomes transparent through "positioning" and the latter through "interactions". The first variant gives hint to how involvement tendencies are handled in the dream. Thus, a conclusion could be that interactions include a high risk or deterioration and finally destruction. The security principle can be detected in the second variant. By avoiding movements, changes and transitions, the dreams appear rather static. The dream process reveals not much more than the positioning of some (often anonymous) objects and no interactions take place. These two principles are moderated via trajectories (movement traces) leading from a positioning to an interaction or out of an interaction back to a positioning. Common to both principles is their ruling by negative and positive affects, i.e. anxiety is the motor for an enlargement of security, regulating involvement by, e.g. interrupting interactions, generating a new situation or interrupting the entire dream. Likewise, hope is active in the security as well as in the involvement principle. It is assumed that problem-solving can only take place and be tested in interactions; therefore, successful dreaming activity tends towards interaction.

Psychoanalytic Enunciation Analysis

The Psychoanalytic Enunciation Analysis (PEA) has been applied to the fields of psychiatry, psychotherapy and psychoanalysis [29] – especially concerning the mental conditions of psychosis, trauma and suicide [30, 31]. PEA can be defined as a method that combines the phenomenology of the dream with a psychoanalytically informed analysis of the structure and dynamics of the dream-telling.

The person who is speaking – telling a dream or another kind of narrative – is at the same time embedded in and structured by the speech he is authoring.

In its simple structure the enunciation is defined as:

> **I** (1st-person) say/tell/inform/ask/command/promise **you** (2nd-person) that **this and this** (3rd-person, reference) is **the case**.

The full model is more complex. "Behind" or "underneath" any manifest utterance are tacit internal enunciation structures working, and they thus give depth to the utterance and define its final structure. When one person is telling his dream by saying "I do not know what I am saying", then it is implied that "[I say to you that] I do not know what I am saying". In the "[I say to you that]" lies an internal object-relational structure which implies at least two modes of intersubjective dimensions: an *imaginary mode* and a *symbolic mode*. Under normal conditions, these two modes are always present in the dialogues between two persons speaking to each other.

The *imaginary mode* concerns the subject's immediate experiential reaction to and/or interaction with the world in its material and spatially conceived scenarios. The speaking person creates in this way a "mirror" which he himself can get a picture of both his own state of mind and the situation referred to.

The symbolic mode appears differently. If the speaker says: "They tortured me again and again and wanted me to confess plans that I did not know of. I tried to imagine how I could convince them that I was innocent", then the utterance makes use of verbal expressions and concepts that are not primarily spatial but rather get their value and meaning through a narrative temporal process (past-present-future) with abstract, symbolic, value-based and context-dependent words. This part of the enunciation structure is called the *symbolic mode,* developed through the person's life experiences; it is partly situation-dependent and partly situation-independent. In the concrete dream-telling, it sometimes appears just as immediate as the fantasies of the imaginary mode, but it is always framed and formed by reflective thoughts and thinking.

The concepts of *imaginary mode* and *symbolic mode* are both related to different processes in the mind's way of working in communication – the imaginary being associated predominantly with automatic, pre-reflected and preverbal processes and the symbolic with self-reflective processes. Both modes are assumed under normal conditions to work together; they are both dimensions in an integrated narrative representation of a dream. As we shall see later, the dreams of the severely traumatized person appear with an enunciation structure in which precisely the linking of the imaginary mode and the symbolic mode is often disconnected or instable.

Results

Polysomnographic Data

The 25 subjects who were investigated in the sleep laboratory[1] spent on the average 464 min in bed (time in bed, TIB), and their average total sleep time (TST) was 397 min.

[1]We would like to express our gratitude to Professor Michael Schredl, Institute for Mental Health, Mannheim, for evaluating EEG data.

As Table 34.1 demonstrates, their waking times were between 26.5 and 154 min leading to an average sleep efficiency of 85.5%.

It is obvious that only three subjects showed lower sleep efficiency than 80%. Thus, the subjects seemed not to be impaired in their amount of sleep, even though interviews were carried out during the night. The laboratory situation did not seem to affect the subjects in a negative way.

Parametric (t-test) and nonparametric (median test, Moses test of extreme reaction, Mann-Whitney U test) tests were used in order to find differences between a subgroup of nine tortured subjects and the rest of the group. No significant difference was found. We wanted to explore other possible effects of types of war-related traumatic experience on sleep parameters. Results are presented in Table 34.2. There is only one significant correlation: between the experience of active combat and REM latency. However, after Bonferroni correction, this correlation didn't remain statistically significant, and we will not discuss its possible meaning. No other type of traumatic experience, including imprisonment and torture, did appear to correlate with any of the sleep parameters.

Dream Analysis

There are two types of dream narratives that are collected during the assessment: (a) dreams that are dreamt in the laboratory, either recorded during the night upon awakening from sleep (spontaneous or initiated), and (b) dream narratives recorded in the morning immediately after the sleep, when subjects were asked to tell dreams that they dreamt during the last night. They are marked as "lab-night" and "lab-morning". In addition, we asked subjects to tell any dream that they had since the war which they consider as important or recurring. These dreams were marked as "dream-remembered".

For the nine subjects identified as victims of torture, we recorded a total of 24 dream narratives, of dreams dreamt during two nights in the laboratory. In addition, we recorded 11 dream narratives of "important or recurring dreams dreamt after the war".

