Review

The potential of epigenetics in stress-enhanced fear learning models of PTSD

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Prolonged distress and dysregulated memory processes are the core features of post-traumatic stress disorder (PTSD) and represent the debilitating, persistent nature of the illness. However, the neurobiological mechanisms underlying the expression of these symptoms are challenging to study in human patients. Stress-enhanced fear learning (SEFL) paradigms, which encompass both stress and memory components in rodents, are emerging as valuable preclinical models of PTSD. Rodent models designed to study the long-term mechanisms of either stress or fear memory alone have identified a critical role for numerous epigenetic modifications to DNA and histone proteins. However, the epigenetic modifications underlying SEFL remain largely unknown. This review will provide a brief overview of the epigenetic modifications implicated in stress and fear memory independently, followed by a description of existing SEFL models and the few epigenetic mechanisms found to date to underlie SEFL. The results of the animal studies discussed here highlight neuroepigenetics as an essential area for future research in the context of PTSD through SEFL studies, because of its potential to identify novel candidates for neurotherapeutics targeting stress-induced pathogenic memories.

Post-traumatic stress disorder (PTSD) is triggered by experiencing or witnessing a traumatic event and is characterized by pathogenic memory (e.g., recurrent, involuntary memories that trigger intense stress), avoidance of reminders, hyperarousal and reactivity, negative mood, cognitive alterations, and a persistence of symptoms for at least 1 mo. Although only a fraction of people exposed to trauma develop PTSD, a history of stress exposure prior to witnessing a traumatic event increases the risk (Breslau et al. 2014). Therefore, some animal models of PTSD use multidimensional stress and fear memory paradigms to model the disorder. In stress-enhanced fear learning (SEFL), a rodent is exposed to a stressor or combination of stressors prior to undergoing classical fear conditioning. Models that utilize SEFL closely reproduce many core symptoms of PTSD, including enhanced fear learning, generalized anxiety, heightened startle, and impaired extinction. Furthermore, therapeutics that alleviate symptoms in some PTSD patients, such as selective serotonin reuptake inhibitors (SSRIs) and D-cycloserine (DCS) (Albucher and Liberzon 2002; de Kleine et al. 2015), also mitigate some of the effects produced by SEFL procedures in rodents (Takahashi et al. 2006; Yamamoto et al. 2008). Finally, animal studies have revealed the importance of several brain regions such as the amygdala, hippocampus, and medial prefrontal cortex (mPFC) in mediating the effects of SEFL (Maren and Holmes 2016), and these regions show abnormal activity in PTSD patients (Milad et al. 2009; Pitman et al. 2012; Stevens et al. 2014; Maren and Holmes 2016). Taken together, SEFL models have relatively high face, construct and predictive validity for PTSD and provide an exciting avenue for the investigation of neurobiological mechanisms, including neuroepigenetics, mediating the debilitating symptoms of this illness.

Epigenetic modifications alter the mRNA and protein expression of a given gene without changing the inherent DNA sequence, allowing cells to fine-tune expression patterns of the genome in a tissue-specific manner. Core histone proteins provide physical control over transcriptional events by winding DNA into a compact, repressive state, or unwinding it into a relaxed, permissive state. Modifications to histone tails, such as acetylation, methylation, and phosphorylation, occur throughout the genome and interact with neighboring chromosomes when DNA is in a folded conformation to yield complex transcriptome patterns within a given cell (Zhou et al. 2011). DNA itself can also be directly modified through covalent modifications of the cytosine pyramidine ring. Addition of a methyl group is typically associated with transcriptional silencing, whereas the opposite is achieved through hydroxymethylation. DNA methylation, once thought to be an irreversible modification, has proven to be highly dynamic in the brain thanks to the process of hydroxymethylation (Miller and Sweatt 2007; Kim et al. 2009; Kriaucionis and Heintz 2009; Guo et al. 2011; Kaas et al. 2013; Li et al. 2013; Rudenko et al. 2013) and can interact with histone modifications to produce a complex transcriptional "code" for any given gene (Miller et al. 2008; Vaissiere et al. 2008). Because epigenetic adaptations have been shown to be induced by stress and also to support the learning and modulation of fear memories (see later sections), deciphering epigenetic mechanisms unique to their interaction in SEFL has significant implications for the treatment of PTSD.

Stress-enhanced fear learning models

Animal models of SEFL measure the effect of a stressor on subsequent fear memory (Fig. 1; Table 1). Fear conditioning is generally performed anywhere from 24 h to 10 d after the stressor and is most commonly a classical fear conditioning procedure involving the temporal pairing of a neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US). In cued fear conditioning, the CS is typically an auditory cue and in contextual fear conditioning, the CS is the context in which the rodent receives the

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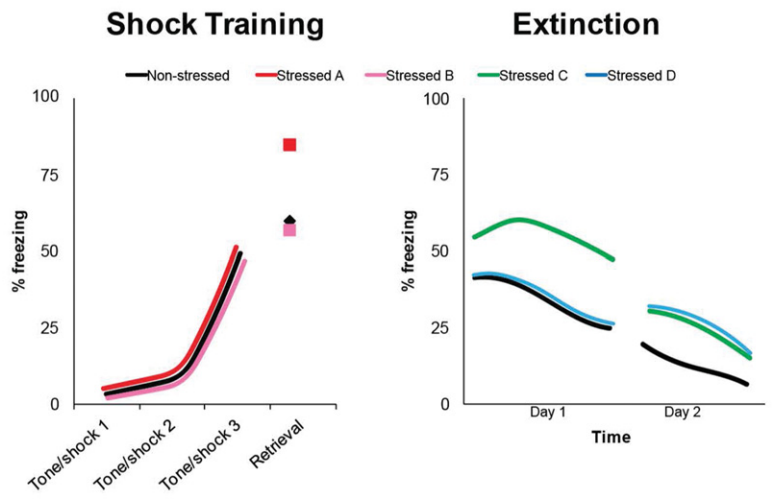

