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Epigenetic Mechanisms of Memory Formation and Reconsolidation

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Abstract

Memory consolidation involves transcriptional control of genes in neurons to stabilize a newly formed memory. Following retrieval, a once consolidated memory destabilizes and again requires gene transcription changes in order to restabilize, a process referred to as reconsolidation. Understanding the molecular mechanisms of gene transcription during the consolidation and reconsolidation processes could provide crucial insights into normal memory formation and memory dysfunction associated with psychiatric disorders. In the past decade, modifications of epigenetic markers such as DNA methylation and posttranslational modifications of histone proteins have emerged as critical transcriptional regulators of gene expression during initial memory formation and after retrieval. In light of the rapidly growing literature in this exciting area of research, we here examine the most recent and latest evidence demonstrating how memory acquisition and retrieval trigger epigenetic changes during the consolidation and reconsolidation phases to impact behavior. In particular we focus on the reconsolidation process, where we discuss the already identified epigenetic regulators of gene transcription during memory reconsolidation, while exploring other potential epigenetic modifications that may also be involved, and expand on how these epigenetic modifications may be precisely and temporally controlled by important signaling cascades critical to the reconsolidation process. Finally, we explore the possibility that epigenetic mechanisms may serve to regulate a system or circuit level reconsolidation process and may be involved in retrieval-dependent memory updating. Hence, we propose that epigenetic mechanisms coordinate changes in neuronal gene transcription, not only during the initial memory consolidation phase, but are triggered by retrieval to regulate molecular and cellular processes during memory reconsolidation.

1. Introduction

The formation of memories, or the process by which specific aspects of an event are encoded and stored in the brain (Nadel, Hupbach, Gomez, and Newman-Smith, 2012), is

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thought to undergo several different stages at both the molecular and cellular level. Hence, a fundamental goal for behavioral neuroscientists has been to understand the molecular, cellular, and genetic basis for memory formation, storage, retrieval, and modification across a lifetime. Following experience-driven memory acquisition, learned associations are transferred from a labile short-term memory state to a stable long-term memory state, through a process referred to as memory consolidation (McGaugh, 2000). This consolidation process is the most studied stage of memory formation and once formed, memories were thought to no longer be susceptible to disruption. However numerous studies have demonstrated that upon memory recall or retrieval, a once consolidated memory enters a labile transient period requiring a process referred to as reconsolidation to restabilize the previously formed memory (Nader, Schafe, and Le Doux, 2000a; Riccio, Millin, and Bogart, 2006). The reconsolidation phase of memory is unique in that it provides an opportunity to erase (Agren et al., 2012; Clem and Haganir, 2010; Monfils, Cowansage, Klann, and LeDoux, 2009; Rao-Ruiz et al., 2011; Schiller et al., 2010) or modify (Chen et al., 2011; Inda, Muravieva, and Alberini, 2011; Lee, 2008; 2010) the existing memory. This suggests that reconsolidation could have major clinical implications as it could serve to alleviate anxiety disorders associated with traumatic events or be used to modify or enhance specific contents of memories. As a result, understanding the molecular, cellular, and genetic mechanisms of reconsolidation is critical for the application of reconsolidation principles to a variety of therapeutic treatments and cognitive enhancement strategies (Alberini and Ledoux, 2013; Stern and Alberini, 2013).

Over the past few decades, a significant amount of evidence demonstrate that memory storage requires alterations in gene transcription and translation and protein degradation in neurons across several brain regions in order to properly store memories following their acquisition (Artinian et al., 2008; Gafford, Parsons, and Helmstetter, 2011; Kwapis, Jarome, Schiff, and Helmstetter, 2011; Reis, Jarome, and Helmstetter, 2013; Schafe and LeDoux, 2000; Taubenfeld, Milekic, Monti, and Alberini, 2001) and retrieval (Duvarci, Nader, and LeDoux, 2008; Inda et al., 2011; Jarome et al., 2012; Jarome, Werner, Kwapis, and Helmstetter, 2011; Lee et al., 2008; Milekic, Pollonini, and Alberini, 2007; Parsons, Gafford, and Helmstetter, 2006b). These transcriptional and translational changes are thought to result in structural and functional changes to synapses, leading to alterations in synaptic efficacy (Finnie and Nader, 2012; Jarome and Helmstetter, 2013; Johansen, Cain, Ostroff, and LeDoux, 2011). In consideration that transcriptional regulation of genes is a critical component of memory storage, a significant amount of research has focused on examining the molecular mechanisms involved in the transcriptional regulation of genes during memory consolidation and reconsolidation. Although much progress has been made in understanding the transcriptional regulators involved in memory consolidation (Alberini, 2009), very little is known about the molecular mechanisms that serve to regulate gene transcription during the reconsolidation process. Importantly, recent research attention has been focused on a persistent mechanism that may serve to stabilize memory during memory reconsolidation.

Epigenetic modifications result in chromatin remodeling around gene regions that can enhance or inhibit gene transcription and, in some cases, can be self-perpetuating (Bird, 1999). Recently, epigenetic modifications have emerged as an attractive molecular genetic

mechanism involved in transient and persistent gene transcriptional regulation during long-term memory formation and storage (Jarome and Lubin, 2013; Parkel, Lopez-Atalaya, and Barco, 2013; Sweatt, 2009; Zovkic, Guzman-Karlsson, and Sweatt, 2013). Although epigenetic mechanisms were once thought to occur only during development and remain static thereafter (Egger, Liang, Aparicio, and Jones, 2004), the definition for epigenetics has evolved to now include the recently observed dynamic nature of epigenetic mechanisms in adulthood, thus epigenetics is now defined as reversible heritable and non-heritable changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence (Day and Sweatt, 2011; Holliday, 1999; Lester et al., 2011).