Dream analyses were performed systematically. Each interview was transcribed in Serbian language and later translated into English. Subsequently, dream narratives were

Table 34.1 Polysomnographic data

Subject	Lights out	Sleep onset	Wake-up	TIB (min)	TST (min)	Sleep efficiency (%)	Sleep latency (min)	REM latency (min)	Waking time (min)
9	22.30	23.34	06.29	479.5	441.5	92	65	67	38
14[a]	22.23	22.27	06.22	479	397.5	83	3.5	63.5	81.5
16	22.00	22.13	06.10	490	446.5	91	13.5	54	43.5
20[a]	22.47	22.54	06.11	444	402	91	7	90	42
35	22.09	22.45	05.39	450	373.5	83	36	53	76.5
97[a]	22.12	22.18	06.02	470.5	437	93	6	73	33.5
116	22.13	23.09	05.11	417	309	74	56.5	58.5	108
157	22.19	22.23	06.13	474	447.5	95	4	56.5	26.5
158	21.59	22.12	05.54	473.5	349	74	13	22.5	124.5
159	22.22	22.33	05.51	448.5	390.5	87	9.5	47	58
161	22.05	22.15	06.04	478.5	419.5	88	9.5	57.5	59
185	22.06	22.31	06.06	480	408	85	25.5	76	72
188	22.32	23.06	05.48	436	316.5	73	34	40.5	119.5
205[a]	21.50	22.02	05.41	471	428	91	12	74.5	43
206[a]	22.04	22.11	05.56	471	394.5	84	6.5	157	77
211[a]	22.04	22.24	05.55	471	406.5	86	20.5	66	44
230[a]	21.42	22.08	05.36	473.5	319.5	68	25.5	58	154
297[a]	22.17	23.04	06.16	479	448.5	94	47.5	57	30.5
303	22.09	22.47	05.29	440	353	80	39	82	87
308[a]	00.14	01.03	06.57	403	330	82	49	33	73
341	22.31	22.46	06.22	471	442	94	15	46	29
348	22.00	22.34	06.14	494	434.5	88	34	44	59.5
352	22.05	22.14	06.03	478	451	94	8.5	141.5	27
399	22.17	22.27	06.07	470	396	84	10	133.5	74
411	22.19	22.42	06.08	469	396.5	85	23	62.5	72.5
414	22.06	22.30	05.50	464	386	83	24	86	78

TIB time in bed, *TST* total sleep time
[a]Participants identified as torture victims

Table 34.2 Correlations between dimensions of war-related stressors and sleep parameters

	Active combat	Witnessing of death or wounding	Loss of organizational/ military structure	War-related deprivation	Injury	Life in hostile surrounding	Imprison ment/torture	Combat exposure
TIB	0.01	−0.095	0.027	−0.062	−0.281	−0.082	−0.195	0.004
TST	0.064	−0.14	0.126	0.172	−0.216	0.043	−0.097	0.118
Sleep efficiency	0.07	−0.134	0.143	0.257	−0.151	0.097	−0.008	0.153
Sleep latency	−0.323	−0.254	−0.234	−0.176	0.121	−0.002	−0.116	−0.288
REM latency	0.532a	0.042	0.295	0.341	0.049	0.005	0.055	0.152
Waking time	−0.111	0.11	−0.142	−0.268	0.08	−0.113	0.013	−0.143

[a]Correlation is significant at the 0.01 level (2 tailed)

marked and defined in the transcripts by one of the research members (SH) and suggested to the group. Unclear cases were discussed until a consensus was reached.

Summary and Interpretations of the Results Obtained with the Zurich Dream Process Coding System of Moser and von Zeppelin

A total of 24 dreams dreamt in the laboratory by nine participants who were detected as torture survivors have been coded with the dream analysis system developed by Moser and von Zeppelin. In order to apply the coding system, the dreams had to be transformed into present tense and afterwards segmented into different scenes. In what follows, a short descriptive summary of the relevant coding of the dreams from torture survivors is given.

We assume that traumatic experiences are relevant to the subjects and that they have to deal with their traumatic experiences in dreams. The main protruding finding of the evaluation of this group of dreams is that there seem to be two ways of coping with potentially frightening dream scenes, which resemble traumatic experiences: in the first option topics of destruction and threat appear in the dreams, above all in the context of interactions with others. Interactions and exchanges with other persons are dreamt, but topics of destruction or negative influence characterize the relations and exchanges. Beating, torturing, killing and lynching take place, but also running, escaping and chasing are very prominent.

The second option seems to be to prevent or stop any kind of relevant development of the dream. These dreams impress by a lack of LTM codings, i.e. situations in which changes take place (which are necessary to initiate movements, development of actions and finally transitions). These dreams remain static and just contain a steady moment, without changes or transformations. In contrast to the first variant, in which the dreamer seems to be more active, the second variant can be characterized as a more passive strategy, not to take risks.

A third feature of the dreams can be found in both variants described: the objects that appear in the dreams are to a large extent described either as anonymous persons or as anonymous groups. Quite rarely real objects with a clear identity and contour appear. This can also be understood as a sign of difficulty to enter into a relational context. The inner world of object representations seems to be impaired, and relational experiences to individuals and their inner representations are hampered.