Figure 1. SEFL outcomes after cued fear conditioning. Stress enhanced fear learning is performed by exposing animals to a stressor prior to fear conditioning. SEFL can induce alterations in fear memory expression, extinction, retention, or combinations of these three behaviors. In this example, stressed animals undergo cued fear conditioning that consists of three shocks, each paired with an auditory cue. Upon retrieval of the fear memory, stressed animals may have heightened fear expression (Stressed A). Depending on the SEFL model, a history of stress may not elevate fear expression (Stressed B), but instead affect the rate of fear extinction (Stressed C) or the retention of extinction between sessions (Stressed D).

shock, or US. The pairing of the CS and US leads to freezing, a defensive behavior characterized by the absence of all movement except for respiration, in response to later presentation of the CS alone. The strength of the fear memory can be measured by quantifying freezing to a brief CS exposure. Extinction is displayed as reduced freezing to the CS and occurs only after repeated, nonreinforced CS exposures. Extinction is not considered a reversal of the fear memory, but at least in part, the formation of a new memory that inhibits expression of the original, fearful conditioned response (Bouton 2002).

SEFL models utilize a variety of environmental, physical and psychological stressors, such as immobilization or restraint stress, swim stress, inescapable shock, elevated platform stress, early-life stress, social stress and exposure to predator odors. One of the most commonly used stressors is restraint stress, where an animal is immobilized by placement in a plastic restraint such as a Falcon tube or Decapicone bag or its limbs are secured to a wooden board. Evidence exists for effects of both a single restraint event and repeated restraints on subsequent fear learning. Several studies have shown increased freezing upon exposure to a context previously paired with shock in rodents that have undergone brief (30 min–2 h) restraint (Cordero et al. 2003; Rodriguez Manzanares et al. 2005; Tronson et al. 2010), whereas other studies utilizing repeated restraint have observed increased freezing upon exposure to a tone previously paired with shock (Meyer et al. 2014; Suvrathan et al. 2014; Baratta et al. 2015). The degree to which restraint stress affects fear learning, generalization, extinction rate, or extinction retention differs, depending on the method and duration of restraint, the varying delays between the stress and fear conditioning and differences in the amount of shock utilized during conditioning (Miracle et al. 2006; Andero et al. 2011, 2013; Chauveau et al. 2012). Although studies of the effectiveness of therapeutics have generally used SEFL models other than restraint, a recent study showed that 7,8-dihydroxyflavone (7,8-DHF), a TrkB agonist, was able to rescue impaired extinction following restraint stress (Andero et al. 2011). TrkB is a receptor for brain-derived neurotropic factor (BDNF), a regulator of neuronal plasticity that supports cognition and learning throughout life (Bramham and Panja 2014; Karpova 2014; Lu et al. 2014) and can accelerate extinction in classical fear learning paradigms (Peters et al. 2010; Rosas-Vidal et al. 2014). The efficacy of this approach is likely to be tested in human studies because 7,8-DHF is safe and can cross the blood–brain barrier, and evidence supports the hypothesis that BDNF signaling is altered in PTSD patients (Dell'Osso et al. 2009; Hauck et al. 2010; Soliman et al. 2010).

One SEFL model known for its predictive and construct validity is the single-prolonged stress (SPS) model. This model involves the presentation of a complex stressor (restraint, 20 min forced swim and exposure to diethyl ether until consciousness is lost) prior to presentation of fear conditioning. This model has the advantage of representing the multidimensional nature of PTSD and results in enhanced fear conditioning and impaired extinction (Iwamoto et al. 2007; Kohda et al. 2007; Knox et al. 2012), as well as increased fear renewal (Yamamoto et al. 2009), exaggerated startle (Khan and Liberzon 2004), enhanced glucocorticoid negative feedback (Liberzon et al. 1997; Iwamoto et al. 2007), deficits in spatial memory, and stress-induced analgesia (Yamamoto et al. 2009). SSRIs can reverse the increase in contextual fear conditioning (Takahashi et al. 2006) and DCS (Yamamoto et al. 2008) ameliorates the impaired extinction in the SPS model, which gives the model good predictive validity, as these drugs alleviate symptoms in some PTSD patients (Albucher and Liberzon 2002; de Kleine et al. 2015). The SPS model produces enhanced contextual fear and is associated with hippocampal abnormalities, although not much is known about the involvement of the mPFC or amygdala in this model (Maren and Holmes 2016). The enhanced contextual fear memory in this model is consistent with the finding that some PTSD patients show increased sensitivity to contextual cues (Grillon 2002), and the impaired extinction and hippocampal abnormalities are consistent with the finding that PTSD patients have difficulty using context to regulate fear (Rougemont-Bucking et al. 2011; Garfinkel et al. 2014).

Another model of SEFL utilizes repeated footshock as a stressor and is similar to SPS in that it produces a very robust phenotype (Rau et al. 2005; Szczytkowski-Thomson et al. 2013). In this model, >90% of outbred rats show a PTSD-like phenotype. When these same rats are given 15 shocks over a 90-min period, subsequent contextual and cued fear conditioning is enhanced, even 90 d following the 15-shock stressor. Reducing the stressor to four shocks instead of 15 results in only 20% of rats developing PTSD-like symptoms, which more closely resembles the human situation. Because repeated footshock enhances cued conditioning, in addition to contextual fear, the effects of this model are likely due to a sensitization of the fear circuitry and not merely generalization to a shock context (Rau et al. 2005). Consistent with this, the model reliably produces changes in the amygdala, a brain region with known pathology in PTSD patients (Maren and Holmes 2016; Perusini et al. 2016). This model is also able to produce a variety of PTSD symptoms, such as reduced exploration, depression, increased propensity to drink alcohol, enhanced reactivity to loud noise, anxiety and disrupted diurnal cycle of corticosterone (Perusini et al. 2016). Tailshock has also been

Table 1. Current SEFL models, including the stress utilized and its effect on fear memory