With respect to neuronal function, there is strong supporting evidence that epigenetic mechanisms are critical regulators of learning-dependent synaptic plasticity (Chwang, Arthur, Schumacher, and Sweatt, 2007; Day et al., 2013; Feng et al., 2010; Guan et al., 2009; Gupta et al., 2010; Haettig et al., 2011; Kaas et al., 2013; Levenson et al., 2004; Lubin, Roth, and Sweatt, 2008; Maddox and Schafe, 2011; McQuown et al., 2011; Miller et al., 2010; Miller and Sweatt, 2007; Monsey, Ota, Akingbade, Hong, and Schafe, 2011; Vogel-Ciernia et al., 2013). Therefore, the field of “neuroepigenetics” proves to be promising for understanding how memories become formed, stored and modified through modification of gene transcription in neurons. In this review, we focus on the currently known epigenetic regulators underlying the processes of memory consolidation and reconsolidation. Additionally, because the idea that an epigenetic transcriptional process underlies memory reconsolidation has only begun to be elucidated, we engage the reader with a discussion of other potential epigenetic modifications involved in memory reconsolidation based on prior implications of epigenetic modifications already implicated as transcriptional regulators of the consolidation process. In doing so, we highlight both known and potential brain region specific differences in the epigenetic mechanisms recruited for the reconsolidation phase and discuss potential differences in the epigenetic regulation of the consolidation and reconsolidation processes. Finally, we discuss the evidence supporting the regulation of these epigenetic mechanisms by signaling pathways known to be involved in memory reconsolidation that may contribute to systems level reconsolidation processes. Collectively, we propose that transcriptional regulation by epigenetic mechanisms may be a powerful tool for understanding how memories become modified and stored following retrieval.

2. Epigenetic marks are dynamically regulated during memory consolidation

Epigenetic mechanisms regulate the chromatin structure, which can promote or inhibit gene transcription depending on the type of modification present (Levenson and Sweatt, 2005; Lubin, 2011; Lubin, Gupta, Parrish, Grissom, and Davis, 2011). For example, posttranslational modifications of histone proteins can bidirectionally regulate gene transcription while DNA methylation is generally associated with a transcriptionally repressive environment. In this section, we briefly summarize some of the identified epigenetic marks and the transcriptional state they are associated with, highlighting how these marks contribute to initial memory formation and storage in neurons.

2.1. Post-translational modification of histone proteins during memory consolidation

A summary of some of the epigenetic mechanisms of memory consolidation are presented in Table 1. In eukaryotes, chromatin is a complex of DNA and associated proteins including histones. Segments of 146-7 base pair of DNA wound around an octamer of proteins containing two copies each of the H2A, H2B, H3 and H4 histone proteins, a complex termed “nucleosome”, which forms the fundamental repeating units of chromatin. Unstructured N-terminal tails of histone proteins are subject to a variety of posttranslational modifications at amino acid residues that result in repression or activation of gene transcription depending on the type of functional group added to the N-terminal tails. For example, the addition of the phosphate group to histones results in disruption of the interaction of the histone octamer with DNA. This leads to chromatin restructuring and exposure of DNA to transcription factor binding at gene promoter regions, which is necessary to initiate the transcriptional machinery (Puckett and Lubin, 2011; Sawicka and Seiser, 2012). Because increased gene transcription is thought to be critical for memory formation (Bailey, Kim, Sun, Thompson, and Helmstetter, 1999), it is not surprising that histone phosphorylation has been demonstrated to be involved in memory consolidation (Chwang, O’Riordan, Levenson, and Sweatt, 2006), supporting that this form of posttranslational modification of histones is a critical regulator of transcriptional activation during memory formation. Similar to phosphorylation, the addition of the acetyl functional group to N-terminal tails of histones is associated with an active transcriptional state of genes. This form of posttranslational modification of histone proteins is the most widely studied in the context of memory formation and it is now widely accepted that histone acetylation in neurons is critical for memory consolidation (Bousiges et al., 2010; Levenson et al., 2004; Oliveira et al., 2011). Acetylation of histone proteins is regulated by a balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) activity, which serve to precisely control transcriptional states at gene regions. Numerous studies have reported that enhancing acetylation of histones via manipulation of specific HDAC isoform activity in neurons limit memory consolidation (Guan et al., 2009; Hawk, Florian, and Abel, 2011; Kim et al., 2012; Malvaez et al., 2013; McQuown et al., 2011; Rogge, Singh, Dang, and Wood, 2013; Stefanko, Barrett, Ly, Reolon, and Wood, 2009), suggesting that a coordinated regulation of histone acetylation is critical for control of memory formation.

Histone methylation is another posttranslational modification that has been demonstrated to be involved in memory formation and nervous system function. Unlike histone phosphorylation and acetylation, histone methylation is associated with both activation and repression of gene transcription, and thus represents a more complex form of gene regulation. Histones can acquire 1, 2,3 methyl groups on the same amino acid residue resulting in mono-, di-, or tri-methylation of lysine and mono- or di-methylation of arginine residues (Jarome and Lubin, 2013; Parkel et al., 2013). Methylation of histone proteins is regulated by histone methyltransferases (HMTs) and histone demethylases (HDMs) that can occur at specific amino acid residues and control the degree of methylation (mono, di, or tri). Similar to acetylation and phosphorylation, histone methylation in neurons has been implicated in memory formation. For example, behavioral training in a contextual fear conditioning paradigm increased dimethylation of histone 3 lysine 9 (H3K9me2), a transcriptional repressor, and trimethylation of histone 3 lysine 4 (H3K4me3), a

transcriptional activator, in the CA1 region of the hippocampus and the lateral entorhinal cortex (Gupta-Agarwal et al., 2012; Gupta et al., 2010). These histone methylation marks were found to parallel transcriptional activity around a number of genes during memory consolidation (Mahan et al., 2012), including *Homer1*, *DNMT3a*, *COMT* and *zif268*. These findings are exciting because for some time histone methylation marks were once considered to be permanent histone modifications, however with the discovery of multiple HDMs, this view has been changed. Interestingly, genetic or pharmacological manipulation of the HMT G9a and MLL enzymes for H3K9me2 and H3K4me3, respectively, in the CA1 interfered with long-term memory formation (Gupta-Agarwal et al., 2012; Gupta et al., 2010; Kerimoglu et al., 2013). Furthermore, G9a/GLP inhibition in the entorhinal cortex enhanced long-term memory formation and was accompanied by increased H3K9 acetylation (Gupta-Agarwal et al., 2012). The interaction and interdependence between different histone modifications and the fact that they can occur in tandem with each other rather than in isolation remains largely unexplored. Additionally, inhibiting LSD1, a HDM for H3K9me2, also altered hippocampus-dependent memory consolidation (Gupta-Agarwal et al., 2012; Neelamegam et al., 2012) and pharmacologically inhibiting or enhancing H3K9me2 levels in the lateral amygdala (LA) alters long-term memory for an auditory fear conditioning task (Gupta-Agarwal, Jarome, Fernandez, and Lubin, 2014), supporting the idea that histone lysine methylation is critical for the process of memory consolidation.

