Neuroscience and Biobehavioral Reviews 131 (2021) 1037–1055

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Environmental certainty influences the neural systems regulating responses to threat and stress

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ARTICLE INFO

Keywords:
Threat
Safety
Stress
Predictability
Controllability
Neural circuits

ABSTRACT

Flexible calibration of threat responding in accordance with the environment is an adaptive process that allows an animal to avoid harm while also maintaining engagement of other goal-directed actions. This calibration process, referred to as threat response regulation, requires an animal to calculate the probability that a given encounter will result in a threat so they can respond accordingly. Here we review the neural correlates of two highly studied forms of threat response suppression: extinction and safety conditioning. We focus on how relative levels of certainty or uncertainty in the surrounding environment alter the acquisition and application of these processes. We also discuss evidence indicating altered threat response regulation following stress exposure, including enhanced fear conditioning, and disrupted extinction and safety conditioning. To conclude, we discuss research using an animal model of coping that examines the impact of stressor controllability on threat responding, highlighting the potential for previous experiences with control, or other forms of coping, to protect against the effects of future adversity.

1. Introduction

Appropriate responding to threats is critical for adaptive behavior. This process involves two distinct, yet highly interrelated processes: identifying *sources* of danger and identifying *the absence* of danger (i.e., safety). The key to generating an appropriate response lies in estimating the likelihood that a certain stimulus or environment predicts a threat along with a scalable estimation of how harmful the outcome may be if the threat is faced. Based on these estimations, an individual can engage a behavioral response that will minimize the likelihood of interacting with a threat while also maintaining other goal-directed behaviors (e.g., exploring the environment, collecting resources, or interacting with social partners). Importantly, these estimations must also be flexible, as the likelihood of encountering a threat readily fluctuates alongside changes in the surrounding environment. This process, which we refer to here as 'threat response regulation' (Box 1), is accomplished through a variety of strategies, relying on distinct, but overlapping, neural circuitry.

A critical factor in determining circuit recruitment in response to a potential threat is the "predictability" of danger, which refers to the strength of the relationship between a stimulus and a threat (i.e. an aversive outcome). For example, during extinction, a stimulus previously predictive of threat (strong stimulus-threat association) comes to be associated with relative safety after repeated presentations in the absence of threat (weak stimulus-threat association). Because of the history of the same stimulus to have both strong and weak associations with threat, the meaning of the extinguished threat stimulus with regard to how safe the animal is can be ambiguous, or *unpredictable*, particularly in certain settings including a change in context, the passage of time, or re-exposure to the initial aversive outcome (Bouton, 1993; Konorski, 1967; Pavlov, 1927). In contrast, a discriminated safety cue is a stimulus separate from a threat-associated cue that has never been paired with an aversive outcome. As a result, such a cue has high predictability for safety.

The degree of predictability of a threat influences which neural circuits are recruited for determining the most appropriate behavioral response to the challenge at hand. When a threat is encountered, animals (human and non-human alike) can exhibit a broad repertoire of active

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https://doi.org/10.1016/j.neubiorev.2021.10.014
Received 1 April 2021; Received in revised form 29 September 2021; Accepted 1 October 2021
Available online 18 October 2021

and passive behaviors. Each type of response involves distinct neurobiological processes, and importantly, influences future responses to the same or similar threats and threat-associated cues. For instance, studies have found that permitting the animal to predict or control elements related to receipt of an aversive stimulus alters subsequent physiological, hormonal and behavioral responses (Abelson et al., 2008; Levine, 2000; Maier and Seligman, 2016; Weiss, 1972). Moreover, recent evidence indicates that engagement in active or passive threat responses differentially affects the long-term ability to regulate fear (e.g., Gruene et al., 2015).

In this review, we discuss the neural systems that mediate how organisms respond to threats in the framework of how the predictability of danger recruits differential circuitry, thus producing distinct behavioral responses. We also discuss how experiential factors, specifically stress exposure, alters threat response regulation to the point that it overpredicts threat. Finally, we extend the concept of predictability in the domain of stress exposure to include controllable versus uncontrollable stressors, noting that previous experiences with control or other forms of coping promotes a broad protection against the effects of future adversity (Fig. 1).

2. Neural systems of threat response regulation

Given that a fast and accurate threat response regulation system is essential for survival, it should not be surprising that a conserved neural system that is both integrative and swift has evolved within mammals. Unique roles in generating and regulating threat responses have been attributed to areas such as the thalamus, hypothalamus, periaqueductal gray (PAG), amygdala, hippocampus, and prefrontal cortex (PFC). For an extensive review of how these regions are connected to orchestrate a threat response we direct readers elsewhere (e.g., Janak and Tye, 2015; Pape and Pare, 2010; Sotres-Bayon and Quirk, 2010). Here, we briefly overview the neural circuitry underlying the generation and suppression of responses to learned threat cues. The recruitment of this circuitry relies in great part on the external environment of the animal. Thus, embedded into the review of literature detailing the neural circuitry is a discussion of environmental factors that mediate neural circuit engagement and resultant threat responding. In particular, we emphasize how variability in the predictability of threat plays into specific circuit recruitment. Our review focuses on findings that have examined the *cessation* of overt behavior in the presence of a threat-associated cue (e.g., freezing or conditioned suppression in response to conditional stimuli (CSs) associated with a threat (unconditional stimulus, US)). Nonetheless, as discussed elsewhere (Diehl et al., 2019; Rodriguez-Romaguera and Quirk, 2017; Sangha et al., 2020), threat response regulation can also engage active avoidance behaviors in response to threat-associated cues (i.e. CS-US association).

The ability to predict threat in response to a sensory cue relies on associative learning processes. Briefly, sensory information from these cues is relayed to the thalamus, which then projects to the lateral nucleus of the amygdala (LA). The dorsal midline thalamus (Li et al., 2004; Padilla-Coreano et al., 2012) and particularly the paraventricular nucleus of the thalamus (PVT) (Li et al., 2014) are highly interconnected with the basal (BA) and central (CeA) nuclei of the amygdala as well as the PFC and have been emphasized for playing a role in regulating conditioned fear. The LA also receives somatosensory information regarding stimuli such as footshocks, thus contributing to learning the association between cue and threat. The LA projects to the BA, an amygdala region particularly rich in projections to and from several other corticolimbic regions involved in valence encoding and which is often described as an integration hub within the amygdala (reviewed in Janak and Tye, 2015). In turn, BA projects to both the lateral and medial portions of the CeA (Pape and Pare, 2010). Additionally, both the LA and BA, as well as the PFC, have projections to the GABAergic intercalated cells (ITCs) of the amygdala (Pape and Pare, 2010). These cells send projections to the CeA and can regulate its output, which is primarily served by the medial CeA.

Whereas many studies have focused on the role of the basolateral amygdala (BLA) in the acquisition of stimulus-threat associations (CS-US association), commonly using the laboratory paradigm "fear conditioning", more recent work suggests that the CeA is also important in this regard. Interestingly, a subpopulation of GABAergic cells in the lateral CeA shows inhibition to a threat-associated stimulus while another subpopulation shows excitation (Ciocchi et al., 2010), a distinction that appears to correspond to the presence or absence of protein kinase C (PKC) delta, respectively (Haubensak et al., 2010). These PKC delta neurons provide tonic inhibition over medial CeA output, and this inhibition is removed during threat cue presentations. In contrast, cells lacking PKC delta (CeA somatostatin-expressing neurons) are excited by threat-associated cues and subsequently drive the medial CeA output that supports threat responding. Together, these findings indicate that valence-defined subpopulations of neurons within the lateral CeA may regulate the excitability of the medial CeA, influencing responding to threat-associated cues. As the next step in the circuit, projections from the medial CeA to the hypothalamus contribute to the integration of innate and learned fear while projections to the PAG contribute to

