Neurobiology of Stress 23 (2023) 100517

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Modeling integrated stress, sleep, fear and neuroimmune responses: Relevance for understanding trauma and stress-related disorders

Larry D. Sanford [a,*], Laurie L. Wellman [a], Austin M. Adkins [a], Ming-Lei Guo [b], Ye Zhang [c], Rong Ren [c], Linghui Yang [c], Xiangdong Tang [c]

[a] Sleep Research Laboratory, Center for Integrative Neuroscience and Inflammatory Diseases, Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

[b] Drug Addiction Laboratory, Center for Integrative Neuroscience and Inflammatory Diseases, Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

[c] Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Mental Health Center, Translational Neuroscience Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Handling Editor: Dr R Victoria Risbrough

Keywords:
Amygdala
Animal models
Conditioned fear
Hippocampus
Neuroimmune system
Rapid eye movement sleep
Stress
Prefrontal cortex

ABSTRACT

Sleep and stress have complex interactions that are implicated in both physical diseases and psychiatric disorders. These interactions can be modulated by learning and memory, and involve additional interactions with the neuroimmune system. In this paper, we propose that stressful challenges induce integrated responses across multiple systems that can vary depending on situational variables in which the initial stress was experienced, and with the ability of the individual to cope with stress- and fear-inducing challenges. Differences in coping may involve differences in resilience and vulnerability and/or whether the stressful context allows adaptive learning and responses. We provide data demonstrating both common (corticosterone, SIH and fear behaviors) and distinguishing (sleep and neuroimmune) responses that are associated with an individual's ability to respond and relative resilience and vulnerability. We discuss neurocircuitry regulating integrated stress, sleep, neuroimmune and fear responses, and show that responses can be modulated at the neural level. Finally, we discuss factors that need to be considered in models of integrated stress responses and their relevance for understanding stress-related disorders in humans.

1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes disorders which are precipitated by specific stressful and potentially traumatic events as "Trauma and Stress-Related Disorders." These include acute stress disorder, posttraumatic stress disorder (PTSD) and adjustment disorders which together encompass a broad range of maladaptive stress responses (American Psychiatric Association, 2013). Discussions in formulating this diagnostic category questioned whether PTSD should be considered an anxiety disorder, a stress induced fear circuitry disorder, an internalizing disorder, or a trauma and stressor-related disorder (Friedman et al., 2011). These considerations likely reflected the difficulty in providing clear diagnostic criteria for stress-related disorders, which can vary widely in symptomology and time courses.

It has also been suggested that there is a need to distinguish between "stress" and "trauma" in order to better define experiences that are likely to be resolved with no lasting negative effects from those that can lead to persisting psychopathology (Richter-Levin and Sandi, 2021). This has proven difficult because of significant overlap in responses across systems and a lack of clear definitions of what constitutes normal and pathological stress responses, or an understanding of their respective time courses. Adding to the complexity of understanding the impact of stress are individual differences in resilience and vulnerability. Nowhere are these differences more significant than in PTSD. It is estimated that 70% of individuals will experience a traumatic event in their lifetime; however, only an estimated 20% of those who experience traumatic stress will develop PTSD.

Different individual reactions to stress and similarities between normal and pathological responses have made it difficult to determine

* Corresponding author. Sleep Research Laboratory, Center for Integrative Neuroscience and Inflammatory Diseases, Pathology & Anatomy, Eastern Virginia Medical School, P.O. Box 1980, VA, 23507, USA.
E-mail address: SanforLD@evms.edu (L.D. Sanford).

https://doi.org/10.1016/j.ynstr.2023.100517
Received 24 June 2022; Received in revised form 30 December 2022; Accepted 19 January 2023
Available online 23 January 2023

the essential factors that drive persisting stress-related psychopathology. Many stress studies have also focused on a limited number of outcome measures that may not fully reflect the range of possible stress responses, and how they may vary across systems. These factors have made it extremely challenging to develop animal models to assess the neurobiological mechanisms that underlie the effects of stressful experiences on responses across systems and their interactions, and to distinguish adaptive and maladaptive stress responses.

The two most common pathologies of fear- and anxiety-based psychiatric disorders are increased neuroinflammation (Najjar et al., 2013) and disrupted sleep (Krystal, 2012). Studies have also shown individuals diagnosed with fear- and anxiety-based psychiatric disorders, are more likely to develop neurodegenerative diseases later in life (Rasmussen et al., 2018). With a primary focus on animal models, our review will discuss the complex relationships between stress, sleep and the neuroimmune system, individual and stressor parameters that appear to be important in determining different post-stress outcomes, and the relationship between stress and fear memory. We will discuss the neuroanatomical substrates important in regulating the relationship between stress, sleep, and neuroimmune responses. We will discuss modeling integrated stress and fear responses and revisit important output measures (behavioral fear, stress responses, sleep and neuroimmune responses) and discuss interpretive weaknesses in individual measures of stress outcomes. Lastly, we will suggest that an integrated model of multi-system responses to stress may provide insight into stress-related disorders and the role that sleep may play in mediating adaptive and maladaptive outcomes relevant for clinical disorders.

2. Stress

Stress is broadly defined as a nonspecific physiological response to a situation or event that is psychologically or physiologically demanding. In response to stressors, neurochemical mediators are released that act acutely to promote adaptive physiological and behavioral responses to the existing challenge (McEwen, 2007). This includes activation of the autonomic nervous system and hypothalamo-pituitary-adrenal (HPA) axis to initiate and regulate behavioral and physiological adaptations to the challenge as well as the restoration of homeostasis when the threat is removed.

The physiological stress response has been selected throughout evolution as an important survival reaction (Bijlsma and Loeschcke, 2005; Arnoldini et al., 2012). Problems can arise when the stress response is inadequate or the stress system is overwhelmed by intense or prolonged stress (Chrousos, 1998). Indeed, stress is implicated in the genesis of neuropsychiatric diseases including PTSD, anxiety and mood disorders as well as being linked to a variety of physical health ailments. Critically, stress influences and interacts with multiple other systems that have significant roles in mental and physical health including sleep, the immune system, and learning and memory in ways that can impact stress outcomes. The impact of stress can also be modulated by individual differences in resilience and vulnerability and by various stress parameters including intensity, duration, and whether or not the stressor is controllable (Reviewed in (Sanford et al., 2015)).

2.1. Sleep as a mediator and index of stress-related psychopathology

Disturbances in sleep, both prior to and after a stressful event, have been implicated in psychopathology (Lavie, 2001; Koren et al., 2002; Bryant et al., 2010), and both early rapid eye movement sleep (REM) disruptions (Mellman et al., 2014) and persisting sleep disturbances after traumatic stress (Lavie, 2001) are predictive of PTSD. It has been suggested that sleep disturbance around the time of stress may limit cognitive resources needed to manage stress, contribute to hyperarousal that may lead to psychiatric disorder, pose as an additional stressor that compounds the effect of a stressful event and/or limit restorative sleep that is required to manage stressful events (Bryant et al., 2010). Thus, there are multiple pathways by which sleep disturbances may negatively impact systems important for adaptive responding to stress.

Both REM and non-REM (NREM) can be impacted by stress, and disturbances, decreases and increases in either state can occur and can vary across stressor type and parameters (Sanford et al., 2015). Of these changes, disruptions and decreases in sleep have been most often, though not always, linked to stress-related pathologies. Our group (Wellman et al., 2016) and others (Ross, 2014) have suggested that disrupted REM may be a biomarker of stress-related pathogenesis. The hypothesis that disrupted REM after stress may be a marker of a failed stress response is consistent with the increases in post-stress REM reported for a variety of stressors (avoidable footshock (Smith, 1995; Sanford et al., 2005), restraint (Rampin et al., 1991; Gonzalez et al., 1995; Meerlo et al., 2001), water maze (Smith, 1995), novel object (Schiffelholz and Aldenhoff, 2002; Tang et al., 2005a), open field (Tang et al., 2004, 2005a), cage change (Tang et al., 2004, 2005a), and social stress (Meerlo et al., 1997; Meerlo and Turek, 2001)) not necessarily linked to enduring psychopathology; thereby, suggesting that increased post-stress REM is normal after many mild to moderately challenging situations. Functionally, REM has been primarily hypothesized to be related to the adaptive processing of emotional and traumatic memories (Mellman et al., 2002; 2007; Walker and van der Helm, 2009; Rasch and Born, 2013) including that it functions to weaken unwanted memory traces in the cortex (Crick and Mitchison, 1983) and that it may aid in "decoupling" aversive memories from their emotional charge during consolidation (Nishida et al., 2009; Walker, 2009). Note, however, that some have suggested that REM may play a negative role in fear memory (Menz et al., 2013).

NREM can also be differentially impacted by stressors with some being followed by decreases and some by increases in NREM amounts and alterations in EEG slow wave amplitude. For example, rats and mice exposed to acute social stress, i.e., a 1 h interaction with an aggressive male conspecific, can show deeper or longer NREM sleep compared to a similar period of non-stressful sleep deprivation (Meerlo et al., 1997; Meerlo and Turek, 2001). Some of the differences across stressors may be related to stress-related learning. Hellman and Abel (2007) reported that fear-conditioned mice trained with a single shock showed a 1 h increase in NREM over 24 h compared to both non-shocked mice and mice that experienced a shock unassociated with conditioning. In humans, Kleim et al. (2016) reported that sleep after an experimental laboratory trauma protocol protected against the occurrence of intrusive trauma memories in healthy young women. Specifically, more time spent in NREM stage N2, greater parietal fast sleep spindle density (mean spindle counts/number of analyzed 30-sec epochs), and decreased REM density (no. rapid eye movements/total REM time) were associated with reduced intrusion frequency.

In addition to roles in intital stress responses, persisting alterations in both NREM and REM have been reported in stress and trauma-related disorders. Both visually scored delta sleep and EEG delta amplitude have been reported to be reduced in patients with PTSD (Neylan et al., 2006), and meta-analyses considering data from multiple studies have also reported persisting alterations in sleep (Kobayashi et al., 2007). In a recent meta-analysis of 31 studies, we (Zhang et al., 2019a) found that patients with PTSD showed decreased total sleep time, NREM amounts, and sleep efficiency and increased wake after sleep onset compared to healthy controls. PTSD severity was associated with decreased sleep efficiency and NREM percentage. Interestingly, although REM sleep percentage did not significantly differ between PTSD patients and controls across the whole sample, it was significantly decreased in PTSD patients in studies where the mean age of participants was below 30 y, but not in studies with greater mean ages (30–40 y and >40 y). We suggested that the significant relationship between younger age and decreased REM sleep percentage in PTSD patients could indirectly support a role for disturbed REM in PTSD as differences across age cohorts could also reflect time since the precipitating trauma.

Thus, available evidence suggests that sleep plays a role in mediating

responses to stressful challenges and that it may also reflect enduring consequences of stressful and traumatic events. However, understanding interactions between sleep and the immediate and long-term consequences of stress has proven to be difficult. Nowhere is this more apparent than in the sleep changes associated with PTSD. Reductions in REM that appear to occur proximal to traumatic stress may be followed by increases in REM in the longer term in PTSD patients (Zhang et al., 2019a). Mellman et al. (2014) suggested that disruptions in REM in the aftermath of trauma may be linked to the development and symptoms of PTSD whereas increases in REM later in its progression may reflect an attempt at adaptive changes within the fear system. By comparison, Ross (2014) suggested that "reconstituted" REM sleep observed years after trauma may be pathological and the source of recurrent nightmares of chronic PTSD. Either suggestion is compatible with sleep and stress systems interacting to mediate the outcomes of challenging experiences.

2.2. Neuroinflammation as a mediator and index of stress-related psychopathology

The neuroimmune system is comprised of a coordinated network of neurons, glial, and immune cells that acts to maintain homeostasis and regulate inflammatory responses in the central nervous system (CNS) (Tian et al., 2012). Microglia are the main resident macrophages in the CNS and they primarily act to maintain homeostasis (Singhal and Baune, 2017). In general, information transfer between microglia and neurons continuously update microglia regarding the activity and state of nearby neurons (Szepesi et al., 2018). Microglial regulation is managed by a select group of intrinsic and extrinsic factors (Kierdorf and Prinz, 2013). Under normal, healthy conditions microglia are in a constant quiescent state. Quiescence is maintained by fractalkine (CX_3CL1) and CD200 expressed by neurons; these bind to the fractalkine receptor (CX_3CR1) and CD200R expressed on microglia. Microglia receive various signals from neurons that direct their response and remain activated and respond until returned to a quiescent state by CX_3CL1 or CD200 (Kierdorf and Prinz, 2013).

When microglia become activated, they rapidly alter their transcriptional profile and produce inflammatory cytokines in order to meet the challenges of immunological, physiological, and psychological stressors (Lund et al., 2017; Singhal and Baune, 2017). However, they are also linked to pathology, and over-activation of microglia has been reported in neurodegenerative diseases (Rojo et al., 2014) and in psychiatric disorders, including anxiety (Wohleb et al., 2013; Wohleb et al., 2014a,b) and depression (Singhal and Baune, 2017). For example, reports have demonstrated that activation of the autonomic nervous system by stress exposure can elevate microglial activity (Bratt et al., 2001), increasing the number of circulating cytokines and leading to phagocytoses of healthy functioning neurons. Depending on the type and duration of the stressor, microglia may not return to a quiescent state (Bratt et al., 2001). This can lead to significant damage, distorting neuronal signaling, and disrupting normal brain function. This has direct implications for PTSD, and may serve as an early indicator for the development of neurodegenerative diseases, as patients with such disorders all show increased neuroinflammation (Najjar et al., 2013). Overall, stress is a well-documented risk factor for the development of mental illness and neuroinflammation, in particular elevated microglial activity, has been proposed to mediate this association (Calcia et al., 2016).

Stress can induce a pro-inflammatory response in the brain and periphery that is characterized by a complex release of cytokines and chemokines (Goncharova and Tarakanov, 2008), prostanoids, free radicals and transcription factors (Garcia-Bueno et al., 2008). Anti-inflammatory pathways can also be activated by stress, a possible endogenous defense against excessive inflammation (Garcia-Bueno et al., 2008). Stress-related immune dysregulation is increasingly being linked to a variety of health risks (Kiecolt-Glaser et al., 2002; Nakata, 2012) and to increased neuroinflammation (Angelidou et al., 2012; Garate et al., 2013), which, in turn, is implicated in neural pathogenesis (Frischer et al., 2009; Karagkouni et al., 2013), and neuropsychiatric disorders (Hagberg et al., 2012; Theoharides et al., 2014). Importantly, psychological stress appears to produce effects on the immune system through the same signaling pathways as physiological stress (Iwata et al., 2013). For example, PTSD, depression, and insomnia in military personnel are associated with higher concentrations of inflammatory proteins including C-reactive protein (Gill et al., 2014). Microglial activation status determines neuroinflammation levels, and they are implicated in neuroinflammation in a variety of stress models (e.g., footshock, swim stress, restraint (Wohleb, 2016)) and are over-activated in a social defeat model of psychosocial stress that produces some features of anxiety and depression in animals (Rojo et al., 2014). Work using the social defeat model has demonstrated that microglia actively recruit $Ly6C^{hi}$ monocytes specifically to threat appraisal regions of the brain (McKim et al., 2017). Once in the brain, these monocytes differentiate into macrophages and increase inflammatory cytokine signaling (Wohleb et al., 2013). Their production of IL-1β and stimulation of IL-1R1 on brain endothelial cells has been reported to be responsible for the development of anxiety during repeated social defeat stress (McKim et al., 2017). Thus, stress-induced immune activation may be a significant mediator of its long-term effects.

2.3. Neuroimmune, sleep and stress interactions

The immune system and sleep are intimately linked (Krueger and Majde, 1990; Toth et al., 1993; Opp, 2005). There is growing evidence that microglia are involved in sleep regulation (Wisor et al., 2011; Ingiosi et al., 2013), as they are activated after sleep loss (Hsu et al., 2003; Bellesi et al., 2017; Wadhwa et al., 2018; Tuan and Lee, 2019; Xie et al., 2020), and improved sleep (based on the Pittsburgh sleep quality index (PSQI) self-report questionnaire) is associated with reductions in inflammation (Heinzelmann et al., 2014; Livingston et al., 2015). Furthermore, short-term (72 h) REM deprivation produces activation of the immune system that can persist after recovery sleep (Yehuda et al., 2009) suggesting a possible role for REM in the neuroimmune responses induced by stress.

