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Neuroepigenetic mechanisms underlying fear extinction: emerging concepts

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Abstract

An understanding of how memory is acquired and how it can be modified in fear-related anxiety disorders, with the enhancement of failing memories on one side and a reduction or elimination of traumatic memories on the other, is a key unmet challenge in the fields of neuroscience and neuropsychiatry. The latter process depends on an important form of learning called fear extinction, where a previously acquired fear-related memory is decoupled from its ability to control behaviour through repeated non-reinforced exposure to the original fear-inducing cue. Although simple in description, fear extinction relies on a complex pattern of brain region and cell-type specific processes, some of which are unique to this form of learning and, for better or worse, contribute to the inherent instability of fear extinction memory. Here we explore an emerging layer of biology that may compliment and enrich the synapse-centric perspective of fear extinction. As opposed to the more classically defined role of protein synthesis in the formation of fear extinction memory, a neuroepigenetic view of the experience-dependent gene expression involves an appreciation of dynamic changes in the state of the entire cell: from a transient change in plasticity at the level of the synapse, to potentially more persistent long-term effects within the nucleus. A deeper understanding of neuroepigenetic mechanisms and how they influence the formation and maintenance of fear extinction memory has the potential to enable the development of more effective treatment approaches for fear-related neuropsychiatric conditions.

Keywords

neuroepigenetics; extinction; learning; epitranscriptomics; memory; epigenetics; DNA modification; DNA structure; Histone modification; RNA modification; RNA editing

Introduction

Theories and models of fear-related memory exist in many forms and, historically, they have been primarily focused on the idea that memories are created by mechanisms that translate an initially labile experience to a persistent state (Muller & Pilzecker 1900; Lechner & Squire 1999; McGaugh 2000) which can then return to a labile state upon reactivation

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("reconsolidation", Misanin et al. 1968; Nader et al. 2000; although see Dudai & Eisenberg 2004). The concept of dynamic memory states is most apparent in fear extinction where it has been observed, since the time of Pavlov, that fear responses can be reduced following repeated exposure to cues related to the original fear evoking experience, but then return with the passage of time (Pavlov 1927; Baum 1988), by a return to original context in which fear was acquired (Bouton & Bolles 1979a; Bouton & Bolles 1979b), and by exposure to an unrelated but stress evoking cue (Rescorla & Heth 1975). However, what has never truly been established following Pavlov's (1927) original observations of extinction is an understanding of whether the reduction in behavioural responding results in the erasure of the original trace, the creation of a new trace, or something else, and a complete picture of what may be happening at the molecular level in the brain has yet to be achieved. In this review, we compare and contrast transient extinction learning-induced electrical signalling events at the level of the synapse with potentially more persistent experience-dependent changes in the capacity for gene expression, which occur against the backdrop of the nuclear environment. We highlight newly emerging neuroepigenetic mechanisms surrounding DNA, RNA and the local chromatin environment, and describe how they contribute to this important form of learning and memory when extinction is considered as a dynamic equilibrium between erasure and inhibition of the original fear memory trace.

Theoretical perspectives on fear extinction and the role of LTP

It is notable that since the early days of investigation into fear extinction as a unique inhibitory learning process, the question of whether fear memories are 'erased' or inhibited following extinction has been strongly debated. Pavlov (1927) rejected any form of erasure as a mechanism for fear extinction learning and proclaimed that only a new inhibitory trace following extinction training was possible due to the observation of spontaneous recovery. But, he also stated that "being a definite circumscribed material system, [a reflex] can only continue to exist so long as it is in continuous equilibrium with the forces external to it: so soon as this equilibrium is seriously disturbed the organism will cease to exist as the entity it was. Reflexes are the elemental units in the mechanism of perpetual equilibrium," suggesting, at the very least, an appreciation of the importance of an equilibrium between different memory states. This idea, as opposed to a dichotomy between fear and extinction, is theoretically attractive because both models, 'erasure of fear' and 'inhibitory control over fear', have repeatedly been observed over the course of 50 years of fear extinction research (Quirk & Mueller 2008; Flavell et al. 2013).