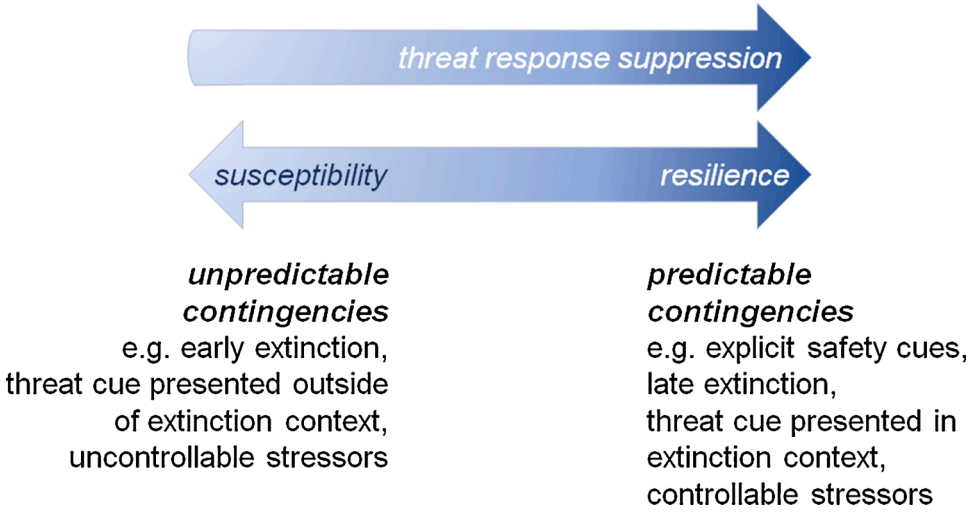

Fig. 1. The flexible calibration of threat responding in accordance with the surrounding environment is a critical feature of adaptive behavior. Integral to this process is a determination of the "predictability" of threat (i.e., the strength of the relationship between a threat-predictive stimulus and an aversive outcome). Similarly, in the domain of stress, experience with controllable or uncontrollable stressors can impact the later resilience or susceptibility (respectively) to adversity.

expression of freezing and suppression of ongoing motivated behaviors (Gross and Canteras, 2012). The extent to which predictability contributes to CeA output is yet to be established. Additional research is necessary to examine whether an absence of neuronal inhibition by the lateral CeA is sufficient to trigger threat response regulation, or if instead CeA neurons actively engage circuitry related to explicit safety.

The primary objective of the threat response system is survival and harm reduction, and the system is highly effective in generating a fast response to reflexively eliminate exposure to threat. Following the initial associative learning process, the threat response system is biased towards generalization of responses to stimuli similar to the original, threatening stimulus. Deploying attentional resources and engaging in threat responding can be adaptive as it allows an animal to avoid harm during encounters that parallel those that have had negative outcomes in the past. However, a balance must be struck between generalization and discrimination of features in the environment that indicate that the anticipated threat will not be encountered. This discrimination is highly influenced by experience, context, and the passage of time since initial associative threat learning took place. Each of these factors greatly impacts how predictable an outcome of threat is, and thus, influences threat responding.

2.1. Extinction and safety conditioning

Two types of responses that involve discrimination that we will consider below are extinction and safety conditioning. Although both methods serve to effectively reduce learned threat responding, they do not necessarily entirely overlap in their mechanisms (Fig. 2).

Extinction is the most common method in both the laboratory and clinic to address inappropriate threat responding. CSs are presented without an aversive outcome (i.e., US) and the goal is that, over repeated trials of CS-noUS exposures, threat responding to the CS will decline (Fig. 2). During extinction learning, the potential for threat is highly unpredictable due to the conflict between expectation (US) and actual experience (no US). This could result in a negative prediction error being created to support learning the CS-noUS association (reviewed in McNally et al., 2011). As training progresses, two additional things occur that impact predictability in favor of threat response suppression. First, the animal likely experiences a greater number of trials where the US does not occur (extinction) than trials where the US occurs (fear conditioning). Second, the more recent experience is with trials where the US does not occur. Both factors seem to be limited to reducing threat responding during extinction learning because with the passage of time, the initial threat association often re-emerges as behaviorally prepotent (Bouton, 1993; Goode and Maren, 2014). In addition, threat responding measured subsequent to extinction is highly contingent upon the similarity between the present context and the context in which extinction took place (Bouton, 1993; Bouton et al., 2021; Goode and Maren, 2014). Testing in the context where the threat was originally encountered, or a novel context distinct from the extinction context, often results in

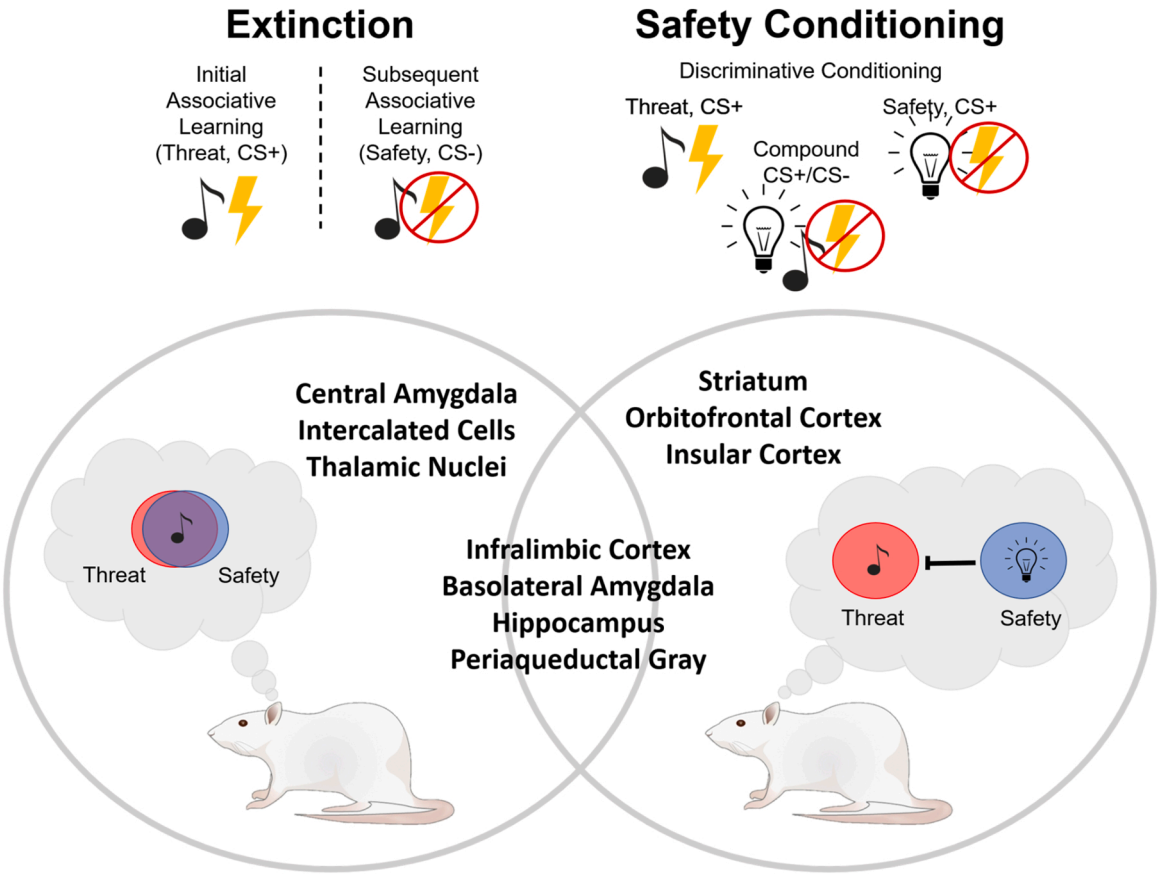

Fig. 2. Extinction and safety conditioning are two methods that effectively serve to reduce learned threat responding. During extinction **(left)**, cues associated with threat (i.e., conditional stimuli, CSs) are presented without an aversive outcome (i.e., unconditional stimulus, US). Threat responding to the CS declines over repeated CS-noUS trials. However, an extinguished CS maintains the initial aversive CS-US association and the recall of the CS-noUS or the CS-US memory is highly dependent on contextual cues and the passage of time since extinction training. Safety conditioning **(right)** occurs when independent threat (CS+) and safety (CS-) cues are presented at the same time and threat responding is reduced in the presence of the safety cue compared to the threat cue alone. A safety cue trained in this manner provides a highly predictable outcome that the threat is absent. Extinction and safety conditioning recruit both overlapping and distinct neural circuitry, indicating that while some regions may play a general role in threat response suppression, others may respond specific to the associative structure under which threat response regulation is learned.

increased threat responding relative to the extinction context.