Species	Stressor	Fear measurement	Citation
Mice	Restraint/immobilization	Enhanced cued fear	Andero et al. (2013), Baratta et al. (2015), Meyer et al. (2014)
		Enhanced context fear	Tronson et al. (2010)
		Impaired cued extinction	Andero et al. (2011), Chauveau et al. (2012)
Rats	Restraint/immobilization	Enhanced cued fear	Suvrathan et al. (2014)
		Enhanced context fear	Rodriguez Manzanares et al. (2005), Cordero et al. (2003)
		Impaired cued extinction	Miracle et al. (2006)
Rats	Single prolonged stress (SPS)	Enhanced context fear	Iwamoto et al. (2007), Kohda et al. (2007)
		Impaired cued and context extinction	Knox et al. (2012)
Rats	Shock	Enhanced cued and context fear	Rau et al. (2005)
		Enhanced eyeblink conditioning	Shors et al. (1992)
		Increased avoidance	Brennan et al. (2005)
Rats	Predator odor	Increased avoidance	Brennan et al. (2006)
Mice	Social stress	Enhanced cued fear	Dubreucq et al. (2012)
Rats	Maternal separation	Enhanced context fear	Toda et al. (2014)
Mice	Swim stress	Impaired cued extinction	Izquierdo et al. (2006)
Rats	Elevated platform stress	Impaired cued and context extinction	Akirav and Maroun (2007)

successfully used to enhance fear learning. When tailshock precedes the pairing of a white noise with periorbital shock, eyeblink conditioning is enhanced (Shors et al. 1992). Furthermore, tailshock has been shown to increase avoidance responding, where rats press a lever to avoid receiving a footshock (Brennan et al. 2005). Measuring avoidance responding rather than freezing behavior in rodents is thought to model the active component of learned fear and represents a coping strategy. This behavior is excessive in PTSD, as patients actively avoid people or places that serve as reminders of the traumatic situation and may impede extinction learning.

Some stressors are used to model a psychological, rather than physical, form of stress. Exposure to trimethylthiazoline (TMT), a component of fox odor, is stressful to rats because the fox is a predator. This stressor is naturalistic and does not involve the presentation of painful stimuli, so it is thought to more closely model a psychological stressor. Avoidance responding has also been shown to increase following the presentation of predator stress (Brennan et al. 2006). Another naturalistic stressor used is social defeat, where a rodent (intruder) is placed into the cage of a larger, dominant (resident) rodent. Although this procedure involves fighting between the two rodents that can be painful, prolongation of the stressor is achieved by caging the intruder inside the resident's cage, where it is protected from physical harm but can still experience stress via visual and olfactory cues. This stress increases cued fear conditioning and anxiety-like behavior in the elevated plus maze (Dubreucq et al. 2012). A third psychological stressor is maternal separation, which more closely models the increased incidence of PTSD in individuals that have experienced childhood stress. This procedure, which involves separation of pups from the mother for a few hours each day in early postnatal life, enhances contextual fear memory in adulthood (Toda et al. 2014).

Models producing extinction deficits may be valuable for screening therapeutics, as studies demonstrate impaired fear extinction in PTSD patients (Blechert et al. 2007; Milad et al. 2009; Norrholm et al. 2011). Restraint, SPS, and shock have all been shown to affect both fear conditioning and extinction. Other stressors, such as swim stress, have been found to have no effect on fear memory, but to impair extinction memory (Izquierdo et al. 2006). Interestingly, stress *after* fear conditioning is also capable of altering fear memory. Indeed, the stress of 30 min spent on an elevated platform is sufficient to produce deficits in extinction when performed after contextual or cued fear conditioning (Akirav and Maroun 2007; Maroun et al. 2013), and these deficits are reversed by intra-amygdala DCS (Akirav et al. 2009).

The neuroepigenetics of stress

Stress elicits both immediate and long-lasting psychological, physical, and emotional strain on an individual, leading to profound neurobiological changes that impact future behavioral responses. Animal models of stress exposure have identified epigenetic modifications in key brain areas known to be critical components of the circuitry responsible for both the expression of anxiety and formation and expression of fear memories, such as the frontal cortex, hippocampus, and amygdala (Gudsnuk and Champagne 2012; Stankiewicz et al. 2013). Because a thorough review of the epigenetics of stress has been described elsewhere (Vialou et al. 2013), emphasis will be placed on the specific stressors utilized in SEFL models, as described in the preceding section.

Exposure to a natural predator or predator odor evokes epigenetic modifications of the *Bdnf* gene. In a complex psychosocial stress paradigm, rats subjected to a combination of restraint stress, live cat exposure, and social housing instability displayed hypermethylation of *Bdnf* exon IV in the dorsal hippocampus (dentate gyrus and CA1), but hypomethylation in the ventral hippocampus (CA3) (Roth et al. 2011). In a milder predator stress paradigm, a genome-wide methylation screen identified a number of differentially methylated regions in the rat hippocampus following exposure to soiled cat litter and highlighted the relevance of *Dlgap2*'s methylation state to anxiogenic behaviors (Chertkow-Deutsher et al. 2010). *Dlgap2*, a gene that encodes a postsynaptic density protein, was more likely to be unmethylated in animals that displayed an anxious phenotype in this predator stress paradigm. Because not all animals exposed to the cat litter developed the anxiety-like phenotype, hypermethylation of *Dlgap2* and decreased mRNA expression of the gene are associated with resilience to stress. Predator stress also induces phenotypic variability in stress coping responses that can be linked to the degree of methylation of the hormone vasopressin (*Avp*) in the amygdala (Bowen et al. 2014). The methylation status of *Avp*, a secreted neuropeptide that can modulate higher cognitive processes such as social behavior (Meyer-Lindenberg et al. 2011), segregates animals into resilient or susceptible phenotypes and is positively correlated with higher levels of corticosterone in the susceptible group. Such epigenetic regulation may be linked to intergroup variability observed in rodent stress paradigms and recapitulates the variability in human stress responses to seemingly equivalent traumatic events.