Although histone phosphorylation, acetylation, and methylation are strongly supported for their role in memory formation, there are other posttranslational modifications or addition of functional groups that occur at N-terminal tails of histone proteins. For example, histones can also be bound by protein-modifiers such as ubiquitin and the ubiquitin-like protein Small Ubiquitin-like Modifier (or SUMO). Similar to methylation, histone ubiquitination can enhance or repress gene transcription and may prove to be as complicated as histone methylation due to its diversity. For example, ubiquitination of histone 2B lysine 120 (ubiH2BK120) promotes transcription while ubiquitination of histone 2A lysine 119 (ubiH2AK119) is a transcriptionally repressive mark (Geng, Wenzel, and Tansey, 2012). The ubiquitination of histones is controlled by specific protein-ligases, which modify histones in the same way that proteins would normally be marked for degradation in the generally proteolytic ubiquitin-proteasome system (Hegde, 2010; Jarome and Helmstetter, 2014; Mabb and Ehlers, 2010). Surprisingly, numerous studies have implicated both proteolytic (Felsenberg, Dombrowski, and Eisenhardt, 2012; Jarome, Kwapis, Ruenzel, and Helmstetter, 2013; Jarome et al., 2011; Lopez-Salon et al., 2001; Pick, Malumbres, and Klann, 2013; Pick, Wang, Mayfield, and Klann, 2013; Reis et al., 2013) and non-proteolytic functions (Jarome, Kwapis, Hallengren, Wilson, and Helmstetter, 2014; Pavlopoulos et al., 2011) of ubiquitin-signaling in memory consolidation, however, no study to date has identified a role for histone ubiquitination in memory formation in neurons. Histone sumoylation is generally associated with an active transcriptional state (Pinder, Attwood, and Dellaire, 2013). While very little is known about the role of protein sumoylation in memory formation (Yang et al., 2012), recent evidence suggests that histone sumoylation may be involved in memory consolidation (Castro-Gomez et al., 2013). Investigation of the relationship between these histone modifications and the already identified phosphorylation,

acetylation, and methylation marks will prove useful in increasing our understanding of epigenetic mechanisms in memory consolidation and reconsolidation processes.

2.2. DNA methylation undergo dynamic changes in neurons during memory consolidation

DNA methylation is another epigenetic modification implicated in memory and neuronal function. DNA contains a large number of cytosine and guanine residues that are adjacent to each other and are linked by phosphodiester bonds. DNA methyltransferases (DNMTs) can transfer the methyl group from the donor S-adenosylmethionine (SAM) to the 5 position of the cytosine pyrimidal ring (Gavin, Chase, and Sharma, 2013; Lubin, 2011; Puckett and Lubin, 2011). CpG sites are generally unmethylated if genes are being actively transcribed and expressed, however, when methylated, CpG dinucleotides serve as docking sites for proteins containing the methyl-binding domain (MBD) that serve to recruit a larger repressive complex. Furthermore, the methyl group on the cytosine can interfere with transcription factor binding. Thus, DNA methylation serves as a powerful mechanism of transcriptional silencing.

A change in DNA methylation at gene regions impacts gene transcription and subsequently long-term memory formation. For example, genetic or pharmacological manipulation of DNMTs in various brain regions impaired memory consolidation for a variety of different behavioral tasks (Day et al., 2013; Feng et al., 2010; Han et al., 2010; Levenson et al., 2006; Miller and Sweatt, 2007; Sultan, Wang, Tront, Liebermann, and Sweatt, 2012; Zhao, Fan, and Frick, 2010). Additionally, several studies have reported changes in DNA methylation levels at numerous genes, including *Bdnf* (Brain-derived neurotrophic factor: Exons I, II, IV, VI and IX), *Arc*, and *zif268* during memory consolidation (Gupta et al., 2010; Koshibu et al., 2009; Lubin et al., 2008; Miller et al., 2010; Mizuno, Dempster, Mill, and Giese, 2012; Munoz, Aspe, Contreras, and Palacios, 2010; Penner et al., 2011; Roth, Zoladz, Sweatt, and Diamond, 2011; Sui, Wang, Ju, and Chen, 2012). Notably, recent reports observed increased learning-induced activity of Ten-eleven translocation 1 (TET1), a methylcytosine dioxygenase that catalyzes the oxidation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), is critical for memory formation (Kaas et al., 2013; Rudenko et al., 2013). A reported mechanism for conversion of 5mC to 5hmC is to promote DNA demethylation, (Ito et al., 2011) which remains to be explored in the context of memory consolidation or reconsolidation. These findings illustrate that various forms of DNA methylation respond to learning and are involved in the memory consolidation process. It should be noted, however, that, like histone modifications, DNA methylation events across the genome do not occur in isolation but rather can influence each other, further emphasizing the point that coordinated epigenetic changes regulate gene transcription during long-term memory formation (Gupta-Agarwal et al., 2012; Miller, Campbell, and Sweatt, 2008).

3. Epigenetic regulation of memory reconsolidation

Reconsolidation is a unique phase of memory storage in which previously acquired memories can be modified following retrieval. Consistent with this, several studies have demonstrated that reconsolidation only occurs in the presence of newly acquired information (Diaz-Mataix, Ruiz Martinez, Schafe, LeDoux, and Doyere, 2013; Sevenster, Beckers, and

Kindt, 2013) and can strengthen (De Oliveira Alvares et al., 2013; Inda et al., 2011; Lee, 2008) or change memory content (Sierra et al., 2013). The reconsolidation process requires dynamic changes in the activity of intracellular signaling molecules thought to be upstream of gene transcription, such as Protein Kinase A (PKA) and ERK-MAPK (Duvarci, Nader, and LeDoux, 2005; Tronson, Wiseman, Olausson, and Taylor, 2006), as well as increased transcription factor and CREB activity (Arguello et al., 2013; Kida et al., 2002; Kim, Kwon, Kim, Josselyn, and Han, 2014; Milekic et al., 2007). Consistent with this, several studies have demonstrated a role for *de novo* gene transcription in the reconsolidation process (Da Silva et al., 2008; Duvarci et al., 2008; Lee, Everitt, and Thomas, 2004) suggesting that increased transcriptional regulation is critical for memory reconsolidation and updating, though some exceptions have been reported (Parsons, Gafford, Baruch, Riedner, and Helmstetter, 2006a; Solntseva and Nikitin, 2012). Currently, very little is known about the mechanisms that regulate this increased demand for transcriptional regulation of neuronal genes during reconsolidation. However, while still in its early stages, an increasing body of literature has highlighted the role for epigenetic mechanisms not only in the memory consolidation process, but potentially as transcriptional regulators of gene expression crucial to the memory reconsolidation process as well. In this section we review the known epigenetic regulators of the reconsolidation process and discuss additional epigenetic mechanisms, originally implicated in memory consolidation that may also play a role in memory reconsolidation. Moreover, we discuss how these mechanisms may be regulated by known intracellular signaling cascades involved in the reconsolidation process and how these epigenetic mechanisms may be involved in a systems level reconsolidation process following memory retrieval.