In contrast, inhibition of threat responding during safety conditioning occurs when a safety cue is explicitly unpaired to an aversive outcome (CS-), while a threat cue is paired to an aversive outcome (CS+). Some studies use separate groups of subjects that learn *either* the CS- or CS + association, while others examine *both* CS- and CS + associations within the same subjects (reviewed in Sangha et al., 2020). Within studies that investigate discrimination between the CS + and CS-, a subset of them also present the threat-associated and safety-associated cues at the same time as a compound cue to examine how threat responding is reduced in the presence of the safety cue compared to the threat cue alone (e.g. Greiner et al., 2019; Meyer et al., 2019, 2021) (Fig. 2). A subset of these safety conditioning paradigms qualify as paradigms producing conditioned inhibition if they can show the CS- can pass both summation and retardation tests as outlined by Rescorla (1969) (e.g. Foilb et al., 2016; Meyer et al., 2021). In each case, though, the intent is to produce inhibition of threat responding to a learned safety cue. Similar to extinction, it is possible a negative prediction error could be elicited early in safety conditioning, facilitating the association of safety with the cue. Ultimately, a successfully extinguished cue and a learned safety cue would produce a negative prediction between cue and threat (US). However, in contrast to extinction learning, where the same stimulus acquires threat and safety meanings, a safety cue has meaning solely related to safety (including the high probability that threat is absent and the affective experience of safety). Thus, the safety cue provides a highly predictable outcome that the individual is safe.

2.2. Neural systems underlying extinction and safety conditioning

Past research on the neural basis for threat response regulation has emphasized the importance of a reciprocally connected tripartite circuit comprising the amygdala, PFC and hippocampus, largely in the context of extinction (for review, see Bouton et al., 2021; Morrison and Ressler, 2014; Myers and Davis, 2002; Orsini and Maren, 2012; Sangha et al., 2020; Sotres-Bayon and Quirk, 2010; Yousuf et al., 2020). More recently though, investigation into other aspects of threat response regulation, such as safety conditioning and threat unpredictability, has revealed the involvement of other contributors, such as the striatum (Ray et al., 2020; Rogan et al., 2005), PAG (particularly the ventral columns; Arico et al., 2017; Assareh et al., 2017; Carrive et al., 1997; Fanselow, 1994; McNally et al., 2011; Vianna et al., 2001; Walker et al., 2020; Wright and McDannald, 2019), the paraventricular nucleus of the thalamus, and the bed nucleus of the stria terminalis (BNST) (Goode et al., 2019, 2020; Ressler et al., 2020). Below, we highlight both overlapping and distinct neural circuits with notable roles in extinction and safety conditioning.

The PFC has by far received the most attention with regard to a facilitatory role in threat response regulation. In particular, the infralimbic (IL) region of the medial PFC (mPFC) has been highlighted as having a role in suppressing threat responding (Sotres-Bayon and Quirk, 2010). Optogenetic activation of IL reduces freezing during extinction (Do-Monte et al., 2015) and electrical stimulation of IL during a CS reduces freezing in non-extinguished rats (Milad et al., 2004; Milad and Quirk, 2002). In a thorough examination of regional contributions to extinction learning, Sierra-Mercado et al. (2011) found that IL inactivation disrupted within-session extinction learning (Sierra-Mercado et al., 2011). Disrupting IL activity prior to extinction also results in higher levels of freezing during an extinction retention test, suggesting that an intact IL is necessary to form an extinction memory (Morgan and LeDoux, 1995; Quirk et al., 2000; Sierra-Mercado et al., 2006, 2011). IL sends glutamatergic projections to a number of regions within the amygdaloid complex and is thought to mediate the suppression of conditioned threat responding by targeting the inhibitory ITC masses and/or the basomedial region (BMA; see discussion by Giustino and Maren, 2015). IL activation (e.g., pharmacological, optogenetic) activates these downstream targets, and IL stimulation inhibits CeA output neurons and reduces threat responding (Adhikari et al., 2015; Berretta et al., 2005).

On the other hand, evidence suggests that inactivation of the prelimbic (PL) region of the mPFC, the dorsal neighbor of IL, disrupts threat responding in the form of freezing, though such inactivation does not disrupt the formation of an extinction memory (Sierra-Mercado et al., 2011). Further supporting the opposing nature of the IL and PL in threat response regulation, Giustino et al. (2016) found that differential firing in PL versus IL predicts freezing behavior such that greater PL activity relative to IL activity correlates with higher freezing (Giustino et al., 2016). Moreover, IL neurons projecting to the BLA (Bloodgood et al., 2018; Bukalo et al., 2015; Knapska et al., 2012) and BMA (Adhikari et al., 2015) support extinction processes, whereas PL (Dejean et al., 2016; Fitzgerald et al., 2014) and reciprocal connectivity between PL and BLA (Burgos-Robles et al., 2009; Karalis et al., 2016; Senn et al., 2014) have been implicated in threat responding to the detriment of extinction.

Interestingly, changes in prefrontal intrinsic excitability occur following extinction. For example, evidence suggests that excitability of BLA-projecting IL neurons increases following extinction in mice (Bloodgood et al., 2018). In contrast, other work found that extinction does not increase IL excitability relative to baseline but reverses the diminished IL excitability observed following fear conditioning (Santini et al., 2008). Furthermore, Santini et al. also found that extinction recall correlates with burst spiking in IL neurons. The observed changes in IL excitability are often interpreted with regard to the important role that IL plays in extinction learning and memory. Thus, an intriguing possibility is that the ramping of activity in this circuit may scale with the increased predictability that threat will *not* occur.

Limitations in threat response regulation have been linked to lower markers of activity in IL. Indeed, reduced immediate early gene expression in IL has been observed alongside disrupted extinction learning in a line of rats bred for high anxiety (Muigg et al., 2008). Following extinction training, failure to retrieve an extinction memory in the form of spontaneous recovery is associated with depressed intrinsic IL excitability relative to elevated post-extinction levels (Cruz et al., 2014). Evidence also suggests that a strain of mouse with poor extinction learning and retention (129S1) has reduced immediate early gene (c-Fos and Zif268) expression in IL and BLA following extinction recall relative to canonical wild type (C57BL/6 J) mice (Hefner et al., 2008), supporting the link between IL-BLA functional activity and threat response regulation. Similarly, prior work found that chemogenetic inhibition of IL-BLA neurons during extinction training impairs subsequent extinction retrieval (Bloodgood et al., 2018).

Evidence also suggests that the BLA plays a key role in extinction. Indeed, although BLA inactivation reduces freezing during extinction, such inactivation leads to higher freezing on a subsequent extinction retention test, indicating disruptions to extinction learning (Sierra--Mercado et al., 2011). NMDAR-mediated plasticity in the amygdala appears to be especially important for extinction learning (Walker and Davis, 2002). Intra-amygdala infusion of d-cycloserine, a partial NMDAR agonist, improves extinction learning (Falls et al., 1992), whereas intra-amygdala infusion of the NMDAR antagonists 2-amino-5--phosphonovaleric acid (AP5) (Falls et al., 1992) or phosphatidylinositol 3-kinase (PI3K) (Lin et al., 2003) disrupts extinction learning. Similarly, intra-amygdala infusion of ifenprodil, which selectively blocks the NMDAR subunit NR2B, also impairs extinction learning as well as extinction recall (Sotres-Bayon et al., 2007). In addition, following fear conditioning, calcium-permeable α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors (AMPARs) increase at thalamic synapses in LA (Clem and Huganir, 2010). Subsequently, removal of calcium-permeable AMPARs has been shown to mediate the strong extinction learning (akin to erasure) that occurs in a reconsolidation update protocol, when one threat stimulus is presented shortly (10 min to 6 h) before extinction training (Clem and Huganir, 2010). This molecular mechanism is believed to reflect a means to reduce threat responding in the absence of cortical regulation. Thus, though evidence

suggests an important role for the BLA in promoting fear conditioning and its expression, it is clear that plasticity within the BLA also supports the extinction of such conditioning.