Summary of PEA Analysis of Torture Survivors' Dreams

Dreams dreamt in the laboratory were characterized by the following:

- The symbolizing function never failed totally: when telling the dream, the dreamer most often was able to narrate the content in a symbolic context. The dreams were at times related to experiences of war and torture but never presented as repetition or replicas of these traumatizing experiences. Elements from other parts of the dreamer's life were intermingled with war experiences and often the traumatizing experiences were hardly present. Some apparent transformations were present, like slaughtering animals to provide food.
- The imaginary mode was dominating: the narration of the dreams where as a rule short, with often insufficient reports of events and often presented concretely, like "this happened, and this happened". When the imaginary mode is structured in time and space modes, the telling of the dream is characterized by a transportation of mental pain to the listener. The dreamer is not reflecting and not inviting the listener to reflect on the dream. When the imaginary space is not structured in time and space modes, then

the telling is more an evacuation of undigested painful mental content. Telling the dream seems to equal getting rid of unwanted and painful mental content.

- Emotions were hardly present in the dream narratives. The reports were emotionally flat, except for reports of anxiety and horror feelings.
- Passivity dominated. When activity was present, it concerned most often trying to escape from dangers and in a few direct aggressive acts towards others. Often active attempts led to being trapped and the fearful wakening occurred.

Dreams remembered were more often more directly about war and torture experiences, but these narrations had as a rule the characteristic of memories rather than dream-telling.

A Case Study: Analysis of Dreams from Subject 308

We have chosen subjects 308 in order to demonstrate the relevance of studying dreams systematically in torture victims.

Personal history Subject 308 is a 46-year-old man of Serbian ethnicity, with basic education (8 years of elementary school); he is married and has one child and is currently unemployed. He was mobilized at the beginning of war into reserve units of JNA (Yugoslav People's Army) and was often deployed to direct fighting; he spent 39 months at the combat line. He was not wounded during the war but was captured and imprisoned for 5 months. During that time, he was physically abused and tortured and witnessed other people being tortured, raped and killed and was forced to hard labour.

Results of the polysomnographic assessment of basic sleep parameters for subject 308 are presented in Table 34.1. What is striking is that subject 308 has a clearly poorer sleep efficiency (66.4%) compared to the other subjects (above 80%). However, waking time was of course extended due to the interviews performed for dream collection.

Narratives of the dreams Table 34.3 contains a direct, uninterrupted dream narrative of subject 308, recorded after the first night in the laboratory (left column). It was broken into four separate dreams (with the narrations between them) and a

Table 34.3 Narratives of dreams from subject 308 together with units of analysis for Moser method and PEA

Recorded material	Units of analysis	
	Moser method: Scenes included in the dream report	The units of the PEA
P: Let me tell you, I slept, but I woke up several times and I had some dreams, not so intense dreams, more or less those were usual things, I woke up, I woke up four times and then I couldn't sleep, I was turning and rolling, so; well, one night passed and that's it Interviewer: Can you remember any of dreams that you dreamt? P: First I dreamt, first I dreamt that		#1 – Let me tell you, I slept, but I woke up several times and I had some dreams, not so intense dreams, more or less those were usual things #2 – I woke up, I woke up four times and then I couldn't sleep, I was turning and rolling, so; well, one night passed and that's it Interviewer: Can you remember any of dreams that you dreamt?
Dream 1		
I should drive my mother somewhere and I sat in the car and opened her door so she could sit – at the same moment, one person approached me, man in the uniform and he said to me: "You have no chance against us, look how many men we have". I managed, as I was turned to the door, to open it for my mother, but instead of my mother, that young guy appeared. I just turned my head and looked in front of the car, and I saw many people in uniform	S1: I shall drive my mother somewhere and I sit in the car and open her door so she can sit – S2: At the same moment, one person approaches me, man in the uniform S3. He says to me: "You have no chance against us, look how many men we have" S1: I manage, as I am turned to the door, to open it for my mother S2: But instead of my mother, that young guy appears S4: I just turn my head and look in front of the car and I see many people in uniform (…) S3: (So when) he says, when he shows up at the door: "Look how many men we have" and when I see that person in uniform I know that I am in danger, that, that my life is threatened, do you understand – and (cough) S4: I instinctively look how many of them are there and they are S5: The car is in the yard, you know, so the car is there, and in front of it there is opened gate and the road is; I have to get out of that yard and S6: They are standing in lines, two by two or three by three, and they all are, that's interesting, in those green military uniforms and they are standing, and after that I wake up	#3 – First I dreamt, first I dreamt that I should drive my mother somewhere and I sat in the car and opened her door so she could sit #4 – At the same moment, one person approached me, man in the uniform and he said to me: "You have no chance against us, look how many men we have" #5 – I managed, as I was turned to the door, to open it for my mother, but instead of my mother, that young guy appeared. #6 – I just turned my head and looked in front of the car and I saw many people in uniform

(continued)

Table 34.3 (continued)