Decreases in global DNA methylation have been observed in the hippocampus, cortex, and periaqueductal gray of stressed

animals (Rodrigues et al. 2015). Furthermore, in the hippocampus of stressed animals, the 3′-UTR of the glucocorticoid receptor gene *Nr3c1* was hyper-hydroxymethylated, a modification associated with increased transcription (Li et al. 2015). These parallel studies also identified a pattern of hydroxymethylation throughout the genome in stressed animals, with many sites of differential hydroxymethylation located on known stress-related genes that were concomitantly changed at the mRNA level (Li et al. 2016). These large-scale data sets suggest that even brief stressors induce epigenetic patterns that are capable of changing the global transcriptional profile of the brain by creating an environment that is permissible for the up-regulation of stress response genes. Conversely, chronic restraint stress imposes inhibitory regulation of the glucocorticoid receptor, presumably through increased methylation of the promotor of the *Npas4* regulatory transcription factor (Furukawa-Hibi et al. 2015). Dissociating the epigenetic effects of acute versus chronic stress will likely yield more information about the long-lasting effects of stress and how resilience can be encoded to cope with acute stressors.

Epigenetic regulation of *Bdnf* by histone modifications has been studied in animal models of restraint stress with conflicting results. Using a 2 h restraint stress paradigm, Fuchikami et al. reported lower histone H3 acetylation of *Bdnf* in the hippocampus, accompanied by corresponding decreases in *Bdnf* mRNA expression (Fuchikami et al. 2010). However, this effect was not reproduced in a more recent study (Ieraci et al. 2015). The latter study also examined the expression of the enzymes responsible for removing acetyl groups, histone deacetylases (HDACs). Levels of the specific HDAC isoforms 4, 5, 7, and 9 were measured at varying time points after stress, with dynamic regulation reported between 2 and 8 h after restraint stress. The mRNA expression of all isoforms returned to baseline at 24 h poststress, suggesting that restraint stress may only briefly regulate histone modifications in the hippocampus to allow for transcription of stress-responsive genes. Studies that have examined histone modifications in other brain regions after restraint stress support this notion; restraint stress has short-lived effects on global histone H3 phosphorylation in the nucleus accumbens and prelimbic cortex, with large increases in phosphorylation that return to baseline in a relatively quick manner (Rotllant et al. 2013). Predator stress also increases phosphorylation of histone H3 in adult dentate gyrus granule cells of the hippocampus (Bilang-Bleuel et al. 2005) and acetylation of histones H3 and H4 in the amygdala (Ragu Varman and Rajan 2015). Perhaps not surprisingly, differences in the duration and severity of the stressor induce differential patterns of lysine methylation on H3 in the CA1 and dentate gyrus regions of the hippocampus (Hunter et al. 2009). These findings are relevant for dissociating the molecular adaptations of chronic depressive states from acute, isolated traumatic exposures because the varying degrees of stress likely have different epigenetic signatures.

Along this same line, a recent study used a combination of stressors to demonstrate that lasting epigenetic changes arising from a chronic stress paradigm may be briefly disrupted with subsequent short-term stress exposures (Nasca et al. 2015). Chronic restraint stress decreased acetylation on lysine residue 27 of the metabotropic glutamate receptor 2 *(Grm2)*, but exposure to a 2 h restraint stress transiently normalized this effect. 24 h later, acetylation levels of *Grm2* returned to below baseline, indicating that multiple stressors can temporarily change the epigenetic landscape of neuronal cells. Stress-induced epigenetic changes such as this likely induce a transcriptional profile that contributes to the behavioral response to stress, including activities such as coping or the expression of anxiety and generalized fear.

Systemic administration of the HDAC inhibitors sodium butyrate (NaB) (Yamawaki et al. 2012; Han et al. 2014; Valvassori et al. 2014, 2015), trichostatin A (Miyagawa et al. 2012), and valproic acid (Wilson et al. 2014), which elevate histone acetylation levels, has therapeutic effects in rodent stress paradigms, improving cognition, and reducing anxiety behaviors. Predator stress elevates expression of histone deacetylases themselves (Wilson et al. 2014; Ragu Varman and Rajan 2015) and knockdown of the *Hdac6* isoform reduces anxiety (Fukada et al. 2012), suggesting that restoring acetylation levels to baseline may improve stress-related behavioral responses. Indeed, treatment with NaB in a model of chronic restraint stress was sufficient to reduce depression and anxiety behaviors, accompanied by restoration of HDAC2 and histone H3 acetylation levels (Han et al. 2014). Likewise, in an acute restraint stress paradigm, pretreatment with trichostatin A prevented stress-induced novelty suppression and increased acetylation of histones H3 and H4 (Miyagawa et al. 2012).

Strikingly, the bulk of epigenetic stress research has focused on expression changes of epigenetic machinery in the cortex and hippocampus. Undoubtedly, these two regions are critically involved in stress responses, but given that the amygdala contributes heavily to the expression of anxiety and is centrally involved in the modulation of emotional fear memories (discussed below), functional characterization of amygdala-driven epigenetic marks would be expected to provide important insight into stress pathologies.

The neuroepigenetics of fear memory

The epigenetics of fear memory have been covered in a number of reviews (Roth et al. 2010; Zovkic et al. 2013; Kwapis and Wood 2014; Rudenko and Tsai 2014), so we will provide just a brief summary here for the purposes of discussion. In the most basic terms, the hippocampus is crucial for contextual fear conditioning and the amygdala for cued fear conditioning. Accordingly, DNA methyltransferase (DNMT) inhibition in Area CA1 following training disrupts consolidation of contextual fear and DNMT inhibition in the lateral amygdala disrupts consolidation of cued fear (Miller and Sweatt 2007; Miller et al. 2008; Monsey et al. 2011). Bidirectional changes in the methylation status of several memory-related genes, including *Pp1cb*, *reelin*, and *Bdnf*, have also been found in the hippocampus following fear learning (Miller and Sweatt 2007; Lubin et al. 2008). Consistent with these findings, mice fed a diet deficient in the methyl donors folate, methionine, and choline from 3 to 6 wk of age to drive a global reduction in DNA methylation levels, have impaired fear memory formation that persists into adulthood (Ishii et al. 2014). Finally, cortical DNA methylation supports the storage of remote (30-d-old) fear memory (Miller et al. 2010), suggesting that targeting this epigenetic mechanism may be useful in treating the pathological persistence of fear memories in PTSD.