Given the close relationship between sleep and the immune system, post-stress sleep may be important for mediating the effects of stress on the immune system, as insufficient sleep can promote pro-inflammatory cytokines (Ingiosi et al., 2013). Experimentally fragmented sleep, even without alterations in total sleep, can impact the immune system (Poroyko et al., 2016) and both sleep disruption (Hurtado-Alvarado et al., 2018; Medina-Flores et al., 2020) and REM restriction (Gomez-Gonzalez et al., 2013) disrupt blood-brain barrier (BBB) functionality by altering its neuroimmune regulation (Hurtado-Alvarado et al., 2016; Medina-Flores et al., 2020). We recently reported that sleep fragmentation may concurrently promote brain inflammation and compromise immune regulation of the barrier that maintains separation of the host and microbiome (Sanford et al., 2021a), which may have significant implications for gut microbiota influences on the stress system (Dinan and Cryan, 2012) and provide an additional path by which sleep, the immune system and stress may interact.

Mounting evidence indicates interactions between microglial systems and stress (Frank et al., 2007; Bollinger et al., 2016; Hellwig et al., 2016; Winkler et al., 2017), and that microglia regulate responses to footshock stress and conditioned fear (Li et al., 2021). Microglia can also have varied phenotypes that produce specialized responses that differ across brain regions and with stress model and duration (Wohleb, 2016). We have found that controllable and uncontrollable stress (modeled by escapable (ES) and inescapable (IS) footshock) also produce differential neuroimmune responses that vary across brain regions [Unpublished Results]. In general, controllable stress has a suppressing effect on neuroinflammation whereas uncontrollable stress promotes neuroinflammation. The different neuroimmune responses are also associated with differences in post-stress sleep as controllable stress is followed by

increased REM and uncontrollable stress by decreased REM (Sanford et al., 2010; Yang et al., 2011a,b).

Various lines of work indicate that neural influences on, and interactions with, the neuroimmune system are important for regulating stress outcomes. The amygdala, prefrontal cortex (PFC), hippocampus (HPC) and hypothalamus have established roles in responding to and regulating responses to stress and fear (e.g., (Kollack-Walker et al., 1997; Maren, 1999; Richmond et al., 1999; LeDoux, 2000; Zhang et al., 2001; Martinez et al., 2002; Bast et al., 2003; Maren and Holt, 2004; Trivedi and Coover, 2004; Rudy and Matus-Amat, 2005; Hobin et al., 2006; Maier et al., 2006; Akirav and Maroun, 2007; Misane et al., 2013; Zhang et al., 2014)). Stress-induced activation in these regions is associated with activation of microglia and increased neuroinflammatory signaling (Wohleb et al., 2015). Of these regions, the amygdala becomes activated and shows local synthesis of pro-inflammatory cytokines shortly after systemic immune challenge with administration of bacterial lipopolysaccharide (Engler et al., 2011; Prager et al., 2013). Furthermore, our work has amply demonstrated that it regulates the effects of footshock stress and fear memories on sleep (Liu et al., 2009, 2011; Wellman et al., 2013, 2014, 2016), and, more recently, that it mediates the effects of controllable and uncontrollable stress on the neuroimmune system [Unpublished Results] and that its regulation of fear memory may be dependent on REM during the consolidation period (Machida et al., 2021a,b). In summary, available evidence indicates that the complex interactions of the immune system, sleep and stress can be explored at functional, mechanistic and neurocircuit levels in ways that can lend new insight into adaptive and maladaptive stress responses. Considerations for these studies are discussed below.

3. Modulators of stress responses

Experimental stressors are often defined, implemented and interpreted from the researcher's point of view. This has led to a literature replete with descriptive studies of the effects of various stressors (e.g., footshock (Roozendaal et al., 1991a,b; Vazquez-Palacios and Velazquez-Moctezuma, 2000), restraint (Rampin et al., 1991; Gonzalez et al., 1995; Vazquez-Palacios and Velazquez-Moctezuma, 2000) and stressor combinations (Iwamoto et al., 2007; Lisieski et al., 2018)). However, both humans and animals can be differentially resilient or vulnerable to the effects of stress (Franklin et al., 2012; Dutcher and Creswell, 2018; Faye et al., 2018) and the need to understand individual differences in the ability to cope with stress and also the effects of heterogeneous stressors is being widely recognized (e.g. (Gordon, 2018)). Stressful situations also provide the opportunity to learn, which may impact both the current response as well as those to future challenges.

One of the major issues in embarking on studies of stress modulators is defining what constitutes adaptive and inadequate or maladaptive coping. Experimental stress paradigms are generally based on the application of presumed aversive stimuli that will produce activation of the classical neuroendocrine stress systems, i.e., the sympatho-adrenal axis and the HPA axis with elevations in noradrenaline and corticosterone being typical assays (Sanford et al., 2015). However, virtually any kind of challenge can induce elevations in these markers (Koolhaas et al., 2011), and they may not differ across stressor types, and may not correlate with other stress-induced changes. That is, activation of the classical stress system may not be predictive of other stress-induced responses.

In our work, we have focused on sleep responses, and more recently on neuroimmune responses, to delineate differential stress responses in animal models of stressor controllability and putative stress vulnerability and resilience. At a conceptual level, the rationale is straightforward: compared to animals that show reduced and/or disrupted sleep and greater neuroinflammation, animals that sleep normally or have increased sleep and reduced neuroinflammation after stress have a more adaptive response that is less likely to lead to long-term stress-related problems. This rationale is consistent with literature that emphasizes roles for disrupted sleep and neuroinflammation in stress-related pathology (e.g., (Kiecolt-Glaser et al., 2002; Angelidou et al., 2012; Nakata, 2012; Garate et al., 2013)). It is also consistent with a return to normalcy when the stressful situation is resolved; i.e., restoration of homeostasis as the stress responses ends (Chrousos, 2009).

3.1. Stressor controllability

Various studies have demonstrated that controllability, or lack thereof (Foa et al., 1992; Bolstad and Zinbarg, 1997), can have significant impact on the behavioral and physiological outcomes of a stressful event. Uncontrollable stress is linked to negative outcomes and can lead to deficits in associative, motivational, and emotional functioning and can also induce significant alterations in a variety of neurochemical systems (learned helplessness is perhaps the best known experimental effect (e.g., (Seligman et al., 1975; Anisman and Merali, 2009)). By comparison, controllability is more generally associated with neutral or positive stress outcomes. Thus, the different processes associated with different perceptions of stress may be important for maladaptive and adaptive coping with stress.

We have utilized a simple paradigm based on training with ES and yoked IS to model controllable and uncontrollable stress, respectively (Liu et al., 2003; Sanford et al., 2003b; Tang et al., 2005c). Training is similar to the yoked paradigm long established in learned helplessness (Seligman et al., 1975; Anisman and Merali, 2009). Animals receive equal amounts of footshock under the control of the ES mouse, which can terminate the footshock simply by moving to the safe side of the shock chamber. ES and IS produce directionally different changes in post-stress REM (Sanford et al., 2010; Yang et al., 2011a,b) (see Fig. 1), differential activation of brain stress-regulatory regions (Liu et al., 2009a,b; Machida et al., 2018), and differential neuroimmune responses [Unpublished Results]. Specifically, uncontrollable stress is associated with decreased sleep/REM, activation in brain stress regulatory regions and increased neuroinflammation in multiple brain regions whereas controllable stress is followed by normal/enhanced sleep/REM, baseline levels of activation in several brain stress regulatory regions and reduced/suppressed neuroinflammation. Critically, these differences are consistent with predictions for maladaptive and adaptive stress responses yet occur despite virtually identical peripheral stress system activation (increased corticosterone and stress induced hyperthermia (SIH) (Maier et al., 1986; Shors et al., 1989; Yang et al., 2011a,b; Machida et al., 2018) and overt fear behavior (freezing (Wellman et al., 2008; Wellman et al., 2016; Wellman et al., 2017a,b; Machida et al., 2021a,b), the standard behavioral index of fear and fear memory in rodents (Rosen, 2004; Roelofs, 2017). Importantly, contextual reminders of ES and IS produce responses very similar to those produced by the initial stress (e.g. (Sanford et al., 2010; Yang et al., 2011a,b); also see Fig. 1) indicating differential learning engaged by the different experiences (discussed below).

3.2. Resilience and vulnerability

Genetic differences in vulnerability and resilience are recognized as important factors in the development of stress-related pathology. Attempts to develop animal models that better represent genetic/individual differences in clinical populations have included comparisons of inbred strains (Crawley et al., 1997; Nadler et al., 2006) and selecting low and high responders to stressors in outbred rat strains (Cohen et al., 2003).

Our work in inbred mice has demonstrated that strains that exhibited greater anxiety-like behaviors in response to challenges in wakefulness exhibited correspondingly greater and longer duration alterations in sleep after training with IS and after fearful cues (Sanford et al., 2003a) and contexts (Sanford et al., 2003b) associated with IS. In general, putative vulnerable mouse strains (e.g., BALB/cJ mice) compared to putative more resilient strains (e.g., C57BL/6J mice) also showed greater

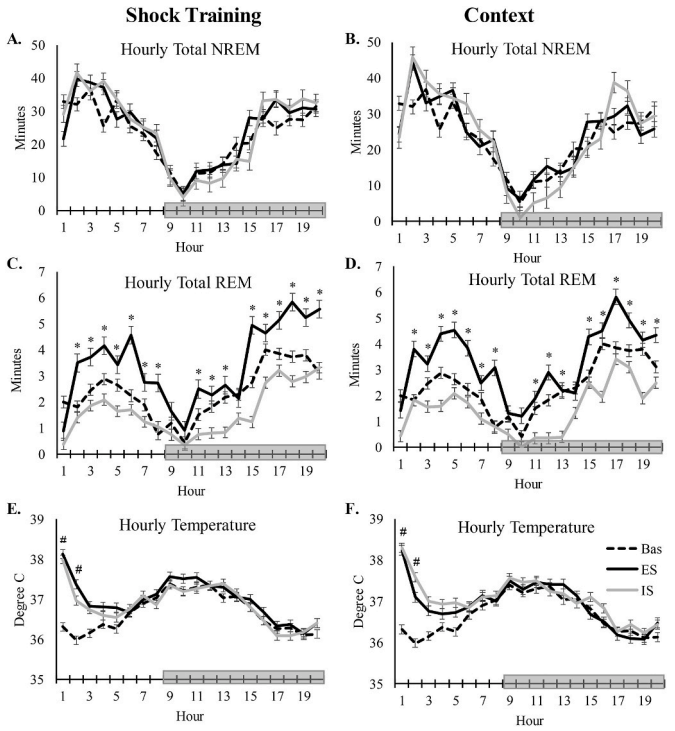

Fig. 1. Hourly NREM (A, B), REM (C, D), and core body temperature (E, F) plotted for escapable shock (ES) and inescapable shock (IS) mice after shock training, context and non-shock baseline (Bas) in C57BL6/J mice (male, n = 9 ES/IS). Mice receiving ES were presented with 20 shocks (0.5 mA; 5.0 s maximum duration) in a shuttlebox. To escape shock, the mice had to learn to enter the non-occupied chamber of the shuttlebox, which terminated the shock for both ES and IS mice. As shown in the figure, NREM amounts did not noticeably differ between conditions whereas REM was increased in ES mice and decreased in IS mice. These increases could begin during periods of stress-induced increases in core body temperature, and were similar for both shock training and context re-exposure. Plots are over 20h; gray bar on X-axis indicates dark period. *ES vs. IS, $p < 0.05$ or greater; # vs. Bas, $p < 0.05$ or greater. REM as an overall percentage change from Bas also differed after training (ES: 58.8 ± 7.1; IS: 32.4 ± 6.8, $p < 0.001$) and after context (ES: 50.1 ± 7.0; IS: 40.2 ± 4.3, $p < 0.001$).

decreases in sleep after stressful situations with unlearned responses including exposure to an open field (Tang et al., 2004), cage change and novel objects placed in the home cage (Tang et al., 2005a,b). BALB/cJ mice also do not show a significant REM sleep increase after restraint stress whereas C57BL/6J mice do (Meerlo et al., 2001). Inbred rat strains also show differences in sleep after IS and novel chamber stressors (Tang et al., 2005a,b,c).

We have found individual differences in the REM response in outbred Wistar strain rats (Wellman et al., 2016, 2017; Sweeten et al., 2020a,b) that parallel those observed with uncontrollable and controllable stress. REM vulnerable (Vul) rats show decreases in REM after training with IS whereas REM resilient (Res) rats showed no decreases, or even increases, in REM after IS (Wellman et al., 2016, 2017; Sweeten et al., 2020a,b). The rapidly normalized and enhanced REM in Res rats suggests a rapid recovery of sleep homeostasis (Wellman et al., 2018) which is consistent with stress resilience. As with our work with controllable and uncontrollable stress, these differences in REM occur even though freezing and SIH are identical in both groups. The Vul and Res phenotypes are also differentially responsive to other stressors (e.g., novel chamber (Sweeten et al., 2020a,b) and simulated space radiation (Britten et al., 2021)) indicating the differences are not limited to footshock stress. Contextual fear memories also produce virtually identical sleep, freezing and SIH responses to those they exhibited to IS in Vul and Res rats (Wellman et al., 2016, 2017; Sweeten et al., 2020a,b). We are currently assessing whether they differ with respect to neuroimmune markers.

3.3. Other stress modulators

A variety of other parameters may have consequence for stress outcomes regardless of stressor modality. These include stressor duration and intensity, whether it has a physical element or is purely psychological, and whether it is predictable or not (Reviewed in (Sanford et al., 2015)). Past experiences with stressors also can modulate future stress responses, and a significant body of work has shown that early life stress as well as sleep deprivation can significantly alter adult behavior (Shaffery et al., 2003). In general, these studies demonstrate the critical role(s) of factors that impact an organism's ability to interpret, respond to, and learn from, challenges play in determining stress outcomes.

4. Stress and fear memory

Stress-related learning provides a mechanism by which organisms can adapt to ongoing challenges and by which stressful experiences can impact future behavior. While stressors may engage different learning types as an organism seeks to cope with the challenges they encounter, fear conditioning has become a key research model for understanding the role of memories in stress-related psychopathology. Fear conditioning occurs when a neutral stimulus or context becomes associated with the occurrence of a significant aversive emotional event (typically IS in standard experimental paradigms). Subsequently, previously neutral stimuli and contexts can elicit behavioral and physiological fear responses similar to those induced by the aversive event itself.

It is important to keep in mind that although conditioned fear is typically interpreted in the context of pathological processes, it most often underlies adaptive behavior that readily extinguishes when the fear-inducing situation or stimulus is no longer present (Kishimoto et al., 2000; Pitman et al., 2001; Bouton, 2004). It is the inappropriate engagement of fear or the failure of fear extinction, a type of new learning that inhibits fear behavior without erasing the fearful memory (Bouton, 2004), that has been linked to psychopathology such as the persisting symptoms of PTSD though the processes that make memories resistant to extinction remain mostly unknown.

It is also important to note that most studies seeking to understand fear memory have measured immediate responses to fearful cues or contexts including behavioral freezing (cessation of all observable activity except respiration (Blanchard and Blanchard, 1969a,b; Phillips and LeDoux, 1992; Paylor et al., 1994)), autonomic responses (e.g., increased heart rate (Davis, 1992a)) or the ability of fearful cues or contexts to modify responses to other stimuli (e.g., fear-potentiated startle (Davis, 1990; Davis, 1992b). Behavioral freezing is the most common outcome measure, with greater time spent freezing being interpreted as stronger fear reactions (Blanchard and Blanchard, 1969a, b; Doyere et al., 2000). However, fear memory can influence responses in multiple systems in different ways depending on the learning context and on how individuals respond, and those influences may also vary across time.

4.1. Stress, fear memory and sleep

Sleep has long been implicated in learning and memory and cognitive performance, including facilitating underlying related neural activity and communication between brain regions. Support for a role for sleep has come from studies in humans and animals using a variety of learning tasks. Conclusions from these studies have often been based on correlations between sleep amounts and subsequent behavioral and performance indices of learning and memory formation. However, there also has been contradictory evidence across studies that may result from differences in learning paradigms, behavioral measures, as well as individual differences in learning and/or in the effects of training and testing. Conclusions can also be impacted by the fact that memories can

alter sleep, indicating potential reciprocal influences between sleep and learning systems that have not often been considered. Thus, even after decades of work, questions remain as to whether sleep subserves fundamental mechanisms across learning types, only certain types of learning, or indeed, reflects activity in circuits underlying memory consolidation and the integration of the various emotional and behavioral responses that memories may subsequently engage and regulate.