If one were to view extinction learning as a process that exists as an equilibrium between erasure and inhibition, it may therefore be posited that any behavioural manipulation which influences fear expression would also have impact on a variety of underlying continuous biological variables, such as intrinsic excitability, which could either promote a return to baseline in the original cells resulting in functional erasure of the original trace, or have permissive effects on new 'inhibitory control' cells leading to the inhibition of the original trace. Behavioural expression also exists on a continuous scale, from absolute fear expression to no expression, and this could be overlaid as a combined model in which sufficient activation of either of these two mechanisms enables the transition from one behavioural state to another, such as from freezing to exploration (Figure 1). The emphasis

would then be placed on the subthreshold variables that summate in both the original fear-related cells and the cells encoding the new inhibitory trace.

To describe how these two processes may operate and functionally interact, the most well supported and utilized model of memory storage and retrieval, the electrochemical model of plasticity, where synapse-related mechanisms play a dominant role, has often been invoked (Poo et al. 2016). The electrochemical model posits that signals in the nervous system originate via membrane depolarization, which then propagate via spreading activation along axons, and transmit their signal to surrounding neurons via chemical messengers. With respect to fear-related learning and memory, this particular model aligns with Hebb's postulate, whereby a collection of neurons representing a memory trace is formed and maintained through modulating mechanisms which allow firing of one neuron to increase the probability of triggering firing in the network of temporally coincident neurons distributed across the brain. This idea has been validated at the cellular level, in part, with the discovery of long-term potentiation (LTP; Bliss & Lomo 1973) and long-term depression (LTD; Ito 1989). Because of its potential link with memory formation, this correlate for experience-dependent plasticity has thus taken hold of our conception of cellular memory, and supporting evidence can be found throughout the literature, supporting a relationship between LTP/LTD like processes and fear-related learning and memory. For example, a synapsin-driven channelrhodopsin called oChIEF, was used to demonstrate that modulation of LTP and LTD in the medial geniculate nucleus and auditory cortex, can either induce or impair fear memory respectively (Saucier & Cain 1995; although see Nabavi et al. 2014 for evidence that LTP is not necessary for the formation of other forms of memory).

Electrophysiological recordings have also been used to define anxiety, fear, and extinction cells in associated brain areas, such as the hippocampus and prefrontal cortex, which have made it possible to examine LTP in neurons selectively activated by fear and extinction learning (Milad & Quirk 2002; Herry et al. 2010; Tovote et al. 2015; Jimenez et al. 2018). It has even been possible to demonstrate that manipulations which appear to completely erase cued fear to either a 7kHz or 2kHz tone which share overlapping cells, can be rescued if just the cells of one representation are activated with oChIEF (Abdou et al. 2018). From this, it is clear that electrophysiological changes must occur in particular regions and cells of the brain for extinction to occur; however, it is still debated as to whether these changes theoretically constitute erasure or inhibition. In a recent extension of this idea, An et al. (2017) demonstrated that the training conditions are critical and the mechanisms of erasure or inhibition can be activated depending on the behavioural protocol employed. Specifically, they found that a single training session resulted in firing in the prelimbic PFC and basal lateral amygdala, which is known to be associated with inhibition of fear. Whereas repeated training sessions, failed to activate these areas and instead resulted in the activation of 'erasure' mechanisms including depotentiation of local circuits in the lateral amygdala.

As indicated, it has been shown that the neuronal circuits responsible for fear memory can be electrophysiologically de-potentiated and therefore relate to 'erasure', or, when alternative inhibitory traces are created, the two processes can compete (Clem & Schiller 2016). Although this conceptual framing of extinction in relation to equilibrium is a step in the right direction, this premise remains incomplete as it fails to integrate molecular

mechanisms, which may serve as primary components of the extinction engram (Lashley 1950; Marshall & Bredy 2016). This is important because there are many instances where LTP-related changes in synaptic efficacy and synaptic structure following fear extinction learning do not persist even when the memory is maintained over long periods of time. For example, following a significant reduction in LTP associated with fear and its extinction, there is typically a return of fear (Nabavi et al. 2014). Mechanisms known to promote LTP such as spine formation (Hayashi-Takagi et al. 2015) have also been shown to be impermanent (Chen et al. 2014; Attardo et al. 2015; Lai et al. 2018). Furthermore, performance, memory and electrophysiological recordings can be decoupled; although recent findings suggest that this may be in part due to not clearly differentiating which outputs, among many, are involved in memory during the manipulation of local synaptic plasticity (Saucier & Cain 1995; Herry et al. 2008; Hong & Kim 2017; Marek et al. 2018). Fortunately, in recent years an entirely new model of molecular memory has emerged, which may advance the understanding of experience-dependent plasticity and address the problem of lingering fear memory following fear extinction.