Histone acetylation has been found to promote fear learning (Korzus et al. 2004; Wood et al. 2005). Systemic administration of NaB prior to contextual fear conditioning strengthened long-term retention of the fear memory, without altering the short-term memory (Levenson et al. 2004). Although this study found acetylation of histone H3 in the hippocampus to be important, other studies have also demonstrated involvement of acetylated histones H4 and H2B (Peleg et al. 2010; Bousiges et al. 2013). Gupta et al. found that NaB can support consolidation of contextual fear memory by increasing methylation at a histone lysine residue associated with active transcription, H3K4me3, at the *Zif268* promoter in the hippocampus (Gupta et al. 2010). In addition, Monsey et al. found that infusion of an HDAC inhibitor into the lateral amygdala increases H3 acetylation and enhances the consolidation of cued fear conditioning (Monsey et al. 2011).

Other studies have shown that histone modifications that increase transcription of *Bdnf* and *Homer1a* in the hippocampus and amygdala promote fear learning (Lubin et al. 2008; Takei et al. 2011; Mahan et al. 2012).

More recently, the study of chromatin in memory formation has gone beyond specific histone lysine modifications to chromatin remodeling, a process in which ATP-dependent nucleosome complexes disrupt the contacts with DNA (Vogel-Ciernia et al. 2013). Similar to the effects of histone modifications, this influences transcription by regulating physical access to regions of DNA. Vogel-Ciernia and colleagues demonstrated that mice haploinsufficient for BAF53b, a neuron-specific chromatin regulatory subunit, had synaptic plasticity and long-term, but not short-term, memory deficits. Importantly, rescuing BAF53b in the adult hippocampus was sufficient to restore memory (Vogel-Ciernia et al. 2013). Furthermore, inhibiting nuclear protein phosphatase 1 in the amygdala can control chromatin remodeling, producing histone modifications and changes in gene expression that correlate with enhanced fear memory (Koshibu et al. 2011).

Epigenetics and the modulation of fear memory

A core feature of PTSD is the presence of a traumatic memory that is long-lasting and persists, despite repeatedly encountering triggers without the traumatic event reoccurring (extinction). Given that the majority of patients are diagnosed with PTSD long after consolidation of the traumatic experience, a practical approach to treatment is to modulate, or even disrupt the existing, pathogenic memories of the event. This can be done through extinction or a blockade of reconsolidation, a brief period of lability following retrieval during which the memory is susceptible to disruption. In the clinic, extinction has been targeted in the form of prolonged exposure (PE) and is commonly used by Veterans Affairs (Kudler et al. 2016). In PE, patients are re-exposed to their trauma through several different methods (e.g., imagery, virtual reality, and discussion of the trauma) as a means of reducing emotional reactivity to the trauma. However, although considered a first-line approach by many clinicians, the results have been mixed; PE improves PTSD symptoms in only a portion of patients and exacerbates them in others (Steenkamp 2016a,b; Yehuda and Hoge 2016). Although PE has not proven to be particularly successful, identifying the mechanisms responsible for successful extinction, including epigenetics, could, theoretically, lead to improved outcomes through pharmacologically enhanced or accelerated extinction.

Because the infralimbic region of the PFC (IL) is crucial for extinction learning (Peters et al. 2010; Sierra-Mercado et al. 2011), the majority of studies investigating the role of DNA methylation in fear extinction have focused here. Gene-specific changes in DNA methylation appear to support extinction learning. Some studies report that demethylation in the IL is associated with extinction learning (Rudenko et al. 2013; Li et al. 2014), whereas others have found an increase in methyl-CpG binding protein (*Mecp2*), a protein known to promote gene silencing through binding to methylated DNA, with extinction (Wei et al. 2012). *Bdnf* is a critical factor in extinction learning (Peters et al. 2010). Interestingly, female mice are more resistant to fear extinction than male mice and exhibit increased cytosine methylation of *Bdnf* exon IV and decreased exon IV mRNA expression within the mPFC (Baker-Andresen et al. 2013).

Histone acetylation also participates in extinction learning. Systemic administration of HDAC inhibitors facilitates extinction of cued and contextual fear memories (Li et al. 2006; Bredy et al. 2007; Lattal et al. 2007; Bredy and Barad 2008; Stafford et al. 2012). Because HDAC inhibitors can also promote fear learning (Levenson et al. 2004; Bredy and Barad 2008; Guan et al. 2009; Gupta et al. 2010), the timing of treatment with an HDAC inhibitor is important, particularly if given systemically, in that its administration must be tightly coupled with extinction training under optimal parameters (e.g., duration of exposure to the CS) to ensure strengthening of the extinction memory and not the original fear memory.

Epigenetic studies of the IL have found that a decrease in HDAC2 levels accompanies extinction (Wei et al. 2012), and NaB induces IL acetylation and an increase in the immediate early gene *Fos* (Stafford et al. 2012). In addition, histone H4 acetylation at *Bdnf*'s exon IV gene promoter and corresponding increases in mRNA in the IL appear to be particularly important for extinction learning (Bredy et al. 2007). Levels of p300/CREB binding protein (CBP)-associated factor (PCAF), a histone acetyltransferase (HAT), also increase in the IL with extinction learning and this HAT has been shown to selectively target extinction processes over acquisition. Interestingly, evidence indicates that PCAF functions as a transcriptional coactivator to repress *Zif268*, thereby promoting fear extinction and limiting fear reconsolidation, the restabilization of a fear memory following its reactivation (Wei et al. 2012).

