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Dopamine regulation of contextual fear and associated neural circuit function

Christine Stubbendorff | **Carl W. Stevenson**

School of Biosciences, University of Nottingham, Loughborough, UK

Correspondence
Carl W. Stevenson, School of Biosciences, University of Nottingham, Sutton Bonington Campus, Loughborough LE12 5RD, UK.
Email: carl.stevenson@nottingham.ac.uk

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Abstract

Learning to associate certain contexts with threat and adapting to changing environmental contingencies by learning that such contexts are no longer associated with threat are both crucial for survival. Research over the last few decades has made considerable progress in determining the brain areas involved in the encoding, retrieval and extinction of contextual fear. These studies have identified the hippocampus and amygdala, along with the prefrontal cortex and other inter-connected brain areas, as key players in contextual fear processing. In contrast to the neural circuit basis of contextual fear, the neurochemical mechanisms involved in its regulation remain poorly understood. Dopamine is well known for its role in appetitive learning but this neurotransmitter is also important for other types of learning, including spatial and aversive memory processing. Dopamine is ideally positioned to regulate contextual fear given that the areas involved receive dopamine input and express dopamine receptors. Moreover, neuronal activity, functional connectivity and synaptic plasticity in this neural circuitry are modulated by dopamine receptor signalling. Here, we review the evidence indicating that dopamine regulates various contextual fear processes, along with the more recent studies that have begun to elucidate the brain areas and neurophysiological mechanisms involved. From a fundamental research perspective, understanding how dopamine regulates contextual fear will lead to novel insights on the neurochemical modulation of neural circuit function underlying memory processing. This research may also have translational relevance given that contextual fear conditioning and extinction also provide useful preclinical models of certain aspects of anxiety-related disorders and their treatment.

KEYWORDS

amygdala, extinction, fear conditioning, hippocampus, prefrontal cortex

Abbreviations: BLA, basolateral amygdala; CeA, central amygdala; DH, dorsal hippocampus; dmPFC, dorsomedial prefrontal cortex; DS, dorsal striatum; IL, infralimbic cortex; La, lateral amygdala; LHb, lateral habenula; LTP, long-term potentiation; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PFC, prefrontal cortex; PL, prelimbic cortex; PTSD, post-traumatic stress disorder; SN, substantia nigra; US, unconditioned stimulus; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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1 | INTRODUCTION

Learning that certain environments, or contexts, predict danger is adaptive and thus enhances survival, as does learning that previously dangerous contexts no longer pose a threat. This phenomenon can be studied using contextual fear conditioning, which serves as a useful model for investigating the general principles underlying the neural circuit basis of learning, memory and associated behaviours (Maren, Phan, & Liberzon, 2013; Rozeske, Valerio, Chaudun, & Herry, 2015). Such research also has clinical relevance given that certain anxiety-related disorders are characterized by abnormally persistent memories of fear-related events and impairments in suppressing maladaptive fear. For example, post-traumatic stress disorder (PTSD) is associated with intrusive emotional memories, re-experiencing of the traumatic event and deficient extinction, which forms the theoretical basis for psychological therapies (Craske et al., 2017; Watkins, Sprang, & Rothbaum, 2018). Importantly, the neural circuitry underpinning contextual fear conditioning and extinction (i.e. hippocampus, amygdala, prefrontal cortex (PFC); see below) is also implicated in the deficits in cognition and emotional regulation that are key features of PTSD (Sevenster, Visser, & D'Hooge, 2018; Tovote, Fadok, & Lüthi, 2015). Therefore, understanding how the brain mediates the encoding, retrieval and extinction of contextual fear may lead to novel insight on the pathophysiology and treatment of PTSD and other anxiety-related disorders.

The neural circuitry mediating these contextual fear processes is subject to modulation by various neurotransmitters (e.g. acetylcholine, noradrenaline, serotonin, dopamine) that are released in different areas throughout the brain. These neurotransmitters play an important role in regulating neuronal excitability locally, as well as synchronized oscillatory activity and synaptic plasticity between inter-connected areas (Bazzari & Parri, 2019). However, the neuromodulatory mechanisms involved in regulating contextual fear processing remain to be fully elucidated (Likhtik & Johansen, 2019). In this narrative review, we focus on the regulation of contextual fear and associated neural circuit function by the neurotransmitter dopamine. We begin by providing overviews on the different aspects of contextual fear processing, the key brain areas that comprise the contextual fear circuit and dopamine modulation of the function of this neural circuitry. We then review the studies, mainly conducted in rodents, which have investigated dopamine regulation of contextual fear processing. We conclude by summarizing the key findings of these studies and outlining future directions for taking this research forward, along with highlighting its potential translational relevance.

2 | OVERVIEW OF CONTEXTUAL FEAR PROCESSING AND THE UNDERPINNING NEURAL CIRCUITRY

Pavlovian fear conditioning is a type of associative learning whereby a neutral conditioned stimulus, which can be a discrete cue (e.g. sound, light) or a distinctive context (e.g. operant chamber), comes to predict threat through its association with an aversive unconditioned stimulus (US; e.g. mild electric shock; Pape & Pare, 2010; Tovote et al., 2015). During contextual fear conditioning, unsignalled presentations of the US (i.e. without a discrete cue) in the conditioning context initially result in the elicitation of fear responding upon later re-exposure to the context in the absence of the US. Freezing behaviour is typically quantified as the measure of contextual fear. This process is known as foreground contextual conditioning. During cued fear conditioning, pairing a discrete cue with the US can also result in later fear expression when returned to the conditioning context in the absence of the US, even without cue presentations. This process is known as background contextual conditioning (Phillips & LeDoux, 1994). Contextual fear conditioning entails the encoding of spatial cues and other elements of the environment into a distinct configural representation of the context, which then becomes associated with the US. As with other types of learning, the contextual representation and context-US association are consolidated into long-term memory after contextual fear conditioning (Maren et al., 2013).