Nowhere is the question regarding a role for sleep more important than in the processing and consolidation of fear memory which is linked to PTSD (Grillon et al., 1996; Shvil et al., 2013) and anxiety (Davis, 1992b; Charney and Deutch, 1996). Reduced and fragmented REM after trauma has been linked to PTSD (Mellman et al., 2007, 2014), and disrupted sleep before and after stressful events is predictive of PTSD and anxiety, as well as depression (Lavie, 2001; Koren et al., 2002; Bryant et al., 2010). REM appears to be important for adaptive processing of emotion and stress (Mellman et al., 2002, 2007; Sanford et al., 2010; Walker, 2010). This may be related to its role in mediating activity in stress and fear neurocircuits as a functional neuroimaging study in humans found that greater baseline REM is associated with reduced fear-related activity in, and connectivity between, the amygdala, ventromedial PFC (vmPFC) and HPC during fear conditioning (Lerner et al., 2017). NREM has also been implicated in fear memory; e.g., post-training optogenetic inhibition of HPC CA1 parvalbumin-expressing interneurons during NREM, but not REM or wakefulness, reduced freezing after single-trial contextual fear learning (Ognjanovski et al., 2018).

Much of the basic research examining fear learning and memory has utilized brief conditioning paradigms and relied on behavioral freezing as the sole output measure of fear memory. However, fear is a complex emotion that can engage a variety of neural, physiological and behavioral responses that this simple behavior does not adequately reflect. Indeed, we have found no specific, predictive relationship between this standard index of fear memory and stress markers, sleep parameters, and neuroinflammation across a variety of fear conditioning paradigms (cued fear and contextual fear and modifications by predictability and controllability) and evaluating strain and individual differences in behavioral responses. In general, equivalent freezing can be associated with subsequent increases or decreases in REM and NREM, enhanced or suppressed neuroinflammation [Unpublished Results], and freezing can extinguish during periods with significantly elevated stress markers (i.e., SIH (Wellman et al., 2018)).

4.2. Stress, fear memory and neuroinflammation

Fear memories associated with previous stressful experiences can persist throughout life and continually or periodically resurface. This is quite common and can lead to an exacerbation of neuroinflammation (Najjar et al., 2013). If neuroinflammation persists, healthy functioning neurons can be destroyed, altering normal brain function (De Felice and Lourenco, 2015). Therefore, stress-induced neuroinflammation has direct implications for the development of neurodegenerative diseases as well as neuropsychiatric disorders (Najjar et al., 2013).

Our lab has found that ES and IS produce differential activation of the immune system (Ciavarra et al., 2018). Pro-inflammatory cytokines released by microglia, endothelial cells, and macrophages in response to stress may alter fear memory, e.g., IL-1β administered intracerebroventricularly after shock training heightened fear memory in rats (Song et al., 2003), while blocking the IL-1 receptor in mice decreased perceived anxiety-type behavior (Wohleb et al., 2014a,b). We found that IL-1β and IL-1r1 (as well as other pro-inflammatory cytokines) are significantly suppressed by ES compared to IS in mice. Our data support the view that uncontrollable stress (modeled by IS) enhances pro-inflammatory neuroimmune responses, that controllable stress (modeled by ES) significantly blunts these responses, and that these differences can occur in conjunction with similar peripheral stress responses (e.g., virtually identical corticosterone and SIH responses). In general, ES appears to be associated with less neuroinflammation and increases in markers associated with neuroprotection whereas IS is associated with a dysregulation of neuroprotection and increased activity in pro-inflammatory pathways [Unpublished Results].

The differences in immune response induced by IS and ES can be functionally significant. This is illustrated by the fact that ongoing training with ES can dramatically increase morbidity and mortality (Ciavarra et al., 2018) after intranasal inoculation of vesicular stomatitis virus, a member of the Rhaboviridae virus family, and a well-established mouse model of acute viral encephalitis (Huneycutt et al., 1993, 1994; Bi et al., 1995). This may seem odd given the putative beneficial effect of reducing neuroinflammation; however, it is consistent with findings that inhibitors of pro-inflammatory cytokines (antibodies, soluble receptors, and anti-inflammatory cytokines) can lead to rapid and overwhelming infection and excess mortality in models utilizing localized infection (Opal et al., 1996). This suggests that the immunosuppression produced by ES may be quite strong.

Additionally, ES and IS elicit regionally different immune responses in the mPFC and HPC [Unpublished Results]. We have observed differences in regional gene expression and immune cell recruitment that may be related to the functions of these regions within the greater stress neurocircuit during the stress response. Since mPFC is more directly involved in working memory, recruitment to this region may be more substantial compared to HPC during the earlier stages of the stress response. Alternatively, training with ES and IS resulted in some similarities in gene expression related to cell cycle regulation and immune signaling and cell recruitment. However, these data do not reveal the precise underlying mechanisms behind the gene expression that may drive these response mechanisms to be inflammatory or not. The differences observed in expression levels related to cellular repair, protein trafficking, and neurotransmission, however, may suggest these processes influence inflammatory outcomes [Unpublished Results].

One of the critical aspects of this work is that fear memories associated with ES can result in less neuroinflammation whereas those associated with IS can result in greater neuroinflammation. Thus, fear memories have the ability to elicit different immune responses dependent upon whether the initial stressor associated with their formation was controllable or not in ways that have relevance to the development of psychopathologies, and potentially neurodegeneration.

4.3. Stress and fear memory extinction

Fear extinction has primarily been examined using freezing to define memory modifications and assess reductions in fear with the general assumption that greater freezing indicates greater fear and stronger fear memory retention (Blanchard and Blanchard, 1969a,b) and that reduced freezing indicates extinguished fear and/or attenuated fear memory. However, freezing does not fully reflect fear behavior and we recently examined fear extinction using multiple behavioral outputs (freezing, locomotion, grooming and rearing), SIH, and effects on subsequent NREM and REM amounts. We also examined NREM-associated EEG delta (δ) activity (NREM-δ) as a measure of potential changes in sleep intensity (Pappenheimer et al., 1975; Borbely, 1982; Borbely et al., 1984) and REM-associated EEG theta (θ) activity (REM-θ) which has been linked to fear memory consolidation and extinction (Boyce et al., 2016). We conducted extinction training at 24 h (a typical time for many fear conditioning studies (e.g. (Seidenbecher et al., 2003; Lesting et al., 2011)) and 48 h after fear conditioning and tested again at one week post conditioning.

This study demonstrated how complex fear memory and extinction can be when multiple outcome measures and time points are evaluated. Critically, freezing was not predictive of behaviors that varied with different extinction delays. Extinction training at 24 h post-conditioning resulted in significantly increased rearing and a nominal increase in locomotion indicating a putatively lower level of anxiety compared to extinction training at 48h post-conditioning whereas freezing was

similar at both times. Freezing also was not predictive of fear conditioned SIH which was lower with extinction training at 24 h (~0.5 °C above baseline) compared to at 48 h (~1.0 °C above baseline). These findings suggest potential differences in the anxiolytic effect of extinction at different post-conditioning times on some behaviors and that early extinction may actually be associated with a reduction in the conditioned stress response, as indicated by SIH.

Early extinction also was associated attenuated REM-θ activity at 2 h after extinction training and also in the following dark period. Reduced REM-θ activity was not found after extinction training at 48 h post-conditioning. By comparison, NREM-δ was increased for 3 h after extinction training at 24 h post-conditioning and for 2 h after extinction training at 48 h post-conditioning. REM and NREM amounts were briefly decreased immediately after extinction training.

The difference in REM-θ across extinction training days is interesting given the hypothesized role(s) of θ oscillations in enabling network-level cooperation (Buzsaki, 1996, 2002), including in memory consolidation (Boyce et al., 2016) and fear extinction (Lesting et al., 2011). For example, Boyce et al. (2016) suggested that *in vivo* hippocampal θ oscillations during REM are necessary for consolidation of contextual fear memory. The general consensus is that the large-scale θ oscillation detected in the EEG, as recorded and analyzed in our study, is primarily produced in the hippocampus (Buzsaki et al., 1983). Additionally, studies using local field potential (LFP) and unit recordings have found phase-locked discharge of neurons responding to hippocampal θ waves in the amygdala and the mPFC (Siapas et al., 2005; Sirota et al., 2008; Popa et al., 2010; Boyce et al., 2016). These structures exhibit "synchronized θ activity" reflecting selective involvement of the hippocampus (Quirk and Mueller, 2008) that has been hypothesized to provide means for connecting neural ensembles temporally and functionally (Buzsaki, 1996; Pape et al., 2005; Lesting et al., 2011). This θ coherence reportedly increases during contextual fear conditioning (Seidenbecher et al., 2003), but declines during extinction learning (Lesting et al., 2011). Accordingly, the reduced REM-θ activity following extinction training 24 h post-conditioning would reflect changes in synchronization within hippocampal-associated neural ensembles acting to regulate the consolidation of fear extinction. However, if this is the case, the lack of a similar reduction in REM-θ activity in mice receiving extinction training at 48 h post-conditioning is difficult to explain.

4.4. Integrated stress and fear responses

The findings presented above demonstrate that fear memory and fear memory extinction, and their relationship to stress, are not adequately represented by a few simple overt behaviors and stress response markers. Instead, stress, fear memory and fear memory extinction induce complex responses that engage multiple systems in ways that can be impacted by individual differences in resilience and vulnerability, available learning opportunities, and potentially, lability of memories. In general, the varying responses for indices of behavioral fear, sleep, brain activity, neuroimmune, and the stress system demonstrate the need to include multiple outcome measures considered as integrated responses to more accurately assess fear memory and its neural regulation.

5. Neural circuits and regulation of integrated stress and fear responses

The amygdala, HPC, and vmPFC have been identified as key structures for fear conditioning. The amygdala has long been recognized as being important for fear expression and extinction (LaBar et al., 1998; Buchel and Dolan, 2000; Phelps et al., 2004; Milad et al., 2007a,b; Sehlmeyer et al., 2009; Linnman et al., 2011). The HPC has been linked to the contextual features associated with fear conditioning and expression and hippocampal activity has been observed during fear behavior in several imaging studies (Kalisch et al., 2006; Milad et al., 2007a,b; Knight et al., 2009; Sehlmeyer et al., 2009). The HPC is also implicated in extinction training and recall of extinction (Milad et al., 2007, 2009). vmPFC activity has been shown to be decreased during acquisition and expression of fear and increased during extinction of fear behavior and recall of extinction (Phelps et al., 2004).

It is important to note here that these regions are also involved in modulation of sleep, and/or are sensitive to sleep disturbances. Neuronal activity of amygdala varies across the sleep-wake states, with increased activity during REM compared to wakefulness (Braun et al., 1997; Nofzinger et al., 2002). It is also interconnected with wakefulness promoting and sleep promoting areas throughout the brain. Regions of mPFC also have interconnections with sleep promoting regions and may be involved in modulation of sleep following fear conditioning. In fact, vmPFC activity during fear conditioning was found to be positively correlated with subsequent REM (Spoormaker et al., 2014). This is interesting given that mPFC is critical for the perception of control and in mediating the consequences of stress (Maier et al., 2006; Smith and Vale, 2006; Akirav and Maroun, 2007). For example, blocking activation of the vmPFC with muscimol did not alter escape behavior in rats presented inescapable shock, but blocking vmPFC in rats presented with escapable shock produced failure in escape learning and greater fear conditioning (Maier et al., 2006). By comparison, activation of vmPFC in rats with picrotoxin prior to inescapable shock promoted subsequent learning of escapable shock in a shuttlebox (Maier et al., 2006). However, part of the influence of mPFC is enacted through its effects on the dorsal raphe nucleus (DRN) and possibly locus coeruleus (LC) (Maier et al., 2006), which have inhibitory effects on REM (Steriade and McCarley, 1990), providing a potential substrate for regulating alterations in REM sleep. For example, activation of mPFC inhibits DRN (Maier et al., 2006; Smith and Vale, 2006).

Of these three regions, the amygdala has the most established role in regulating fear- and stress-induced alterations in sleep, especially REM (Liu et al., 2009, 2011; Wellman et al., 2013) as well as in the acquisition and consolidation of fear conditioning (e.g. (Helmstetter and Bellgowan, 1994; Maren et al., 1996; Muller et al., 1997; Cousens and Otto, 1998; Maren, 1998; Sacchetti et al., 1999; Koo et al., 2004)). In addition to its roles in mediating fear memory and fear responses, the amygdala is important in the regulation of behavioral, physiological and neuroendocrine responses to stress (Roozendaal et al., 1991a,b; Bohus et al., 1996; Roozendaal et al., 1991a,b) and it appears to be a vital interface between stressful events, stressful memories and their impact on sleep and arousal as evidenced by regulation of differential sleep responses in Res and Vul rats (Wellman et al., 2016, 2018). For example, pharmacological inactivation of the basolateral nucleus of the amygdala (BLA) during shock training can block fear conditioned REM reductions in Vul rats without altering either SIH or freezing, and do not alter fear conditioned changes in REM, SIH or freezing in Res rats (Wellman et al., 2016). We also have found, in mice, that excitatory optogenetic stimulation of BLA during post-conditioning REM, but not NREM, can significantly reduce EEG theta activity (Machida et al., 2021a,b) whereas inhibitory optogenetic stimulation of BLA during REM can enhance EEG theta (Machida et al., 2021a,b). Excitatory optogenetic stimulation during REM also resulted in significantly reduced contextual freezing and enhanced subsequent REM, but did not significantly alter fear conditioned SIH (Machida et al., 2021a,b).

Various lines of work indicate that neural influences on, and interactions with, the neuroimmune system are important for regulating stress outcomes. The amygdala, PFC, HPC, as well as the hypothalamus, have established roles in responding to and regulating responses to stress and fear (e.g., (Kollack-Walker et al., 1997; Maren, 1999; Richmond et al., 1999; LeDoux, 2000; Zhang et al., 2001; Martinez et al., 2002; Bast et al., 2003; Maren and Holt, 2004; Trivedi and Coover, 2004; Rudy and Matus-Amat, 2005; Hobin et al., 2006; Maier et al., 2006; Akirav and Maroun, 2007; Misane et al., 2013; Zhang et al., 2014)). Stress induces activation of microglia and increases neuroinflammatory signaling in these areas (Wohleb et al., 2015). The amygdala becomes activated and

shows local synthesis of pro-inflammatory cytokines shortly after systemic immune challenge with administration of bacterial lipopolysaccharide (Engler et al., 2011; Prager et al., 2013). Furthermore, we recently found that it also mediates stress-induced neuroimmune responses as demonstrated by findings that optogenetic inhibition of BLA of mice during shock training blocks stress-induced neuroinflammatory responses in HPC and mPFC (see Fig. 2). Thus, the amygdala, appears to be a critical node in the neurocircuit(s) coordinating multiple stress, sleep and neuroimmune responses (see Table 1).

It should be noted that interactions between the amygdala, mPFC and HPC occur within the context of reciprocal influences with brainstem regions that regulate arousal and sleep (e.g., REM regulatory and generator regions in the pons: LC; DRN; nucleus subcoeruleus (SubC); laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) and the reticularis pontis oralis (RPO) (Morrison et al., 2000; Xi et al., 2011; Zhang et al., 2012). See Fig. 3 for simplified diagram of connections. For example, noradrenergic and serotonergic neurons in the stress-responsive LC and DRN, respectively, are virtually silent during REM, and their activation has long been thought to inhibit its generation (Reviewed in (Steriade and McCarley, 1990)). The amygdala projects to these regions (Krettek and Price, 1978; Price et al., 1987; Bernard et al., 1993; Petrov et al., 1994; Peyron et al., 1998), and we recently demonstrated that optogenetic activation of central nucleus of the amygdala (CNA) projections to RPO, but not SubC and PPT, could enhance dark period REM (Wellman et al., 2022). Optogenetic activation of CNA projections into LC of rats inhibits neuronal firing which could assist in promoting REM (Wellman et al., 2017a,b), and its projections into other regions could play a role in modulating other REM related phenomena (Reviewed in (Wellman et al., 2022). A variety of studies implicate these brainstem regions in mediating various aspects of the stress response. Most work on stress has focused on the LC and DRN which are impacted by stress-induced neuroinflammation (Reviewed in (Finnell and Wood, 2016)) and the LC is also thought to play a role in modulating neuroinflammatory responses (Finnell et al., 2019).