Neuroepigenetics: a new frontier in the molecular underpinnings of fear extinction

An emerging perspective that may overcome current limitations in fully understanding the process of fear extinction involves recent discoveries in the burgeoning field of cognitive neuroepigenetics. Broadly defined, neuroepigenetic mechanisms represent a variety of molecular processes traditionally associated with cell lineage specification during early development, which have been co-opted in the adult brain to facilitate experience-dependent gene expression (Day & Sweatt 2011; Marshall & Bredy 2016). These mechanisms are rapid, long lasting and are well suited to govern the fine tuning of experience-dependent gene expression and memory in ways that are potentially independent, yet complementary, to protein synthesis-dependent changes in synaptic plasticity and behavioural performance at the time of learning.

DNA Modification

The first neuroepigenetic mechanism that satisfies these criteria is DNA methylation, which is known to be directly involved in memory formation (Ashapkin et al. 1982; Miller & Sweatt 2007; Stafford & Lattal 2011; Baker-Andresen et al. 2013). Importantly, this molecular process does not simply turn on and off genes necessary for fear learning or for its extinction. The accumulation of 5-methylcytosine (5mC) on DNA can both activate and inhibit gene expression associated with fear extinction depending on its position within the genome (Figure 2). In gene promoters, 5mC often silences gene expression and when it accumulates in gene bodies, this epigenetic mark tends to be permissive (Day & Sweatt 2010; Vanyushin & Ashapkin 2017). Other recently identified DNA modifications, including 5-hydroxymethylcytosine (5hmC) and N6-methyldeoxyadenosine (m6da), appear to be biased towards gene activation in fear extinction (Li et al. 2014; Li et al. 2018).

Beyond on-off states, DNA modification can also influence the rate of transcription (Roundtree & Selker 1997). If one were to consider fear extinction as a process that involves

a dynamic equilibrium between erasure and inhibition, perhaps in this context, changes in DNA methylation and the regulation of transcription rates would be important. In the case of functional erasure, this might involve transcriptional repression by DNA methylation or, similar to depotentiation, active DNA demethylation may occur as a function of fear extinction learning, which may then functionally erase transcriptional blocks that occur during fear learning (Li et al. 2013; Rudenko et al. 2013; Li et al. 2014). For inhibitory control, transcription rate may be controlled along an analogue scale with many DNA modifications required to govern gene expression associated with the new trace. DNA modifications could therefore serve to tune gene expression and behavioural outcomes in a manner akin to a dimmer switch, dialling down the original fear, or dialling up inhibitory control, with the behavioural impact depending on both sequence context, and surrounding DNA modifications (Figure 1 and Figure 2).

However, much in the way that LTP is only observed after repeated stimulation, there are many cases when the effect of DNA modification on gene expression and behavioural regulation is only evident at the time of reactivation (Baker-Andresen et al. 2013; Liu et al. 2017). This has led to the intriguing hypothesis that DNA modification may serve as a form of genomic meta-plasticity where it can effectively tune the genome in response to experience, which could then dynamically modify the strength of fear extinction memory and performance depending on the context and future experience (Baker-Andresen et al. 2013). For example, it is possible that one reason why only repeated training leads to fear erasure is because fear cells must first be epigenetically primed. Future studies may explore the conditions under which this may occur in order to facilitate more permanent changes.