Although the studies above demonstrate that general increases in acetylation support extinction, extinction is also associated with gene-specific decreases in acetylation. For example, extinction decreases H3 acetylation around the promoter region of the *Bdnf* exon 1 gene in the PFC (Bredy et al. 2007), suggesting that exon-specific regulation of *Bdnf* may be important. Additionally, levels of the HAT p300/CBP decrease with extinction and its inhibition enhances extinction consolidation and LTP in the IL (Marek et al. 2011). Finally, mice overexpressing *Hdac1* in the dorsal hippocampus display enhanced extinction of contextual fear memory, whereas HDAC1 inhibition results in a blockade of extinction. In this study, *Hdac1* overexpression resulted in decreased H3K9 acetylation and increased H3K9 trimethylation at the *Fos* promoter in the hippocampus, with a concomitant decrease in *Fos* mRNA (Bahari-Javan et al. 2012). This case highlights the different effects that may result from inhibition of a single HDAC, rather than multiple isoforms with existing pharmacological HDAC inhibitors.

Extinction can inhibit fear expression, but return of the fear memory is always a possibility through spontaneous renewal (Bouton 2002). This is particularly relevant because PE therapy is context specific, such that the fear memory can return when the context is changed. In consideration of these features, extinction alone may be unable to produce the long-lasting effects required to permanently abolish the influence of traumatic memories. Indeed, some have suggested the persistence of traumatic memories in PTSD arises from frequent re-experiencing of the trauma, creating an "overconsolidated" memory trace. Thus, another approach being considered is direct disruption of memory trace by preventing reconsolidation following retrieval.

It is widely accepted that a memory is formed in a stabilized, time-dependent manner, thereby rendering the memory resistant to loss (McGaugh 2000; Alberini 2005). Importantly, while being stabilized, these memories can be strengthened or updated (Lee 2008; Forcato et al. 2011; Gräff et al. 2014). Reconsolidation is thought to be a way for the brain to incorporate new information into existing memory traces (Alberini and Ledoux 2013). Following a reactivation trial, consolidated memories become labile and sensitive to disruption by protein synthesis inhibitors, behavior modification, brain lesions, and a variety of small-molecule inhibitors (Nader et al. 2000; Miller and Sweatt 2006; Bredy and Barad 2008; Monfils et al. 2009; Maddox and Schafe 2011). Many have successfully used pharmacological agents such as the FDA-approved β-adrenergic antagonist, propranolol, in preclinical studies to prevent reconsolidation of fear memories

as a means of memory "erasure" (Debiec and Ledoux 2004). However, translating these achievements to the clinic has come with varying levels of success (Soeter and Kindt 2012; Steenen et al. 2016). This has motivated investigations of additional mechanisms, including epigenetic modifications.

Although additional work is needed, DNA methylation has emerged as one possible negative regulator of reconsolidation. Maddox and colleagues demonstrated that the DNMT inhibitors, 5-aza-2′-deoxycytidine and RG108, impaired reconsolidation when infused into the lateral amygdala after reactivation (Maddox et al. 2014). This corresponded with a reduction in neural plasticity in the lateral amygdala.

Similar to initial consolidation, increased acetylation appears to enhance reconsolidation. In work by Lubin and Sweatt, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway was found to participate in reconsolidation in a manner independent of NF-κB's role as a transcription factor. Reactivation of a fear memory induced phosphorylation and acetylation of histone H3 at the promoter of the immediate early gene, *Zif268*, which was attenuated when rats were treated with the IKKα inhibitor, diethyldithiocarbamate (DDTC). Because IKKα interacts with CBP, an HAT, the authors postulated that IKKα mediates its chromatin modulating effects by inducing histone acetylation via enhanced CBP activity (Lubin and Sweatt 2007). Intra-lateral amygdala infusions of the p300/CBP inhibitor, C646, also impair reconsolidation when administered shortly after fear memory retrieval (Maddox et al. 2013b). This was not limited to newly consolidated memories, as 2-wk-old memories were also sensitive to disruption by C646. Furthermore, memories disrupted by C646 did not display spontaneous recovery, reinstatement, or renewal (Maddox et al. 2014), strengthening the argument for disruption of the original memory trace, rather than an extinction-related effect. Consistent with this, a similar reconsolidation deficit has been reported with garcinol, a compound with several pharmacological actions, including HAT inhibition (Maddox et al. 2013a).

Although epigenetic manipulations of reconsolidation appears to be an attractive avenue for targeting traumatic memories in stress-induced disorders such as PTSD (Kwapis and Wood 2014), the boundary conditions of reconsolidation (e.g., age of memory, length of activation trial, and time of post-activation intervention) should be kept in mind. For instance, older (remote) memories are less likely to undergo reconsolidation after memory reactivation (Milekic and Alberini 2002; Gräff et al. 2014). Further, although extinction and reconsolidation are distinct processes (Suzuki et al. 2004; Miller and Sweatt 2006), the duration of reactivation (where the US is not present) plays a significant role in determining which process is recruited (Pedreira and Maldonado 2003; Suzuki et al. 2004), with shorter durations skewing toward reconsolidation. Finally, reconsolidation occurs within a finite temporal window, ranging from 10 min to 6 h postreactivation, depending on the exact mechanism (Monfils et al. 2009). This restricts the use of pharmaceuticals to ones that reach peak bioavailability inside the window appropriate for the given mechanism of action.

Recent work has shown that strategies combining elements of extinction and reconsolidation may have synergistic effects, while overcoming some of their individual obstacles. Gräff and colleagues found that HDAC2-specific inhibition with CI-994 induced hippocampus-dependent plasticity, which is required to update a fear memory trace during extinction, even when the memory was weeks old (Gräff et al. 2014). This suggests that HDAC inhibitors may have the potential to induce plasticity in deeply engrained traumatic memories, enabling their disruption through appropriately timed behavioral therapy.