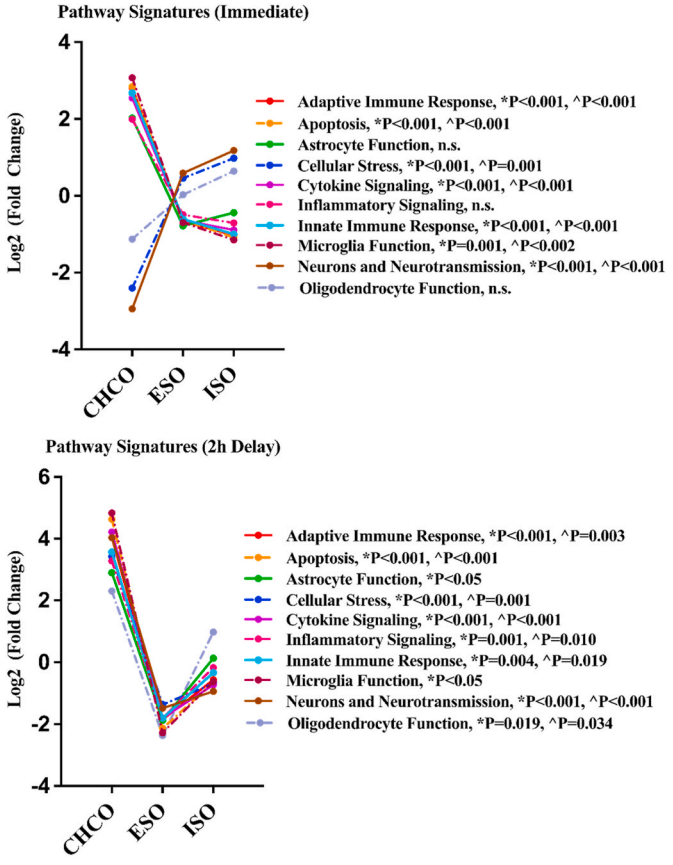

Fig. 2. Optogenetic inhibition of BLA blunts neuroimmune relevant pathway signatures (based on principal component analysis) in mPFC after ES and IS. C57BL/6J mice (n = 5/group) were prepared for optogenetic inhibition of BLA with CaMKIIα-eNpHR3.0-eYFP-WPRE (NpHR) and optic cannulas bilaterally, and after recovery, were trained in our yoked ES-IS paradigm over two days (20 shocks: 0.5 mA, 5.0 s maximum duration, 1.0 min intervals). During training on each day, BLA was optogenetically inhibited for the duration of training. On day 1 of training, the mice were returned to their home cage and left undisturbed. On day 2, the mice were sacrificed immediately (A) or 2 h (B) after training, and the mPFC was processed for assessing chemokine and cytokine responses. CHCO, home cage controls with control opsin. ESO: ES with optogenetic inhibition. ISO: IS with optogenetic inhibition. Significant differences relative to CHCO indicated by ESO (*) and ISO (^) next to pathway label.

Table 1
Summary showing general effects of uncontrollability/controllability on stress outcome measures and involvement of the amygdala. Gray shading: Similar for IS and ES. No shading: Differences between IS and ES.

Parameter	IS	ES	Amygdala
Behavioral freezing	↑	↑	+
Corticosterone	↑	↑	≠
Stress-induced hyperthermia	↑	↑	≠
REM amounts	↓	↑	√
Neuroinflammatory response	Enhanced	Suppressed	√
Antiviral response*	Enhanced	Suppressed	---
Morbidity and mortality*	↔	↑	---
c-Fos in paraventricular n.	↑↑	↑	√
c-Fos in amygdala	↑	↔	---
c-Fos in locus coeruleus	↑	↔	√
c-Fos in dorsal raphe n.	↑	↔	---

↓, ↑, ↔: decrease, increase or no change relative to home cage control; √: amygdala can influence; ≠, no demonstrated effects in our hands; +, we have found the amygdala to be involved in the acquisition of fear learning, but not to otherwise impact freezing in the extensive fear learning paradigms we us in our studies. —: data not available; IS: inescapable shock; ES: escapable shock; REM: rapid eye movement sleep; *, Response to a neurotropic virus (vesicular stomatitis virus) compared to infected home cage control. The enhanced and suppressed antiviral response and related morbidity and mortality demonstrate that the altered immune responses after ES and IS can have significant consequences for immune function.

6. Modeling integrated stress and fear responses

The aphorism "all models are wrong, but some are useful" is attributed to the statistician, George E. P. Box (Box and Draper, 1987). This statement is also appropriate outside of statistics and serves a reminder to be aware of the limitations of models, and the need to ensure that the models chosen are useful for the questions that are being asked. This is especially true when simple models are used in attempts to understand complex processes that involve the engagement of multiple systems and interactions that evolve over time, as has been the case for much of the work examining the relationships between fear memory, stress and sleep. Typical studies of fear memory use a simple approach that assesses behavioral or physiological responses in the immediacy of a stressful event, and then use the findings to extrapolate regarding fear memory, stress and their relationship to sleep and role in psychopathology. However, as discussed above, fear and fear memory are complex, can be impacted both stress parameters and organismic variables, and interact with and regulate multiple systems in synergistic ways that are not fully reflected in these proximal responses. This has sometimes led to diametrically opposed hypotheses regarding the potential role of specific

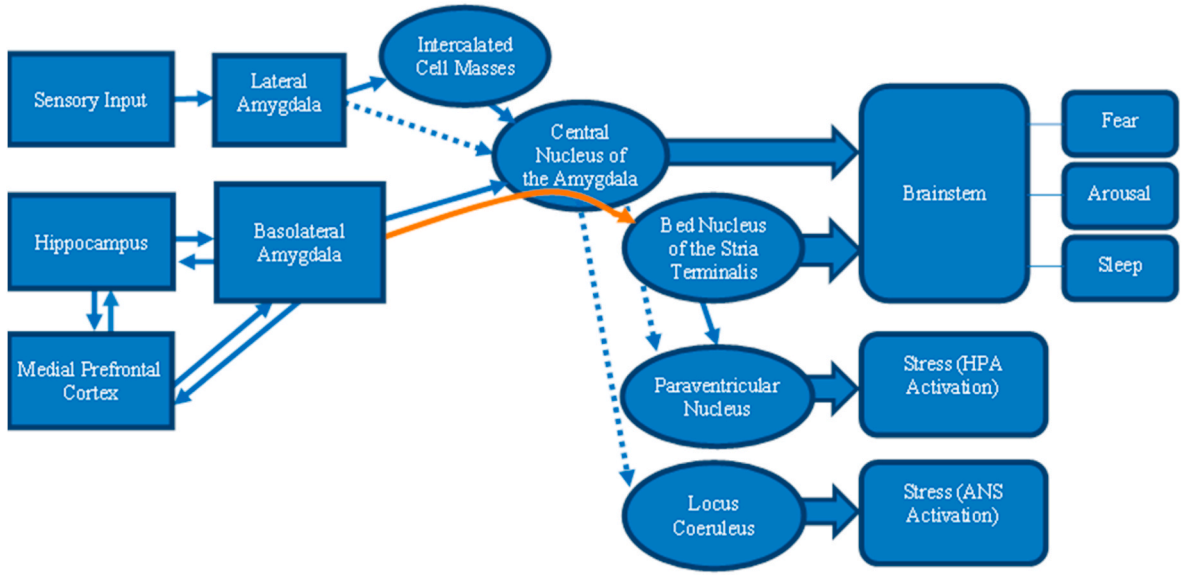

Fig. 3. Simplified diagram of circuitry regulating fear-conditioned behavior and fear-conditioned changes in sleep, arousal and stress. The lateral nucleus of the amygdala (LA) receives afferent sensory input during fear conditioning. The LA projects, via the intercalated cell masses, to the central nucleus (CNA), which has outputs to brainstem regions (locus coeruleus, dorsal raphe nucleus, n. subcoeruleus, laterodorsal tegmental nucleus, pedunculopontine tegmental nucleus, periqueductal gray, reticularis pontis oralis) that control the expression of the fear, arousal and REM sleep. Projections from the hippocampus to the basolateral nucleus of the amygdala (BLA) process contextual information during conditioning and BLA regulates fear expression and the influence of contextual fear memory on sleep via projections to CNA and bed nucleus of the stria terminalis (BNST) which has similar descending outputs to those of CNA. Projections from BLA to BNST travel through CNA (orange line), which may be the source of conflicting data regarding the influence of the CNA on brainstem regions. BNST also has influence on the hypothalamic paraventicular nucleus which regulates the hypothalamo-pituitary-adrenal (HPA) stress axis. The medial prefrontal cortex also receives and supplies input to the amygdala which has been linked to fear extinction. Dashed blue line indicates a direct connection of LA to CNA in some models of fear, and for a projection from CNA to PVN in some models of stress regulation. CNA also has inhibitory input into the locus coeruleus which regulates the autonomic (ANS) branch of the stress system. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sleep states in the consolidation and extinction of fear memory.

One of the critical problems in studying the effects of stress on sleep in animals with respect to modeling the development of PTSD and other stress-related disorders is the lack of a clear understanding of the nature of the alterations in sleep that are associated with the development of pathology as opposed to those associated with a normal, and therefore non-pathological, stress response. As noted above, virtually all stressors produce alterations in sleep and it is highly unlikely that all, or even most, reflect pathological processes. The same is likely true for stress-induced neuroimmune responses. It is also not known whether the initial stress-induced alterations in sleep and neuroinflammation are the same as those that occur in later stages of disorders such as PTSD or how they may be modified over time by subsequent life experiences or drug usage. Potential longer-term changes in sleep and neuroinflammation and their relationship to maladaptive behaviors have received much less attention. This is important, as it also is not clear whether the enhanced REM that appears to develop over time after a traumatic event is adaptive, pathological, or a reflection of failed adaptive responses.

Genetic differences are an important factor in the development of stress-related pathology as approximately 20–30 percent of individuals who experience traumatic events may develop PTSD (Cohen et al., 2003; Kerns et al., 2004). Attempts to develop animal models that better represent individual differences in clinical populations have included selecting low and high responders to stressors in outbred rat strains (Cohen et al., 2003; Kerns et al., 2004; Bush et al., 2007). However, the potential role of individual differences in resilience and vulnerability has been minimally explored, particularly in studies that involve sleep. The differences in sleep amongst those who develop PTSD and those that adequately cope with significant stress are not known. We have demonstrated that mouse strains that exhibit greater anxiety-like behaviors in response to challenges in wakefulness also show greater and longer duration alterations in sleep after training with IS and after fearful cues (Sanford et al., 2003a) and contexts (Sanford et al., 2003b). We have also found significant individual differences in stress and conditioned changes in sleep within outbred Wistar strain rats (Wellman et al., 2016).

Thus, significant limitations in animal models of stress and fear induced sleep disturbances arise from an imperfect understanding of which stressful experiences can lead to persisting psychopathology, how those may interact with individual differences in resilience and vulnerability, and of the role that sleep may play in adaptive coping with stress. These factors suggest that refinement is needed in the way that stress and sleep are studied if truly successful models are to be developed.

Despite many common responses across species, animal models of fear conditioning have not yet provided the insight needed to understand human fear-related psychopathology. Part of this failure is likely due to the fact that adaptive and maladaptive fear responses have not been adequately defined and thus do not guide work on fear mechanisms. Our thesis is also that the primary reliance on a single behavioral output (freezing) as the defining, and often only, index of fear memory has promoted examination of correlational relationships between fear output variables and has limited understanding of fear memory expression and circuitry. This has been particularly true for sleep and stress where much of the effort has been focused on determining whether and how they promote fear memory as defined by freezing.

7. Animal models of fear memory

Fear memory in animal models has typically been treated as a simple construct that can be evaluated based on overt behavior (usually freezing) that presumably reflects the strength of fear responses and extinction of fear memories. However, fear is a complex emotion that interacts with multiple neural and physiological systems and that can be modulated by both situational factors and an individual's ability to cope with challenges. This complexity has been recognized. LeDoux

distinguished fear dependent on survival circuits from that associated with other types of challenges and suggested that conscious fear emotions should be considered separately from nonconscious mechanisms that regulate defense responses (LeDoux, 2014). There also has generally been insufficient consideration of the different ways that fear can be manifested, and what fear responses mean within the behavioral repertoire of subject animals. Below, we discuss some considerations for measures of fear memory, stress, sleep and neuroimmune responses that may impact the long-term effects of stressful experiences.

7.1. Behavioral fear

Behavioral freezing is the standard measure of fear memory in rodent studies (Blanchard and Blanchard, 1969a,b; Phillips and LeDoux, 1992; Paylor et al., 1994), and greater behavioral freezing is considered to indicate greater associative learning (Havekes et al., 2015), as well as stronger fear reactions (Blanchard and Blanchard, 1969a,b; Phillips and LeDoux, 1992; Paylor et al., 1994). The ease of evaluating this simple behavior makes it a very attractive outcome measure, and it has become virtually synonymous with fear memory in the literature. Numerous studies have used its presence and absence, or reduction, to draw conclusions regarding fear circuitry; unfortunately, freezing has limited ability to reflect other fear related behaviors and responses, and even activity in the brain (Liu et al., 2009a,b; Machida et al., 2018). It can be virtually eliminated pharmacologically and optogenetically, and behaviorally extinguished, without having a consistent, predictive relationship to alterations in other fear-related activity and behavior. It also has little translational construct validity as enhanced freezing is not a common symptom of psychopathology in humans (it is not listed in the DSM-5 (American Psychiatric Association, 2013), as a characteristic of any psychiatric disorder), and it is actually decreased in patients with severe PTSD (Fragkaki et al., 2017).

The lack of a predictive relationship of enhanced freezing to human psychopathology and its inability to predict conditioned stress and immune responses and disturbances in sleep (which are associated with psychopathology) are especially disconcerting as much of the basic work linking fear memory to mood, anxiety and stress disorders is based on mechanistic examinations of fear circuitry using freezing as the outcome measure. Additionally, even though the failure of current conditioned fear models to explain pathological fear has been generally recognized; studies that purport to study PTSD-related fear memory processes in animal models most often do so using outputs such as enhanced freezing (Kaouane et al., 2012) or impaired extinction of freezing (Debiec et al., 2011). However, the use of freezing as the sole or most important index of fear memory is likely preventing insight into the mechanisms by which it produces the disruptions in sleep, neuroimmune, and the stress system observed with fear-related psychopathology.

Interestingly, limitations of behavioral measures in shock training paradigms such as commonly used in fear conditioning have long been recognized. Bolles (1970) noted that placing an animal in a chamber and presenting shock limited its behavioral repertoire to that typically seen in the face of danger, i.e., fleeing, freezing or defensive aggression. The confinement of the chamber and lack of direct threat for the animal to engage may further constrain behavior and make freezing the most likely response. More recently, Trott et al. (2022) argued that freezing was "the purest reflection of associative learning" in fear conditioning, but found that novel stimuli could induce movement in freezing animals. This suggests that even during freezing, animals are continuing to surveil their environment and processing information that could impact their memories and subsequent behavior. Thus, given constrained behavior and continued sensory surveillance, it should not be surprising that freezing in experimental fear conditioning does not fully reflect fear learning and memory. Behavioral constraints may be a factor in differences in fear memory associated with ES and IS as constraints on fleeing (escape) are lifted in the ES condition.

7.2. Stress response

The stress system regulates physiological and behavioral adaptations to external and internal stimuli that organisms interpret as challenging or threatening, with the ultimate goal of restoring homeostasis (Kazakou et al., 2022). However, as noted above, ES and IS produce virtually identical increases in corticosterone (Machida et al., 2018), an index of HPA activation (Maier et al., 1986), and SIH (Yang et al., 2011a,b), an increase in core body temperature that parallels the time course of corticosterone (Groenink et al., 1994; Veening et al., 2004). Others have also reported that ES and IS produce similar inductions of corticosterone (Maier et al., 1986). Thus, standard indices of the stress response may not distinguish controllable and uncontrollable stress.

We have focused most of our efforts on SIH as an index of the stress response because it does not require handling animals for blood draws and can be continuously monitored in conjunction with recording sleep and, with appropriate equipment, conjointly collected in association with freezing. This work has demonstrated that SIH responses can be fear conditioned. We have observed that similar SIH responses occur with either decreases or increases in subsequent REM (Yang et al., 2010; Wellman et al., 2016, 2017) and that freezing can extinguish during periods of enhanced SIH (in our paradigm, freezing can significantly decrease across two repeated context exposures whereas SIH is similar in both exposures (Wellman et al., 2018). Thus, stress responses induced by fear memories also are not necessarily associated with freezing, and are not predictive of specific changes in sleep. These findings are problematic for the hypothesis that activation of the stress system is solely responsible for pathological conditions, and suggest that its activation needs to be considered in context of multiple system responses.