During memory retrieval induced by brief re-exposure to the context without the US, contextual fear memory can be rendered labile via destabilization of the memory engram. This allows for the maintenance, strengthening or updating of memory before its restabilization through the process of reconsolidation (Lee, 2009). In contrast, longer or repeated context re-exposure alone results in contextual fear extinction, which is a form of inhibitory learning that competes with the original context-US memory to suppress fear expression. Context also plays an important role in the extinction of cued fear, such that repeated cue presentations result in the reduction of cue-induced fear responding but only when the cue is presented in the extinction context. After cued fear extinction, fear can return when the cue is presented outside of the context in which extinction occurred, a process known as fear renewal. Cue-induced fear can also return with the passage of time after extinction. This process is known as spontaneous fear recovery and occurs because the cue is presented outside of the temporal extinction context. Finally, contextual or cued fear can also return after extinction with exposure to the US alone. This process is known as fear reinstatement and is triggered by the association between the context and US (Bouton, Westbrook, Corcoran, & Maren, 2006; Maren et al., 2013).

Studies investigating the brain areas involved have identified a neural circuit comprising the hippocampus, amygdala and PFC as being crucial for contextual fear processing. One influential view on contextual fear conditioning is that the dorsal hippocampus (DH) encodes the contextual representation that is then conveyed via the ventral hippocampus (VH) and/or the medial PFC (mPFC) to the basolateral amygdala (BLA), where it is associated with US-related somatosensory input (Fanselow, 2010; Maren et al., 2013; Rudy, Huff, & Matus-Amat, 2004). However, more recent evidence suggests that encoding of the context-US association may also involve the hippocampus, such that the initial consolidation of contextual fear memory in BLA might be followed by further consolidation in VH and DH (Chaaya, Battle, & Johnson, 2018). The hippocampus is normally the dominant region involved in contextual fear conditioning but other brain areas can compensate in the absence of a functioning hippocampus to allow for learning to occur (Fanselow, 2010). For example, mPFC is recruited to mediate contextual fear in compensating for damage to DH (Zelikowsky et al., 2013), in keeping with evidence indicating a role for mPFC in mediating both context and context-US association encoding during contextual fear conditioning (Zelikowsky, Hersman, Chawla, Barnes, & Fanselow, 2014). This circuit is also crucial for contextual fear retrieval and extinction, as well as the contextual regulation of cued fear after its extinction (Maren et al., 2013; Rozeske et al., 2015). Other brain areas (e.g. dorsal striatum (DS), nucleus accumbens (NAc), lateral habenula (LHb)) that are inter-connected with hippocampus, amygdala and PFC also form part of the wider neural circuitry underlying contextual fear processing (Fanselow, 2000; González-Pardo, Conejo, Lana, & Arias, 2012; Kathirvelu & Colombo, 2013).

3 | NEUROCHEMICAL MODULATION OF CONTEXTUAL FEAR CIRCUIT FUNCTION: THE CASE FOR DOPAMINE

While much research has elucidated the neural circuit mechanisms underlying contextual fear processing, lagging behind this is our understanding of the role that neurotransmitters play in regulating the function of this circuitry (Likhtik & Johansen, 2019). One such neurotransmitter is dopamine, which is crucial for regulating various facets of behaviour, including motor function, motivation, emotion, cognition and executive function (Nieoullon & Coquerel, 2003). However, dopamine is also important for spatial and aversive learning (Brandão & Coimbra, 2019; Pezze & Feldon, 2004; Werlen & Jones, 2015), which are key aspects of contextual fear conditioning. Dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) send ascending projections to the hippocampus, amygdala, PFC and other inter-connected areas (e.g. DS, NAc, LHb) involved in different contextual fear processes (Dahlstrom & Fuxe, 1964; Gasbarri, Sulli, & Packard, 1997; Oades & Halliday, 1987). Dopamine signalling is mediated by D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors, which are expressed in these brain areas (Missale, Nash, Robinson, Jaber, & Caron, 1998). Therefore, dopamine is well placed to modulate the function of this neural circuitry and, consequently, contextual fear processing. Descending dopaminergic projections from the medial zona incerta to the midbrain tectum (e.g. superior colliculus, periaqueductal gray) are also important for regulating innate fear and anxiety (Brandão & Coimbra, 2019) but this topic is beyond the scope of the present review.

Dopamine modulates neuronal activity by tuning the balance between excitatory and inhibitory inputs received from different afferents. This modulation of neuronal excitability allows dopamine to exert a strong influence on activity locally but also on functional coupling between the inter-connected areas of the contextual fear circuit (Grace & Rosenkranz, 2002; Werlen & Jones, 2015). Communication within this neural circuitry is mediated in part by synchronized rhythmic oscillations in these areas, which play a key role in fear conditioning and its extinction by facilitating synaptic plasticity underlying their encoding (Lesting et al., 2011; Pape, Narayanan, Smid, Stork, & Seidenbecher, 2005; Popa, Duvarci, Popescu, Léna, & Paré, 2010; Taub, Perets, Kahana, & Paz, 2018). Importantly, dopamine modulates theta oscillations and spike firing at theta frequencies in these brain areas (Benchenane, Tiesinga, & Battaglia, 2011; Kowski, Veh, & Weiss, 2009; Lemaire et al., 2012; Lorétan, Bissière, & Lüthi, 2004; Matulewicz, Kasicki, & Hunt, 2010; Werlen & Jones, 2015). Theta oscillations in DH are disrupted by VTA inhibition and spatial learning is impaired by dopamine receptor blockade in DH (Werlen & Jones, 2015), suggesting a mechanism by which dopamine regulates the encoding of the context representation during contextual fear conditioning. Therefore, dopamine modulation of theta oscillations in, or theta synchrony between, these areas may also regulate other contextual fear processes.

Synchronized theta oscillations within this neural circuitry are thought to facilitate the synaptic plasticity that underpins fear conditioning and its extinction (Pape & Pare, 2010). Associative learning, such as when the context is associated with the US during contextual fear conditioning, requires both Hebbian and neuromodulatory processes for its encoding. This form of learning initially involves the NMDA receptor-dependent strengthening of convergent homosynaptic glutamatergic inputs to post-synaptic neurons that underpins memory formation. However, neurotransmitters such as dopamine are also needed for the later heterosynaptic stabilization of memory that leads to its persistence over time. Long-term potentiation (LTP) is a cellular model of