The neuroepigenetics of stress-enhanced fear learning

Several recent reviews have covered the broad array of neurobiological players that have been found to mediate SEFL, such as glucocorticoids, glutamate, glycine, and cytokines (Cordero et al. 2003; Akirav and Maroun 2007; Iwamoto et al. 2007; Kohda et al. 2007; Yamamoto et al. 2009; Tronson et al. 2010; Jones et al. 2015; Maren and Holmes 2016; Perusini et al. 2016). However, in spite of the contribution of epigenetic mechanisms to stress and numerous aspects of fear memory independently, very little work has been done in the realm of epigenetics at the crossroads between stress and fear memory. Epigenetic-driven synergy between stress and fear could occur through a variety of routes, which are not mutually exclusive. Epigenetic mechanisms are particularly intriguing candidates to explore in SEFL because even transient modifications can produce persistent gene and protein expression changes (Weaver et al. 2004; Kumar et al. 2005). Further, DNA methylation and some chromatin modifications associated with both stress and fear memory can, themselves, persist for very long periods of time (Miller et al. 2010; Stankiewicz et al. 2013; Halder et al. 2016). The brain may be made more vulnerable to "overconsolidation" of a pathological memory by a stressful experience through transient or persistent, gene-specific epigenetic changes triggered by the stressor in brain regions affected by both stress and fearful associations, such as the amygdala (e.g., epigenetic repression of memory suppressors, such as PP1 and calcineurin; Miller and Sweatt 2007; Baumgartel et al. 2008; Herzog et al. 2008; Miller et al. 2010). This same stressor could raise the transcriptional threshold of genes utilized by the brain's extinction circuit, such that pro-extinction genes are epigenetically repressed through DNA methylation and histone methylation at inhibitory lysine residues.

Another area of SEFL and PTSD that has rich potential for epigenetic involvement is susceptibility versus resilience in the face of trauma. Despite the majority of the population experiencing at least one traumatic event in their lifetime, the lifetime prevalence of PTSD is only ∼7% (Kessler et al. 2005). This suggests that there may be protective factors, both environmental and molecular, that lend resilience to some when exposed to a traumatic event, whereas other factors confer vulnerability to develop PTSD. For example, early-life adversity, such as maternal stress, loss of or separation from a parent, and chronic environmental stress, is a significant environmental risk factor for the development of PTSD (Koenen et al. 2007). A number of human and animal studies have established a clear, potentially causal, epigenetic link between early-life stress and altered stress responses later in life (Daskalakis et al. 2013; Vaiserman 2015; Yehuda et al. 2015b). Some SEFL protocols use an early-life stressor, such as maternal separation, rather than an acute stressor in adulthood, and find that it prevents the infantile amnesia that typically occurs when fear conditioning is performed in early life (Callaghan et al. 2013; Quinn et al. 2014). Unfortunately, the effects of early-life stress on fear conditioning performed in adulthood are mixed, with some reporting an enhancement (Toda et al. 2014) and others an impairment (Stevenson et al. 2009). Additional work is needed to clarify the parameters of an SEFL model that reflects the effect of early-life adversity on later trauma. However, once established, studying the underlying epigenetic mechanisms will be extremely important (Toda et al. 2014). Another SEFL approach has been to use Long Evans rats, an outbred strain, to identify the individual rats that are susceptible or resilient to the effects of stress in adulthood on fear conditioning (Rau et al. 2005). An advance here would involve identification of a susceptible and resilient population in response to SEFL within an inbred strain, as it would provide a powerful tool for interrogating the underlying epigenetic contributions by removing genetic vulnerability factors.

Although researchers are just beginning to identify the neuroepigenetic players involved in SEFL, a few studies have been published (Table 2). For instance, SPS before fear conditioning results in a delayed extinction profile (Yamamoto et al. 2009; Chauveau et al. 2012; Sawamura et al. 2016), an effect that can be rescued by treatment with an HDAC inhibitor (Matsumoto et al. 2013). This is not surprising, given that HDAC inhibitors increase acetylation to support extinction learning and decrease anxiety in animal stress paradigms (Yamawaki et al. 2012; Valvassori et al. 2014). The perseverant nature of these stress-enhanced traumatic memories may be due to a very strong epigenetic-regulated learning experience, as this model can also result in "overconsolidation" and enhanced acetylation of the *Bdnf* promoter by histones H3 and H4 (Takei et al. 2011).

Only two studies, to date, have examined DNA methylation in SEFL, focusing on *Ntsr1* and *Fkbp5*. *Ntsr1* encodes the receptor for neurotensin 1, an endogenous neuropeptide implicated in anxiety and densely expressed in the amygdala. The authors report that an SEFL model involving maternal separation was associated with decreased *Ntsr1* mRNA and increased methylation of its promoter (Toda et al. 2014). *Fkbp5* is a crucial regulator of glucocorticoid receptor (GR) and in turn, the sensitivity of the hypothalamic pituitary axis that mediates stress responses. A reduction in FKBP5 levels have been reported in PTSD patients (Yehuda et al. 2009), and changes in methylation of the *FKBP5* gene have been found in holocaust survivors and their offspring (Yehuda et al. 2015a). Pretreatment with the synthetic corticosteroid dexamethasone prior to extinction not only rescued stress-induced fear extinction deficits but also regulated the expression of *Fkbp5* mRNA and expression of the DNA methylation regulators *Dnmt3a* and *3b* and *Tet1*, *2*, and *3* (Sawamura et al. 2016). The correlative data from this study demonstrate a pattern of *Fkbp5* methylation linked to an accelerated extinction profile in an SEFL model, strengthening the notion that DNA methylation of key genes involved in both stress and memory may impact the degree of stress-enhanced fear learning, extinction, and retention.