7.3. Sleep

Experiments in animals have shown that virtually any stressful experience can significantly impact subsequent sleep (Reviewed in (Pawlyk et al., 2008)). Exposure to many experimental stressors induces a stress-induced period of arousal (Chrousos, 1998) followed by subsequent rebound sleep (increases in REM and/or NREM) that occur at various latencies after the stressor is removed. REM appears to be particularly susceptible to the effects of stress and can either be decreased or increased depending on stressor characteristics, e.g., controllability (Sanford et al., 2010; Yang et al., 2010) and/or putative individual resilience or vulnerability to stress (Wellman et al., 2016, 2018; Sweeten et al., 2020a,b;). Increases in REM can also occur several hours after a stressor has been experienced, e.g., in rodents, REM can be increased in the dark period after restraint has been administered in the light period (Meerlo et al., 2001).

In addition to the direct effects of stress, we have demonstrated that changes in sleep, particularly REM, can be fear conditioned. This is illustrated by the fact that re-exposure to shock contexts without representing shock can produce virtually identical changes in REM to those produced by shock (Wellman et al., 2014, 2016, 2017) and the fact that these changes in REM can extinguish with repeated exposures to the shock context (Wellman et al., 2008). We have also shown that fear conditioned alterations in REM can be independent of behavioral freezing and SIH (Wellman et al., 2016, 2017). That is, REM can be either increased or decreased following enhanced freezing and a significant stress response. NREM can also be altered by fear memory (Tang et al., 2005c), but the relationship has received much less attention.

While the significance of the differences are not fully understood, several lines of work suggest that REM is important for adaptive processing of emotion and stress (Mellman et al., 2002, 2007; Sanford et al., 2010; Walker, 2010) and disrupted REM soon after trauma is associated with the development of PTSD (Mellman et al., 2014). A recent functional neuroimaging study in humans also indicates that greater baseline REM is associated with reduced fear-related activity in, and connectivity between, the HPC, amygdala and vmPFC during conditioning using a

"highly annoying but not painful" shock as the unconditioned stimulus (Lerner et al., 2017). This finding is consistent with the hypothesis that REM is associated with stress resilience, though this type of experimental paradigm likely does not fully model fear learning associated with traumatic experiences. The rapidly normalized REM in Res rats also suggests a more rapid restoration of sleep homeostasis (Wellman et al., 2018) which is consistent with stress resilience.

Thus, REM disturbances, and likely general sleep disturbances, appear to have predictive validity for subsequent psychopathology though unfortunately the mechanisms are not known. However, it is also important to consider sleep-related activity in addition to the presence, absence or relative duration of given sleep states. REM-dependent activity including synchronized θ activity among brain regions (Popa et al., 2010), REM-θ amplitude (Boyce et al., 2016; Machida et al., 2021a,b) and phasic pontine-waves (P-waves) (Datta and O'Malley, 2013) have been suggested to be associated with the successful consolidation of fear memory. However, the story may be more complex. In ongoing work, we have found that Res rats showed decreased correlations in LFP signal recorded between BLA-HPC regions during REM after ST and after fear recall whereas Vul rats showed strong correlations between BLA and HPC (Sanford et al., 2021a,b). Res and Vul rats show virtually identical freezing and stress responses, but different stress and fear conditioned sleep responses, thereby reinforcing our hypothesis that reliance on a single behavioral output does not provide sufficient representation of fear memory processing.

7.4. Neuroimmune system

It has long been known that immune function could be conditioned, i.e., the field of psychoneuroimmunology was founded with the discovery that alterations in immune function could be associated with conditioned taste aversion (Ader and Cohen, 1975). However, immune responses have rarely been considered in the context of conditioned fear, but the continued intrusion of fear memories activates stress response mechanisms, and can increase neuroinflammation (Grippo and Scotti, 2013; Calcia et al., 2016; Kim and Won, 2017; Muhie et al., 2017) which is thought to play negative roles in fear memory extinction and the development of stress-related mood and anxiety disorders (Myers and Davis, 2007; Hefner et al., 2008; Furini et al., 2014). Assessing differences in neuroimmune responses elicited by controllable and uncontrollable stress, and their respective fear memories, may help to understand the role fear memory in mediating maladaptive and adaptive outcome of stress. The close relationship between the immune system and sleep (Krueger and Majde, 1990; Toth et al., 1993; Opp, 2005) may be important to consider.

In a study using NanoString® panels that assessed multiple immune pathways, we found that contextual fear memories associated with ES resulted in a down-regulation in HPC of many genes associated with neuroinflammation and an up-regulation of genes associated with neuroprotection (Adkins et al., 2022) (see Fig. 4). By comparison, fear memories associated with IS mice showed a down-regulation of genes associated with neuronal protection, but an up-regulation of genes involved in pro-inflammatory pathways. Similarly, within BLA, contextual fear memories associated with ES resulted in an up-regulation of genes involved in neuronal signaling and neuroprotection, whereas fear memories associated with IS resulted in a down-regulation of genes associated with neuronal signaling and neuroprotection and an up-regulation of genes involved in pro-inflammatory signaling. These differences were associated with greater amounts of REM in ES trained mice and less REM in IS trained mice. Freezing and SIH did not differ regardless of whether the stress was controllable or not.

8. Relevance of integrated models for understanding trauma and stress-related disorders

In general, current models of stress, sleep, fear memory and neuroinflammation have failed to provide sufficient answers regarding their roles in stress-related psychopathology. However, the weakness is not necessarily in the markers that have been used, but in the fact that their use in relatively simple models have provided incomplete representations of the complex systems level interactions that can occur in organisms facing, and dealing with the consequences of, significant stress. This suggests that more comprehensive models are needed to better understand given disorders at the neurobiological level, which also will require better understanding of clinical conditions.

Much of our work has been focused on using animal models in trying to understand the interactions between stress, sleep, and fear memory, and more recently neuroinflammation, in the development of PTSD. However, determining precise system level changes in disorders such as

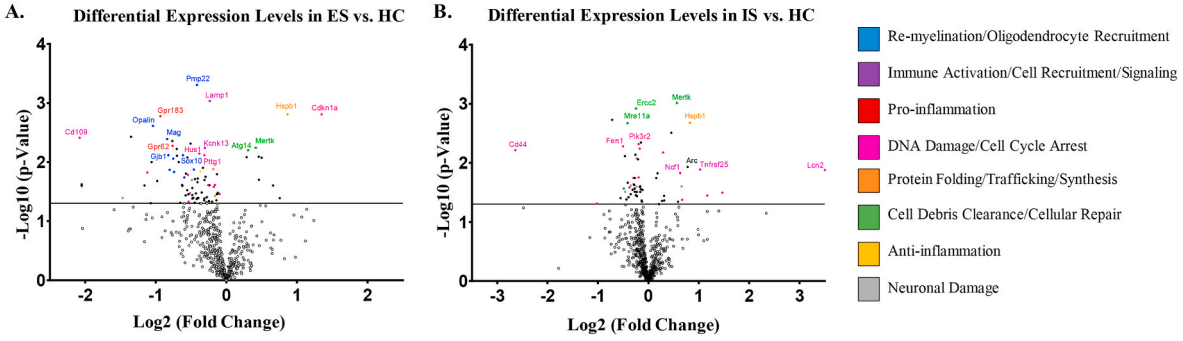

Fig. 4. Volcano plots displaying gene expression levels in hippocampus compared to home cage (HC) control following fearful context for A. escapable shock (ES) and B. inescapable shock (IS) groups. Statistically significant genes fall above the horizontal line, and highly differentially expressed genes fall to either side of the zero on the x-axis. Genes are colored coded based on their related pathway. The most statistically significant genes are labeled in the plot. Overall, compared to HC, ES showed decreases in markers of NI and less innate immune system activation following fearful context while IS showed increases in markers of NI and more innate immune system activation. ES mice showed down-regulation of many genes associated with re-myelination (Mag, p = 0.000406; Opalin, p = 0.00244; Pmp22, p = 0.000493; Sox10, p = 0.00762); oligodendrocyte differentiation (Opalin, p = 0.00244; Gjb1, p = 0.00764); DNA damage (Hus1, p = 0.0072; and Pttg1, 0.00761); immune cell recruitment/activation (Lamp1, 0.000923 and Gpr183, p = 0.00167); and inflammation (Gpr183, p = 0.00167). ES mice also showed an up-regulation of genes associated with the clearance of dead cells and debris (Mertk, p = 0.00571 and Atg14, p = 0.00627), proper protein folding (Hspb1, p = 0.00155), microglial protection of neurons (Kcnk13, p = 0.00574), and the regulation of cell growth (Cdkn1a, p = 0.00156) in response to stress. Compared to HC, IS showed down-regulation of genes associated with DNA repair and protection from neurodegeneration (Mre11a, p = 0.00213; ErCC2, p = 0.0012; Fen1, p = 0.00523); microglial protection of neurons (Kcnk13, p = 0.00668); cell survival and differentiation (Pik3r2, p = 0.00482); and blood brain barrier (BBB) protection (CD44, p = 0.00609). IS showed up-regulation of genes involved in cytokine signaling (Tnfrsf25, p = 0.013); activation of the innate immune response (Lcn2, p = 0.0132); recruitment of neutrophils (Lcn2, p = 0.0132 and Ncf1, p = 0.0149); and the Arc gene. Adapted from Adkins et al., (2022).

PTSD needed to ascertain the accuracy of models has proven to be incredibly difficult. Variations in results across studies of PTSD patients may involve demographic heterogeneity (e.g., age and gender), clinical variables (e.g., PTSD severity, comorbidities and medication status), trauma-related factors (e.g., trauma type, duration and number of trauma exposures, and the time between trauma and sleep and neuroimmune assessment) (Mellman et al., 2002, 2014; Hall Brown et al., 2015; Shalev et al., 2017; Mysliwiec et al., 2018; Peruzzolo et al., 2022), and experimental methodology (e.g., whether there was an adaptation night and sleep scoring rules). The relative influence of these factors can be examined with meta-analytic procedures, but requires sufficient data for given variables, which is not always available. The lack of data means that it is difficult to determine endophenotypes (e.g., changes in fear-related neural circuits) and exophenotypes (e.g., clinical manifestation such as sleep disorders) underlying individual reactions to stress, similarities between normal and pathological responses, and the essential factors that drive persisting stress-related psychopathology. Such data are needed both to guide basic experimental research as well as to guide efforts in precision medicine for psychiatric disorders.

Determining differences in sleep may be central to understanding stress-related and potentially other disorders. Sleep has been considered an especially important target for interventions in PTSD, and successful alleviation of disorders commonly seen in trauma survivors and patients with PTSD (i.e., insomnia, trauma-related nightmares, and obstructive sleep apnea) (Zhang et al., 2019a,b; Zhang et al., 2022) is associated with improved overall posttraumatic stress symptoms (Hertenstein et al., 2022). Additionally, in a recent umbrella review (which summarizes, assesses, and grades the findings of multiple meta-analyses (Ioannidis, 2009; Fusar-Poli et al., 2018) of 27 neuropsychiatric disorders, we found that no two diseases had the same pattern of altered sleep (Zhang et al., 2022). This is important as it suggests that specific sleep profiles might distinguish neuropsychiatric disorders, and by extension, that the origins of the profiles might also be different. While additional work needs to be conducted on this possibility, if true, different sleep profiles, as opposed to simple changes in relative amounts, might provide markers for adaptive and maladaptive outcomes of stress. This is consistent with the role we have assigned for sleep in hypotheses guiding our basic work, but these hypotheses need clinical validation or disproval.

9. Conclusion

Our basic contention in this paper is that stressful challenges induce integrated responses across multiple systems that are inadequately modeled by simple overt fear behaviors or physiological responses that occur in the immediacy of stressful/fearful stimuli. Instead, we propose that stress and associated fear learning memory orchestrate integrated responses in multiple systems that can vary depending on situational variables in which the initial stress was experienced, and with the ability of the individual to cope with the fear-inducing challenges. Differences in coping may involve differences in resilience and vulnerability and/or whether the stressful context allows adaptive learning and responses that can change parameters within the integrated multi-system response.

We have concentrated on stress, sleep, fear and neuroimmune responses and how they are impacted by stressor controllability and differences in putative stress resilience and vulnerability. This work, while far from complete, demonstrates both common (corticosterone, SIH and fear behaviors) and distinguishing (sleep and neuroimmune) responses based on an individual's ability to respond and relative resilience and vulnerability. Critically, different integrated responses across systems are replicable, can subsequently be induced by fear memory, and they can be modulated at the neurocircuit level; thus, providing avenues for manipulating and exploring the mechanisms and relative roles of factors that regulate different components of the responses. Experimental models that consider how an organism responds to stress, and how that impacts responses across systems, may have the potential to provide insight into stress-related disorders not possible with simple descriptive models.

CRediT authorship contribution statement

Larry D. Sanford: Conceptualization, Writing – original draft, Funding acquisition. **Laurie L. Wellman:** Conceptualization, Writing – review & editing, Funding acquisition. **Austin M. Adkins:** Investigation, Writing – review & editing. **Ming-Lei Guo:** Writing – original draft. **Ye Zhang:** Writing – original draft, Writing – review & editing. **Rong Ren:** Writing – review & editing. **Linghui Yang:** Investigation. **Xiangdong Tang:** Conceptualization, Writing – review & editing, Funding acquisition.

Declaration of competing interest

None.

Acknowledgments

Portions of this work were supported by NIH research grant MH64827, NASA research grant 80NSSC19K1582, National Natural Science Foundation of China research grant 82120108002, and an EVMS Multidisciplinary Research (MDR) Grant.

References

Ader, R., Cohen, N., 1975. Behaviorally conditioned immunosuppression. Psychosom. Med. 37, 333–340.
Adkins, A.M., Wellman, L.L., Sanford, L.D., 2022. Controllable and uncontrollable stress differentially impact fear conditioned alterations in sleep and neuroimmune signaling. Life (submitted for publication).
Akirav, I., Maroun, M., 2007. The role of the medial prefrontal cortex-amygdala circuit in stress effects on the extinction of fear. Neural Plast., 30873
Angelidou, A., Asadi, S., Alysandratos, K.D., Karagkouni, A., Kourembanas, S., Theoharides, T.C., 2012. Perinatal stress, brain inflammation and risk of autism-review and proposal. BMC Pediatr. 12, 89.
Anisman, H., Merali, Z., 2009. Learned helplessness induced in mice. In: Gould, T.D. (Ed.), Mood and Anxiety Related Phenotypes in Mice. Humana Press, New York, pp. 177–196.
Arnoldini, M., Mostowy, R., Bonhoeffer, S., Ackermann, M., 2012. Evolution of stress response in the face of unreliable environmental signals. PLoS Comput. Biol. 8, e1002627.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Arlington, VA.
Bast, T., Zhang, W.N., Feldon, J., 2003. Dorsal hippocampus and classical fear conditioning to tone and context in rats: effects of local NMDA-receptor blockade and stimulation. Hippocampus 13, 657–675.
Bellesi, M., de Vivo, L., Chini, M., Gilli, F., Tononi, G., Cirelli, C., 2017. Sleep loss promotes astrocytic phagocytosis and microglial activation in mouse cerebral cortex. J. Neurosci. 37, 5263–5273.
Bernard, J.F., Alden, M., Besson, J.M., 1993. The organization of the efferent projections from the pontine parabrachial area to the amygdaloid complex: a Phaseolus vulgaris leucoagglutinin (PHA-L) study in the rat. J. Comp. Neurol. 329, 201–229.
Bi, Z., Barna, M., Komatsu, T., Reiss, C.S., 1995. Vesicular stomatitis virus infection of the central nervous system activates both innate and acquired immunity. J. Virol. 69, 6466–6472.
Bijlsma, R., Loeschcke, V., 2005. Environmental stress, adaptation and evolution: an overview. J. Evol. Biol. 18, 744–749.
Blanchard, R.J., Blanchard, D.C., 1969a. Crouching as an index of fear. J. Comp. Physiol. Psychol. 67, 370–375.
Blanchard, R.J., Blanchard, D.C., 1969b. Passive and active reactions to fear-eliciting stimuli. J. Comp. Physiol. Psychol. 68, 129–135.
Bohus, B., Koolhaas, J., Luiten, P., Korte, S., Roozendaal, B., Wiersma, A., 1996. The neurobiology of the central nucleus of the amygdala in relation to neuroendocrine outflow. Prog. Brain Res. 107, 447–460.
Bolles, R.c., 1970. Species-specific defense reactions and avoidance learning. Psychol. Rev. 77, 32–48.
Bollinger, J.L., Bergeon Burns, C.M., Wellman, C.L., 2016. Differential effects of stress on microglial cell activation in male and female medial prefrontal cortex. Brain Behav. Immun. 52, 88–97.
Bolstad, B.R., Zinbarg, R.E., 1997. Sexual victimization, generalized perception of control, and posttraumatic stress disorder symptom severity. J. Anxiety Disord. 11, 523–540.
Borbely, A.A., 1982. Sleep regulation. Introduction. Hum. Neurobiol. 1, 161–162.