3.1. Histone modification changes during memory reconsolidation

A summary of the epigenetic mechanisms of memory reconsolidation is listed in Table 2. The first evidence that posttranslational modification of histone proteins was involved in the reconsolidation process came from a study that found that global histone H3 phosphorylation and acetylation were increased in area CA1 of the hippocampus following the retrieval of a contextual fear memory (Lubin and Sweatt, 2007). This observed increase in histone H3 phosphorylation and acetylation was dependent on the Nuclear Factor kappa B (NF- κ B) signaling pathway, which has been shown to be a critical regulator of memory reconsolidation (Boccia et al., 2007; Merlo, Freudenthal, Maldonado, and Romano, 2005; Si et al., 2012). Additionally, memory retrieval increased H3 phosphorylation and acetylation at the *zif268* and *Ikb* promoters, two genes critical for the reconsolidation process (Lee et al., 2004; Lubin and Sweatt, 2007; Maddox, Monsey, and Schafe, 2011), supporting increased transcription of these genes following retrieval (Hall, Thomas, and Everitt, 2001). Interestingly, increasing histone acetylation with the HDAC inhibitor sodium butyrate did not enhance memory following retrieval but it did rescue memory impairments resulting from NF- κ B blockade. This suggests that while histone acetylation is critical for memory reconsolidation, HDACs do not limit memory strength following retrieval. Consistent with this, a recent study found that inhibiting HDAC activity with sodium butyrate could rescue memory impairments that resulted from inhibiting the NF- κ B pathway in the amygdala following retrieval but did not improve memory retention (Si et al., 2012). Collectively,

these results suggest that NF- κ B signaling regulates modifications of histone proteins that are important regulators of memory reconsolidation in neurons.

Since this initial demonstration, other studies have implicated histone acetylation in the reconsolidation process. For example, the HDAC inhibitor valproic acid has been shown to enhance the reconsolidation of an auditory fear memory when injected systemically prior to retrieval (Bredy and Barad, 2008), suggesting that HDACs act to limit memory strengthening during reconsolidation. This result is surprising since systemic injections of sodium butyrate, another HDAC inhibitor, did not enhance retention of contextual or auditory fear memories (Lubin and Sweatt, 2007; Si et al., 2012). While it is unclear why the HDAC inhibitors produced different behavioral outcomes since they have similar mechanisms of action, one possibility is that valproic acid targets other molecules in addition to HDACs when compared to sodium butyrate (Backliwal et al., 2008). However, sodium butyrate has been shown to enhance memory in an invertebrate model of reconsolidation (Federman, Fustinana, and Romano, 2012), suggesting that it can enhance the reconsolidation process. Nonetheless, these results suggest that HDACs may serve to limit memory strengthening during the reconsolidation process under certain conditions.

Posttranslational modification of histones has also been demonstrated to regulate the reconsolidation of fear memories in the amygdala. For example, retrieval of auditory fear memory transiently increases histone H3 but not H4 acetylation in the LA (Maddox and Schafe, 2011). Inhibiting HDAC activity in the LA after retrieval with Trichostatin-A (TSA) enhanced the increases in histone H3 acetylation and memory retention, suggesting that HDACs limit memory strengthening in the LA during the reconsolidation process. Consistent with a role for histone acetylation in the amygdala, infusions of a naturally occurring histone acetyltransferase inhibitor Garcinol into the LA impaired the reconsolidation of an auditory fear memory (Maddox, Watts, Doyere, and Schafe, 2013a). Inhibiting the HAT p300/CBP in the LA prevented retrieval-induced increases in histone acetylation and impaired memory retention, suggesting that the p300/CBP HAT is required for the reconsolidation of an auditory fear memory in the amygdala. Additionally, retrieval of a contextual fear memory, which reconsolidates in the amygdala (Jarome et al., 2011; Mamiya et al., 2009), increases the phosphorylation of histone H3 at Ser10 (Antoine, Serge, and Jocelyne, 2014), suggesting that histone phosphorylation may be important in the reconsolidation of this type of memory in the amygdala. However, very little is known about the epigenetic mechanisms that regulate the reconsolidation of contextual fear memories in both the amygdala and hippocampus.

While the focus has remained on the role of histone acetylation, it currently is unknown if other histone modifications regulate gene transcription during the reconsolidation process. For example, as discussed above, histone methylation is a critical regulator of memory consolidation in the hippocampus (Gupta-Agarwal et al., 2012; Gupta et al., 2010; Kerimoglu et al., 2013; Mahan et al., 2012) and amygdala (Gupta-Agarwal et al., 2014) but it is unknown if histone methylation contributes to the reconsolidation process. However, several lines of evidence suggest that histone methylation may be a dynamic regulator of gene transcription during memory reconsolidation (Jarome and Lubin, 2013). First, histone lysine methylation (HKM) has been shown to bidirectionally regulate gene transcription

during the consolidation process (Gupta-Agarwal et al., 2012; Gupta et al., 2010). Importantly, HKM promoted the transcription of *zif268*, a critical regulator of memory reconsolidation (Lee et al., 2004; Maddox et al., 2011). Thus, it is interesting to consider a potential role for HKM as a critical regulator of gene transcription during memory reconsolidation. Second, HKM marks are the only histone posttranslational modification, to date, that has been demonstrated to be persistently impacted long after a learning experience. Indeed, there are persistent changes in H3K9me2 and H3K4me3 levels in the CA1 region and entorhinal cortex following contextual fear conditioning and H3K9me2 levels in the LA following auditory fear conditioning that are still present 24 hrs after training (Gupta-Agarwal et al., 2012; Gupta-Agarwal et al., 2014; Gupta et al., 2010), when the consolidation process has already been completed, suggesting long-term changes in transcriptional regulation mediated by HKM. Given that reconsolidation is thought to occur in the same neurons involved in the initial consolidation of the memory (Han et al., 2009; Kim et al., 2014), these interesting results indicate that persistent changes in HKM present at the time of memory retrieval could influence gene transcription during the reconsolidation process. Finally, manipulation of HKM alters changes in other histone modifications such as acetylation (Gupta-Agarwal et al., 2012; Warren, Chia, Warren, Brooks, and Gabrielli, 2010; Zhang, Siino, Jones, Yau, and Bradbury, 2004) which further supports the idea that HKM likely works in concert with other histone modifications to effectively control gene transcription during memory reconsolidation. Together, the evidence highlights a potential crucial role for histone methylation in memory reconsolidation that remains to be directly tested.