Adjacent to the BLA, recent evidence has highlighted ITC neurons of the amygdala for their role in balancing threat responding and its inhibition, through opposing contributions of dorsal and ventral ITC clusters (Hagihara et al., 2021). Hagihara et al. found that ventral ITC neurons increase responsivity as extinction progresses and their suppression disrupts both extinction learning and extinction retrieval, while activation facilitates extinction retrieval. The opposite effects were seen following manipulation of activity in dorsal ITC neurons. Notably, a bidirectional, inhibitory relationship is seen between the two clusters, supporting the theory that these neurons contribute to the interplay of calibrating threat responding. Dorsal and ventral ITC clusters also differentially modulate activity in other fear circuitry components, consistent with their opposing roles in threat responding. In particular, ventral clusters provide inhibitory regulation over PL-projecting BLA neurons and ventrolateral PAG (vlPAG)-projecting CeA neurons, while dorsal clusters target IL-projecting BLA neurons.

Pathways from the PFC to the amygdala via thalamic nuclei have also been identified as playing a role in fear extinction learning and retrieval (Ferrara et al., 2021; Ramanathan et al., 2018; Tao et al., 2021). One study using c-FOS analyses and bi-directional chemogenetic manipulations found that an IL-PVT-amygdala circuit positively mediated extinction retrieval (Tao et al., 2021). Another study found that optogenetic suppression of projections from the medial geniculate nucleus to the BLA decreased fear during extinction learning, an effect that persisted during a later retrieval test in the extinction context, though fear returned in both the conditioning context and a novel context (Ferrara et al., 2021). Finally, chemogenetic suppression of projections from the mPFC to the thalamic nucleus reuniens disrupted extinction learning and retrieval in the extinction context (Ramanathan et al., 2018). These studies suggest a strong and complementary role of thalamic nuclei to reinforce and possibly fine-tune prefrontal and amygdala based mechanisms for responding to threat.

Following extinction, there are "threat" and "safety" neurons coexisting within the same regions. For example, within the BLA, "extinction" neurons have been reported (Herry et al., 2008). These neurons are unresponsive to a threat-associated cue before extinction, but with extinction training, and as fear subsides, these neurons become increasingly responsive to the extinguished threat cue. Moreover, during an extinction retention test, silencing "extinction" neurons (those active during extinction learning) promotes the spontaneous recovery of threat responding, whereas silencing "threat" neurons (those active during initial CS-US conditioning) decreases threat responding (Lacagnina et al., 2019). The authors also found that stimulation of the same populations produces the opposite effect. Additional work is necessary to establish which environmental and neurobiological factors determine which populations of neurons will be called to action. It may be the case that valence-differentiated populations of neurons in the same region exhibit differential connectivity (Beyeler et al., 2016; Meyer et al., 2019; Senn et al., 2014; Shpokayte et al., 2020). For example, previous work has linked projection-defined sub-populations of neurons in the basal amygdala to threat responding (PL-projecting) or extinction (IL-projecting) processes (Senn et al., 2014). Similarly, evidence suggests differentiable roles for ventral hippocampal neurons, with those projecting to PL, but not those projecting to IL or BLA, correlating with safety conditioning (Meyer et al., 2019).

Context is another factor that plays an integral role in mediating threat responding, particularly in terms of determining extinction recall. Context appears to gate threat or safety responding by acting as an "occasion setter" for CS-US relationships (Bouton, 1993). As a consequence, after extinction training, the predictability of threat will be weak in the extinction context, but strong in the fear conditioning context or a novel context. Maren et al. reported that specific neuronal populations in the amygdala exhibit increased activation to the fear conditioning context, whereas IL neurons are more responsive to the extinction context (Knapska and Maren, 2009; Orsini et al., 2013). Notably, this effect appears to be specific to rats that have undergone extinction, as rats that did not undergo extinction training exhibited greater amounts of overlapping cells reactive to both contexts (Orsini et al., 2013). Although the authors did not observe differences in the hippocampus in these studies, previous work from the same laboratory suggests that amygdala-projecting hippocampal neurons are preferentially activated in the fear conditioning context (Orsini et al., 2011). This is in line with much other work highlighting context-dependent recruitment of hippocampal circuitry following extinction (Maren et al., 2013). Indeed, hippocampal inactivation disrupts the return of fear that commonly occurs when an animal is exposed to the original fear conditioning context (i.e., renewal) (Hobin et al., 2006; Maren et al., 2013; Maren and Holt, 2000; Preston and Eichenbaum, 2013). Additional work indicates that this role of the hippocampus involves communication with the amygdala and PFC (Knapska and Maren, 2009; Orsini et al., 2011; Wang et al., 2016), in some cases with the same hippocampal neurons projecting to both regions (Jin and Maren, 2015). A recent study by Marek et al. (2018) provided a mechanism for this effect, indicating that fear renewal is mediated by ventral hippocampal inhibition of amygdala-projecting neurons in the IL (Marek et al., 2018). They further found that the ventral hippocampus inhibits IL neurons through a specific class of parvalbumin-positive interneurons.

A growing literature in rodents has begun to delineate the neural correlates of safety conditioning (Foilb and Christianson, 2018; Kong et al., 2014; Krueger and Sangha, 2021; Sangha et al., 2020). Similar to extinction, safety cues have been associated with reduced activity in the amygdala (Genud-Gabai et al., 2013; Kazama et al., 2012; Ng et al., 2018; Ostroff et al., 2010). Reports of convergence of circuitry between safety conditioning and extinction have found that a subset of BLA neurons that were responsive to explicit safety cues also developed a similar response to an extinguished threat cue as extinction progressed, highlighting overlapping neuronal ensembles for safety conditioning and extinction within the amygdala (Sangha, 2015; Sangha et al., 2013). However, the circuitry involved in safety cue learning also diverges markedly from that necessary for extinction. For example, unique contributions of the striatum to the modulation of amygdalar responses to a threat context have been observed during safety cue presentations (Rogan et al., 2005). In addition, the posterior insular cortex is necessary for the development of a safety cue (Christianson et al., 2008a, 2011; Foilb et al., 2016). Subsequently, when threat and safety cues are presented together, a key role has been identified for the ventral hippocampus and its communication with the PL for the implementation of safety conditioning, a finding detailed in neural circuitry in the mouse brain and paralleled by functional neuroimaging in humans (Meyer et al., 2019).

At a larger level, whereas safety conditioning involves a strong negative association that a safety cue predicts the absence of threat (i.e., a highly predictable CS-no US outcome), this predictability is typically attained following substantial training in which a safety cue is presented in the explicit absence of a US. For example, explicit unpairing may be accomplished by contrasting the safety cue with either a threat cue (i.e., a cue that is paired with an aversive US) or a threatening context (i.e., a context in which the animal has experienced US exposures but with ample temporal separation between presentations of the US and presentations of the safety cue) (Foilb and Christianson, 2018; Wagner and Rescorla, 1972). Because of this contrast, safety training is often referred to as discriminative conditioning. Only when a strong predictive relationship between the CS- and the absence of threat has been established can the CS- serve as an effective safety cue. After safety training, the IL, but not the PL, is important for discriminating between cues signaling threat versus safety during recall (Sangha et al., 2014). The ventrolateral orbitofrontal cortex has also been implicated in recalling the meaning of the safety cue, with damage to this structure resulting in reduced discrimination between threat and safety cues (Sarlitto et al., 2018).

In concert with the tripartite system of the PFC, amygdala, and hippocampus, contributions from several other brain regions are necessary to tailor threat responding based on dynamic environmental information. The nucleus accumbens has recently emerged as having an important role in the scaling of threat responding as a result of threat predictability (Ray et al., 2020). Ray et al. found that nucleus accumbens core lesions reduce discrimination between distinct auditory cues that predict footshocks at probabilities of 1, 0.25, or 0 in rats. Optogenetic inhibition of the nucleus accumbens core subsequent to discrimination training abolishes the ability to discriminate uncertain threat (footshock probability of 0.25) from safety (footshock probability of 0) (Ray et al., 2020).