synaptic plasticity underlying learning, and dopamine plays a crucial role in stimulating the protein synthesis required for late LTP that corresponds to memory persistence (Bazzari & Parri, 2019; Lisman, Grace, & Duzel, 2011). Dopamine receptor blockade in DH impairs both spatial learning and local LTP (Lisman et al., 2011; Werlen & Jones, 2015). Similarly, blocking dopamine receptors in BLA disrupts cued fear learning and LTP in this area resulting from stimulation of cortical afferents (Li, Dabrowska, Hazra, & Rainnie, 2011; Li & Rainnie, 2014; Pezze & Feldon, 2004). Moreover, dopamine receptor activation modulates synaptic plasticity in an inhibitory circuit within amygdala to regulate cued fear expression (Lee & Kim, 2016). Dopamine modulation of LTP in mPFC is also thought to be crucial for synaptic plasticity that underlies the encoding of certain types of long-term memory in this area (Otani, Bai, & Blot, 2015). For example, hippocampal and amygdala projections to mPFC might be involved in encoding the context representation and/or the association between the context and US during contextual fear conditioning. Interestingly, synaptic plasticity in the hippocampo-prefrontal and amygdala-prefrontal pathways is disrupted by dopamine depletion or receptor blockade (Jay et al., 2004; Onozawa, Yagasaki, Izawa, Abe, & Kawakami, 2011). Therefore, dopamine modulation of synaptic plasticity in this neural circuitry may also play an important role in regulating contextual fear conditioning and extinction.

4 | DOPAMINE REGULATION OF THE ACQUISITION OF CONTEXTUAL FEAR

Several studies have investigated the effects of systemically administering different dopamine-acting drugs on the acquisition of contextual fear. Various drugs that act as dopamine (and noradrenaline) reuptake inhibitors have been shown to reduce foreground and background contextual fear conditioning. Cocaine was found to have dose-related effects on fear conditioning to background contextual cues. A very low dose given before cued fear learning increased freezing in the conditioning context during later retention testing. In contrast, a moderate dose had the opposite effect and decreased freezing to the background contextual cues at retention test. These results were not attributable to its local anaesthetic properties, given that cocaine had no effect on shock reactivity, and instead indicate that the very low dose enhanced while the moderate dose reduced contextual fear conditioning (Wood, Fay, Sage, & Anagnostaras, 2007). Bupropion was reported to have dose-dependent effects on fear conditioning to background contextual cues as higher doses inhibited the acquisition of contextual fear (Portugal & Gould, 2007). Amphetamine and methylphenidate given before contextual fear conditioning have been shown to decrease freezing during retention testing, indicating that these drugs reduced foreground contextual fear conditioning (Byun et al., 2014; Calzavara et al., 2009). Taken together, these findings suggest that elevated levels of synaptic dopamine result in reduced contextual fear conditioning, although noradrenaline may also be involved in the effect of these non-selective drugs as central noradrenaline depletion has been shown to enhance fear conditioning to background contextual cues (Selden, Everitt, & Robbins, 1991; Selden, Robbins, & Everitt, 1990).

Other studies have determined the effects of different neuroleptic drugs, which typically have D2-like receptor antagonist properties but also act at various other targets, on contextual fear conditioning. Inoue, Tsuchiya, and Koyama (1996) found that the atypical antipsychotics clozapine and olanzapine reduced the acquisition of contextual fear in a dose-dependent manner. Typical antipsychotics such as haloperidol were also shown to inhibit contextual fear conditioning but these were more effective at moderate, compared to high, doses. The inhibitory effect of these different neuroleptics was thought to be related to their D4 receptor antagonist properties. Inhibition of contextual fear conditioning by haloperidol and clozapine has been replicated in other studies (Inoue et al., 2005; Calzavara et al., 2009; but see also Colombo, de Oliveira, Reimer, & Brandão, 2013). Conversely, the atypical antipsychotics ziprasidone, risperidone and amisulpride were found to enhance the acquisition of contextual fear (Calzavara et al., 2009). The varied effects of these different antipsychotic drugs on contextual fear conditioning may involve differences in the non-dopaminergic targets at which these non-selective drugs act.

Studies examining the effects of more selective dopamine-acting drugs have shown that D1-like and, to a lesser extent, D2-like receptor signalling is involved in the acquisition of contextual fear. Several studies have shown that the D1-like receptor antagonist SCH23390 inhibits contextual fear conditioning (Calzavara et al., 2009; Heath et al., 2015; Inoue et al., 2005; Inoue, Izumi, Maki, Muraki, & Koyama, 2000; Stubbendorff, Hale, Cassaday, Bast, & Stevenson, 2019). This effect was not attributable to altered nociception, given that shock sensitivity was unaffected by SCH23390 (Heath et al., 2015; Inoue et al., 2000). Nor could this effect be accounted for by state-dependent learning (Overton, 1985), as SCH23390 inhibited conditioning either when given before acquisition or before both acquisition and retention testing (Stubbendorff et al., 2019). SCH23390 has also been shown to potentiate the inhibitory effect of haloperidol on contextual fear conditioning (Inoue et al., 2005). However, the D1-like receptor agonist SKF38393 had no effect on the acquisition of contextual fear (Inoue et al., 2000). Taken together, these studies indicate that dopamine activation of D1-like receptors facilitates contextual fear conditioning. In contrast, the evidence from systemic drug administration studies indicating a

role for D2-like receptors in regulating contextual fear conditioning is mixed. Raclopride, a D2/3 receptor antagonist, has been shown to reduce the acquisition of contextual fear (Inoue et al., 1996) but no effect was found with metoclopramide, a non-selective D2-like receptor antagonist that also acts on serotonin receptors (Calzavara et al., 2009).

Gene knockout studies have been conducted to determine the specific dopamine receptor subtypes involved in contextual fear conditioning. No effect of D1 or D5 receptor knockout on contextual fear conditioning has been reported in some studies (El-Ghundi et al., 1999; Holmes et al., 2001). However, a more recent study found that D1 receptor knockouts that underwent cued fear conditioning showed decreased freezing to the background contextual cues during retention testing, compared to wild-type controls, which did not involve an effect on shock sensitivity (Ortiz et al., 2010). Conditional knockout of cannabinoid CB1 receptors selectively in neurons expressing D1-like receptors was also shown to increase freezing to background contextual cues during retention testing, compared to wild-type controls (Terzian, Drago, Wotjak, & Micale, 2011). This suggests that interactions between endocannabinoid and dopaminergic signalling are involved in background contextual conditioning. D3 receptor knockouts subjected to contextual fear conditioning have been shown to express decreased freezing at retention test, compared to wild-type controls, which did not involve differences in locomotor activity (Song et al., 2018). Taken together, these results suggest the involvement of D1 and D3 receptors in the acquisition, consolidation and/or retention of contextual fear. D4 receptor knockout was found to have no effect on fear conditioning to background contextual cues (Falzone et al., 2002). This result seems to be at odds with the previous findings suggesting that D4 receptor signalling is involved in the inhibitory effect of neuroleptics on contextual fear conditioning (Inoue et al., 1996) and instead adds weight to the argument that their effects also involve non-dopaminergic targets.