DNA Structure State

DNA structure states represent another level of DNA that may follow this concept of dynamic tuning. Initially thought to be static, based on the original double-helix structure proposed by Watson and Crick, there is now a long history of observation of alternate and dynamic DNA structures, which may functionally regulate transcription and, possibly, memory traces (Watson & Crick 1953; Felsenfeld et al. 1957). Specifically, particular structures like particular DNA modifications, have been observed to both impair or promote transcription rate, suggesting a non-binary structure-switch potentially playing a role in tuning fear memory (Figure 2 and Figure 1; Naylor & Clark 1990; Siddiqui-Jain et al. 2002). In addition, like DNA modification, it has been proposed that these structures once induced can modify the probability of future structure-switch induction in this genomic context thus providing further support for the idea of genomic priming and tuning (Pohl 1987). The idea of a structure switch has been demonstrated in the context of regulation of the immediate early gene expression thought to be important for fear conditioning. Specifically, Top2B activation is required to cut and repair DNA to promote the expression of immediate early genes (Madabhushi et al. 2015). In unpublished experiments, we have also found that DNA breaks produced by Top2B generate changes in DNA methylation, which must be actively removed to produce multiple waves of transcription, which are then critical for the formation of fear memory (Li et al. 2018). Further work will be required to determine the extent of structure-function relationships, and their interaction with other layers such as DNA modification in fear extinction regulation.

Histone Modification

Histone modifications represent another layer in which epigenetic modification appears to play a role in the formation of extinction memory. Schmitt & Matthies (1979) first observed a relationship between histones and learning, and since then histone modifications have become some of the best established epigenetic mediators of behaviour ranging from acetylation to methylation of histone proteins (Swank & Sweatt 2001; Gupta-Agarwal et al. 2012; Damez-Werno et al. 2016). Furthermore, histone acetylation and methylation are also specifically engaged during reconsolidation (Gupta-Agarwal et al. 2014; Webb et al. 2017; Jarome et al. 2018), and extinction (Itzhak et al. 2012; Stafford et al. 2012; Li et al. 2014). As a result of these marks transcriptional activity is enhanced or inhibited by modifying chromatin accessibility, specifically methylation tends to inhibit transcription by closing the chromatin, while acetylation tends to do the opposite (Rice & Allis 2001). Thus, blocking proteins which promote acetylation such as PCAF impairs extinction (Wei et al. 2012). Similarly, facilitating acetylation by blocking enzymes which remove acetylation either indirectly with histone deacetylase inhibitor drugs (Bredy et al. 2007; Bredy & Barad 2008), or directly by knocking down specific histone deacetylases (HDACs) such as HDAC1 (Bahari-Javan et al. 2012) HDAC2 (Morris et al. 2013) or HDA3 (Malvaez et al. 2013) facilitates extinction.

More interestingly, like DNA modifications, histone modifications have also been shown to be involved in epigenetic priming. Specifically, HDAC inhibitors when given alone appear to have no effect on destabilizing or stabilizing memory, but when given just before or after behavioural experience, or in conjunction with other memory modulators, they can drastically alter memory memory updating (Gräff & Tsai 2013; Gräff et al. 2014). Furthermore, early studies demonstrated that massed vs. spaced extinction training in the presence of an HDAC inhibitor biased the expression of memory from extinction to the enhanced reconsolidation of the original fear (Bredy & Barad 2008). Thus, these reversible modifications appear also to interact with the behavioural conditions, and through these interactions modulate both the original trace and the fear extinction trace by modifying transcription.

Histone Variant Exchange

In addition to posttranslational modification of histone proteins, a variety of histone variants including: H3.3, H2A.Lap1, H2Az and H2BE have been shown to regulate experience dependent gene expression within the context of learning and memory. While H2BE, has been shown to be mainly for learning in the olfactory bulb (Santoro & Dulac 2012) H3.3 (Maze et al. 2015) H2A.Lap1 (Anuar 2018), and H2A.Z (Zovkic et al. 2014) appear to be critical for fear learning. Additionally, like RNA and DNA there appear to be 100’s of unexplored variants that may also participate in extinction learning, each with a potentially specialized role (Draizen et al. 2016). For example, H2A.Z appear to regulate the equilibrium of chromatin architecture such that it biases regions to remain in a transcriptionally poised state (Subramanian et al. 2015).