PAG has been shown to play a role in threat and safety prediction (Arico et al., 2017; Assareh et al., 2017; Carrive et al., 1997; Fanselow, 1994; Vianna et al., 2001; Walker et al., 2020; Wright and McDannald, 2019), perhaps facilitated by inputs from the amygdala (Dejean et al., 2015; Fanselow, 1994; Tovote et al., 2015; Walker et al., 1997). In a recent study performing single unit recordings from vlPAG, Wright and McDannald (2020) found neural responding scaled to the degree of threat. Neurons were most responsive during presentations of a threat-associated stimulus (always followed by a footshock), least responsive to a safety stimulus (never followed by a footshock), and showed intermediate responsiveness to an uncertain stimulus (followed by a footshock 37.5 % of the time). Notably, neural activity was more directly linked to threat probability than the overt expression of fear (conditioned suppression). Other work has suggested that vlPAG may play a role in signaling the temporal proximity of danger. Indeed, one sub-population of vlPAG neurons shows a strong onset-locked responsivity to threat-associated stimuli (Ozawa et al., 2017; Tovote et al., 2016; Watson et al., 2016; Wright and McDannald, 2019), while a distinct subpopulation ramps activity leading up to shock delivery (Wright and McDannald, 2019).

Neural activity in vlPAG has also been linked to prediction error signaling (Cole and McNally, 2009; Johansen et al., 2010; McNally et al., 2011; McNally and Cole, 2006; McNally and Westbrook, 2006; Ozawa et al., 2017; Walker et al., 2020). Walker et al. (2020) found that vlPAG activity related to shock delivery was elevated to uncertain stimuli relative to threat-associated stimuli, despite the physical experience of the shock delivery being identical. Moreover, the authors found that optogenetic inhibition of vlPAG around the shock delivery following uncertain stimuli diminishes later threat responding to these stimuli. Together, the authors make a strong case for the role of vlPAG in updating threat predictability via prediction error signaling.

2.3. Sex as a biological variable impacting extinction and safety conditioning

Recent research on the neural mechanisms of threat response regulation has disproportionately focused on male subjects (Shansky, 2015), making it difficult to conclude whether and to what degree the above circuitry and behavioral observations apply to females. We do know that female mice display greater fear generalization to novel and safe contexts compared to males, which correlates with increased activity within the BLA (Keiser et al., 2017). In cued paradigms, it appears, overall, that females and males perform similarly in discriminating threat from safety, though females seem to show consistent deficits in suppressing fear when threat and safety cues are presented together compared to males (reviewed in Krueger and Sangha, 2021). However, it is important to point out that it is too early to make broad generalizations given the general lack of inclusion of female subjects in studies of threat response regulation. For example, Foilb et al. have shown that females show greater threat versus safety cue discrimination than males and this behavioral difference may be correlated with differences in activity within the CeA and BNST (Foilb et al., 2018, 2021). In addition, neither males nor female mice bred for high alcohol preference showed significant safety conditioning unless subjected to a juvenile stressor (Müller et al., 2021). It is possible that males and females may have different thresholds for generalizing and estimating, or scaling, threat, with females more likely to have a lower threshold for threat responding. From an evolutionary perspective, this may be adaptive for sexually differentiated reproductive, gestational, and/or maternal behavior (Carter et al., 2001). Notably, estradiol levels markedly affect threat responding in females. Studies in female rats, and parallel studies conducted in humans, found that states of high estrogen are associated with facilitated extinction (Zeidan et al., 2011). Estradiol fluctuations also correspond to altered cortico-amygdala functional activity. In female rats, estradiol administration immediately following extinction learning increases functional activity in IL and decreases functional activity in the amygdala, an effect linked to facilitated consolidation of the extinction memory (Zeidan et al., 2011). Interestingly, inhibiting estrogen production by using hormonal contraceptives in both healthy women and female rats resulted in poor extinction recall (Graham and Milad, 2013). Moreover, inhibiting estradiol synthesis in male rats also impaired extinction recall (Graham and Milad, 2014). There is evidence to suggest that sex differences also emerge when considering the impacts of stress on threat response regulation (e.g., Baran et al., 2009; Schroeder et al., 2018), though substantial further research in this area is necessary, including validation of stress paradigms for use in female subjects (Lopez and Bagot, 2021).

The lifetime prevalence of anxiety disorders is markedly higher for women, and women often experience an increased intensity of symptoms (Kessler et al., 2005). A crucial caveat to note is that investigations of the impact of sex on psychiatric disease progression in non-human animal models are limited to biological sex, leaving a need to consider the influences of gender in human work that go beyond purely biological influences (e.g., Eliot et al., 2021; Polderman et al., 2018). Thus, in addition to being a critical area of additional research for basic science advancements, consideration of sex as a biological variable, and gender identity, in the invesitgation of threat response regulation has important implications for understanding and treating psychiatric disease.

3. The impacts of stress on threat response regulation

In this section we discuss evidence showing that exposure to stress can enhance fear conditioning and interfere with processes that support threat response regulation, such as extinction and safety conditioning. Also apparent following stress exposure are dramatic changes in the circuitry outlined above, particularly PFC and amygdala (for additional details, see (Deslauriers et al., 2018; Maren and Holmes, 2016; McEwen and Morrison, 2013; Stockhorst and Antov, 2016; Wellman and Moench, 2019). Structural changes at circuit and synaptic levels can alter how threat stimuli are processed and how responses are regulated. It may be that stress inflates the calculation of threat probability, leading to generalized fear and susceptibility to stress disorders (Fig. 1). At the level of discussion here, studies using stress exposure typically assess the effects of unpredictable and uncontrollable stressors on subsequent fear conditioning. A more detailed discussion of predictability and controllability of stressors is included in Section 4.

3.1. Stress and glucocorticoids prime neural circuits for threat responding

The effects of stress on threat responding have in many cases been linked to altered signaling in prefrontal regions in both rodents and humans, largely supporting the role of IL in extinction efficacy discussed in the rodent studies above. Recordings from the PFC have shown that while control mice exhibit decreased PL and increased IL activity following extinction, stressed counterparts show neither of these effects (Wilber et al., 2011). Other studies have also shown prefrontal dendritic remodeling in pyramidal neurons in rats following both one week (Brown et al., 2005) and three weeks (Cook and Wellman, 2004; Liston et al., 2006; Radley et al., 2004) of restraint stress. Repeated stress also decreases dendritic spine density and volume of individual spines

(Radley et al., 2008), likely through non-transcriptional and canonical signaling pathways involving activation of glucocorticoid receptor/LIM kinase-cofilin pathway and mineralocorticoid receptor, respectively (Liston et al., 2013). The PFC appears to be highly susceptible to even brief stress exposure. Application of single prolonged stress diminished prefrontal excitatory tone in rats (i.e., glutamatergic and glutaminergic signaling; Knox et al., 2010), whereas just one episode of swim stress induced retraction of dendrites on IL neurons in mice (Izquierdo et al., 2006). Notably, reductions in prefrontal activity occurred alongside increased sensitivity in the amygdala, reflected in spinogenesis (Maroun et al., 2013; Mitra et al., 2005) and elevated immediate early gene response (Hoffman et al., 2014; Toledo-Rodriguez et al., 2012). In addition, exposure to elevated platform stress has been shown to cause a shift in cortico-amygdala plasticity, such that activation of IL induces long term potentiation, but not long term depression, in downstream BLA neurons (Maroun, 2006). The result appears to be a compounded disruption to dynamics of cortico-amygdala circuitry that facilitate threat response regulation in non-stressed mice.

Additional evidence suggests that glucocorticoids are capable of recapitulating many of the impacts of stress exposure on brain and behavioral function. Similar effects on this circuitry, as well as disruptions to extinction, are observed following enhancements in basal corticosterone levels (e.g., after administration of high levels in the drinking water) (Gourley et al., 2009, 2013). Three weeks of corticosterone administration produced dendritic remodeling (Wellman, 2001), and long-lasting dendritic spine morphological changes (Anderson et al., 2016), similar to that seen following repeated stress exposure. Time lapse imaging studies have further revealed that long-term exposure to glucocorticoids leads to increased dendritic spine elimination, rather than diminished formation (Liston et al., 2013; Liston and Gan, 2011).