One of the first studies to investigate the brain areas involved in mediating dopamine regulation of contextual fear conditioning found no effects of dopamine (and noradrenaline) depletion in BLA on fear conditioning to background contextual cues, as measured by the time spent in the conditioning context compared to a neutral context (Selden, Everitt, Jarrard, & Robbins, 1991). However, more recent studies have established a role for amygdala dopamine in regulating contextual fear conditioning. Guarraci, Frohardt, and Kapp (1999) found that D1-like receptor antagonism in the central amygdala (CeA) before cued fear conditioning decreased freezing in response to the background contextual cues during later retention testing, an effect which was not attributable to state-dependent learning. Similarly, D1-like receptor agonism in this area before cued fear conditioning increased freezing elicited by the conditioning context during the retention test. These results indicate that blocking CeA D1-like receptors reduced contextual fear conditioning, while activating D1-like receptors in this area enhanced contextual fear conditioning. In contrast, D2-like receptor antagonism in CeA had no effect on freezing in response to the conditioning context during retention testing (Guarraci, Frohardt, Falls, & Kapp, 2000), suggesting a lack of involvement of D2-like receptor signalling in CeA in contextual fear conditioning. D1-like receptors in BLA have also been found to regulate the acquisition of contextual fear in a similar manner. While D1-like receptor activation potentiated contextual fear conditioning (Biedenkapp & Rudy, 2008), D1-like receptor blockade reduced the acquisition of contextual fear (Heath et al., 2015). Taken together, these studies indicate that D1-like receptor activation in amygdala facilitates contextual fear conditioning. The inhibitory effect of blocking D1-like receptors in BLA on contextual fear conditioning is at odds with the lack of effect of dopamine depletion in this area reported by Selden, Everitt, Jarrard, et al. (1991). However, noradrenaline depletion also occurred in that study and central noradrenaline depletion has been shown to enhance contextual fear conditioning (Selden, Everitt, & Robbins, 1991; Selden et al., 1990). Therefore, it is possible that dopamine and noradrenaline depletion in BLA had opposing effects on the acquisition of contextual fear, resulting in no net effect. Differences in the behavioural measures used to quantify contextual fear between the studies may also explain these discrepant findings.

The hippocampus is another important site of action for dopamine in regulating contextual fear conditioning. Dopamine depletion in the CA3 subregion of DH was found to have no effect on fear conditioning to background contextual cues, although freezing levels during retention testing were also very low in the controls and suggest the possibility of a floor effect (Wen et al., 2015). However, infusion of the non-selective dopamine receptor agonist apomorphine into the CA1, but not the CA3, subregion of DH reduced background contextual fear conditioning (Vago, Bevan, & Kesner, 2007). D1-like receptor blockade in DH was shown to reduce the acquisition of contextual fear (Heath et al., 2015), in keeping with the role of D1-like receptors in this area in modulating spatial learning (Werlen & Jones, 2015). The inhibitory effect of D1 knockout on background contextual fear encoding (see above) was associated with reduced LTP within DH (Ortiz et al., 2010). Knockout of D1, but not D5, receptors selectively in dentate gyrus granule cells of DH has been shown to inhibit contextual fear conditioning (Sarinana, Kitamura, Künzler, Sultzman, & Tonegawa, 2014). Taken together, these studies indicate that D1-like receptor activation in DH facilitates contextual fear conditioning. It is unclear how non-selective dopamine receptor activation by apomorphine and D1-like receptor blockade or D1 receptor knockout can have similar inhibitory effects on contextual

fear conditioning. It is possible that apomorphine reduces the acquisition of contextual fear by activating post-synaptic D2-like receptors, although a role for these receptors in DH in regulating contextual fear conditioning has yet to be established. Apomorphine might also reduce D1-like receptor signalling and the acquisition of contextual fear indirectly by activating presynaptic autoreceptors that decrease dopamine release locally (Missale et al., 1998). In contrast to DH, blockade of D1-like receptors in VH was found to have no effect on contextual fear conditioning (Stubbendorff et al., 2019).

Recent evidence indicates that D1-like receptor signalling in dorsomedial PFC (dmPFC), which includes the prelimbic (PL) and anterior cingulate cortices, is involved in contextual fear conditioning. Blocking D1-like receptors in dmPFC has been reported to reduce the acquisition of contextual fear (Stubbendorff et al., 2019). Similarly, D1-like receptor activation in dmPFC was found to enhance fear conditioning involving weaker contextual cues (Castillo Díaz, Kramar, Hernandez, & Medina, 2017; Pezze, Marshall, Domonokos, & Cassaday, 2016). The role of D2-like receptors in dmPFC in regulating contextual fear conditioning remains to be examined. Striatal D1 receptors have also been implicated in the acquisition of contextual fear, given that selective knockout of D1, but not D2, receptors in this area was shown to inhibit contextual fear conditioning (Ikegami, Uemura, Kishioka, Sakimura, & Mishina, 2014). D1-like receptor antagonism in NAc had no effect on the acquisition of contextual fear in another study (Stubbendorff et al., 2019), raising the possibility that the inhibitory effect of striatal D1 receptor knockout on contextual fear conditioning is mediated by D1 receptor signalling in DS. D1-like receptors in LHb were recently shown to be involved in contextual fear conditioning as their activation or blockade inhibited the acquisition of contextual fear. Moreover, D1-like receptor agonism or antagonism in LHb reduced LTP in DH, suggesting that LHb dopamine regulation of contextual fear conditioning may have occurred indirectly by modulating hippocampal synaptic plasticity (Chan et al., 2017). Taken together, these studies indicate that D1-like receptor signalling in mPFC, striatum and LHb is involved in the acquisition of contextual fear.