Furthermore, recent data has made clear that variant presence or absence is not all that governs their function. The turnover rate of these histone variants is also critical to their

function such that impairing histone turnover impairs: expression of genes critical for fear expression, cell to cell signalling, and fear expression itself (Maze et al. 2015). Additionally, as animals age the distribution of these variants also changes (Stefanelli et al. 2018). Both of these data can be interpreted within the proposed framework that these variants specify regions of transcriptional activity or silencing (Hake & Allis 2006). Thus one shift that may be observed following repeated behavioural training is local variants composition, such that genomic regions containing transcriptional repressors are activated in fear cells, and disinhibited in inhibitory control cells following extinction training. Together this suggests this epigenetic mechanism can modify transcriptional rate through bidirectionally modifying the histone code, and tune the activity of both the original fear and inhibitory control cells involved in extinction learning.

RNA Modification

A bidirectional and graded regulatory signal driving fear extinction may also extend to RNA-mediated regulatory processes (Figure 3 and Figure 1). For example, RNA methylation in the form of N6-methyldeoxyadenosine (m6A) has been implicated in fear learning (Widagdo et al. 2016; Walters et al. 2017) and that this occurs in part as a consequence of RNA degradation. But with over 140 RNA modifications identified to date (Machnicka et al. 2013), “epitranscriptomic” mechanisms may expand beyond just acting as transcription termination signals by directly modifying the rate of RNA degradation (Machnicka et al. 2013; Nainar et al. 2016; Widagdo et al. 2016) and the efficiency of translation (Wang et al. 2015). RNA modifications may also serve modify the localization of the RNA itself (Wang et al. 2015; Ohtan Wang) or other yet to be characterized interactions in the context of fear extinction learning (Nainar et al. 2016). It is therefore likely that we will see the emergence of novel RNA modifications that influence both the rate of translation and RNA degradation during fear extinction learning, which could then facilitate or inhibit the extinction processes via altering the molecular pathways underlying the memory trace. Theoretically speaking, this might serve to enhance the formation of extinction trace substrates in new inhibitory cells, while enhancing RNA degradation in the cells supporting the original fear trace, which could lead to memory erasure, suggesting yet another opportunity for the continuous tuning of gene expression to control behaviour (Figure 1) which may arise independent of local changes in synaptic activity.

RNA Editing

Interestingly, the potential impact of RNA modification on fear extinction may not end here. Another mechanism of RNA metabolism that may play a critical role in fear extinction is RNA editing. This is a biochemical process that enzymatically converts one nucleotide to another to produce diverse types of transcripts without altering the genetic code. For example, ADAR-mediated-editing of the AMPA receptor subunit GluR2, in which conversion of adenosine to inosine changes a glutamine to arginine, can dramatically modify channel permeability and, therefore, fear extinction learning (Clem & Huganir 2010; Wright & Vissel 2012). In addition, the RNA editing-related molecule ADAR3 has recently been shown to be critical for the formation of contextual fear memory (Mladenova et al. 2018). Furthermore, in a series of recent studies, we have found a functional role for another RNA editing enzyme, activation-induced cytidine deaminase (AID), in the regulation of gene

expression (Ratnu et al, 2014) and in the formation of fear extinction memory (Marshall, unpublished observations).

These observations are not surprising given the fact that RNA editing has increased throughout evolution in organisms with increased cognitive complexity (Mattick & Mehler 2008). RNA editing may therefore be playing a direct role in fear and extinction memory by regulating translational efficiency such that the presence or absence of critical proteins for inhibiting and facilitating extinction are being bidirectionally 'tuned'. In this case, the biological variable impacting fear extinction could be described as a ratio of edited to non-edited RNA, such that the complete absence of RNA editing facilitates plasticity and behaviour whereas a ratio above a certain threshold may lead to a reduction in plasticity and behavioural inhibition. This process could have its most relevant impact in the context of a new trace model for extinction by facilitating the expression of functionally distinct proteins, which could impact the stability of the original fear memory and/or the instability of the fear extinction trace.