Glucocorticoid activity seems to prime brain regions to respond to salient features of their environment allowing both threat responding and threat response regulation to take place (de Quervain et al., 2017). Much of this work has focused on the role of glucocorticoids in memory enhancement during the post-training phase after initial acquisition (e.g., McGaugh, 2000; McGaugh and Roozendaal, 2002; Roozendaal et al., 1996) or extinction training (Berlau and McGaugh, 2006), given the expected time course of endogenous increases in glucocorticoid levels in the aftermath of a threat exposure (Cordero et al., 1998). Nevertheless, exposure to acute stress, or administration of corticosterone (and other glucocorticoid receptor agonists) may also facilitate the extinction of threat responding (Barrett and Gonzalez-Lima, 2004; Cai et al., 2006). For example, extinction learning was disrupted in mice receiving systemic injections of metyrapone, a corticosteroid synthesis inhibitor, yet this disruption was rescued by administering corticosterone immediately following extinction (Clay et al., 2011). In addition, extinction was facilitated in rats receiving either systemic or intra-amygdala injections of glucocorticoid receptor agonists dexamethasone and RU28362, respectively (Yang et al., 2006). Interestingly, the effect appeared to be bidirectional - blocking glucocorticoid function entirely also produced disruptions in extinction. Indeed, systemic administration of metyrapone, as well as intra-amygdala infusion of mifepristone, a glucocorticoid receptor antagonist, disrupted extinction learning (Yang et al., 2006). In slight contrast, another study found that systemic administration of metyrapone did not impact extinction learning, though later increases in spontaneous recovery and renewal were observed, suggesting that blocking corticosterone synthesis disrupts extinction memory consolidation (Barrett and Gonzalez-Lima, 2004). These and further studies highlighted below, raise the interesting possibility that endogenous glucocorticoid activity scales with threat predictability, whereby a lack of glucocorticoids disrupts threat response regulation by impairing learning processes about the actual likelihood of threat, whereas elevated glucocorticoid levels lead to generalization of threat assignment.

In some cases, stress exposure may disrupt threat response regulation by enhancing the original threat memory. For example, one week of daily restraint stress led to elevated freezing during later fear conditioning (Wilber et al., 2011). Implementation of even a single period of stress has been shown to produce a sequelae of behavioral and endocrine changes that resemble to what is observed in post-traumatic stress disorder (PTSD), such as the formation of strong and resistant threat responses (Knox et al., 2016; Liberzon et al., 1997; Long and Fanselow, 2012; Maras et al., 2014; Rau et al., 2005). One recent example is the stress-enhanced fear learning (SEFL) model (Perusini et al., 2016), which has been shown to enhance future fear conditioning (Rau and Fanselow, 2009), be resistant to extinction learning (Rau et al., 2005), result in increased voluntary alcohol consumption (Meyer et al., 2013), and cause long-lasting changes in gene expression in relevant brain regions like the amygdala (Ponomarev et al., 2010) that are consistent with genes implicated in human PTSD (Ressler et al., 2011). Interestingly when male and female mice receiving SEFL underwent extinction training to reduce contextual fear to the same levels as control mice, their activity in an open field returned to the same levels as control mice, whereas unconditioned fear to a novel tone remained elevated (Hassien et al., 2020). This highlights that even though some aspects of threat responding can be 'normalized' with extinction, the beneficial effects of extinction may not always transfer to other threat-associated situations.

Different studies have found impacts specific to extinction learning (i.e., the reduction in threat responding across extinction training; (Chauveau et al., 2012; Ganon-Elazar and Akirav, 2013; Green et al., 2011; Izquierdo et al., 2006; Judo et al., 2010; Wilson et al., 2013; Yamamoto et al., 2008) *or* extinction memory recall (Deschaux et al., 2013; Garcia et al., 2008; Knox et al., 2012; Wilber et al., 2011; Zheng et al., 2013), when tested subsequent to extinction training, while others have observed effects in both (Saito et al., 2012; Skelly et al., 2015). These apparent disparities are likely a result of methodological differences in stressor type, intensity, and frequency, as well as the ability of the animal to predict or control stressor administration (discussed further in Section 4). Nonetheless, the overarching picture suggests that stress exposure has detrimental effects on threat response regulation through extinction (for review, see (Maren and Holmes, 2016). Findings in rodents are largely consistent with what is observed in humans. Indeed, humans with a history of stress exposure or trauma commonly exhibit impaired extinction, alongside disruptions in the inhibitory capacity of the PFC and alterations in corticolimbic signaling (Maren and Holmes, 2016; Raio and Phelps, 2015). Likely related to changes in how threats are processed and responded to, exposure to stress can also dramatically increase the risk for psychiatric disease, particularly anxiety disorders or PTSD (Charney et al., 1993; Karstoft et al., 2015; Radley et al., 2011; Zlotnick et al., 2008). The result is a double-hit, as individuals with a history of significant stress or trauma will be more likely to develop psychopathology and less likely to respond to methods of treatment that engage neural circuitry mediating processes of affective regulation.

Despite substantial research considering the impacts of stress on extinction learning and recall, fewer studies have examined safety conditioning following stress exposure. Safety cues have been examined for their ability to reduce stress responding (Christianson et al., 2008a, 2011; Pollak et al., 2008), though these studies did not include a stress-free condition and thus it is not possible to determine the relative efficacy of safety conditioning in stressed and non-stressed animals. From those papers directly examining the impacts of stress exposure on safety conditioning, it appears that different forms of threat response regulation (i.e., extinction or safety conditioning) may be differentially impacted by duration of stress exposure. Indeed, in one study using adult male rats, acute stress (SEFL) surprisingly had no observable impact on safety conditioning, however the same subjects showed no evidence of extinction to the threat cue in a subsequent extinction session (Woon et al., 2020). The authors concluded that since the explicit safety cue had always been tied to safety it was not disrupted by prior stress, while, in order to observe extinction, the subject needed to update expectancies

regarding potential for threat to the threat cue and this was negatively impacted by the prior stress.

3.2. Neurodevelopmental considerations

Though not the focus of this review, the interaction between neurobiological development and exposure to stress for determining patterns of future threat responding is an area of important focus (for review, see (Callaghan and Tottenham, 2016; Gee et al., 2018; Gerhard et al., 2020; Meyer and Lee, 2019; Pattwell and Bath, 2017; Schroeder et al., 2018). Briefly, the impacts of stress exposure on brain and behavioral functioning appear to be greater during development than when the same stress occurs during adulthood. This evidence has been taken to support the idea of "sensitive windows" wherein the heightened plasticity that sets the foundation for rapid neural change during development also leaves developing circuits susceptible to environmental impacts that can permanently alter circuit structure and function.

The precise age at the time of stress exposure(s) is a major mediator of the impact of stress on threat response regulation systems. From other reviews considering the impact of stress during infancy on developing threat processing systems (Callaghan et al., 2019; Chen and Baram, 2016; Opendak and Sullivan, 2019; Walker et al., 2017) it has been delineated that from early infancy in rodents (postnatal day, PND, 0 through 21), the mother serves as a source of safety and her presence buffers the infant from the impacts of stress. Seminal studies in this area have shown that the presence of an anesthetized adult conspecific attenuates heart rate and vocalizations increases otherwise elicited by an unfamiliar environment in young rats at PND16 (Hofer and Shair, 1987; Richardson et al., 1989). Similar attenuating effects of an anesthetized dam were seen on elevations in corticosterone levels apparent in unfamiliar environments across multiple ages (PND 12, 16, and 20) in rats (Stanton et al., 1987). In addition, the wall climbing response to painful aversive stimuli (shocks) rapidly habituates and remains blunted in the presence of nest odors in PND10 rats (Barrett et al., 1982), as well as an anesthetized dam in PND16 rats (Richardson et al., 1989). Notably, 16 day old rats maintain a blunted response to shock, including heart rate and wall climbing, even following removal of anesthetized dam (Richardson et al., 1989). Similar effects are not observed in rats older than PND20 (Richardson et al., 1989).