5 | DOPAMINE REGULATION OF CONTEXTUAL FEAR MEMORY CONSOLIDATION

Using gene knockouts or drug administration to investigate the neurobiological basis of contextual fear encoding has certain disadvantages. Knockout of one gene can be compensated for by other redundant genes with overlapping functions or patterns of expression (El-Brolosy & Stainier, 2017); therefore, negative findings do not conclusively rule out the involvement of a given gene. Moreover, any reported effects might be due to the gene knockout affecting the acquisition, consolidation and/or retention of contextual fear. Gene knockouts can also potentially have non-specific effects on shock sensitivity during acquisition and/or locomotor activity during retention testing, which can obscure the precise role of the gene in question. There are also disadvantages of examining drug effects on contextual fear conditioning. Any reported effects of a drug given before acquisition may involve state-dependent learning if retention is later tested in the absence of the drug (Overton, 1985). Non-specific drug effects on shock sensitivity can also potentially alter contextual fear conditioning. To avoid some of these drawbacks, the effects of drugs given systemically or centrally immediately after conditioning can be determined. The advantage of this approach is that acquisition and retention remain unaffected, meaning that any observed effect of drug treatment is selective to the consolidation process.

Studies have investigated the role of dopamine in regulating the consolidation of contextual fear. Temporary inactivation of SN was found to reduce the consolidation of background contextual memory (Baldi, Mariottini, & Bucherelli, 2007). Infusing amphetamine into DH or DS has been shown to enhance the consolidation of fear conditioning to background contextual cues (White & Salinas, 2003). Systemic D1-like receptor blockade was shown to have no effect on contextual fear consolidation (Heath et al., 2015; Inoue et al., 2000), suggesting that D1-like receptors are not necessary for the consolidation of contextual fear memory. This raises the possibility that the effects of SN inactivation and local amphetamine infusions on contextual fear consolidation are mediated by D2-like receptors, which are also involved in the consolidation of spatial and inhibitory avoidance memory (Brown, Bardo, Mace, Phillips, & Kraemer, 2000; Gasbarri, Introini-Collison, Packard, Pacitti, & McGaugh, 1993). However, D1-like receptor signalling can regulate contextual fear consolidation in some circumstances. Males exposed to females after contextual fear conditioning showed reduced memory consolidation, an effect which was blocked by systemic D1-like receptor antagonism. This inhibitory effect of exposure to females on contextual fear consolidation was mimicked by systemic D1-like receptor activation after conditioning (Bai, Cao, Liu, Xu, & Luo, 2009). Liao, Shi, Liu, and Zhao (2013) found that D1-like receptor blockade in DH had no effect on the consolidation of contextual fear in controls but it did block the facilitatory effect of corticosterone on contextual fear consolidation. In contrast, blocking D2-like receptors in DH had no effect on the consolidation of contextual fear in controls or on its enhancement by corticosterone given after conditioning. Another study found no involvement of D1-like or D2-like receptor signalling in CA3 in the consolidation of fear conditioning to background cues, although freezing was also very low in the controls (Wen et al., 2015). The potential roles of other brain areas in mediating dopamine regulation of contextual fear consolidation have yet to be established. Taken

together, these studies suggest that dopamine might be involved in the consolidation of contextual fear memory but the underlying receptor signalling and neural circuit mechanisms remain unclear.

6 | DOPAMINE REGULATION OF CONTEXTUAL FEAR RETRIEVAL

Evidence indicates that dopamine is released in various brain areas during the retrieval of foreground and background contextual fear. In one study, dopamine release was elicited in mPFC, but not DS, during contextual fear retrieval (Matsumoto et al., 2005). Dopamine release in NAc has been shown during the retrieval of foreground and background contextual fear (Fulford & Marsden, 1998; Saul'skaya & Gorbachevskaya, 1998; Saulskaya & Marsden, 1995). Another study found differences in dopamine release in the core and shell subregions of NAc during cued and background contextual fear retrieval (Pezze, Heidbreder, Feldon, & Murphy, 2001). Dopamine release was elicited during contextual but not cued fear retrieval in NAc core, while dopamine was released during cued but not contextual fear retrieval in NAc shell. In contrast, Martinez, Oliveira, Macedo, Molina, and Brandão (2008) found that dopamine release was elicited in both NAc core and shell during the retrieval of foreground contextual fear. Thus, it is possible that NAc core and shell dopamine play different roles in foreground and background contextual fear retrieval.

Few gene knockout studies have investigated dopamine regulation of contextual fear retrieval, possibly due to some of the drawbacks inherent to such studies (see above). Knockout of the ghrelin receptor, which is co-expressed and can heterodimerize with D1-like and D2-like receptors, was found to reduce contextual fear retrieval 30 days, but not 24 hr, after conditioning, indicating a selective reduction in the retention of remote fear memory (Albarran-Zeckler, Brantley, & Smith, 2012). Various studies have examined the effects of systemic administration of different dopaminergic drugs on contextual fear retrieval. Bupropion has been shown to reduce the retrieval of fear to background contextual cues (Portugal & Gould, 2007). Haloperidol and clozapine were found to have no effect on contextual fear retrieval (Inoue et al., 1996). A more recent study examined the effects of haloperidol on the emission of ultrasonic vocalizations and freezing as measures of contextual fear retrieval. In that study, Colombo et al. (2013) found that haloperidol reduced ultrasonic vocalizations but enhanced freezing, indicating a dissociation in the affective and locomotor effects of this drug. The atypical antipsychotic aripiprazole, which acts mainly as a partial D2-like receptor agonist, was shown to reduce the retrieval of contextual fear at a low, but not a high, dose without affecting locomotor activity (Biojone et al., 2011). No effects of D1-like receptor activation or blockade were found on contextual fear retrieval (Heath et al., 2015; Inoue et al., 2000; de Souza Caetano, de Oliveira, & Brandão, 2013), whereas both agonism and antagonism of D2-like receptors have been shown to reduce the retrieval of contextual fear (de Souza Caetano et al., 2013).

A disadvantage of examining the effects of dopamine-acting drugs on contextual fear retrieval, which is typically inferred from freezing behaviour, is that any reported drug effects may also be confounded by non-specific effects on locomotor activity. Indirect (e.g. bupropion) and direct dopamine receptor agonists enhance locomotor activity, which may resemble a reduction in contextual fear retrieval (Beninger, 1989; Nielsen, Shannon, Bero, & Moore, 1986). Moreover, non-selective (e.g. haloperidol, clozapine) and selective dopamine receptor antagonists reduce locomotor activity (Beninger, 1989; Coward, 1992; Heath et al., 2015), which could mask any potential inhibitory effects of these drugs on the retrieval of contextual fear. To address this limitation of systemically administered dopaminergic drugs, several studies have examined the effects of their local infusion on contextual fear retrieval.