Limitations of a cognitive neuroepigenetic perspective

Epigenetic modifications may contribute to our understanding of how the formation of fear extinction memory could proceed by either 'erasure' of the original trace, the formation of inhibitory memory traces, or the tuning of both in real-time during behaviour. However, much akin to the fact that at the psychological level one cannot differentiate between a lack of retrieval due to permanent erasure or a lack of appropriate retrieval cues, a limitation of this neuroepigenetic view is the inability to determine whether the degradation of the substrates of epigenetic modifications are complete and can therefore be deemed 'erasure', or whether the processes have been tuned temporarily to zero. We predict that similar to the electrophysiological perspective, there exists an equilibrium in epigenetic states that can be pushed in one direction or another at multiple levels of molecular control within the cell; likely leading to both erasure and new inhibitory traces depending on: the context, time since acquisition, length of training, or time between sessions (Cain et al. 2003; Myers 2006; Auber et al. 2013; Flavell et al. 2013; Clem & Schiller 2016).

This leads to the second limitation around what to call this process, as acknowledging that retrieval can activate both original fear cells and new inhibitory cells blurs the line between classical definitions of extinction and reconsolidation (Hemstedt et al. 2017). This said, there is little debate that retrieval activates a variety of epigenetic mechanisms that seem to be critical for storage of the fear memory including enzymes which promote DNA and histone modifications (Zhao et al. 2014; Liu et al. 2017). Thus, to overcome this limitation in future, as opposed to labelling manipulations as solely effecting reconsolidation or extinction, it may prove useful to find drugs which can be combined without interfering with each other to maximally potentiate changes in both populations of cells.

Predicting behavioural strength from neuroepigenetic changes within the nucleus

The most significant problem with fear extinction is the persistence or re-emergence of fear after extinction learning and, therefore, clinical preference is given to treatments that aim to achieve total erasure. One way in which total erasure may be achieved is to utilize manipulations which engage genomic priming in conjunction with both behavioural and electrophysiological manipulations, such that they prime the epigenome for a more permanent change. For example, a mechanism which initially only partially modifies the transcription rate, may poise the same locus to be disengaged more robustly thereby leading to a complete cessation of transcription, and resultant electrophysiological activity, which we may present itself as cellular erasure. However, this strategy presents an issue, such that global manipulations which would favourably prime gene activation in extinction cells might also reactive the fear cells, or treatments that prime fear cells for erasure may also erase inhibitory cells. Thus, to achieve the desired behavioural balance with minimal side-effects one must selectively target the cells in which these behavioural relevant changes occur. More specifically, in addition to electrophysiologically defined “fear”, “extinction”, and “anxiety” cells (Milad & Quirk 2002; Herry et al. 2010; Tovote et al. 2015; Jimenez et al. 2018), the precise molecular marks within a cell that allow it to compete more effectively for resources leading to aforementioned behavioural tuning must be identified and linked to neuroepigenetic mechanisms.

One attractive explanation that has been described among others is that higher levels of CREB are critical for inclusion into a fear memory engram, specifically higher levels of CREB predict the cells where the largest changes in intrinsic membrane excitability occur (Silva et al. 1998; Kida et al. 2002; Kim et al. 2013). These observations are likely to represent the physiological correlate of the dominant trace hypothesis that proposes there are mechanisms, which bias a memory trace towards one that commands resources to update or modify a memory, hence guiding which cells are tuned and when (Eisenberg et al. 2003). Recent observations from our laboratory suggest this may be the case for neuroepigenetic states. Specifically, higher levels of Activity-regulated cytoskeleton-associated protein, which occurs in cells with high CREB expression, tend to co-occur in neurons that exhibit higher rates of RNA editing and the accumulation of DNA modifications such as m6dA (Li et al, 2018). Other marks which can differentiate between reconsolidation and consolidation of new extinction traces such as zif268 and BDNF, may also co-occur with neuroepigenetic changes, but this remains to be investigated (Lee et al. 2004). Together, the data suggest the intriguing possibility that if these markers are experimentally specified and utilized, certain neuroepigenetic mechanisms may be selectively engaged in these two discrete population of cells and lead to more permanent behavioural changes.