Similar to memory consolidation, it is unknown if histone ubiquitination is involved in memory reconsolidation, which is surprising considering the well documented role of ubiquitin-signaling in the reconsolidation process (Artinian et al., 2008; Jarome et al., 2011; Lee et al., 2008; Lee et al., 2012; Ren et al., 2013). While it is difficult to speculate on what possible role histone ubiquitination would play in memory reconsolidation, it is intriguing to hypothesize that this histone modification may serve to regulate crosstalk between other epigenetic mechanisms. Supporting this, ubiH2BK120 has been shown to regulate histone methylation and acetylation in cell cultures (Ma, Heath, Hair, and West, 2011), though it is unknown if this occurs *in vivo*. Future studies will need to examine this non-proteolytic function of ubiquitin-signaling in transcriptional regulation during the reconsolidation process.

3.2. DNA methylation in memory reconsolidation

In regards to the role of other non-histone epigenetic modifications, DNA methylation has also been implicated in the memory reconsolidation process. One pioneering study found that infusion of the DNMT inhibitors Decitabine (5-Aza-2'-deoxycytidine) or RG108 into the LA after retrieval impaired the reconsolidation of an auditory fear memory (Maddox and Schafe, 2011). Consistent with this, after retrieval inhibiting DNMT activity in the LA with Decitabine and RG108 impaired training-related changes in auditory-evoked field potentials and interfered with long-term memory formation, without altering short-term memory for the task (Maddox, Watts, and Schafe, 2014). These results suggest that DNA methylation in the amygdala is an important regulator of memory reconsolidation. To date, these are the

only known studies that have examined the role of DNA methylation in the reconsolidation process. Therefore, it remains unknown if active DNA methylation or demethylation at memory permissive genes in other brain regions such as the hippocampus or contributes to the reconsolidation of other types of declarative memories. Additionally, while DNMT activity is important for memory reconsolidation, we do not know what genes are being regulated through this epigenetic mechanism. Furthermore, the relationship between DNA methylation and modification of histone proteins is currently underexplored during the process of memory reconsolidation. For these reasons, it is clear that we are only at the early stages of discovery and much work remains for understanding the contribution of DNA methylation mechanisms to memory reconsolidation.

3.3. Regulation of epigenetic mechanisms during the reconsolidation process

While several studies have demonstrated a role for epigenetic mechanisms in the reconsolidation process, very little is known about how these mechanisms are regulated following retrieval. NMDA receptor (NMDAR) activity is a critical component of memory reconsolidation as it regulates the “destabilization” of memories and the initiation of the reconsolidation process (Ben Mamou, Gamache, and Nader, 2006; Wang, de Oliveira Alvares, and Nader, 2009). While it has not been directly tested if NMDAR activity is an upstream regulator of epigenetic modifications following retrieval, it is likely that histone modifications and DNA methylation occur downstream of NMDAR activation. Consistent with this, inhibiting NMDAR activity can prevent increases in histone H3 acetylation and phosphorylation in striatal tissue extracts (Li et al., 2004). Additionally, NMDAR stimulation can result in decreases in H3K9me2 and increases in H3K4 dimethylation and H3K9/14 acetylation at *Bdnf* gene promoters in cultured hippocampal neurons, resulting in enhanced *Bdnf* expression (Tian et al., 2009). Furthermore, NMDAR activation reduced HDAC1 and methyl-cytosine-binding protein 2 (MeCP2) occupancy of the promoter region of *Bdnf* in hippocampal cultures, which correlated with increased *Bdnf* expression (Tian, Marini, and Lipsky, 2010), supporting that NMDAR activity could potentially regulate epigenetic mechanisms following memory retrieval. Supporting this, NMDAR activity regulates the recruitment of HMT and HDM complexes to the *G9a* promoter in the LA following auditory fear conditioning and enhancing H3K9me2 levels by pharmacologically inhibiting HDM-LSD1 activity rescues fear memory deficits resulting from NMDAR blockade (Gupta-Agarwal et al., 2014). This evidence demonstrates that NMDAR activity regulates histone methylation in the LA during memory consolidation, supporting a potential involvement of NMDARs in epigenetic regulation during the reconsolidation process.

PKA is also a critical component of the reconsolidation process (Arguello et al., 2014; Kemenes, Kemenes, Michel, Papp, and Muller, 2006; Sanchez, Quinn, Torregrossa, and Taylor, 2010; Tronson et al., 2006) and can bidirectionally regulate H3K9 dimethylation and H3 acetylation in striatal tissue (Li et al., 2004). Considering that PKA activators and HDAC inhibitors can both enhance memory reconsolidation, this suggests that PKA could regulate histone acetylation during the reconsolidation process. Additionally, other intracellular signaling molecules implicated in the reconsolidation process have been found to regulate epigenetic mechanisms *in vitro*, including ERK (Sunahori et al., 2013) and CaMKII (Awad et al., 2013; Mukwevho et al., 2008), and ERK signaling regulates histone methylation

levels in the LA during the consolidation of an auditory fear memory (Gupta-Agarwal et al., 2014). Therefore, while it is currently unknown how epigenetic mechanisms are regulated during the reconsolidation process, there are a number of potential signaling molecules that could control gene transcription through regulation of histone modifying enzymes.

3.4. Epigenetic regulation of systems reconsolidation

While reconsolidation has often been studied in a single brain region at a time, evidence suggests that some memories simultaneously reconsolidate in multiple brain regions. Consistent with this, context fear memories simultaneously reconsolidate in the amygdala, hippocampus, and anterior cingulate cortex after retrieval (Debiec, LeDoux, and Nader, 2002; Einarsson and Nader, 2012; Gafford et al., 2011; Jarome et al., 2011). Interestingly, *de novo* protein synthesis underlies the reconsolidation process in all three regions, suggesting that increased transcriptional regulation likely contributes to the reconsolidation of contextual fear memories in multiple brain regions following retrieval. While it is currently unknown if these brain regions directly interact to reconsolidate a retrieved memory and very little is known about how epigenetic mechanisms might regulate this process, some evidence does suggest that histone modifications might regulate a systems or circuit level reconsolidation of contextual fear memories following retrieval. Evidence for this comes from the studies described above demonstrating that manipulation of histone methylation in one brain region can alter gene transcription at other points in the fear circuit and that persistent changes in histone methylation have been observed following the completion of the consolidation process. This raises the intriguing idea that histone methylation in multiple brain regions may have to interact to properly destabilize and reconsolidate the retrieved memory. Thus, directly testing whether histone methylation, or any other epigenetic mechanism, regulates a systems or circuit level reconsolidation process will be of interest in future studies.