Blocking D1-like receptors in CeA resulted in a marginal reduction in the retrieval of fear to background contextual cues, whereas D1-like receptor activation in this area was without effect (Guarraci et al., 1999). D2-like receptor blockade in CeA was found to have no effect on background contextual fear retrieval, although freezing was also very low in the controls (Guarraci et al., 2000). D2-like receptors in VTA and BLA were shown to play opposing roles in the retrieval of contextual fear (de Souza Caetano et al., 2013). Activation, but not blockade, of D2-like receptors in VTA inhibited contextual fear retrieval. This raises the possibility that activating presynaptic D2-like autoreceptors in this area reduces the retrieval of contextual fear by decreasing dopamine release in other brain areas. In contrast, D2-like receptor blockade, but not activation, in BLA reduced contextual fear retrieval. This suggests that antagonism of post-synaptic D2-like receptors in this region inhibits the retrieval of contextual fear. Blocking, but not activating, D1-like receptors in NAc shell was found to reduce contextual fear retrieval, whereas D2-like receptor signalling in this area was not involved (Albrechet-Souza, Carvalho, & Brandão, 2013). The role of dopamine receptors in other areas in regulating contextual fear retrieval remains to be elucidated. Taken together, these studies indicate that activation of D1-like receptors in NAc and D2-like receptors in BLA facilitates the retrieval of contextual fear.

7 | DOPAMINE REGULATION OF CONTEXTUAL FEAR EXTINCTION

Gene knockout studies have shown that dopamine is involved in contextual fear extinction. El-Ghundi, O'Dowd, and George

(2001) found that knockout of the D1 receptor reduced extinction memory resulting from repeated extinction sessions, compared to wild-type controls. Another study reported that D1 receptor knockouts treated with a D1-like receptor agonist after extinction showed an enhancement of extinction memory, suggesting that D5 receptor activation enhanced the consolidation of contextual fear extinction (Abraham, Neve, & Lattal, 2016a). The ClockΔ19 mutation, which results in increased dopamine transmission, was found to enhance extinction memory resulting from repeated extinction sessions, compared to wild-type controls. ClockΔ19 mutants also showed increased locomotor activity but this did not affect freezing during the first extinction session, suggesting that the effect of this mutation on extinction was not due to its non-specific locomotor effect (Bernardi & Spanagel, 2014).

Studies have also examined the effects of systemically administering different dopamine-acting drugs on contextual fear extinction. The dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was found to have no effect on the extinction of weaker contextual fear or on locomotor activity but it was reported to enhance the extinction of stronger contextual fear (Kinoshita, Tada, Muroi, Unno, & Ishii, 2015). However, MPTP also reduced the expression of stronger contextual fear with repeated retention tests that were likely too brief (3 min) to engage the extinction process (Cassini, Flavell, Amaral, & Lee, 2017), making it unclear if MPTP enhanced the extinction or reduced the retrieval of contextual fear. Methylphenidate given before or immediately after extinction was found to enhance extinction memory (Abraham, Cunningham, & Lattal, 2012). Modafanil, another dopamine reuptake inhibitor, was also shown to enhance extinction memory when given at a low dose before repeated extinction sessions; modafanil had no effect on locomotor activity at this dose (Bernardi & Spanagel, 2014). Systemic administration of the dopamine precursor L-DOPA after contextual fear extinction training was shown to reduce the later spontaneous recovery and reinstatement of fear, possibly by enhancing extinction consolidation (Haaker et al., 2013). A D1-like receptor agonist given before or immediately after contextual fear extinction was found to enhance extinction memory. This effect of D1-like receptor activation immediately after contextual fear extinction was not observed in the absence of extinction training (Abraham, Neve, & Lattal, 2016b). Taken together, these studies indicate that dopamine and D1-like receptor activation facilitate the extinction of contextual fear. The effects of systemically administered drugs acting at D2-like receptors on contextual fear extinction remain unknown.

Different brain areas have been implicated in mediating dopamine regulation of contextual fear extinction. D1-like or D2-like receptor antagonism in BLA before cued fear extinction was shown to decrease freezing to background contextual cues during extinction memory testing, suggesting that blocking BLA dopamine receptors enhanced contextual fear extinction (Pavlova, Rysakova, & Sergeeva, 2016). However, Fiorenza, Rosa, Izquierdo, and Myskiw (2012) found no effects of D1-like receptor activation or blockade in BLA on the consolidation of contextual fear extinction. Methylphenidate infused into DH before contextual fear extinction was shown to enhance extinction memory, an effect which was blocked by co-infusion with a D1-like receptor antagonist (Furini et al., 2017). In DH, D1-like receptor activation enhanced and blockade inhibited the consolidation of contextual fear extinction (Fiorenza et al., 2012). The potential role of D2-like receptors in DH in regulating the extinction of contextual fear remains unexplored. Dopamine (and serotonin) depletion in mPFC was reported to delay contextual fear extinction by reducing the retention of extinction memory with repeated testing (Fernandez Espejo, 2003). However, the retention tests were likely too brief (5 min) to engage extinction, making it unclear if mPFC dopamine depletion inhibited the extinction or enhanced the retrieval of contextual fear. Another study found no effects of D1-like receptor activation or blockade in mPFC on the consolidation of contextual fear extinction (Fiorenza et al., 2012). In a study conducted in humans, L-DOPA given after contextual fear extinction training had no effect on later spontaneous fear recovery or reinstatement. However, L-DOPA did enhance activation of the ventromedial PFC (vmPFC), which is the human homologue of the rodent infralimbic cortex (IL) that is important for extinction, during reinstatement testing (Haaker, Lonsdorf, & Kalisch, 2015). The receptor signalling mechanisms involved in mPFC dopamine regulation of contextual fear extinction remain poorly understood. Fear reinstatement after the extinction of contextual fear in rodents has been shown to activate VTA dopaminergic neurons projecting to IL. Moreover, D1-like receptor blockade in IL, but not PL, was found to block fear reinstatement and enhance local neuronal excitability. These effects were also associated with increased activation of amygdala intercalated neurons and decreased activation of CeA, which are implicated in the extinction and expression of learned fear, respectively (Hitora-Imamura et al., 2015). Taken together, these results indicate that D1-like receptors in DH are involved in contextual fear extinction, whereas D1-like receptors in mPFC might be involved in the later return of contextual fear after its extinction.