Implications, impact and future directions

Based on a neuroepigenetic perspective, promising new directions to answer long held questions about the stability of fear extinction memory, and how to target it, are emerging. For example, if epigenetic priming is required for long-term erasure, as has been suggested,

re-consolidation protocols with epigenetic modifiers as adjuncts to therapy could be implemented in the clinic (Gräff et al. 2014). In addition, if one accepts that memory is not primarily contained within the synapse, a cognitive neuroepigenetic view leaves room for Lamarkian-like phenomena where information can be acquired in one generation and passed on to the next (Franklin et al. 2010; Fischer 2014). Although the evidence is inconclusive, it has been shown that paternal sperm of defeated mice, potentially through a miRNA-mediated signal effecting DNA methylation, can bias the next generations towards a similar fearful phenotype (Dietz et al. 2011; Rodgers et al. 2015). In this case adolescent behaviour associated with mental health issues may therefore be viewed as epigenetic tendencies, which can be predicted and thus tuned behaviourally in order to minimise the future development of anxiety disorders.

But with so many levels and interactions, where might development of new therapies begin testing? Because of the large amount of data on HDAC effects in animal models and limited side effects (Gräff & Tsai 2013), these have been some of the first epigenetic targets to be tested clinically (Whittle & Singewald 2014). But there still remains a variety of other actionable epigenetic targets which can enhance the tuning of fear memory traces at every level. For example, with respect to RNA, it has been shown that increasing either miR-128b in the prefrontal cortex or miR144–3p in the amygdala can enhance extinction learning (Lin et al. 2011; Murphy et al. 2017). With respect to DNA modification, it has been demonstrated that activity of Tet3, which leads to the accumulation of 5hmC, can also enhance the formation of extinction memory (Li et al. 2014). The problem remains that unlike globally manipulating HDACs global manipulation of these targets can have detrimental side effects. Thus in order to alter these and other levels mentioned it will require the development of more targetted manipulations ranging from specific drugs to gene editing tools like CRISPR (Adli 2018). As well as advancing delivery systems such as self-deleting viral vectors (Russ et al. 1996) or nanoparticles (Gao 2016) to deliver these directly to the affected areas. Treatments of the future may also take this one step further by developing tools which apply knowledge of which molecular markers occur in fear and extinction cells and use this to differentially target these areas following central infusion.

In conclusion, a neuroepigenetic view of fear extinction suggests that, although the formation and stability of fear extinction memory occurs at more levels within the cell than currently appreciated, a better understanding of this tunable equilibrium and how to target it may be another key step to addressing the issue of lingering fear.

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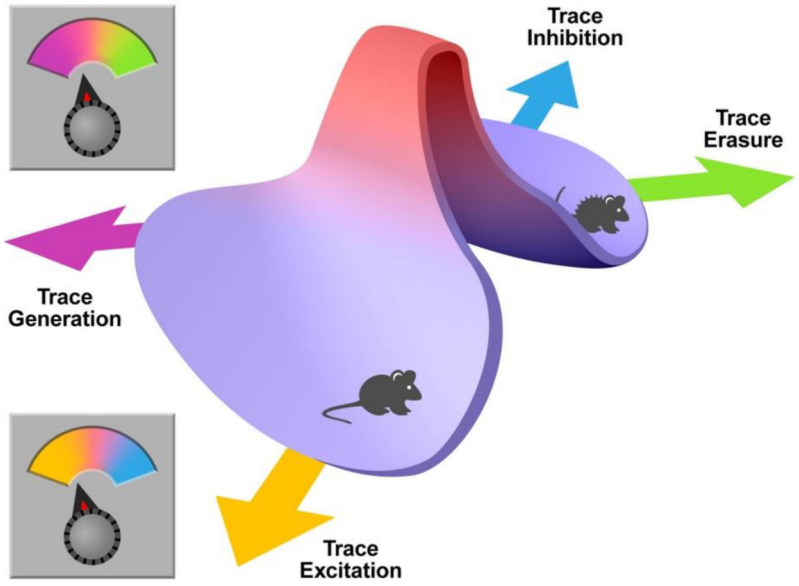

Figure 1.

Visual representation of behavioural tuning where modulation of both fear cells and inhibitory control cells can occur along a continuum. When erasure of original fear (green) and/or fear trace inhibition (blue) occurs, animals may transition from fear behaviours such as freezing and escape behaviours, to normal grooming and exploratory behaviour. However, when original fear traces are activated (purple) and/or engagement of inhibitory control is low (yellow) animals will fail to overcome the threshold to re-engage normal behaviours and remain freezing or performing escape behaviours. Thus, the dynamic equilibrium of behavioural expression relies on mechanisms which modulate either of these aspects.