This work has been extended in recent years to interrogate the neurobiological underpinnings of buffering effects. The presence of the mother during odor-shock conditioning prevents (prior to PND16; Moriceau and Sullivan, 2006) or attenuates (after PND 16; Upton and Sullivan, 2010) fear conditioning in rats, despite pups at both ages acquiring the aversive association in the absence of the mother. This effect has been linked to reduced corticosterone release (Moriceau and Sullivan, 2006) and a blunting of learning-related plasticity in the amygdala (Opendak et al., 2019) when the pup is conditioned in the presence of the mother. Notably, if a pup has previous stress exposure (e.g., adverse rearing conditions), the capacity of the mother to buffer the stress response is greatly reduced (Opendak et al., 2019; Robinson--Drummer et al., 2019).

Some studies have shown that threat responding profiles in infant rats with previous early life stress exposure recapitulate what is seen in adult animals, exhibiting a marked departure from the infantile amnesia and 'permanent' (i.e., relapse-resistant) extinction that are commonly observed in infant rodents reared under normal (non-stressed) conditions (Cowan et al., 2013). Following daily maternal separation from PND2-14, infant rats (PND17) retain threat associative memories for substantially longer than non-stressed counterparts (30 days relative to less than 10 days; (Callaghan and Richardson, 2012) and are much more likely to exhibit relapse following extinction (Callaghan and Richardson, 2011). These findings have been taken to suggest that exposure to stress during infancy can result in precocious development of cortico-amygdala connectivity (Callaghan and Tottenham, 2016; Cowan et al., 2013). The altered timing of windows of increased neuroplasticity can dramatically alter the later ability to regulate threat responding and cope with stressful experiences, though whether it serves an adaptive or maladaptive function is yet to be determined (Bath, 2020; Callaghan and Tottenham, 2016).

A variety of stressful experiences (social isolation, footshock stress, unpredictable mild stress) during the juvenile (PND21-28) and adolescent (PND29-50) periods of development have been linked to altered threat response regulation in adulthood, including disruptions to both extinction (Ishikawa et al., 2012; Judo et al., 2010; Naert et al., 2011; Novick et al., 2016; Skelly et al., 2015; Toledo-Rodriguez et al., 2012; Zhang and Rosenkranz, 2013) and safety conditioning (Meyer et al., 2021). For example, both chronic unpredictable stress during pre-adolescence (PND22-28) in mice (Meyer et al., 2021), and exposure to mild footshock stress through fear conditioning during adolescence (PND30-32) in rats (Müller et al., 2018), led to later impairments in safety conditioning during adulthood. However, in a study of male and female high-alcohol preferring mice, three days of variable stressors was applied during the juvenile stage (PND25-27) before assessing for the inhibition of fear-potentiated startle in the presence of a safety cue in adulthood (Müller et al., 2021). All mice, regardless of sex or stress group, were able to discriminate between the threat and safety cues. Interestingly though, it was only the previously stressed male and female mice that were able to inhibit their threat responding when the threat cue was co-presented with the safety cue. Some of these data are consistent with mounting evidence that early life exposure to stress can be particularly detrimental for adaptive responding in the face of threat. However, prior stress can have variable effects on the effectiveness of safety conditioning. It is clear that further research is needed to clarify the parameters regarding stress that determine the ability to later learn about and use safety cues effectively.

In sum, it seems that stress anytime during early development can leave an indelible mark on maturing threat response systems. Additional studies are needed to determine which aspects of neural circuit development are most sensitive, how this changes with developmental stage, and the implications for later affective functioning.

4. Stressor controllability and calibrating the response to threat

The research reviewed above has not only led to gains in understanding how stress exposure enhances fear conditioning, but also how it interferes with processes that support threat response regulation, including extinction and safety conditioning. The nature and magnitude of the effects of stress on threat processing and responding can vary widely, often depending on the characteristics of the stressor (its predictability, controllability, duration, modality; see (Anisman and Matheson, 2005; Mcewen, 2004). Despite being a significant risk factor, the development of anxiety-related disorders is not an inevitable sequela to trauma. A majority of individuals "bounce back" or recover positive functioning following extreme adversity (resilience) and/or show resistance to its initial impact (Bonanno et al., 2011).

Genetic factors undoubtedly contribute to resilience/resistance, however factors such as stressor predictability can potently impact an organism's response to repeated stress exposure. When an animal is exposed to a repeated, homotypic stressor (e.g., noise, air puff, restraint), they can learn to predict the time course of the stressor, resulting in a habituated or attenuated stress response (Bhatnagar et al., 2002; Nyhuis et al., 2016; Viau and Sawchenko, 2002). For example, the reactivity of the hypothalamic–pituitary–adrenal (HPA) axis can readily decline during successive stimulus exposures to the same threat stimulus. This response is thought to be adaptive, insofar as it would limit exposure to circulating glucocorticoids, and this is not due to an exhaustion of the response capacity of the HPA axis (see e.g., Dallman et al., 1992). In contrast, following chronic *unpredictable* stress, rats subsequently exposed to a novel challenge do not show habituation in corticosterone output observed in counterparts repeatedly exposed to

the same stimulus (Herman et al., 1995; Magariños and McEwen, 1995; Radley and Sawchenko, 2015). Furthermore, rodents subjected to chronic, but predictable, stress has been shown to be accompanied by less robust behavioral sequelae akin to depressive- and anxiety-like phenotypes as compared to those following unpredictable stress (Christoffel et al., 2011; Pollak et al., 2008; Willner, 2017; Zhu et al., 2014).

In addition, human studies have identified appraisal and coping processes as critical in determining individual outcomes to traumatic life events (Agaibi and Wilson, 2005; Iacoviello and Charney, 2014). Coping refers to an individual's cognitive and behavioral efforts designed to manage (master, reduce, or tolerate) adverse experiences. It has been argued that coping strategies serve two major functions: managing the problem that is the source of the distress (problem-focused coping) and regulating the emotions associated with the problem (emotion-focused coping) (Lazarus and Folkman, 1984). In animal research, coping strategies or styles are often defined by the subject's behavioral, physiological, and neuroendocrine characteristics in response to an environmental challenge (Keay and Bandler, 2001; Koolhaas et al., 1999, 2010). An animal is typically considered to be coping proactively if it behaves in an active manner in response to a stressor, and tends to involve elevations in sympathetic activity, whereas reactive coping involves passivity (e.g., freezing, immobility, low level of aggression) and elevated HPA activity. From a teleological standpoint, different coping styles provide divergent means for successful adaptation to similar environmental conditions (Bohus et al., 1987; Henry and Stephens, 1977; Walker et al., 2009). Nevertheless, there is evidence that each coping style may confer differential susceptibility to disease, with passive coping more commonly associated with stress-related psychopathologies (e.g., de Boer et al., 2017; Henry and Stephens, 1977; Wood, 2014).

An individual's ability to perceive or exert actual control over some aspect of an adverse event (its termination, onset/offset, temporal pattern, intensity) is central to active coping. Indeed, the degree of behavioral control that an organism has over an aversive experience can profoundly alter the neurobiological and behavioral impact of that experience (Maier and Seligman, 2016). Thus, the remainder of this section will focus on stressor controllability, as this represents a key aspect of active coping that can be experimentally manipulated in animal models in order to better understand how resilience is mediated at a neural level.

4.1. Stressor controllability phenomena

There are several different paradigms that have been used to compare subjects, typically rats, with or without control over some dimension of an aversive stimulus (e.g., onset, duration, termination, etc.). For the data discussed below, the experimental arrangement involves placement of rats in a small wheel-turn apparatus where they receive either escapable (ES) or yoked inescapable (IS) tailshocks (Fig. 3). One group of subjects (ES) is exposed to a series of tailshocks in which each shock is terminated when the subject performs a given instrumental escape response (e.g., turning a wheel). A second group of subjects (IS) is yoked to the first and is given a series of unpredictable tailshocks that are physically identical (amount, duration, intensity, pattern) to those received by the ES group, but these subjects have no control over terminating the shock. A third group either remains in its cage in the colony or is placed into the wheel-turn apparatus and does not receive tailshock (No Stress). Any observed difference between subjects with (ES) or without (yoked IS) control must be a result of the impact of active coping, rather than stressor exposure *per se*, because the shocks are physically equivalent for the two groups. Indeed, this is why tailshock is employed in controllability studies. Other stressor modalities (e.g., restraint, social defeat) can't be manipulated in such a way that subjects with or without control experience the identical physical event.