Recorded material	Units of analysis	
	Moser method: Scenes included in the dream report	The units of the PEA
Comment		
That was the first dream, then I, immediately after that I woke up, then I turned round and round, and I analysed it, then I fall asleep and		#7 – That was the first dream, then I, immediately after that I woke up, then I turned round and round, and I analysed it,
Dream 2		
I dreamt that my aunt died, in fact my uncle came and asked me to drive him somewhere, that something; to let somebody know that aunt has died	S1: My aunt dies, in fact S2: My uncle comes and asks me to drive him somewhere, that something; to let somebody know that aunt died	#8 – Then I fall asleep and I dreamt that my aunt died, #9 – In fact my uncle came and asked me to drive him somewhere, that something; to let somebody know that aunt has died and I woke up again
Comment		
And I woke up again; I mean those devices weren't problem I was able to turn over – Then I fall asleep again and dreamt the 3rd dream		#10 – I mean those devices weren't problem I was able to turn over – #11 – Then I fall asleep again and dreamt the third dream
Dream 3		
We were driving some material, me and my neighbour, two neighbours, and we had to cross some water, and wondered will we get through or we won't, will we succeed or we won't, and this and that, somebody was shouting: "Go this way" and others: "Go that way"	S1: We are driving some material, me and my neighbour, two neighbours, and S2: We have to cross some water, ---: And wonder will we get through or we won't, will we succeed or we won't, and this and that, S3: Somebody is shouting: "Go this way" and others: "Go that way"	#12 – We were driving some material, me and my neighbour, two neighbours, and we had to cross some water, #13 – And wondered will we get through or we won't, will we succeed or we won't, and this and that, #14 – Somebody was shouting: "Go this way" and others: "Go that way"
Comment		
That was it and then I woke up and the fourth was		
Dream 4		
I dreamt my cousin, my uncle's daughter. Somehow we were surprised, she surprised me and I surprised her, something happened that surprised the both of us. We were in the room and some people passed through that room, mostly women, they were dressed in black, I don't know, they all were in black	S1: I dream my cousin, my uncle's daughter. Somehow we are surprised, she surprises me and I surprise her, something happens that surprises the both of us S2: We are in the room and some people pass through that room, mostly women, they were dressed in black, I don't know, they all are in black	#15 – That was it and then I woke up and the fourth was, I dreamt my cousin, my uncle's daughter #16 – Somehow we were surprised, she surprised me and I surprised her, something happened that surprised the both of us #17 – We were in the room and some people passed through that room, mostly women, they were dressed in black, I don't know, they all were in black
Comment		
And then I woke up and fall asleep again and I didn't dream anymore, so I had four dreams, but it wasn't something that is usual for me, because I told doctor last night, sometimes happens that one night, two nights in a row I don't dream, but the third night		#18 – And then I woke up and fall asleep again and I didn't dream anymore, #19 – So I had four dreams, but it wasn't something that is usual for me, because I told doctor last night, sometimes happens that one night, two nights in a row I don't dream, but the third night;

(continued)

Table 34.3 (continued)

Recorded material	Units of analysis	
	Moser method: Scenes included in the dream report	The units of the PEA
Night terror		
Recently I thought that I will die, it was, I felt really; – I lost my breath, my heart was in my mouth, I lost strength, my wife slept beside me and I put my hand on her and tapped and tapped her and she woke up and I managed to say: "Give me water and sugar" – and then when I couldn't; it was horrible; we were in offensive/that was horrible	S1: I think that I will die, it is, I feel (it) really; – I lose my breath, my heart is in my mouth, I loose strength S2: My wife sleeps beside me and I put my hand on her and tap and tap her S3: And she wakes up and S4: I manage to say: "Give me water and sugar" S5: And then when I can't – It is horrible S6: We are in offensive – That is horrible	#20 – Recently I thought that I will die, it was, I felt really; – I lost my breath, my heart was in my mouth, I lost strength #21 – My wife slept beside me and I put my hand on her and tapped and tapped her and she woke up #22 – And I managed to say: "Give me water and sugar" – and then when I couldn't; it was horrible; we were in offensive/that was horrible

night terror that the subject was referring to at the end of his report. The middle column depicts material transformed into "scenes" as they are used in Moser and von Zeppelin's method of analysis: the entire dream narratives are transformed into sentences in present tense and subsequently divided into whole circumscribed scenes. In the right column, similar material is given for the PEA: narratives of the manifest dream are divided into enunciation "units" (see Table 34.3).

Analysis of Dreams from Subject 308 with the Zurich Dream Process Coding System of Moser and von Zeppelin

To facilitate transparency of the coding, three columns are being used: (1) the positioning field (PF), (2) the field of trajectories (called "loco time motion", LTM) and (3) the interaction field (IAF). The positioning field contains all objects or rather cognitive elements (CE) as well as their attributes and their position. In the field of trajectories, all movements of objects and CEs are coded, and interactions with others are coded in the interaction field column specifying changes to the self, reaction relations and response relations of the objects while specifying whether they are happening to the dreamer himself or to others or are only observed by the dreamer. It is assumed that the more elements are used in the dream scene (mirrored in different subjects and objects summarized in the positioning field), the more possibilities are available for the dreamer to regulate his affects and contents processed in the dream. If the dream remains in the positioning field, security aspects dominate, indicating that the dreamer is hesitant to get involved in interactions. Codes appearing in the second column, i.e. field of trajectories, signify what has been named by the authors "loco time motion" (LTM) and indicate preparations for interaction that will follow. These interactions can be summarized as changes that develop during the dream scene without interrupting the scene. Finally, all types of interactions are summarized in the third column, the IAF: codes in this column signify the ability of the dreamer to get involved with others, even if the interaction might fail or end in a destructive way.

A fourth element normally ignored by dream researchers is so-called interrupts. It comprises all kinds of abrupt endings or interruptions of the dream situation, but also cognitive processes (CP) like commenting on a dream situation in an emotional or cognitive way may to some extent create a distance and interrupt the dream experience.