Borbely, A.A., Tobler, I., Hanagasioglu, M., 1984. Effect of sleep deprivation on sleep and EEG power spectra in the rat. Behav. Brain Res. 14, 171–182.
Bouton, M.E., 2004. Context and behavioral processes in extinction. Learn. Mem. 11, 485–494.
Box, G.E.P., Draper, N.R., 1987. Empirical Model-Building and Response Surfaces. John Wiley & Sons, Hoboken, NJ.
Boyce, R., Glasgow, S.D., Williams, S., Adamantidis, A., 2016. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 352, 812–816.
Bratt, A.M., Kelley, S.P., Knowles, J.P., Barrett, J., Davis, K., Davis, M., Mittleman, G., 2001. Long term modulation of the HPA axis by the hippocampus. Behavioral, biochemical and immunological endpoints in rats exposed to chronic mild stress. Psychoneuroendocrinology 26, 121–145.
Braun, A.R., Balkin, T.J., Wesenten, N.J., Carson, R.E., Varga, M., Baldwin, P., Selbie, S., Belenky, G., Herscovitch, P., 1997. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 120 (Pt 7), 1173–1197.
Britten, R.A., Wellman, L.L., Sanford, L.D., 2021. Progressive increase in the complexity and translatability of rodent testing to assess space-radiation induced cognitive impairment. Neurosci. Biobehav. Rev. 126, 159–174.
Bryant, R.A., Creamer, M., O'Donnell, M., Silove, D., McFarlane, A.C., 2010. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. Sleep 33, 69–74.
Buchel, C., Dolan, R.J., 2000. Classical fear conditioning in functional neuroimaging. Curr. Opin. Neurobiol. 10, 219–223.
Bush, D.E., Sotres-Bayon, F., LeDoux, J.E., 2007. Individual differences in fear: isolating fear reactivity and fear recovery phenotypes. J. Trauma Stress 20, 413–422.
Buzsaki, G., 1996. The hippocampo-neocortical dialogue. Cerebr. Cortex 6, 81–92.
Buzsaki, G., 2002. Theta oscillations in the hippocampus. Neuron 33, 325–340.
Buzsaki, G., Leung, L.W., Vanderwolf, C.H., 1983. Cellular bases of hippocampal EEG in the behaving rat. Brain Res. 287, 139–171.
Calcia, M.A., Bonsall, D.R., Bloomfield, P.S., Selvaraj, S., Barichello, T., Howes, O.D., 2016. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacology (Berl) 233, 1637–1650.
Charney, D., Deutch, A., 1996. A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit. Rev. Neurobiol. 10, 419–446.
Chrousos, G.P., 1998. Stressors, stress, and neuroendocrine integration of the adaptive response. Ann. N. Y. Acad. Sci. 851, 311–335.
Chrousos, G.P., 2009. Stress and disorders of the stress system. Nat. Rev. Endocrinol. 5, 374–381.
Ciavarra, R.P., Machida, M., Lundberg, P.S., Gauronskas, P., Wellman, L.L., Steel, C., Aflatooni, J.O., Sanford, L.D., 2018. Controllable and uncontrollable stress differentially impact pathogenicity and survival in a mouse model of viral encephalitis. J. Neuroimmunol. 319, 130–141.
Cohen, H., Zohar, J., Matar, M., 2003. The relevance of differential response to trauma in an animal model of posttraumatic stress disorder. Biol. Psychiatr. 53, 463–473.
Cousens, G., Otto, T., 1998. Both pre- and posttraining excitotoxic lesions of the basolateral amygdala abolish the expression of olfactory and contextual fear conditioning. Behav. Neurosci. 112, 1092–1103.
Crawley, J.N., Belknap, J.K., Collins, A., Crabbe, J.C., Frankel, W., Henderson, N., Hitzemann, R.J., Maxson, S.C., Miner, L.L., Silva, A.J., Wehner, J.M., Wynshaw-Boris, A., Paylor, R., 1997. Behavioral phenotypes of inbred mouse strains: implications and recommendations for molecular studies. Psychopharmacology (Berl) 132, 107–124.
Crick, F., Mitchison, G., 1983. The function of dream sleep. Nature 304, 111–114.
Datta, S., O'Malley, M.W., 2013. Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. J. Neurosci. 33, 4561–4569.
Davis, M., 1990. Animal models of anxiety based on classical conditioning: the conditioned emotional response (CER) and the fear-potentiated startle effect. Pharmacol. Therapeut. 47, 147–165.
Davis, M., 1992a. The role of the amygdala in conditioned fear. In: Aggleton, J. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Wiley-Liss, Inc, New York, pp. 255–305.
Davis, M., 1992b. The role of the amygdala in fear and anxiety. Annu. Rev. Neurosci. 15, 353–375.
De Felice, F.G., Lourenco, M.V., 2015. Brain metabolic stress and neuroinflammation at the basis of cognitive impairment in Alzheimer's disease. Front. Aging Neurosci. 7, 94.
Debiec, J., Bush, D.E., LeDoux, J.E., 2011. Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats–a possible mechanism for the persistence of traumatic memories in PTSD. Depress. Anxiety 28, 186–193.
Dinan, T.G., Cryan, J.F., 2012. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. Psychoneuroendocrinology 37, 1369–1378.
Doyere, V., Gisquet-Verrier, P., de Marsanich, B., Ammassari-Teule, M., 2000. Age-related modifications of contextual information processing in rats: role of emotional reactivity, arousal and testing procedure. Behav. Brain Res. 114, 153–165.
Dutcher, J.M., Creswell, J.D., 2018. The role of brain reward pathways in stress resilience and health. Neurosci. Biobehav. Rev. 95, 559–567.
Engler, H., Doenlen, R., Engler, A., Riether, C., Prager, G., Niemi, M.B., Pacheco-Lopez, G., Krugel, U., Schedlowski, M., 2011. Acute amygdaloid response to systemic inflammation. Brain Behav. Immun. 25, 1384–1392.
Faye, C., McGowan, J.C., Denny, C.A., David, D.J., 2018. Neurobiological mechanisms of stress resilience and implications for the aged population. Curr. Neuropharmacol. 16, 234–270.
Finnell, J.E., Moffitt, C.M., Hesser, L.A., Harrington, E., Melson, M.N., Wood, C.S., Wood, S.K., 2019. The contribution of the locus coeruleus-norepinephrine system in the emergence of defeat-induced inflammatory priming. Brain Behav. Immun. 79, 102–113.
Finnell, J.E., Wood, S.K., 2016. Neuroinflammation at the interface of depression and cardiovascular disease: evidence from rodent models of social stress. Neurobiol. Stress 4, 1–14.
Foa, E.B., Zinbarg, R., Rothbaum, B.O., 1992. Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model. Psychol. Bull. 112, 218–238.
Fragkaki, I., Roelofs, K., Stins, J., Jongedijk, R.A., Hagenaars, M.A., 2017. Reduced freezing in posttraumatic stress disorder patients while watching affective pictures. Front. Psychiatr. 8, 39.
Frank, M.G., Baratta, M.V., Sprunger, D.B., Watkins, L.R., Maier, S.F., 2007. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav. Immun. 21, 47–59.
Franklin, T.B., Saab, B.J., Mansuy, I.M., 2012. Neural mechanisms of stress resilience and vulnerability. Neuron 75, 747–761.
Friedman, M.J., Resick, P.A., Bryant, R.A., Strain, J., Horowitz, M., Spiegel, D., 2011. Classification of trauma and stressor-related disorders in DSM-5. Depress. Anxiety 28, 737–749.
Frischer, J.M., Bramow, S., Dal-Bianco, A., Lucchinetti, C.F., Rauschka, H., Schmidbauer, M., Laursen, H., Sorensen, P.S., Lassmann, H., 2009. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 132, 1175–1189.
Furini, C., Myskiw, J., Izquierdo, I., 2014. The learning of fear extinction. Neurosci. Biobehav. Rev. 47, 670–683.
Fusar-Poli, P., Hijazi, Z., Stahl, D., Steyerberg, E.W., 2018. The science of prognosis in psychiatry: a review. JAMA Psychiatr. 75, 1289–1297.
Garate, I., Garcia-Bueno, B., Madrigal, J.L., Caso, J.R., Alou, L., Gomez-Lus, M.L., Mico, J. A., Leza, J.C., 2013. Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway. Biol. Psychiatr. 73, 32–43.
Garcia-Bueno, B., Caso, J.R., Leza, J.C., 2008. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. Neurosci. Biobehav. Rev. 32, 1136–1151.
Gill, J., Lee, H., Barr, T., Baxter, T., Heinzelmann, M., Rak, H., Mysliwiec, V., 2014. Lower health related quality of life in U.S. military personnel is associated with service-related disorders and inflammation. Psychiatr. Res. 216, 116–122.
Gomez-Gonzalez, B., Hurtado-Alvarado, G., Esqueda-Leon, E., Santana-Miranda, R., Rojas-Zamorano, J.A., Velazquez-Moctezuma, J., 2013. REM sleep loss and recovery regulates blood-brain barrier function. Curr. Neurovascular Res. 10, 197–207.
Goncharova, L.B., Tarakanov, A.O., 2008. Why chemokines are cytokines while their receptors are not cytokine ones? Curr. Med. Chem. 15, 1297–1304.
Gonzalez, M.M., Debilly, G., Valatx, J.L., Jouvet, M., 1995. Sleep increase after immobilization stress: role of the noradrenergic locus coeruleus system in the rat. Neurosci. Lett. 202, 5–8.
Gordon, J.A., 2018. Moving Stress Research Forward. Director's Message. https://www.nimh.nih.gov/about/director/messages/2018/moving-stress-research-forward.shtml.
Grillon, C., Southwick, S.M., Charney, D.S., 1996. The psychobiological basis of posttraumatic stress disorder. Mol. Psychiatr. 1, 278–297.
Grippo, A.J., Scotti, M.A., 2013. Stress and neuroinflammation. Mod. Trends Pharmacopsychiatry 28, 20–32.
Groenink, L., van der Gugten, J., Zethof, T., van der Heyden, J., Olivier, B., 1994. Stress-induced hyperthermia in mice: hormonal correlates. Physiol. Behav. 56, 747–749.
Hagberg, H., Gressens, P., Mallard, C., 2012. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. Ann. Neurol. 71, 444–457.
Hall Brown, T.S., Akeeb, A., Mellman, T.A., 2015. The role of trauma type in the risk for insomnia. J. Clin. Sleep Med. 11, 735–739.
Havekes, R., Meerlo, P., Abel, T., 2015. Animal studies on the role of sleep in memory: from behavioral performance to molecular mechanisms. Curr. Top Behav. Neurosci. 25:183-206.
Hefner, K., Whittle, N., Juhasz, J., Norcross, M., Karlsson, R.M., Saksida, L.M., Bussey, T. J., Singewald, N., Holmes, A., 2008. Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain. J. Neurosci. 28, 8074–8085.
Heinzelmann, M., Lee, H., Rak, H., Livingston, W., Barr, T., Baxter, T., Scattergood-Keepper, L., Mysliwiec, V., Gill, J., 2014. Sleep restoration is associated with reduced plasma C-reactive protein and depression symptoms in military personnel with sleep disturbance after deployment. Sleep Med. 15, 1565–1570.
Hellman, K., Abel, T., 2007. Fear conditioning increases NREM sleep. Behav. Neurosci. 121, 310–323.
Hellwig, S., Brioschi, S., Dieni, S., Frings, L., Masuch, A., Blank, T., Biber, K., 2016. Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. Brain Behav. Immun. 55, 126–137.
Helmstetter, F.J., Bellgowan, P.S., 1994. Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. Behav. Neurosci. 108, 1005–1009.
Hertenstein, E., Trinca, E., Wunderlin, M., Schneider, C.L., Zust, M.A., Feher, K.D., Su, T., Straten, A.V., Berger, T., Baglioni, C., Johann, A., Spiegelhalder, K., Riemann, D., Feige, B., Nissen, C., 2022. Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: a systematic review and meta-analysis. Sleep Med. Rev. 62, 101597.