8 | ROLE OF DOPAMINE IN THE CONTEXTUAL REGULATION OF CUED FEAR AFTER ITS EXTINCTION

Systemic L-DOPA treatment after cued fear extinction training was found to reduce later spontaneous fear recovery,

possibly due to an enhancement of extinction consolidation. L-DOPA also reduced fear renewal, suggesting that extinction consolidation was enhanced to the extent that extinction became context-independent. Moreover, the reduction in fear renewal by L-DOPA was associated with increased IL activation and decreased CeA activation. Similar results were found in humans, where L-DOPA also reduced fear renewal and increased vmPFC activity. Furthermore, vmPFC activity was negatively correlated with amygdala activity, which, in turn, was positively correlated with the proxy fear measure (skin conductance response) in subjects treated with L-DOPA. Finally, L-DOPA increased the functional connectivity between the dopaminergic midbrain and vmPFC after extinction training, and this coupling predicted vmPFC activation during later fear renewal testing (Haaker et al., 2013). A caveat to these results obtained from human subjects is that conditioning and extinction occurred on the same day, raising the possibility that L-DOPA could have affected fear and/or extinction memory. In a follow-up study where cued fear conditioning and extinction occurred over consecutive days, there were no effects of L-DOPA given after extinction training on later spontaneous fear recovery or reinstatement. However, despite the lack of effect of L-DOPA on these fear measures, it did result in less activation of the amygdala and posterior hippocampus, which is homologous to the rodent DH, during spontaneous fear recovery testing (Haaker et al., 2015). In terms of the receptor signalling mechanisms involved, systemic D1-like receptor agonism immediately after cued fear extinction was found to reduce fear renewal in rodents (Abraham et al., 2016b). Activation of SN dopamine neurons or D1-like receptors in DS was also shown to inhibit fear renewal after the extinction of cued fear (Bouchet et al., 2018). Taken together, these results indicate that dopamine and D1-like receptor activation reduce fear relapse after cued fear extinction by modulating the function of the contextual fear circuit. The role of D2-like receptors in the contextual regulation of fear after extinction remains unknown.

9 | SUMMARY AND FUTURE DIRECTIONS

The studies reviewed above provide clear evidence that dopamine is important for regulating contextual fear processing. They have also begun to identify the receptor signalling and neural circuit mechanisms involved, which are summarized in Figure 1. Overall, these studies indicate that dopamine acting at D1-like receptors is important for the encoding and extinction of contextual fear. D1-like receptor signalling throughout the contextual fear circuit mediates contextual fear conditioning, whereas the brain areas mediating D1-like receptor regulation of contextual fear extinction and the contextual regulation of cued fear after extinction require further characterization. In contrast, the role of D2-like receptors in regulating contextual fear encoding and extinction remains unclear. Less research has investigated dopamine regulation of contextual fear retrieval but both D1-like and D2-like receptors in different brain areas are involved. Determining how dopamine regulates contextual fear will lead to a better understanding of neuromodulation of neural circuit function underlying associative learning in general but this may also be relevant to understanding the pathophysiology and treatment of anxiety-related disorders such as PTSD. Below we suggest various lines of enquiry for further research on this topic.

Although various studies have shown that dopamine reuptake inhibitors and neuroleptics regulate contextual fear conditioning, it is unclear if their effects are mediated by dopamine receptor signalling. Dopamine reuptake inhibitors reduce the acquisition of contextual fear, which appears to conflict with the evidence indicating that D1-like receptor activation mediates contextual fear conditioning. These drugs also inhibit noradrenaline reuptake, and noradrenaline depletion enhances the acquisition of contextual fear, suggesting the involvement of non-dopaminergic mechanisms. It is possible that D2-like receptors mediate the effects of dopamine reuptake inhibitors on contextual fear conditioning. However, there is little evidence indicating that D2-like receptors are involved in the encoding of contextual fear. Different neuroleptics reduce or enhance contextual fear conditioning but these drugs also act on non-dopaminergic targets. Further research is needed to examine the role of D2-like receptor signalling in the encoding of contextual fear, along with the potential brain areas involved.

The neurophysiological mechanisms underlying dopamine regulation of contextual fear via D1-like receptor signalling remain to be fully elucidated. The encoding, retrieval and extinction of learned fear involve functional connectivity within the contextual fear circuit, which is mediated partly by synchronized theta oscillations. D1-like receptors in DH, BLA and mPFC regulate contextual fear conditioning and also modulate theta activity (Benchenane et al., 2011; Lorétan et al., 2004; Werlen & Jones, 2015). This raises the possibility of a causal link between D1-like receptor signalling, theta synchrony in this neural circuitry and contextual fear conditioning, although examining this directly requires further study. Dopamine modulation of this theta synchrony via D1-like receptors may also be involved in contextual fear extinction, which, again, needs to be examined in future studies. Synchronized theta oscillations in this circuit are thought to facilitate synaptic plasticity underlying contextual fear conditioning. D1-like receptor signalling modulates LTP in DH, BLA and mPFC (Li et al., 2011; Li & Rainnie, 2014; Lisman et al., 2011; Otani et al., 2015) but how this modulation is involved in different aspects of contextual fear conditioning remains to be determined. D1-like receptors in DH