Comments on the Moser and von Zeppelin Findings

Results of analysis of dreams with the dream analysis method developed by Moser and von Zeppelin are presented in Table 34.4. Most striking is that except for the first dream, all the other dreams are very short. Relational involvements and deeper interactions with other objects are not developing. On the contrary, very shortly after the initial scene, the dream process is interrupted and the dreamer wakes up.

In the first dream the threatening situation is replacing the initial scene with the mother. The dreamer tries to handle and deal with the powerful affect that is developing in his first dream and which continues to prevail throughout the other dreams during the rest of the night. The self remains passive as if experiencing an unsolved situation and tries to escape. In the first dream, an interrupt occurs when the affect is becoming too threatening. It is not possible to escape or somehow handle the threatening situation expressed by the soldiers. Thus, the dreamer interrupts the dream. Trying to escape, to move to another place or to solve an uncertain situation continues to bother the dreamer. Less and less flexibility leads to earlier interrupts, i.e. ending the dreams and waking up. Death and destruction are becoming more and

Table 34.4 Analysis of dreams of subject 308 with the Moser method

Situation	Positioning field (PF)	Field of trajectories (LTM)	Interaction field (IAF)
Dream 1			
S1	SP OP1 (mother) CEU1 (car) CEU2 (door)		IR.C
S2	SP OP2 (man) ATTR (uniform) CEU3 (uniform)	LTM OP2	V.R. OP2 → SP
S3	SP OP2 (man)		IR.C res OP2 → SP
S1	SP OP1 (mother) CEU2 (door)		IR.C SP ← → CEU2
S2	SP OP2 (man) ATTR (young)	LTM OP2	
S4	SP ATTR (my head) CEU1 (car) OP3 (G) (many people) ATTR (uniform)	LTM SP	
S3	SP OP2 (man) CEU2 (door)	LTM OP2	V.R.
/C.P./ /EX AFF-R./			
S4	SP OP3 (G)		
S5	SP CEU1 (car) CEU3 (gate) CEU4 (road)		
S6	SP OP3 (G) ATTR (standing in lines: two by two; three by three; uniform) CEU4 (green military uniform)		
Wake-up			
Dream 2			
S1	SP OP1 (aunt)		IR.D
S2	SP OP2 (uncle) OP3 (somebody) OP1 (aunt) ATTR (dead)	LTM OP2	V.R.
Wake-up			
Dream 3			
S1	SP OP1 (G) (neighbours) CEU1 (material)	LTM SP, OP1, OP2	
S2	SP OP1 (G) CEU2 (water)		
/C.P./			
S3	SP OP2 (somebody) OP3 (others)		V.R.

(continued)

Table 34.4 (continued)

Situation	Positioning field (PF)	Field of trajectories (LTM)	Interaction field (IAF)
Wake-up			
Dream 4			
S1	SP OP1 (cousin) ATTR (uncle's daughter)		IR.C res
S2	SP PLACE (room) OP2 (G) (some people) ATTR (women dressed in black)		IR.C kin
Wake-up			
Night terror			
S1	SP ATTR ATTR AFF		IR.S
S2	SP OP1 (wife) ATTR		IR.C
S3	SP OP1 (wife)		IR.S
S4	SP OP1 (wife)		V.R.
S5	SP		IR.S *FAIL*
/EX AFF-R./			
S6	SP OP2 (G) (we)	LTM	
/EX AFF-R. wake-up/			

Agenda: *SP* subject processor (the dreamer), *OP* object processor (other persons in the dream), *CEU* inanimate cognitive element, *IR.C* relation, not specified, *ATTR* attribute, *LTM* loco time motion trajectory, *V.R.* verbal relation, *IR.C res* resonance relation, */C.P./* cognitive process, */EX AFF-R./* explicit affective reaction, *IR.D* displacement relation, *Wake-up* awakening from the dream, *IR.C kin* interaction/interplay with body feelings, *IR.S* relation of self-change, *ATTR AFF* affective attribute, *IR.S fail* relation of self-change failed, */EX AFF-R. Wake-up/* affective reaction with awakening from the dream

more overwhelming. As a consequence, the dreamer reports a night terror at the end of the interview in which the pure affect is overwhelming the dreamer. Interactions are enacted in order to reach security and safety again. The terror is becoming clear when at the end the process merges into the feeling of being still on the battlefield. In this last report of the nightmare the difference to the symbolized content of the dream processes in dreams 1–4 becomes apparent. A minimum of symbolization activity remains intact, making it possible to find pictures and scenes for the frightening content. In the night terror, no content is left, only the threatening affect is dominating and felt on a physiological level.

PEA of the Dreams of Subject 308

The main aim of PEA in our investigation is to evaluate the levels of symbolization of the manifest dream, i.e. the cohesion of the imaginary and the symbolic dimensions and to evaluate the internal subject-other relations (internal object relations) implicitly present in the dream-telling.

The method of PEA implies (1) division of the manifest dream text into enunciation "units" (Table 34.3 above), (2) analysis of the structure of enunciation for each of these "units", (3) analysis of each "unit" for its manifest and latent content (especially the latent content as emotional content) and (4) evaluation of the transferential relationship implied in the dreaming.

Assessing Levels of Symbolization

Symbolization may be seen as qualitatively different modes of making language expressions meaningful for oneself or another. We evaluate three dimensions of symbolization and "score" them on a Likert scale from 1 to 5.