3.5. Alternative interpretation: accelerated extinction

Memory deficits observed in the face of post-retrieval pharmacological manipulations are interrupted as disruption of the reconsolidation process. However, an alternative hypothesis is that these memory impairments are actually a result of enhanced extinction learning (Duvarci and Nader, 2004; Fischer, Sananbenesi, Schrick, Spiess, and Radulovic, 2004; Myers and Davis, 2002). This suggests that the alterations in memory retention observed following manipulation of epigenetic mechanisms during retrieval could be a result of enhanced or impaired extinction learning rather than alterations in the reconsolidation process. Consistent with this, epigenetic mechanisms have been shown to be involved in the extinction process for certain types of memories (Lattal and Wood, 2013; Malvaez, Barrett, Wood, and Sanchis-Segura, 2009; Malvaez et al., 2013; Raybuck, McCleery, Cunningham, Wood, and Lattal, 2013). Though it is plausible that epigenetic mechanisms implicated in the reconsolidation process are actually regulating extinction, some evidence suggests that this is not likely. For example, memory impairments resulting from DNMT inhibitors in the amygdala after retrieval are not susceptible to spontaneous recovery (Maddox and Schafe, 2011). Whether memory impairments spontaneously recover following the blockade of memory reconsolidation has traditionally been the criteria for determining if the reduction in memory performance is due to reconsolidation or extinction processes (Duvarci, Mamou,

and Nader, 2006; Duvarci and Nader, 2004; Power, Berlau, McGaugh, and Steward, 2006). Based on this criteria, this suggests that the alterations in memory retention from manipulation of epigenetic mechanisms during memory retrieval are likely due to changes in the reconsolidation process and not extinction learning. Additionally, while HDAC inhibitors can enhance both the reconsolidation and extinction processes, they often produce opposite effects on behavioral performance depending on which process is being manipulated (Bredy and Barad, 2008; Bredy et al., 2007). Similar results have been observed with HAT inhibitors, where blocking histone acetylation during reconsolidation reduces fear responses while the same manipulation increases fear responses following extinction training (Maddox, Watts, and Schafe, 2013b; Wei et al., 2012). Thus, while reconsolidation and extinction may require some of the same epigenetic mechanisms, the net result of manipulating these transcriptional regulators is different, suggesting that the epigenetic regulation of the reconsolidation and extinction processes may be vastly different. Consequently, we argue that alterations in memory retention as a result of manipulation of epigenetic mechanisms during the reconsolidation process cannot be attributed to altered extinction learning.

3.6. Epigenetic regulation of memory updating

Reconsolidation is thought to be a phase of memory storage in which previously acquired associations can be modified, strengthened, weakened or erased (Alberini and Ledoux, 2013; Flavell, Lambert, Winters, and Bredy, 2013; Jarome and Helmstetter, 2013). Indeed, several studies have shown that reconsolidation can act to modify memories under certain conditions (Diaz-Mataix et al., 2013; Lee, 2008; 2010; Sekeres et al., 2012). One of the most studied forms of reconsolidation-dependent memory updating is the reconsolidation-update procedure in which an isolated retrieval event is followed by a massed extinction session (Monfils et al., 2009). This precise spacing of reconsolidation and extinction procedures results in a persistent attenuation of fear responses to specific cues in both rodents (Baker, McNally, and Richardson, 2013; Jones, Ringuet, and Monfils, 2013; Pineyro, Ferrer Monti, Alfei, Bueno, and Urcelay, 2013) and humans (Oyarzun et al., 2012; Schiller, Kanen, Ledoux, Monfils, and Phelps, 2013; Schiller et al., 2010; Warren et al., 2013) and is regulated by dynamic changes in AMPA receptor expression (Clem and Huganir, 2010; Rao-Ruiz et al., 2011). However, while this reconsolidation-update procedure is effective at attenuating fear responses to newer memories, the paradigm is much less effective with older memories (Clem and Huganir, 2010). Consistent with this, while retrieval of a recent contextual fear memory transiently increases histone acetylation and S-nitrosylation of HDAC2 in the hippocampus, these changes are absent in the hippocampus following the retrieval of a remote contextual fear memory (Graff et al., 2014). Interestingly, infusions of an HDAC inhibitor CI-994 into the CA1 region prior to the retrieval-extinction of a remote contextual fear memory resulted in increased histone acetylation in the hippocampus and persistently attenuated fear responses, suggesting that HDACs may act to limit the “updating” of memories following retrieval. Collectively, these results suggest that epigenetic modifications may be a critical regulator of memory updating during the reconsolidation process, though this remains the only study to date that has examined how epigenetic mechanisms regulate memory updating following retrieval.

4. Summary

The studies described above provide strong evidence that epigenetic mechanisms contribute to gene transcription control during both memory consolidation and reconsolidation following retrieval. Since the start of the renewed interest in molecular mechanisms underlying memory reconsolidation over a decade ago, much debate has surrounded research studies testing whether or not the reconsolidation process is a recapitulation of the consolidation process at the molecular level (Dudai and Eisenberg, 2004; Nader and Einarsson, 2010). Indeed, while some studies have identified unique differences between the cellular mechanisms of memory consolidation and reconsolidation (e.g., Lee et al., 2004; Lee et al., 2008; Parsons et al., 2006a), a majority of studies have suggested that they are very similar processes (reviewed in, Jarome and Helmstetter, 2013; Johansen et al., 2011). Therefore, it is difficult to speculate if the epigenetic regulation of the consolidation and reconsolidation processes is identical. Still, the available evidence does suggest that these processes could be vastly similar. For example, histone acetylation is increased following both initial learning and after memory retrieval, and inhibiting HAT activity can adversely affect the consolidation and reconsolidation processes (e.g., Maddox and Schafe, 2011; Miller et al., 2008). Additionally, pharmacological manipulations of DNMT activity impairs both the consolidation and reconsolidation processes (e.g., Maddox et al., 2014; Miller and Sweatt, 2007), and some of the same genes (*zif268*) are epigenetically regulated following the initial learning event and after memory retrieval (Gupta et al., 2010; Lubin and Sweatt, 2007). Interestingly, the consolidation work has largely focused on the hippocampus while reconsolidation studies have almost exclusively focused on epigenetic regulation in the amygdala.