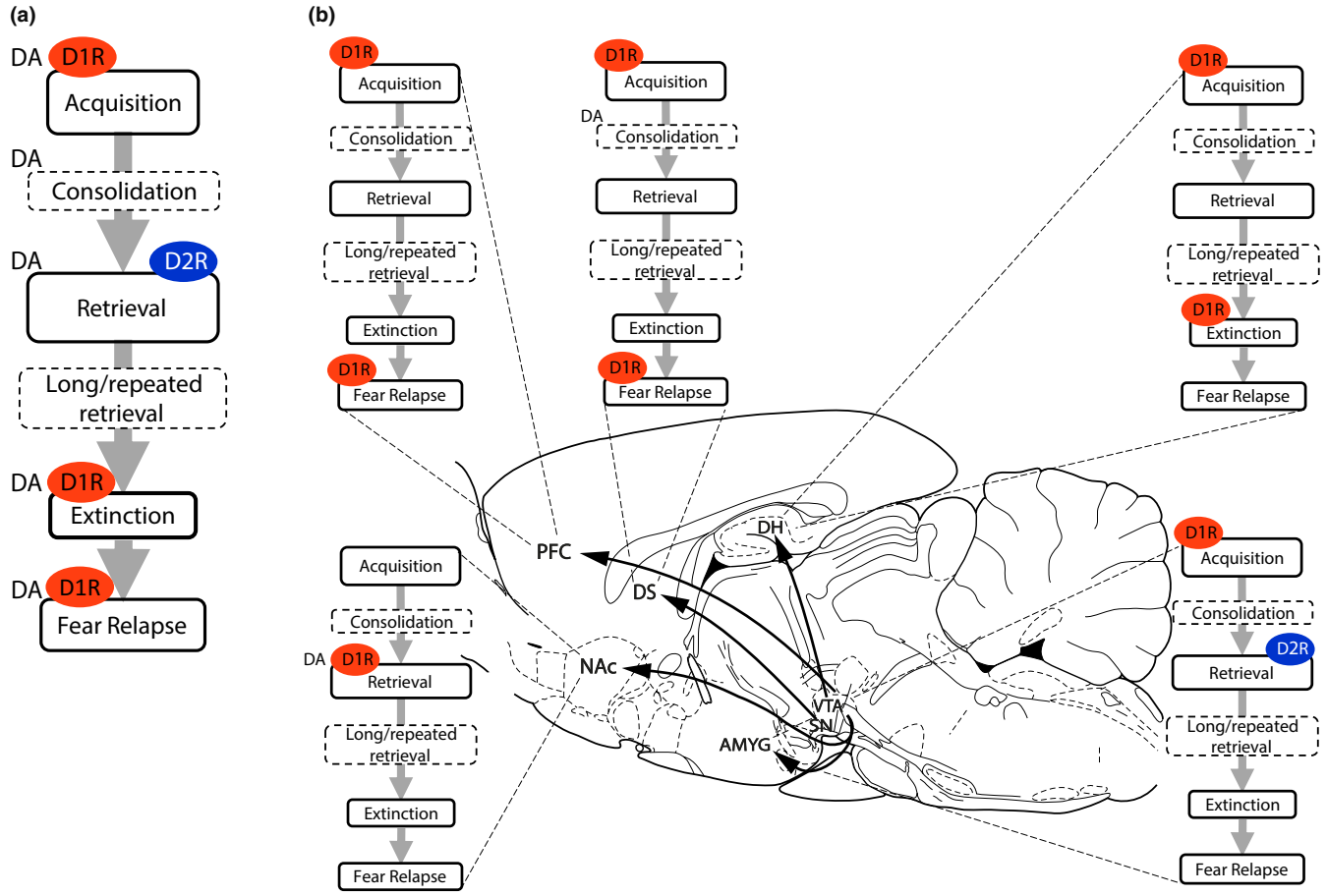

FIGURE 1 Summary of the signalling and brain mechanisms involved in dopamine regulation of contextual fear. (a) Schematic overview of the role of dopamine (DA) and its signalling via D1-like (D1R) and D2-like (D2R) receptors globally in regulating the different stages of contextual fear processing. (b) Dopamine projections to the main brain areas comprising the contextual fear circuit. The schematic inserts provide an overview of the role of DA, D1R, and D2R signalling in each brain area in regulating the different stages of contextual fear processing. DH, dorsal hippocampus; DS, dorsal striatum; NAc, nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area

may regulate encoding of the contextual representation given their role in spatial learning, although they might also be involved in encoding the context-US association. In BLA, dopamine was recently shown to encode the US representation during cued fear conditioning (Tang, Kochubey, Kintscher, & Schneggenburger, 2020), which may involve D1-like receptor modulation of plasticity mediated by somatosensory cortex input. D1-like receptors in BLA might also play a role in associating the context with the US during contextual fear conditioning by modulating plasticity mediated by converging hippocampal and somatosensory cortical input. In mPFC, D1-like receptors may modulate plasticity related to encoding the context representation and context-US association mediated by hippocampal and amygdala input (Jay et al., 2004; Onozawa et al., 2011). Plasticity underlying contextual fear extinction may also involve D1-like receptor signalling in this neural circuitry. Future studies are needed to address these various possibilities.

In terms of the translational relevance of such research, using dopaminergic pharmacotherapies to regulate contextual fear encoding or retrieval in the treatment of PTSD is unlikely to be feasible. The window for targeting fear memory consolidation after the traumatic event is limited, while chronic treatment with dopamine-acting drugs to suppress learned fear may have motor side effects and/or addictive potential. However, using such drugs acutely in combination with psychological therapies to enhance extinction and limit later fear relapse is a realistic opportunity that holds promise for treating PTSD in the future. Another possibility is to use dopaminergic drugs to target destabilization of the fear memory trace, such that the memory is weakened or updated to reduce or possibly even remove its aversive association before it is then reconsolidated in its modified form. While MPTP or D1-like receptor blockade was found to have no effect on the reconsolidation of contextual fear memory (Heath et al., 2015; Kinoshita et al., 2015), studies have shown that dopamine and D1-like receptor signalling play a role in the destabilization of other types of memory and allow for their disruption via the subsequent pharmacological impairment of reconsolidation (Flavell & Lee, 2019; Merlo et al., 2015; Reichelt,

Exton-McGuinness, & Lee, 2013; Rossato et al., 2014). Understanding how dopamine regulates memory destabilization is particularly relevant to trauma-related memories given that strong or persistent memories are thought to be resistant to disruption by reconsolidation impairment (Lee, 2009).

10 | CONCLUSION

Converging lines of evidence indicate that dopamine plays a key role in regulating contextual fear processing. Future studies employing chemogenetic, optogenetic and other contemporary neuroscience research techniques are needed to fully elucidate the underlying receptor signalling and neural circuit mechanisms. This research will inform our understanding of the general principles underpinning neuromodulation of associative learning and may also provide novel insights on potential new treatment approaches for anxiety-related disorders.

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

CS and CWS drafted and revised the paper and approved the final version.

DATA AVAILABILITY STATEMENT

Not applicable (this review reports no primary data).

ORCID

Christine Stubbendorff https://orcid.org/0000-0003-0888-6988

Carl W. Stevenson https://orcid.org/0000-0001-8143-8415

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