1. Differentiation of descriptions of dreams (1–5). The assessment includes details and nuances of the presentation of perceived phenomena (locations, persons, scenarios), qualities of what is seen and what is heard and coherence of the description.

2. Interactions and intersubjective relations (1–5). This variable is assessed by the following criteria: the telling of intentions and actions involving self and/or other and the modes and nuances of the exchange between self and other.
3. The presence of emotions (1–5). This variable is assessed by the general impression of whether emotions are available or absent in the dream.
4. Relation to interviewer is rated dichotomously based on whether the utterances are predominantly in the symbolic or imaginary mode.

The imaginary and the symbolic modes both consist of two dimensions that signify the presentation of different in-depth relationships between the first and second person on the manifest/verbal level of the utterances. The dimensions in the imaginary mode are labelled D1 and D2. The dimensions in the symbolic mode are labelled D3 and D4 (Table 34.5).

In the imaginary mode, the dimensions are scored in the following way:

D1: the utterance is non-contextualized and fragmented (e.g. in cry of pain, bodily sensation, feeling of emptiness).

D2: the utterance is dominated by spatial organization of the content (interactions, description of events and course of events).

In the symbolic mode, the dimensions are scored as:

D3: the utterance is dominated by descriptions, definitions, teaching-like ideas, universals and common sense.

D4: the utterance has the character of a question-setting and self-reflective dialogue.

Furthermore, each utterance is assessed whether the imaginary and the symbolic modes are integrated or disintegrated. We used the label [+] for integration and the label [−] for disintegration.

The global assessment of the dream:

Degree of differentiation = 3
Degree of interactions = 3
Emotions expressed = 3

As to the quality of the emotions, the dreamer had many feelings of being abandoned, not surviving and being helpless

Table 34.5 Summaries of PEA

Sequence/PEA	Manifest level	Latent level
#1 D4;+;D2	I wish to tell you some of my dreams	A desire after being taken care of and accepted. Need for support
#2 D1;+;D4	I slept in an disquiet way	Apprehension over survival. Hopelessness
#3 D2;+;D4	I should transport my mother to some place and opened the door in my car for her	Need for closeness and protection but also need to be the active, the one who protects
#4 D2;+;D4	A man in uniform threatened us	Fear of persecution Fear of helplessness, and being made a passive victim
#5 D2;+;D4	I wanted my mother to be with me	Feelings of insecurity and inability to see control the consequences
#6 D2;+;D4	Uniformed people were around me	Feelings of insecurity and inability to see control the consequences. Fear of helplessness
#7 D4;+;D1	I analysed my dream I am active	Attempts at coping with underlying fear of being pacified and helpless
#8 D4;+;D1	I felt asleep. My aunt died	Fear of abandonment and death
#9 D2;+;D4	My uncle wanted me to help him inform others about my aunt's death	Desire to help and fear of not being able to do so
#10 D4;+;D2	Describing the dream lab conditions	Neutral
#11 D4;+;D1	I fell asleep	Neutral
#12 D2;+;D4	I was driving and had to cross a river	Challenges and how to cope with them
#13 D2;+;D4	I was uncertain that we would succeed	Apprehension of survival and abandonment
#14 D2;+;D4	Different messages were conveyed to me	Fear of lack of support
#15 D4;+;D1	A new dream about my uncle's daughter	Fear of attachment or loss of it
#16 D4;+;D1	Surprise was in both of us	Feelings of mirroring and of being together
#17 D2;+;D4	Women dressed in black passed through the room	Fear of being entrapped and touched by uncanny situation
#18 D4;+;D1	I woke up after that dream	
#19 D4;+;D1	Dreaming many dreams is not unusual for me	Wanting to feel closeness and understanding
#20 D1;+;D4	Recently I dreamt that I lost strength and should die	Fear of dying
#21 D2;+;D4	I tried to wake up my wife	Desperation
#22 D1;+;D4	I asked for help but could not get it	Being left alone, not surviving

and persecuted. In spite of the anxiety present it did not overwhelm the dreamer to the extent that the link between symbolic and imaginary became interrupted. In spite of some insecurity, his presentation preserved coherence all the way through.

We thus estimated that the dream was characterized by a dominance of symbolic anchored representation linked with the subjective/bodily presence in the narrative account of the dreams. The dream-teller seems to have the interviewer internalized as a safe object. However, the underlying feeling of being abandoned, losing the attachment and the fear of being helpless and not surviving makes the person strive for attaining safety and closeness from sentence to sentence.

Discussion

We have presented two different methods for qualitative analysis of narratives of dreams that are related to two different theoretical backgrounds developed within the psychoanalytical framework. They have been used to analyse dream reports of nine participants of the study who were identified as torture survivors, i.e. they were imprisoned and tortured at one point of their war-related experiences. In addition, we presented as an example analysis of one, uninterrupted narrative of a torture survivor. Both methods of analysis (the Zurich Dream Process Coding System of Moser and von Zeppelin and PEA) differ significantly from the technique that is used in a clinical practice and have relatively strict rules for application that limit possible subjective interpretations. Therefore, we argued that they could be used for systematic studies of dreams and more specifically for systematic studies of traumatic dreams, which are needed for better understanding of posttraumatic states and of processes of dreaming itself.