5. Future directions

While the idea that a balance between increased and decreased gene transcription is needed to reconsolidate memories after retrieval has been around for over a decade (Nader et al., 2000a; Nader, Schafe, and LeDoux, 2000b; Sara, 2000), very little is known about the mechanisms that regulate the increased demand for transcription during the reconsolidation process. The studies reviewed here suggest that epigenetic mechanisms likely contribute to dynamic transcriptional regulation during the reconsolidation of memories (Figure 1). However, a number of important questions remain unanswered. For example, a majority of the available data supports that histone acetylation is a critical regulator of the reconsolidation process (Maddox and Schafe, 2011; Maddox et al., 2013b) and some evidence also suggests a role for histone phosphorylation and DNA methylation (Lubin and Sweatt, 2007; Maddox et al., 2014). However, it is unknown if other covalent modifications of histones, such as methylation and ubiquitination, are involved in the reconsolidation process. Identification of other histone modifications is particularly important since these types of epigenetic mechanisms often work in concert with DNA methylation to regulate memory storage in neurons (Gupta et al., 2010; Lubin et al., 2008; Miller et al., 2008). Additionally, while some studies have implicated DNA methylation in the reconsolidation process, it is not yet explored if DNA demethylation is also involved in the storage of memories after retrieval. An example of this is that TET1, which is involved in active DNA demethylation, has been shown to regulate the consolidation of memories following

acquisition (Kaas et al., 2013; Rudenko et al., 2013). Whether or not TET1 plays a similar role during the reconsolidation process is unknown. Nonetheless, it is still likely that the reconsolidation process requires simultaneous methylation and demethylation of DNA to properly control gene transcription following retrieval, and thus should remain the focus of future investigations into epigenetic mechanisms of memory reconsolidation.

In light of our limited understanding of the molecular regulators of the reconsolidation process, additional insights into the contribution of additional epigenetic mechanisms to this phase of memory storage might prove useful. For example, micro-RNAs (miRNAs) have well-documented epigenetic influences and can reversibly regulate translation by targeting mRNA to silence their expression (Saab and Mansuy, 2014). While it is currently unknown if miRNAs contribute to memory reconsolidation, several studies have begun to implicate miRNA-mediated transcriptional regulation in the initial consolidation process (e.g., Gao et al., 2010; Griggs, Young, Rumbaugh, and Miller, 2013; Lin et al., 2011; Wang et al., 2013). Thus, it is plausible that miRNAs and other non-coding RNAs mediated transcriptional regulation might be involved in the reconsolidation process, though this remains to be tested. With regard to histone subunit exchange, individual isoforms of histone monomers can be exchanged in and out of the histone octamer assembly. This histone subunit exchange can result in increased or decreased transcription, which depends on not only the histone isoform involved but also the context of other histone modifications (Sweatt, 2013). While the “genetic code” for gene expression is derived from information within DNA, the “histone code” is a second level of transcription that dictates which genes will be expressed in a given cell type. In the context of memory formation, the “histone code” is in part regulated by chemical modifications to histone proteins, is hypothesized to regulate gene transcription in specific neurons in response to learning to encode a memory. Currently, it is unknown how histone subunit exchange alters the “histone code” to promote or inhibit gene transcription during the consolidation and reconsolidation processes.

Another important direction for future studies is to identify gene-specific changes that are controlled by epigenetic modifications during memory reconsolidation and determining whether they differ from those observed during the consolidation process. This is particularly important because research studies have suggested that the consolidation and reconsolidation processes differ at the molecular level. For example, one gene that undergoes extensive epigenetic regulation during the consolidation process is the *Bdnf* gene (Lubin et al., 2008). However, it remains to be determined if the *Bdnf* gene is epigenetically regulated following retrieval. Interestingly, there are conflicting reports regarding the role of BDNF in the reconsolidation process as some evidence suggests that BDNF is involved (Samartgis, Schachte, Hazi, and Crowe, 2012), is only involved under certain conditions (Wang et al., 2012), or is not involved at all (Lee et al., 2004; Lee and Hynds, 2013) in the reconsolidation process. Therefore, a better understanding how certain genes, implicated in the consolidation process, are differentially and epigenetically controlled following retrieval could help identify differences in the underlying cellular and molecular process involved in memory consolidation and reconsolidation.

As previously stated, reconsolidation is thought to be a phase of memory storage in which previously acquired memories can be modified following retrieval (Nader and Einarsson,

2010). One of the most widely used paradigms demonstrating the potential therapeutic relevance of the reconsolidation process is the reconsolidation-update procedure described above. While some evidence now supports a role for histone acetylation in the successful use of this paradigm, a number of unanswered questions remain. For example, it is unknown if other epigenetic mechanisms are involved in memory modification using the reconsolidation-update procedure. Histone methylation is one attractive mechanism, as enhancing histone methylation with HDM inhibitors can enhance histone acetylation and memory consolidation (Gupta-Agarwal et al., 2012), suggesting that, similar to histone acetylation, promoting histone methylation could facilitate the reconsolidation-update effect. Additionally, of particular importance is whether reconsolidation-update procedures recruit epigenetic modifications similar to that of reconsolidation or extinction processes. Understanding the epigenetic regulation of the reconsolidation-update process is crucial for the implementation of this paradigm as a therapeutic procedure, especially considering this paradigm may rely on mechanisms that are different than that of normal memory reconsolidation or extinction. Consequently, future studies should further explore the epigenetic mechanisms that regulate the reconsolidation-update of fear memories and determine whether they differ from those normally recruited for the reconsolidation and extinction processes.

6. Conclusions

While a large body of work continues to implicate epigenetic mechanisms in transcriptional control of gene expression crucial to memory consolidation, recent studies have begun to implicate similar epigenetic mechanisms in the reconsolidation of memories following retrieval. Although we are at the early stages of discovery, still accumulating evidence indicate that epigenetic mechanisms such as posttranslational modification of histones and DNA methylation may serve as important regulators of gene transcription during the reconsolidation process. Further, neuroepigenetic mechanisms can be linked to upstream signaling pathways and potentially regulate a systems level reconsolidation process; however, there is much that remains to be understood about the epigenetic regulation of memory reconsolidation. Indeed, unraveling the complex regulation of gene transcription by epigenetic mechanisms during memory reconsolidation represents an interesting future direction for the emerging subfield of neuroepigenetic in the context of long-term memory formation that last for a lifetime.