Hobin, J.A., Ji, J., Maren, S., 2006. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. Hippocampus 16, 174–182.
Hsu, J.C., Lee, Y.S., Chang, C.N., Chuang, H.L., Ling, E.A., Lan, C.T., 2003. Sleep deprivation inhibits expression of NADPH-d and NOS while activating microglia and astroglia in the rat hippocampus. Cells Tissues Organs 173, 242–254.
Huneycutt, B.S., Bi, Z., Aoki, C.J., Reiss, C.S., 1993. Central neuropathogenesis of vesicular stomatitis virus infection of immunodeficient mice. J. Virol. 67, 6698–6706.
Huneycutt, B.S., Plakhov, I.V., Shusterman, Z., Bartido, S.M., Huang, A., Reiss, C.S., Aoki, C., 1994. Distribution of vesicular stomatitis virus proteins in the brains of BALB/c mice following intranasal inoculation: an immunohistochemical analysis. Brain Res. 635, 81–95.
Hurtado-Alvarado, G., Becerril-Villanueva, E., Contis-Montes de Oca, A., Dominguez-Salazar, E., Salinas-Jazmin, N., Perez-Tapia, S.M., Pavon, L., Velazquez-Moctezuma, J., Gomez-Gonzalez, B., 2018. The yin/yang of inflammatory status: blood-brain barrier regulation during sleep. Brain Behav. Immun. 69, 154–166.
Hurtado-Alvarado, G., Dominguez-Salazar, E., Pavon, L., Velazquez-Moctezuma, J., Gomez-Gonzalez, B., 2016. Blood-brain barrier disruption induced by chronic sleep loss: low-grade inflammation may Be the link. J. Immunol. Res. 2016, 4576012.
Ingiosi, A.M., Opp, M.R., Krueger, J.M., 2013. Sleep and immune function: glial contributions and consequences of aging. Curr. Opin. Neurobiol. 23, 806–811.
Ioannidis, J.P., 2009. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ (Can. Med. Assoc. J.) 181, 488–493.
Iwamoto, Y., Morinobu, S., Takahashi, T., Yamawaki, S., 2007. Single prolonged stress increases contextual freezing and the expression of glycine transporter 1 and vesicle-associated membrane protein 2 mRNA in the hippocampus of rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31, 642–651.
Iwata, M., Ota, K.T., Duman, R.S., 2013. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav. Immun. 31, 105–114.
Kalisch, R., Wiech, K., Critchley, H.D., Dolan, R.J., 2006. Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. Neuroimage 30, 1458–1466.
Kaouane, N., Porte, Y., Vallee, M., Brayda-Bruno, L., Mons, N., Calandreau, L., Marighetto, A., Piazza, P.V., Desmedt, A., 2012. Glucocorticoids can induce PTSD-like memory impairments in mice. Science 335, 1510–1513.
Karagkouni, A., Alevizos, M., Theoharides, T.C., 2013. Effect of stress on brain inflammation and multiple sclerosis. Autoimmun. Rev. 12, 947–953.
Kazakou, P., Nicolaides, N.C., Chrousos, G.P., 2022. Basic concepts and hormonal regulators of the stress system. Horm. Res. Paediatr.
Kerns, J.G., Cohen, J.D., MacDonald 3rd, A.W., Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. Science 303, 1023–1026.
Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Annu. Rev. Psychol. 53, 83–107.
Kierdorf, K., Prinz, M., 2013. Factors regulating microglia activation. Front. Cell. Neurosci. 7, 44.
Kim, Y.K., Won, E., 2017. The influence of stress on neuroinflammation and alterations in brain structure and function in major depressive disorder. Behav. Brain Res. 329, 6–11.
Kishimoto, T., Radulovic, J., Radulovic, M., Lin, C.R., Schrick, C., Hooshmand, F., Hermanson, O., Rosenfeld, M.G., Spiess, J., 2000. Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. Nat. Genet. 24, 415–419.
Kleim, B., Wysokowsky, J., Schmid, N., Seifritz, E., Rasch, B., 2016. Effects of sleep after experimental trauma on intrusive emotional memories. Sleep 39, 2125–2132.
Knight, D.C., Waters, N.S., Bandettini, P.A., 2009. Neural substrates of explicit and implicit fear memory. Neuroimage 45, 208–214.
Kobayashi, I., Boarts, J.M., Delahanty, D.L., 2007. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology 44, 660–669.
Kollack-Walker, S., Watson, S.J., Akil, H., 1997. Social stress in hamsters: defeat activates specific neurocircuits within the brain. J. Neurosci. 17, 8842–8855.
Koo, J.W., Han, J.S., Kim, J.J., 2004. Selective neurotoxic lesions of basolateral and central nuclei of the amygdala produce differential effects on fear conditioning. J. Neurosci. 24, 7654–7662.
Koolhaas, J.M., Bartolomucci, A., Buwalda, B., de Boer, S.F., Flugge, G., Korte, S.M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wohr, M., Fuchs, E., 2011. Stress revisited: a critical evaluation of the stress concept. Neurosci. Biobehav. Rev. 35, 1291–1301.
Koren, D., Arnon, I., Lavie, P., Klein, E., 2002. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. Am. J. Psychiatr. 159, 855–857.
Krettek, J.E., Price, J.L., 1978. Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. J. Comp. Neurol. 178, 225–254.
Krueger, J.M., Majde, J.A., 1990. Sleep as a host defense: its regulation by microbial products and cytokines. Clin. Immunol. Immunopathol. 57, 188–199.
Krystal, A.D., 2012. Psychiatric disorders and sleep. Neurol. Clin. 30, 1389–1413.
LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., Phelps, E.A., 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron 20, 937–945.
Lavie, P., 2001. Sleep disturbances in the wake of traumatic events. N. Engl. J. Med. 345, 1825–1832.
LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.
LeDoux, J.E., 2014. Coming to terms with fear. Proc. Natl. Acad. Sci. U. S. A 111, 2871–2878.
Lerner, I., Lupkin, S.M., Sinha, N., Tsai, A., Gluck, M.A., 2017. Baseline levels of rapid-eye-movement sleep may protect against excessive activity in fear-related neural circuitry. J. Neurosci. 37, 11233–11244.
Lesting, J., Narayanan, R.T., Kluge, C., Sangha, S., Seidenbecher, T., Pape, H.C., 2011. Patterns of coupled theta activity in amygdala-hippocampal-prefrontal cortical circuits during fear extinction. PLoS One 6, e21714.
Li, S., Liao, Y., Dong, Y., Li, X., Li, J., Cheng, Y., Cheng, J., Yuan, Z., 2021. Microglial deletion and inhibition alleviate behavior of post-traumatic stress disorder in mice. J. Neuroinflammation 18, 7.
Linnman, C., Rougemont-Bucking, A., Beucke, J.C., Zeffiro, T.A., Milad, M.R., 2011. Unconditioned responses and functional fear networks in human classical conditioning. Behav. Brain Res. 221, 237–245.
Lisieski, M.J., Eagle, A.L., Conti, A.C., Liberzon, I., Perrine, S.A., 2018. Single-prolonged stress: a review of two decades of progress in a rodent model of post-traumatic stress disorder. Front. Psychiatr. 9, 196. -196.
Liu, X., Tang, X., Sanford, L.D., 2003. Fear-conditioned suppression of REM sleep: relationship to Fos expression patterns in limbic and brainstem regions in BALB/cJ mice. Brain Res. 991, 1–17.
Liu, X., Tang, X., Sanford, L.D., 2009a. Stressor controllability and Fos expression in stress regulatory regions in mice. Physiol. Behav. 97, 321–326.
Liu, X., Wellman, L.L., Yang, L., Ambrozewicz, M.A., Tang, X., Sanford, L.D., 2011. Antagonizing corticotropin-releasing factor in the central nucleus of the amygdala attenuates fear-induced reductions in sleep but not freezing. Sleep 34, 1539–1549.
Liu, X., Yang, L., Wellman, L.L., Tang, X., Sanford, L.D., 2009b. GABAergic antagonism of the central nucleus of the amygdala attenuates reductions in rapid eye movement sleep after inescapable footshock stress. Sleep 32, 888–896.
Livingston, W.S., Rusch, H.L., Nersesian, P.V., Baxter, T., Mysliwiec, V., Gill, J.M., 2015. Improved sleep in military personnel is associated with changes in the expression of inflammatory genes and improvement in depression symptoms. Front. Psychiatr. 6, 59.
Lund, H., Pieber, M., Harris, R.A., 2017. Lessons learned about neurodegeneration from microglia and monocyte depletion studies. Front. Aging Neurosci. 9, 234.
Machida, M., Lonart, G., Sanford, L.D., 2018. Effects of stressor controllability on transcriptional levels of c-fos, Arc, and brain-derived neurotrophic factor in mouse amygdala and medial prefrontal cortex. Neuroreport 29, 112–117.
Machida, M., Sweeten, B.L.W., Adkins, A.M., Wellman, L.L., Sanford, L.D., 2021a. The basolateral amygdala mediates the role of rapid eye movement sleep in integrating fear memory responses. Life 12.
Machida, M., Sweeten, B.L.W., Adkins, A.M., Wellman, L.L., Sanford, L.D., 2021b. Basolateral amygdala regulates EEG theta-activity during rapid eye movement sleep. Neuroscience 468, 176–185.
Maier, S.F., Amat, J., Baratta, M.V., Paul, E., Watkins, L.R., 2006. Behavioral control, the medial prefrontal cortex, and resilience. Dialogues Clin. Neurosci. 8, 397–406.
Maier, S.F., Ryan, S.M., Barksdale, C.M., Kalin, N.H., 1986. Stressor controllability and the pituitary-adrenal system. Behav. Neurosci. 100, 669–674.
Maren, S., 1998. Overtraining does not mitigate contextual fear conditioning deficits produced by neurotoxic lesions of the basolateral amygdala. J. Neurosci. 18, 3088–3097.
Maren, S., 1999. Neurotoxic or electrolytic lesions of the ventral subiculum produce deficits in the acquisition and expression of Pavlovian fear conditioning in rats. Behav. Neurosci. 113, 283–290.
Maren, S., Aharonov, G., Fanselow, M.S., 1996. Retrograde abolition of conditional fear after excitotoxic lesions in the basolateral amygdala of rats: absence of a temporal gradient. Behav. Neurosci. 110, 718–726.
Maren, S., Holt, W.G., 2004. Hippocampus and Pavlovian fear conditioning in rats: muscimol infusions into the ventral, but not dorsal, hippocampus impair the acquisition of conditional freezing to an auditory conditional stimulus. Behav. Neurosci. 118, 97–110.
Martinez, M., Calvo-Torrent, A., Herbert, J., 2002. Mapping brain response to social stress in rodents with c-fos expression: a review. Stress 5, 3–13.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87, 873–904.
McKim, D.B., Weber, M.D., Niraula, A., Sawicki, C.M., Liu, X., Jarrett, B.L., Ramirez-Chan, K., Wang, Y., Roeth, R.M., Sucaldito, A.D., Sobol, C.G., Quan, N., Sheridan, J. F., Godbout, J.P., 2017. Microglial recruitment of IL-1beta-producing monocytes to brain endothelium causes stress-induced anxiety. Mol. Psychiatr.
Medina-Flores, F., Hurtado-Alvarado, G., Contis-Montes de Oca, A., Lopez-Cervantes, S. P., Konigsberg, M., Deli, M.A., Gomez-Gonzalez, B., 2020. Sleep loss disrupts pericyte-brain endothelial cell interactions impairing blood-brain barrier function. Brain Behav. Immun. 89, 118–132.
Meerlo, P., Easton, A., Bergmann, B.M., Turek, F.W., 2001. Restraint increases prolactin and REM sleep in C57BL/6J mice but not in BALB/cJ mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R846–R854.
Meerlo, P., Pragt, B.J., Daan, S., 1997. Social stress induces high intensity sleep in rats. Neurosci. Lett. 225, 41–44.
Meerlo, P., Turek, F.W., 2001. Effects of social stimuli on sleep in mice: non-rapid-eye-movement (NREM) sleep is promoted by aggressive interaction but not by sexual interaction. Brain Res. 907, 84–92.
Mellman, T.A., Bustamante, V., Fins, A.I., Pigeon, W.R., Nolan, B., 2002. REM sleep and the early development of posttraumatic stress disorder. Am. J. Psychiatr. 159, 1696–1701.
Mellman, T.A., Kobayashi, I., Lavela, J., Wilson, B., Hall Brown, T.S., 2014. A relationship between REM sleep measures and the duration of posttraumatic stress disorder in a young adult urban minority population. Sleep 37, 1321–1326.

Mellman, T.A., Pigeon, W.R., Nowell, P.D., Nolan, B., 2007. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. J. Trauma Stress 20, 893–901.
Menz, M.M., Rihm, J.S., Salari, N., Born, J., Kalisch, R., Pape, H.C., Marshall, L., Buchel, C., 2013. The role of sleep and sleep deprivation in consolidating fear memories. Neuroimage 75, 87–96.
Milad, M.R., Pitman, R.K., Ellis, C.B., Gold, A.L., Shin, L.M., Lasko, N.B., Zeidan, M.A., Handwerger, K., Orr, S.P., Rauch, S.L., 2009. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol. Psychiatr. 66, 1075–1082.
Milad, M.R., Quirk, G.J., Pitman, R.K., Orr, S.P., Fischl, B., Rauch, S.L., 2007a. A role for the human dorsal anterior cingulate cortex in fear expression. Biol. Psychiatr. 62, 1191–1194.
Milad, M.R., Wright, C.I., Orr, S.P., Pitman, R.K., Quirk, G.J., Rauch, S.L., 2007b. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol. Psychiatr. 62, 446–454.
Misane, I., Kruis, A., Pieneman, A.W., Ogren, S.O., Stiedl, O., 2013. GABA(A) receptor activation in the CA1 area of the dorsal hippocampus impairs consolidation of conditioned contextual fear in C57BL/6J mice. Behav. Brain Res. 238, 160–169.
Morrison, A.R., Sanford, L.D., Ross, R.J., 2000. The amygdala: a critical modulator of sensory influence on sleep. Biol. Signals Recept. 9, 283–296.
Muhie, S., Gautam, A., Chakraborty, N., Hoke, A., Meyerhoff, J., Hammamieh, R., Jett, M., 2017. Molecular indicators of stress-induced neuroinflammation in a mouse model simulating features of post-traumatic stress disorder. Transl. Psychiatry 7, e1135.
Muller, J., Corodimas, K.P., Fridel, Z., LeDoux, J.E., 1997. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. Behav. Neurosci. 111, 683–691.
Myers, K.M., Davis, M., 2007. Mechanisms of fear extinction. Mol. Psychiatr. 12, 120–150.
Mysliwiec, V., Brock, M.S., Creamer, J.L., O'Reilly, B.M., Germain, A., Roth, B.J., 2018. Trauma associated sleep disorder: a parasomnia induced by trauma. Sleep Med. Rev. 37, 94–104.
Nadler, J.J., Zou, F., Huang, H., Moy, S.S., Lauder, J., Crawley, J.N., Threadgill, D.W., Wright, F.A., Magnuson, T.R., 2006. Large-scale gene expression differences across brain regions and inbred strains correlate with a behavioral phenotype. Genetics 174, 1229–1236.
Najjar, S., Pearlman, D.M., Alper, K., Najjar, A., Devinsky, O., 2013. Neuroinflammation and psychiatric illness. J. Neuroinflammation 10, 43.
Nakata, A., 2012. Psychosocial job stress and immunity: a systematic review. Methods Mol. Biol. 934, 39–75.
Neylan, T.C., Otte, C., Yehuda, R., Marmar, C.R., 2006. Neuroendocrine regulation of sleep disturbances in PTSD. Ann. N. Y. Acad. Sci. 1071, 203–215.
Nishida, M., Pearsall, J., Buckner, R.L., Walker, M.P., 2009. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cerebr. Cortex 19, 1158–1166.
Nofzinger, E.A., Buysse, D.J., Miewald, J.M., Meltzer, C.C., Price, J.C., Sembrat, R.C., Ombao, H., Reynolds, C.F., Monk, T.H., Hall, M., Kupfer, D.J., Moore, R.Y., 2002. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain 125, 1105–1115.
Ognjanovski, N., Broussard, C., Zochowski, M., Aton, S.J., 2018. Hippocampal network oscillations rescue memory consolidation deficits caused by sleep loss. Cerebr. Cortex 28, 3711–3723.
Opal, S.M., Cross, A.S., Jhung, J.W., Young, L.D., Palardy, J.E., Parejo, N.A., Donsky, C., 1996. Potential hazards of combination immunotherapy in the treatment of experimental septic shock. J. Infect. Dis. 173, 1415–1421.
Opp, M.R., 2005. Cytokines and sleep. Sleep Med. Rev. 9, 355–364.
Pape, H.C., Narayanan, R.T., Smid, J., Stork, O., Seidenbecher, T., 2005. Theta activity in neurons and networks of the amygdala related to long-term fear memory. Hippocampus 15, 874–880.
Pappenheimer, J.R., Koski, G., Fencl, V., Karnovsky, M.L., Krueger, J., 1975. Extraction of sleep-promoting factor S from cerebrospinal fluid and from brains of sleep-deprived animals. J. Neurophysiol. 38, 1299–1311.
Pawlyk, A.C., Morrison, A.R., Ross, R.J., Brennan, F.X., 2008. Stress-induced changes in sleep in rodents: models and mechanisms. Neurosci. Biobehav. Rev. 32, 99–117.
Paylor, R., Tracy, R., Wehner, J., Rudy, J., 1994. DBA/2 and C57BL/6 mice differ in contextual fear but not auditory fear conditioning. Behav. Neurosci. 108, 810–817.
Peruzzolo, T.L., Pinto, J.V., Roza, T.H., Shintani, A.O., Anzolin, A.P., Gnielka, V., Kohmann, A.M., Marin, A.S., Lorenzon, V.R., Brunoni, A.R., Kapczinski, F., Passos, I. C., 2022. Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis. Mol. Psychiatr.
Petrov, T., Krukoff, T.L., Jhamandas, J.H., 1994. Chemically defined collateral projections from the pons to the central nucleus of the amygdala and hypothalamic paraventricular nucleus in the rat. Cell Tissue Res. 277, 289–295.
Peyron, C., Petit, J.M., Rampon, C., Jouvet, M., Luppi, P.H., 1998. Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. Neuroscience 82, 443–468.
Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43, 897–905.
Phillips, R.G., LeDoux, J.E., 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav. Neurosci. 106, 274–285.
Pitman, R.K., Shin, L.M., Rauch, S.L., 2001. Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. J. Clin. Psychiatr. 62 (Suppl. 17), 47–54.
Popa, D., Duvarci, S., Popescu, A.T., Lena, C., Pare, D., 2010. Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc. Natl. Acad. Sci. U. S. A. 107, 6516–6519.
Poroyko, V.A., Carreras, A., Khalyfa, A., Khalyfa, A.A., Leone, V., Peris, E., Almendros, I., Gileles-Hillel, A., Qiao, Z., Hubert, N., Farre, R., Chang, E.B., Gozal, D., 2016. Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice. Sci. Rep. 6, 35405.
Prager, G., Hadamitzky, M., Engler, A., Doenlen, R., Wirth, T., Pacheco-Lopez, G., Krugel, U., Schedlowski, M., Engler, H., 2013. Amygdaloid signature of peripheral immune activation by bacterial lipopolysaccharide or staphylococcal enterotoxin B. J. Neuroimmune Pharmacol. 8, 42–50.
Price, J., Russchen, F., Amaral, D., 1987. The limbic region. II: the amygdaloid complex. In: Swanson, L. (Ed.), Handbook of Chemical Neuroanatomy. Integrated Systems of the CNA, Part I. Elsevier, New York, pp. 279–375.
Quirk, G.J., Mueller, D., 2008. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 33, 56–72.
Rampin, C., Cespuglio, R., Chastrette, N., Jouvet, M., 1991. Immobilisation stress induces a paradoxical sleep rebound in rat. Neurosci. Lett. 126, 113–118.
Rasch, B., Born, J., 2013. About sleep's role in memory. Physiol. Rev. 93, 681–766.
Rasmussen, H., Rosness, T.A., Bosnes, O., Salvesen, Ø., Knutli, M., Stordal, E., 2018. Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer's disease: the HUNT study. Dementia and geriatric cognitive disorders extra 8, 414–425.
Richmond, M.A., Yee, B.K., Pouzet, B., Veenman, L., Rawlins, J.N., Feldon, J., Bannerman, D.M., 1999. Dissociating context and space within the hippocampus: effects of complete, dorsal, and ventral excitotoxic hippocampal lesions on conditioned freezing and spatial learning. Behav. Neurosci. 113, 1189–1203.
Richter-Levin, G., Sandi, C., 2021. Title: "labels matter: is it stress or is it trauma? Transl. Psychiatry 11, 385.
Roelofs, K., 2017. Freeze for action: neurobiological mechanisms in animal and human freezing. Philos. Trans. R. Soc. Lond. B Biol. Sci. 372.
Rojo, A.I., McBean, G., Cindric, M., Egea, J., Lopez, M.G., Rada, P., Zarkovic, N., Cuadrado, A., 2014. Redox control of microglial function: molecular mechanisms and functional significance. Antioxidants Redox Signal. 21, 1766–1801.
Roozendaal, B., Koolhaus, J., Bohus, B., 1991a. Attenuated cardiovascular, neuroendocrine, and behavioral responses after a single footshock in central amygdaloid lesioned male rats. Physiol. Behav. 50, 771–775.
Roozendaal, B., Koolhaus, J., Bohus, B., 1991b. Central amygdala lesions affect behavioral and autonomic balance during stress in rats. Physiol. Behav. 50, 777–781.
Rosen, J.B., 2004. The neurobiology of conditioned and unconditioned fear: a neurobehavioral system analysis of the amygdala. Behav. Cognit. Neurosci. Rev. 3, 23–41.
Ross, R.J., 2014. The changing REM sleep signature of posttraumatic stress disorder. Sleep 37, 1281–1282.
Rudy, J.W., Matus-Amat, P., 2005. The ventral hippocampus supports a memory representation of context and contextual fear conditioning: implications for a unitary function of the hippocampus. Behav. Neurosci. 119, 154–163.
Sacchetti, B., Lorenzini, C.A., Baldi, E., Tassoni, G., Bucherelli, C., 1999. Auditory thalamus, dorsal hippocampus, basolateral amygdala, and perirhinal cortex role in the consolidation of conditioned freezing to context and to acoustic conditioned stimulus in the rat. J. Neurosci. 19, 9570–9578.
Sanford, L.D., Suchecki, D., Meerlo, P., 2015. Stress, arousal, and sleep. Curr. Top Behav. Neurosci. 25, 379–410.
Sanford, L. D., Tang, X., Ross, R. J., Morrison, A. R. 2003a. Influence of shock training and explicit fear-conditioned cues on sleep architecture in mice: strain comparison. Behav Genet, 2003. 33, 43-58.
Sanford, L.D., Wellman, L.L., Ciavarra, R.P., Oldfield, E.C.t., Shams, R., Copare, J.L., Johnson, D.A., 2021a. Differential effect of light and dark period sleep fragmentation on composition of gut microbiome and inflammation in mice. Life 11. Basel.
Sanford, L.D., Wellman, L.L., Pharande, M.V., Y, H., Britten, R.A., 2021b. Assessment of neural networks regulating emotion and neurocognition: implications for understanding effects of space radiation and stressors. In: NASA Human Research Program Investigators' Workshop. Galveston, Texas.
Sanford, L.D., Xiao, J., Liu, X., Yang, L., Tang, X., 2005. Influence of avoidance training (AT) and AT cues on sleep in C57BL/6J (B6) and BALB/cJ (C) mice. Sleep 28, A6.
Sanford, L.D., Yang, L., Tang, X., 2003b. Influence of contextual fear on sleep in mice: a strain comparison. Sleep 26, 527–540.
Sanford, L.D., Yang, L., Wellman, L.L., Liu, X., Tang, X., 2010. Differential effects of controllable and uncontrollable footshock stress on sleep in mice. Sleep 33, 621–630.
Schiffelholz, T., Aldenhoff, J.B., 2002. Novel object presentation affects sleep-wake behavior in rats. Neurosci. Lett. 328, 41–44.
Sehlmeyer, C., Schoning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V., Konrad, C., 2009. Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS One 4, e5865.
Seidenbecher, T., Laxmi, T.R., Stork, O., Pape, H.C., 2003. Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 301, 846–850.
Seligman, M.E., Rosellini, R.A., Kozak, M.J., 1975. Learned helplessness in the rat: time course, immunization, and reversibility. J. Comp. Physiol. Psychol. 88, 542–547.
Shaffery, J., Hoffmann, R., Armitage, R., 2003. The neurobiology of depression: perspectives from animal and human sleep studies. Neuroscientist 9, 82–98.
Shalev, A., Liberzon, I., Marmar, C., 2017. Post-traumatic stress disorder. N. Engl. J. Med. 376, 2459–2469.
Shors, T.J., Seib, T.B., Levine, S., Thompson, R.F., 1989. Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science 244, 224–226.