The fact that traumatic events are repeatedly represented in dreams of survivors is of no surprise. In a clinical everyday practice, we see persons suffering from PTSD who are struggling to avoid any reminders of trauma during the day and dreams of horrible events from their past during the night. But in this sample of 24 dreams dreamt in the laboratory by nine of our participants, we could not identify a single case of "exact replica", instead fragments of war-related images were entangled with fragments of the everyday life. This may indicate that the symbolizing function was not totally destroyed even after a trauma with such a magnitude or destructive impact as can be assumed for experiences of imprisonment and torture. On the other hand, when we analysed dream narratives remembered from the past, it appeared that these dream narratives have more characteristics of memories of traumatic events than of dreams just dreamt in the lab. There is a possibility that the person, due to course of time, focuses more on the traumatic memory that is engrained in the dream and forgets other aspects of the dream. In other words, it is possible that other cognitive mechanisms interfere with the memory to the dream.

Despite the fact that we saw dream work in operation even with severely traumatized individuals, through the analysis of their dreams, we could observe some indications for other mechanisms which could be attributed to the effects of trauma. Restricted or flattened affect could be observed in dreams as it could be observed in everyday expressions of these patients. There was an overwhelming presence of passivity of the dreamers – as it was observed through PE analysis – they are presented as passive participants, or if they are engaged, their action does not produce effective change and relief within the dream. This factual resemblance to the notion of "learned helplessness" would need a further investigation, as it seems that this might be one of the major differences between individuals with PTSD and traumatized persons without PTSD (a statement for which we still need additional confirmation). Results from the Moser and von Zeppelin method offer more detailed picture to this phenomena: the person in the dream is not only passive, he is engaged in action and interaction with others but this leads only to destructive and violent outcomes. We can argue that within the dream processes, there is no resolution to the repetition of aggressive outcomes of interactions with others and as a consequence that results in reduction of movements, in few and poorly equipped places, and in transformation of persons into anonymous characters. All of these could be seen as defensive strategies aimed at coping with the interpersonal space which is perceived as ultimately dangerous.

Another finding from the PEA could have a practical value: in telling the dream narrative, an imaginery mode is dominant. Furthermore, the dream narrative can be structured differently in time and space, which is of relevance to the listener as well. Results from PEA demonstrate how painful emotions/psychic material is transported to the listener: a scene from the dream, structured more or less well in time and space, is told in a way that suggests no possibilities for general reflections: "you just keep this" seems to be the underlying message. When time and space are not structured (this is scored as D1), then evacuation of undigested material takes place, which tends to create more strain in the listener. As we know from the clinical work with torture survivors, their narratives may have a potential emotionally disturbing effect on the helpers which can sometimes lead to severe burn-out syndromes and psychosomatic reactions. A better understanding of the mechanisms underlying this phenomenon might be of great importance.

In the single case description presented here, we could observe some of the described mechanisms and how the dreamer is fighting with strong affects related to trauma. At the beginning, scenes from the everyday life were merged with war-related material, and we may conclude that the dream was not a replica of the traumatic event itself. But even

at that stage, narratives were disclosing strong feelings of fear and hesitations to engage in emotional relations with others. At this stage of the evaluation process, it is just an assumption, but we believe that these dynamics correlate with another important characteristic of PTSD and feelings of detachment from the others.

The subject is repeatedly awakened – sometimes after short dreams – and that is obviously contributing to the poor sleep efficiency (see Table 34.1). We could also observe a gradual shift during the interview – the subject told four dreams that were short but packed up with strong affects and finally ends his narrative with a "nightmare" – an event in which affects are presented in a pure somatic form and the subject seems to be dreaming traumatic experience ("we were in offensive"). It is possible that this event is related to the interview itself: telling other affect-laden dreams triggers an episode of re-experiencing. In this single episode, there is a representation of a dynamic that we could see with our patients: avoidance of emotional relations to others mixed with repeated recourse for help and support.