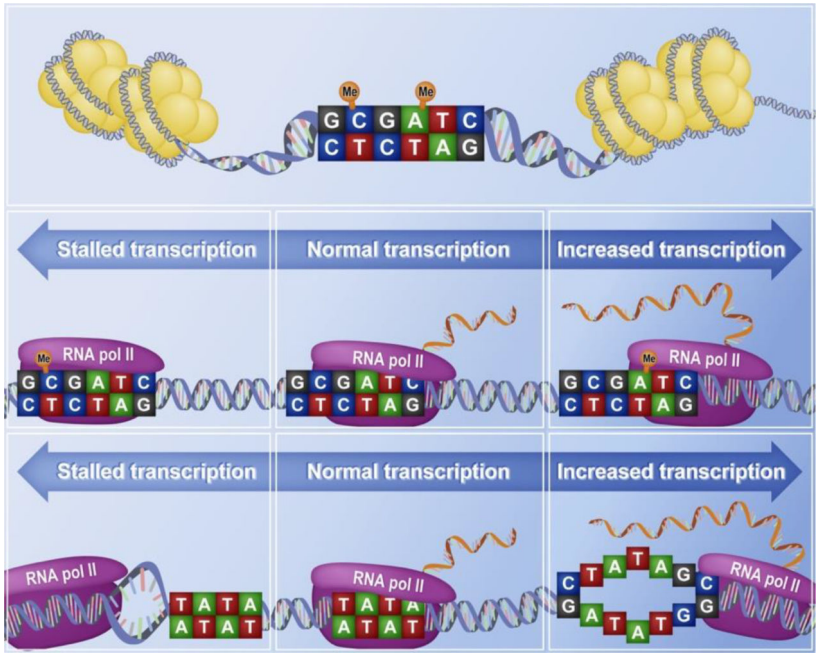

Figure 2.

A proposed mechanism for controlling behavioural equilibrium during fear extinction is genomic tuning. This is a process in which both DNA modifications and DNA structure can modulate transcription rate along a continuum. In the case of DNA modifications, while 5mC may entirely inhibit transcription, m6dA enhances transcription rate above baseline. Similarly DNA structure can completely stall RNA polymerase II (RNA pol II) and block transcription, or facilitate RNA pol II by opening DNA and thus enhance transcription rate above baseline. Combination of either of these mechanisms may thus dial transcription rate up or down.

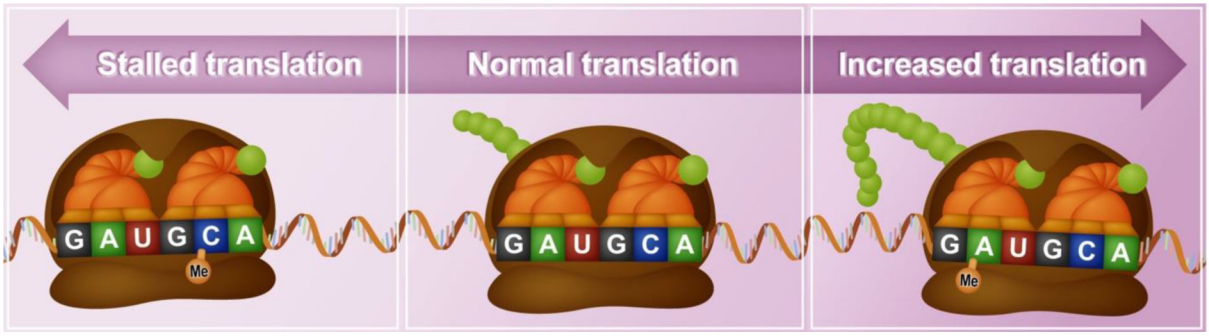

Figure 3.

A second proposed mechanism for controlling behavioural equilibrium during fear extinction is translational tuning in which RNA modifications can modulate translation rate along a continuum. RNA modifications are shown altering physical interactions with the ribosome machinery to modify its translation rate. Here, 5mC methylation in RNA may stall translation, while m6A methylation may enhance translation rate. Thus RNA modifications may dial translation rate up or down depending on the presence of absence of these marks.