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Highlights

- Epigenetic mechanisms regulate the memory consolidation and reconsolidation processes
- Epigenetic mechanisms can regulate memory updating during the reconsolidation process
- Epigenetic mechanisms may be regulated by NMDA-mediated plasticity during reconsolidation

Figure 1. Hypothetical epigenetic regulation of memory reconsolidation

Memory retrieval could lead to dynamic changes in the chromatin structure, resulting in increased (histone acetylation, methylation and ubiquitination) and decreased (histone methylation, ubiquitination and DNA methylation) gene transcription that is necessary for the reconsolidation process. Manipulation of the enzymes that regulate these histone and DNA modifications can have opposing effects on the reconsolidation process, resulting in impaired or enhanced memory. Red arrows indicate impaired memory following retrieval. Blue arrows indicate enhanced memory following retrieval. HAT: histone acetyltransferase; HDAC: histone deacetylase; HDM: histone demethylase; HMT: histone methyltransferase; DNMT: DNA methyltransferase.

Epigenetic mechanisms of fear memory consolidation

Table 1

Structure	Task	Histone/DNA modification	Gene(s)	Manipulation	Time of Injection	Effect on Memory	Citation
Hippocampus (CA1)	CFC	↑ H3 phosphorylation	-	-	-	-	Chwang et al. (2006)
Hippocampus (CA1)	CFC	↑ H3 acetylation	-	HDAC inhibitor	Pre-Training	Enhanced	Levenson et al. (2004)
Hippocampus (CA1)	CFC	↑ H3K4 trimethylation	↑ <i>zif268</i> , <i>BDNF</i>	Genetic KO of MLL	Pre-Training	Impaired	Gupta et al. (2010)
Hippocampus (CA1)	CFC	↑ H3K9 dimethylation	↓ <i>DNMT3a</i> , <i>cFOS</i> , <i>G9a</i>	<i>G9a</i> inhibitor	Pre-Training	Impaired	Gupta-Agawal et al. (2012)
Hippocampus	CFC	↑ H3 acetylation	↑ <i>Homer1</i>	HDAC inhibitor	Post-Training	Enhanced	Mahan et al. (2012)
Hippocampus (CA1)	CFC	↓ DNA methylation	↓ <i>BDNF</i>	DNMT inhibitor	Pre-Training	Impaired	Lubin et al. (2008)
Hippocampus (CA1)	CFC	↓ DNA methylation	↑ <i>Redin</i> ↓ <i>PPI</i>	DNMT inhibitor	Post-Training	Impaired	Miller & Sweatt (2007)
Hippocampus (CA1)	CFC	↓ DNA demethylation	↓ <i>Zif268</i> , <i>NPAS4</i> , <i>cFOS</i>	Tet1 knockdown	Pre-Training	Impaired	Kaas et al. (2013)
Entorhinal cortex	CFC	↑ H3K9 dimethylation	↓ <i>G9a</i>	<i>G9a</i> inhibitor	Pre-Training	Enhanced	Gupta-Agawal et al. (2012)
Amygdala (LA)	DFC	↑ H3 acetylation	-	HDAC inhibitor	Post-Training	Enhanced	Monsey et al. (2011)
Amygdala (LA)	DFC	DNA methylation	-	DNMT inhibitor	Post-Training	Impaired	Monsey et al. (2011)
Amygdala	DFC	H3K9 methylation	↑ <i>Homer1a</i>	HDAC inhibitor	Post-Training	No effect	Mahan et al. (2012)
Amygdala (LA)	DFC	Histone acetylation	-	HAT inhibitor	Post-Training	Impaired	Maddox et al. (2013)
Amygdala (LA)	DFC	H3K9 dimethylation	↓ <i>G9a</i>	<i>G9a</i> inhibitor	Pre-Training	Impaired	Gupta-Agawal et al. (2014)
mPFC (ACC, PLC)	CFC	↑ DNA methylation	↑ <i>CaN</i>	DNMT inhibitor	Post-Training (29 days)	Impaired	Miller et al. (2010)
mPFC	TFC	Histone acetylation	-	HDAC/HAT inhibitor	Post-Training	Enhanced/Impaired	Sui et al. (2012)
mPFC	TFC	DNA methylation	-	DNMT inhibitor	Post-Training	Impaired	Sui et al. (2012)

CFC: contextual fear conditioning; **DFC**: auditory delay fear conditioning; **TFC**: auditory trace fear conditioning; **ACC**: anterior cingulate cortex; **PLC**: prelimbic cortex; **LA**: lateral amygdala; **Zif268**: zinc finger protein 225; **BDNF**: brain-derived neurotrophic factor; **DNMT3a**: DNA methyltransferase 3a; **G9a**: Euchromatic histone lysine N-methyltransferase 2; **Homer1**: Homer protein homolog 1; **PPI**: protein phosphatase 1; **NPAS4**: neuronal PAS domain protein 4; **CaN**: Calcineurin/protein phosphatase 3; **mPFC**: medial prefrontal cortex; **HDAC**: histone deacetylase; **MLL**: mixed lineage leukemia; **DNMT**: DNA methyltransferase; **Tet1**: Ten-eleven translocation methylcytosine dioxygenase 1; **HAT**: histone acetyltransferase

Table 2

Epigenetic mechanisms of fear memory reconsolidation

Structure	Task	Histone/DNA modification	Gene	Manipulation	Time of Injection	Effect on Memory	Citation
Hippocampus (CA1)	CFC	H3 phosphorylation, H3K14, H4K5, K8, K12, K16 (Pan Ab)	<i>zif/268, IrfBα</i>	HDAC inhibitor	Pre-Retrieval	Enhanced NF-κB-mediated memory deficits	Lubin & Sweat (2007)
	CFC	H3K9/14 acetylation		HDAC inhibitor	Pre-Retrieval	Enhanced	Graff et al. (2014)
Amygdala	CFC	H3S10 phosphorylation	-	-	-	-	Antonie et al. (2014)
Amygdala (LA)	DFC	H3 acetylation	-	HDAC inhibitor	Post-Retrieval	Enhanced	Maddox & Schafe (2011)
Amygdala (LA)	DFC	Histone acetylation	-	HAT inhibitor	Post-Retrieval	Impaired	Maddox et al. (2013)
Amygdala (LA)	DFC	DNA methylation	-	DNMT inhibitor	Post-Retrieval	Impaired	Maddox et al. (2014)
Systemic	DFC	Histone acetylation	-	HDAC inhibitor	Pre-Retrieval	Enhanced	Bredy & Barad (2008)
Systemic	DFC	Histone acetylation	-	HDAC inhibitor	Pre-Retrieval	No change	Si et al. (2012)

CFC: contextual fear conditioning; DFC: auditory delay fear conditioning; **Zif268**: zinc finger protein 225; **IrfBα**: inhibitory kappa B alpha; **HDAC**: histone deacetylase; **DNMT**: DNA methyltransferase; **HAT**: histone acetyltransferase