In conclusion, PTSD and its chronic consequences are a potentially extremely harmful condition and also very challenging to clinicians. We tried to offer a different perspective in understanding of traumatic dreams. The dreams, which are one of the core symptoms, could help us to elucidate focal areas in each individual's suffering. Dreams can also help to develop new perspectives on posttraumatic mechanisms: instead of understanding PTSD symptomatology as a "broken machine", with replicas of the past events representing unintegrated memories, another way of conceptualizing the phenomenon would be to look at traumatic dreams as complex processes which more or less successfully aim at integrating traumatic experience into the mind's normal communicative and problem-solving ways of functioning.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth ed. Washington, DC: American Psychiatric Association; 2013.
2. van der Kolk B, Britz R, Burr W, Sherry S, Hartmann E. Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry. 1984;141(2):187–90. doi:10.1176/ajp.141.2.187.
3. Pigeon WR, Carr M. Comprehensive guide to post-traumatic stress disorder. In: Martin RC, Preedy RV, Patel BV, editors. . Cham: Springer International Publishing; 2014. p. 1–13. doi:10.1007/978-3-319-08613-2_71-1.
4. Freud S. Die Traumdeutung. Frankfurt: S. Fischer Verlag; 1900.
5. Hartmann E. The central image makes "big" dreams big: the central image as the emotional heart of the dream. Dreaming. 2008; 18(1):44–57.
6. Fosshage JL. The organizing functions of dream mentation. Contemp Psychoanal. 1997;33:429–58.
7. Weinstein L, Ellman SJ. "It's only a dream": physiological and developmental contributions to the feeling of reality. In: Fonagy P, Kächele H, Leuzinger-Bohleber M, Taylor D, editors. The significance of dreams. Bridging clinical and extraclinical research in psychoanalysis. London: Karnac Books; 2012. p. 126–46.
8. Fischmann T. Einsturz bei Nacht : Verarbeitung traumatischer Erlebnisse im Traum. In: Schlaf Und Traum. Wellcome c. Köln: Böhlau; 2007:51–58.
9. Ellman SJ, Weinstein L. When theories touch: an attempted integration and reformulation of dream theory. In: Fonagy P, Kächele H, Leuzinger-Bohleber M, Taylor D, editors. The significance of dreams. Bridging clinical and extraclinical research in psychoanalysis. London: Karnac Books; 2012. p. 109–25.
10. Hölzer M, Zimmermann V, Pokorny D, Kächele H. The dream as a relationship paradigm. Psychother Psychosom Med Psychol. 1996;46(3–4):116–23.
11. Hartmann E. Träumen kontextualisiert Emotionen. Eine neue Theorie über das Wesen und die Funktionen des Träumens. In: Bareuther H, Brede K, Ebert-Saleh M, Grünberg K, Hau S, editors. Traum, Affekt Und Selbst. Tübingen: Edition diskord; 1999. p. 115–57.
12. Laub D, Podell D. Art and trauma. Int J Psychoanal. 1995;76(Pt 5):991–1005.
13. Fosse MJ, Fosse R, Hobson JA, Stickgold RJ. Dreaming and episodic memory: a functional dissociation? J Cogn Neurosci. 2003;15(1):1–9.
14. Phelps AJ, Forbes D, Creamer M. Understanding posttraumatic nightmares: an empirical and conceptual review. Clin Psychol Rev. 2008;28(2):338–55.
15. Leys R. Trauma: a genealogy. Chicago: University of Chicago Press; 2000.
16. Freud S. Beyond the pleasure principle. In: The standard edition of the complete psychological works of Sigmund Freud, Volume XVIII (1920–1922): beyond the pleasure principle, Group Psychology and Other Works.1920:1–64.
17. Lansky M, Bley CR. Post traumatic night mares. Psychodynamic explorations. Hilsdale: The Analytic Press; 1995.
18. Freud S. Inhibitions, symptoms and anxiety. In: The standard edition of the complete psychological works of Sigmund Freud, Volume XX (1925–1926): an autobiographical study, inhibitions, symptoms and anxiety, the question of lay analysis and other works. 1926:75–176.
19. Opacic G, Knezevic G, Jovic V, Radovic B. Concomitants of repatriation – the case of former Yugoslavia. In: Traue HC, Johler R, Jancovic Gavrilovic J, editors. Migration, integration and health. Lengerich: Pabst; 2010. p. 83–97.
20. Radović B. A brief retrospective on the problem of refugees in the Yugoslav wars 1991–99. In: Opačić G, Vidaković I, Vujadinović B, editors. Living in post-war communities. Belgrade: International Aid Network; 2005. p. 11–26.
21. Opacic G, Jovic V, Radovic B, Knezevic G. Redress in action: consequences of forcible mobilization of refugees in 1995. International Aid Network: Belgrade; 2006.
22. Savic D, Knezevic G, Damjanovic S, Spiric Z, Matic G. The role of personality and traumatic events in cortisol levels – where does PTSD fit in? Psychoneuroendocrinology. 2012;37(7):937–47.
23. Savic D, Knezevic G, Damjanovic S, Spiric Z, Matic G. Is there a biological difference between trauma-related depression and PTSD? DST says "NO.". Psychoneuroendocrinology. 2012;37(9): 1516–20.
24. Jovic V. Psychosocial assistance in humanitarian interventions – six years of experience in IAN (1997–2003). In: Špiric Ž, Knežević G, Jović V, Opačić G, editors. Torture in war: consequences and rehabilitation of victims – Yugoslav experience. Belgrade: International Aid Network; 2003. p. 73–93.

25. Blake DD, Weathers FW, Nagy LM, et al. Clinician administered PTSD scale for DSM-IV: current and lifetime diagnostic version. Boston: National Centre for Posttraumatic Stress Disorder; 1996.
26. First MB, Gibbon M, Spitzer RL, Janet BW, Williams JBW. User's guide for the SCID-I, structured clinical interview for DSM-IV axis I disorders, research version. New York: Biometrics Research Department, New York State Psychiatric Institute; 2002.
27. Jovic V, Opacic G, Knezevic G, Tenjovic L, Lecic-Tosevski D. War stressors assessment questionnaire – psychometric evaluation. Psihijatr Danas. 2002;35:51–75.
28. Moser U, v Zeppelin I. Der Geträumte Traum. Stuttgart: Kohlhammer; 1996.
29. Rosenbaum B, Varvin S. The influence of extreme traumatisation on body, mind and social relations. Int J Psychoanal. 2007;88:1527–42.
30. Varvin S. Mental survival strategies after extreme traumatisation. Copenhagen: Multivers; 2003.
31. Rosenbaum B. Semiotic reflections on suicidal behaviour: a I kill myself – who is self and who is I? In: Fleischer E, editor. Elements of a cross-scientific paradigm for suicide research. Odense: Center for selvmordsforskning; 1994. p. 65–83.

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