Shvil, E., Rusch, H.L., Sullivan, G.M., Neria, Y., 2013. Neural, psychophysiological, and behavioral markers of fear processing in PTSD: a review of the literature. Curr. Psychiatr. Rep. 15, 358.
Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal phase locking to hippocampal theta oscillations. Neuron 46, 141–151.
Singhal, G., Baune, B.T., 2017. Microglia: an interface between the loss of neuroplasticity and depression. Front. Cell. Neurosci. 11, 270.
Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., Buzsaki, G., 2008. Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. Neuron 60, 683–697.
Smith, C., 1995. Sleep states and memory processes. Behav. Brain Res. 69, 137–145.
Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin. Neurosci. 8, 383–395.
Song, C., Phillips, A.G., Leonard, B., 2003. Interleukin 1 beta enhances conditioned fear memory in rats: possible involvement of glucocorticoids. Eur. J. Neurosci. 18, 1739–1743.
Spoormaker, V.I., Gvozdanovic, G.A., Samann, P.G., Czisch, M., 2014. Ventromedial prefrontal cortex activity and rapid eye movement sleep are associated with subsequent fear expression in human subjects. Exp. Brain Res. 232, 1547–1554.
Steriade, M., McCarley, R., 1990. Brainstem Control of Wakefulness and Sleep. Plenum Press, New York.
Sweeten, B.L.W., Adkins, A.M., Wellman, L.L., Sanford, L.D., 2020a. Group II metabotropic glutamate receptor activation in the basolateral amygdala mediates individual differences in stress-induced changes in rapid eye movement sleep. Progress in Neuropsychopharmacology & Biological Psychiatry.
Sweeten, B.L.W., Sutton, A.M., Wellman, L.L., Sanford, L.D., 2020b. Predicting stress resilience and vulnerability: brain-derived neurotrophic factor and rapid eye movement sleep as potential biomarkers of individual stress responses. Sleep 43.
Szepesi, Z., Manouchehrian, O., Bachiller, S., Deierborg, T., 2018. Bidirectional microglia-neuron communication in health and disease. Front. Cell. Neurosci. 12, 323.
Tang, X., Liu, X., Yang, L., Sanford, L.D., 2005a. Rat strain differences in sleep after acute mild stressors and short-term sleep loss. Behav. Brain Res. 160, 60–71.
Tang, X., Xiao, J., Liu, X., Sanford, L.D., 2004. Strain differences in the influence of open field exposure on sleep in mice. Behav. Brain Res. 154, 137–147.
Tang, X., Xiao, J., Parris, B.S., Fang, J., Sanford, L.D., 2005b. Differential effects of two types of environmental novelty on activity and sleep in BALB/cJ and C57BL/J mice. Physiol. Behav. 85, 419–429.
Tang, X., Yang, L., Sanford, L.D., 2005c. Rat strain differences in freezing and sleep alterations associated with contextual fear. Sleep 28, 1235–1244.
Theoharides, T.C., Conti, P., Economu, M., 2014. Brain inflammation, neuropsychiatric disorders, and immunoendocrine effects of luteolin. J. Clin. Psychopharmacol. 34, 187–189.
Tian, L., Ma, L., Kaarela, T., Li, Z., 2012. Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases. J. Neuroinflammation 9, 155.
Toth, L.A., Tolley, E.A., Krueger, J.M., 1993. Sleep as a prognostic indicator during infectious disease in rabbits. Proc Soc Exp Biol Med 203, 179–192.
Trivedi, M.A., Coover, G.D., 2004. Lesions of the ventral hippocampus, but not the dorsal hippocampus, impair conditioned fear expression and inhibitory avoidance on the elevated T-maze. Neurobiol. Learn. Mem. 81, 172–184.
Trott, J.M., Hoffman, A.N., Zhuravka, I., Fanselow, M.S., 2022. Conditional and unconditional components of aversively motivated freezing, flight and darting in mice. Elife 11.
Tuan, L.H., Lee, L.J., 2019. Microglia-mediated synaptic pruning is impaired in sleep-deprived adolescent mice. Neurobiol. Dis. 130, 104517.
Vazquez-Palacios, G., Velazquez-Moctezuma, J., 2000. Effect of electric foot shocks, immobilization, and corticosterone administration on the sleep-wake pattern in the rat. Physiol. Behav. 71, 23–28.
Veening, J.G., Bouwknecht, J.A., Joosten, H.J., Dederen, P.J., Zethof, T.J., Groenink, L., van der Gugten, J., Olivier, B., 2004. Stress-induced hyperthermia in the mouse: c-fos expression, corticosterone and temperature changes. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28, 699–707.
Wadhwa, M., Chauhan, G., Roy, K., Sahu, S., Deep, S., Jain, V., Kishore, K., Ray, K., Thakur, L., Panjwani, U., 2018. Caffeine and modafinil ameliorate the neuroinflammation and anxious behavior in rats during sleep deprivation by inhibiting the microglia activation. Front. Cell. Neurosci. 12, 49.
Walker, M.P., 2009. The role of sleep in cognition and emotion. Ann. N. Y. Acad. Sci. 1156, 168–197.
Walker, M.P., 2010. Sleep, memory and emotion. Prog. Brain Res. 185, 49–68.
Walker, M.P., van der Helm, E., 2009. Overnight therapy? The role of sleep in emotional brain processing. Psychol. Bull. 135, 731–748.
Wellman, L.L., Fitzpatrick, M.E., Hallum, O.Y., Sutton, A.M., Williams, B.L., Sanford, L. D., 2016. Individual differences in animal stress models: considering resilience, vulnerability, and the amygdala in mediating the effects of stress and conditioned fear on sleep. Sleep 39, 1293–1303.
Wellman, L.L., Fitzpatrick, M.E., Hallum, O.Y., Sutton, A.M., Williams, B.L., Sanford, L. D., 2017a. The basolateral amygdala can mediate the effects of fear memory on sleep independently of fear behavior and the peripheral stress response. Neurobiol. Learn. Mem. 137, 27–35.
Wellman, L.L., Fitzpatrick, M.E., Machida, M., Sanford, L.D., 2014. The basolateral amygdala determines the effects of fear memory on sleep in an animal model of PTSD. Exp. Brain Res. 232, 1555–1565.
Wellman, L.L., Fitzpatrick, M.E., Sutton, A.M., Williams, B.L., Machida, M., Sanford, L.D., 2018. Antagonism of corticotropin releasing factor in the basolateral amygdala of resilient and vulnerable rats: effects on fear-conditioned sleep, temperature and freezing. Horm. Behav. 100, 20–28.
Wellman, L.L., Lonart, G., Adkins, A.M., Sanford, L.D., 2022. Regulation of dark period sleep by the Amygdala: a microinjection and optogenetics study. Brain Res. 1781, 147816.
Wellman, L.L., Sutton, A.M., Kim, M.H., Koech, O.K., Fitzpatrick, M.E., Williams, B.L., Machida, M., Yoon, H., Lonart, G., Sanford, L.D., 2017b. Optogenetic stimulation and inhibition of the central nucleus of the amygdala (CNA) alters firing in locus coeruleus (LC) neurons. Sleep 40 (Suppl. 1). A51-A51.
Wellman, L.L., Yang, L., Ambrozewicz, M.A., Machida, M., Sanford, L.D., 2013. Basolateral amygdala and the regulation of fear-conditioned changes in sleep: role of corticotropin-releasing factor. Sleep 36, 471–480.
Wellman, L.L., Yang, L., Tang, X., Sanford, L.D., 2008. Contextual fear extinction ameliorates sleep disturbances found following fear conditioning in rats. Sleep 31, 1035–1042.
Winkler, Z., Kuti, D., Ferenczi, S., Gulyas, K., Polyak, A., Kovacs, K.J., 2017. Impaired microglia fractalkine signaling affects stress reaction and coping style in mice. Behav. Brain Res. 334, 119–128.
Wisor, J.P., Schmidt, M.A., Clegern, W.C., 2011. Evidence for neuroinflammatory and microglial changes in the cerebral response to sleep loss. Sleep 34, 261–272.
Wohleb, E.S., 2016. Neuron-microglia interactions in mental health disorders: "for better, and for worse. Front. Immunol. 7, 544.
Wohleb, E.S., McKim, D.B., Shea, D.T., Powell, N.D., Tarr, A.J., Sheridan, J.F., Godbout, J.P., 2014a. Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain. Biol. Psychiatr. 75, 970–981.
Wohleb, E.S., McKim, D.B., Sheridan, J.F., Godbout, J.P., 2015. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. Front. Neurosci. 8, 447.
Wohleb, E.S., Patterson, J.M., Sharma, V., Quan, N., Godbout, J.P., Sheridan, J.F., 2014b. Knockdown of interleukin-1 receptor type-1 on endothelial cells attenuated stress-induced neuroinflammation and prevented anxiety-like behavior. J. Neurosci. 34, 2583–2591.
Wohleb, E.S., Powell, N.D., Godbout, J.P., Sheridan, J.F., 2013. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. J. Neurosci. 33, 13820–13833.
Xi, M., Fung, S.J., Sampogna, S., Chase, M.H., 2011. Excitatory projections from the amygdala to neurons in the nucleus pontis oralis in the rat: an intracellular study. Neuroscience 197, 181–190.
Xie, Y., Ba, L., Wang, M., Deng, S.Y., Chen, S.M., Huang, L.F., Zhang, M., Wang, W., Ding, F.F., 2020. Chronic sleep fragmentation shares similar pathogenesis with neurodegenerative diseases: endosome-autophagosome-lysosome pathway dysfunction and microglia-mediated neuroinflammation. CNS Neurosci. Ther. 26, 215–227.
Yang, L., Wellman, L.L., Ambrozewicz, M.A., Sanford, L.D., 2010. Effects of stressor predictability and controllability on sleep, temperature and fear behavior in mice. Sleep 34, 759–771.
Yang, L., Wellman, L.L., Ambrozewicz, M.A., Sanford, L.D., 2011a. Effects of stressor predictability and controllability on sleep, temperature, and fear behavior in mice. Sleep 34, 759–771.
Yang, L., Wellman, L.L., Tang, X., Sanford, L.D., 2011b. Effects of corticotropin releasing factor (CRF) on sleep and body temperature following controllable footshock stress in mice. Physiol. Behav. 104, 886–892.
Yehuda, S., Sredni, B., Carasso, R.L., Kenigsbuch-Sredni, D., 2009. REM sleep deprivation in rats results in inflammation and interleukin-17 elevation. J. Interferon Cytokine Res. 29, 393–398.
Zhang, J., Xi, M., Fung, S.J., Sampogna, S., Chase, M.H., 2012. Projections from the central nucleus of the amygdala to the nucleus pontis oralis in the rat: an anterograde labeling study. Neurosci. Lett. 525, 157–162.
Zhang, W.N., Bast, T., Feldon, J., 2001. The ventral hippocampus and fear conditioning in rats: different anterograde amnesias of fear after infusion of N-methyl-D-aspartate or its noncompetitive antagonist MK-801 into the ventral hippocampus. Behav. Brain Res. 126, 159–174.
Zhang, W.N., Bast, T., Xu, Y., Feldon, J., 2014. Temporary inhibition of dorsal or ventral hippocampus by muscimol: distinct effects on measures of innate anxiety on the elevated plus maze, but similar disruption of contextual fear conditioning. Behav. Brain Res. 262, 47–56.
Zhang, Y., Ren, R., Sanford, L.D., Yang, L., Zhou, J., Zhang, J., Wing, Y.K., Shi, J., Lu, L., Tang, X., 2019a. Sleep in posttraumatic stress disorder: a systematic review and meta-analysis of polysomnographic findings. Sleep Med. Rev. 48, 101210.
Zhang, Y., Ren, R., Yang, L., Zhang, H., Yuan, S., Vitiello, M.V., Sanford, L.D., Tang, X., 2022. Patterns of polysomnography parameters in 27 neuropsychiatric diseases: an umbrella review. Psychol. Med. (in press).
Zhang, Y., Ren, R., Yang, L., Zhou, J., Sanford, L.D., Tang, X., 2019b. The effect of treating obstructive sleep apnea with continuous positive airway pressure on posttraumatic stress disorder: a systematic review and meta-analysis with hypothetical model. Neurosci. Biobehav. Rev. 102, 172–183.