Implications for PTSD

The contribution of neuroepigenetics to PTSD is essentially untapped in the human brain, because of several limitations. Such studies are beginning to take into account the relevance of epigenetic modifications to disease state and therapeutic potential (Norrholm et al. 2013; Labonte et al. 2014; Malan-Muller et al. 2014; Rampp et al. 2014; Yehuda et al. 2015b), but the majority are limited to measurements from peripheral fluids (e.g., blood, plasma, and saliva). The stability and longevity of epigenetic mechanisms allows for correlations to stress history in a retrospective fashion and associations with other epidemiological data, such as disease risk, drug history, and genetic background. However, methylation status and histone modifications in peripheral blood and saliva have not yet been shown to accurately represent neuroepigenetic states in PTSD subjects, especially considering subregion-specific modifications in the brain. Measurement of epigenetic marks in post-mortem PTSD brains will be necessary to reconcile these issues and provide additional insight regarding the contribution of epigenetics to disease duration and outcome.

Another significant challenge to patient studies is controlling for the wide range of stressors that individual study participants incur throughout the course of their lifetime, which can alter a person's response to a traumatic event, as well as the brain's molecular landscape, particularly in terms of persistent epigenomic changes. Further, a number of neuropsychiatric disorders, such as major depressive disorder and substance use disorder, have a strong co-morbidity with PTSD and are accompanied by an element of stress associated with the chronicity of the disease (e.g., major depressive disorder, substance abuse disorder). Thus, the interpretation of such human studies is limited and often cannot be purely dissociated from other psychiatric illnesses. This latter point reiterates the strong need to understand the epigenetic effects of stress on the brain's memory systems because, ultimately, these changes may push an individual into a more severe disease state, such as PTSD.

Although the field's understanding of neuroepigenetic contributions to PTSD from patient studies is extremely limited, findings from animal models hint at the importance of these molecular processes and should eventually be translated to human studies to further characterize potential targets in the treatment of PTSD. One such area that can be addressed relates to gender-specific mechanisms of PTSD pathology. In humans, females are twice as likely to develop PTSD, yet the majority of animal studies have been performed in males. Therefore, SEFL paradigms performed in both genders simultaneously are expected to provide insight into the elevated vulnerability of females to develop PTSD. For example, female mice subjected to subchronic variable stress are susceptible to a depression phenotype, whereas males are resilient (Hodes et al. 2015). This gender discrepancy was linked to the expression levels of the DNA methyltransferase *Dnmt3a*, which is elevated in the nucleus accumbens in females, but not males, after stress. In terms of sex differences in fear memory, the results are mixed and difficult to extrapolate to the human condition of PTSD. For instance, male rats freeze more than female rats in memory retention tests of cued fear conditioning (Maren et al. 1994), and female rats extinguish faster than their male counterparts (Dalla and Shors 2009; Glover et al. 2015). This picture is complicated by recent work showing that female mice cope differently in behavioral assays such as fear conditioning, which may confound interpretation of their behavioral output (Jones and Monfils 2016). Despite this, there is evidence that the sexual bias seen in PTSD may have epigenetic underpinnings. For example, the neuropeptide, PACAP, a regulator of the

Table 2. Known neuroepigenetic mechanisms of SEFL

Species	Stressor	Finding	Epigenetic mark	Brain region	Citation
Rats	Maternal separation	Increased methylation of the neurotensin receptor	DNA methylation of Ntsr1	Amygdala	Toda et al. (2014)
Rats	Single-prolonged stress (SPS)	HDAC inhibitor vorinostat facilitates contextual fear extinction	General histone H3 acetylation	Hippocampus	Matsumoto et al. (2013)
Rats	Single-prolonged stress (SPS)	SEFL induces epigenetic regulation of BDNF	Histones H3/H4 are hyperacetylated at BDNF promoters	Hippocampus	Takei et al. (2011)
Mice	Restraint/ immobilization	Dexamethasone alters *Dnmt*/*Tet* genes and Fkbp5 methylation status in SEFL	DNA methylation of intron 5 CpG4/5 of Fkbp5	Amygdala	Sawamura et al. (2016)

brain's stress response, has been associated with PTSD in human patients. Not only is PACAP differentially regulated in women exposed to trauma, its expression is increased in the amygdala and mPFC following cued fear conditioning. Interestingly, hypermethylation of the gene responsible for encoding PACAP's receptor, PAC1, is predictive of PTSD in a sex-specific manner (Ressler et al. 2011). This work highlights the importance of studying sexual dimorphism in PTSD, as sex-specific epigenetic differences may provide an important avenue for identifying susceptibility mechanisms that can be targeted for therapies.

ALthough the existing literature on the epigenetics of SEFL is limited, data on the epigenetics of stress and fear conditioning separately are likely to shed light on the epigenetics of SEFL. For example, epigenetic modifications of the exon IV region of *Bdnf* are linked to both stress and learning and memory events (Bredy et al. 2007; Lubin et al. 2008; Roth et al. 2011), suggesting that epigenetic modification of *Bdnf* will likely modulate behavior in an SEFL model as well. Support for BDNF participating in emotional learning has been recently translated from animal studies to PTSD in humans. Individuals with the *BDNF* polymorphism Val66Met have impaired fear memory extinction (Soliman et al. 2010). The extensive work on *Bdnf* in animal models has been influential in establishing a role for epigenetic mechanisms in PTSD and *Bdnf* is, by far, the most neuroepigenetically studied gene in emotional behaviors. Most likely, it represents a broad spectrum of neuroepigenetic molecular targets waiting to be identified in PTSD.

However, it is important to go beyond the current animal literature on stress and fear conditioning separately and further examine neuroepigenetics in the context of the SEFL models discussed in this review. Figure 1 depicts the different ways in which stress can influence subsequent fear learning in SEFL models. Stress results in epigenetic modifications, and it is likely that the nature and location of the stress-induced epigenetic change dictates the subsequent effect on memory. Deciphering epigenetic mechanisms mediating SEFL is likely to reveal unique molecular players and brain regions that participate specifically in the interaction between stress and fear memory and reveal new therapeutic targets for the treatment of PTSD.

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