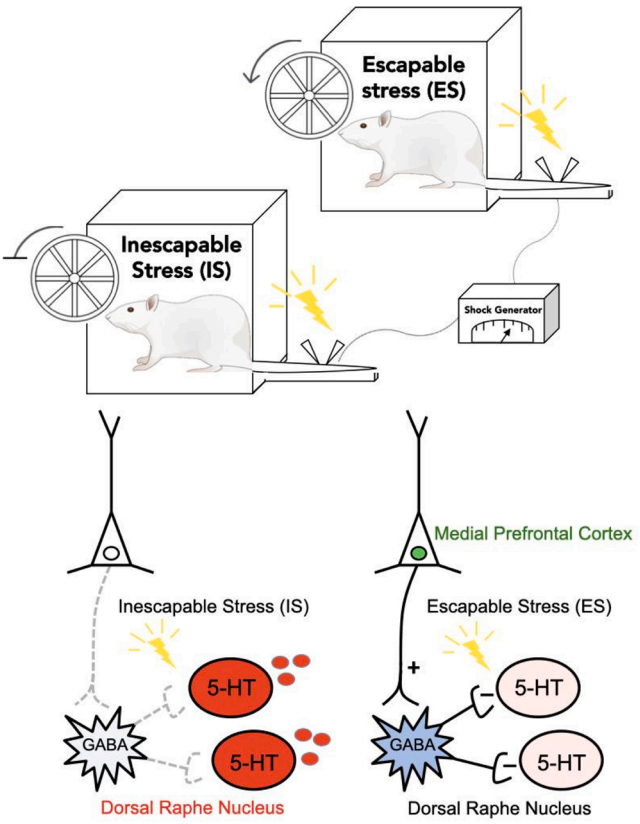

Fig. 3. Stressor controllability and resilience/vulnerability to stressor outcome. **Top:** Schematic diagram of the wheel-turn escape/yoked inescapable tailshock procedure. Subjects (typically rats) are assigned to either escapable stress (ES), inescapable stress (IS), or no stress. Subjects receive a series (usually 80–100 trials) of tailshocks while restrained in a chamber with a wheel mounted in the front and their tail secured to a rod extending from the back of the chamber. ES subjects can perform an instrumental wheel-turn escape response to terminate each of the shocks. IS subjects are "yoked" to ES subjects, such that shock is simultaneously terminated for the IS subject when the ES subject achieves the wheel-turn requirement. Importantly, each rat in the pair receives exactly equal tailshock (same duration, onset/offset, intensity, number of shocks, etc.). **Bottom:** Proposed model by which stressor controllability regulates the dorsal raphe nucleus. Inescapable shock leads to intense activation of the serotonergic (5-HT) dorsal raphe nucleus. In contrast, escapable shock leads to top–down inhibition of dorsal raphe 5-HT neurons, thereby blunting the behavioral impact of tailshock.

Numerous behavioral sequelae are produced in the group of subjects that receive IS, but not in the group of subjects that are allowed to exert behavioral control over stressor termination (ES). For example, IS, but not ES, leads to social avoidance, neophobia towards different types of novelty (such as objects and locations), increased submissive behaviors following social defeat, enhanced morphine-conditioned place preference, and profound impairment of shuttlebox escape behavior (Christianson et al., 2008b; Maier and Watkins, 2005; Minor, 1990; Rozeske et al., 2009; Will et al., 1998). It should be noted that testing for behavioral outcomes is typically carried out in an environment that is very different from where the controllability procedure was administered. Thus, it has been argued that IS produces behavioral changes that are mediated by non-associative rather than associative processes (Maier and Watkins, 1998). The distinction is important, as both the time course and the circuits responsible for supporting stress-induced outcomes differ if the testing environment is exactly the same or shares common cues with the stress treatment environment (see discussion below).

4.2. Neural mediation of controllability

Efforts directed at understanding the neural mechanisms underlying the numerous behavioral changes observed following IS have focused on several broad-projecting neural systems. Both the brainstem serotonergic (5-HT) dorsal raphe nucleus (DRN) and noradrenergic locus coeruleus impart broad modulatory influences over a range of stress-induced behaviors through their innervation of limbic and cortical structures (Lowry et al., 2005; Weiss, 1970; Weiss et al., 1975). Of note, many of the behavioral consequences of IS are due to a selective activation of 5-HT neurons in the DRN, which does not occur with ES (Grahn et al., 1999; Maswood et al., 1998). The large and prolonged elevation of extracellular 5-HT within the DRN by IS results in a period of sensitization (lasting several days) during which inputs to the DRN produce an exaggerated release of 5-HT both within the DRN and in DRN terminal regions, thereby modifying the behavioral response (see reviews by (Christianson and Greenwood, 2014; Hammack et al., 2012; Maier and Watkins, 2005). The hyperexcitability of 5-HT neurons induced by IS is argued to be dependent on functional desensitization of inhibitory 5-HT_{1A} autoreceptors in the DRN (Rozeske et al., 2011).

With regard to fear conditioning, IS-exposed subjects display exaggerated freezing levels in response to two brief footshocks delivered the following day in a novel context (shuttlebox apparatus). Similarly, IS, but not ES, increases extracellular 5-HT in the amygdala (a projection region of the DRN) in response to the same two brief footshocks (Amat et al., 1998). Furthermore, lesions to the DRN or pharmacological inhibition of DRN 5-HT activity, at the time of IS or at the time of behavioral testing, blocks the IS-induced potentiation of threat responding (Maier et al., 1995b). Conversely, pharmacological activation of the DRN *in the absence* of tailshock produces the same exaggerated freezing upon subsequent footshock exposure, providing a necessary and sufficient link between DRN 5-HT activation and behavioral changes produced by IS (Maier et al., 1995a).

The contribution of DRN 5-HT to IS outcomes highlights one of the key features of the stressor controllability paradigm in which the experience of uncontrollable stress impacts how the subject responds in novel unrelated circumstances ('transsituational'). That is, in a typical controllability experiment, behavioral testing is conducted in a context that is distinct and removed from the original tailshock experience. This is in direct contrast to other protocols in which uncontrollable shock (stress treatment) and behavioral testing occur in the very same apparatus. In both scenarios, the behavioral change may be the same (poor shuttlebox escape learning, exaggerated freezing, social avoidance, etc.) but the underlying neural processes are quite different. For example, when IS and testing are carried out in the same environment, blockade of DRN 5-HT activity either before IS or before testing is *without effect*. The foregoing demonstrates that DRN 5-HT is critical for mediating the induction and expression of a *state change* (non-associative process) that transfers the effects of the IS experience to novel environments and unrelated task demands. When the contextual relationship is similar, IS outcomes are instead governed by an associative process (i.e., conditional fear) that is dependent on amygdala but not DRN activity (Greenwood et al., 2010; Greenwood and Fleshner, 2008; Maier and Watkins, 2005).

Although the DRN is a key structure in the mediation of behavioral changes following IS, the computation of controllability is a process unlikely to be intrinsic to the DRN. Behavioral control over shock is formally defined as a comparison between two conditional probabilities: the probability of shock given that the instrumental response (e.g., wheel turn) has occurred and the probability of shock given that the instrumental response has not occurred (Maier et al., 1969). When the two probabilities are equal, behavioral control is absent – there is nothing the subject can do to modify shock presentation. However, any inequality between the two probabilities indicates that the subject has some degree of control. The ability to detect causal relationships between actions and outcomes (instrumental contingency) is largely a corticostriatal function (Balleine and O'Doherty, 2010; Corbit and Balleine, 2003) and recent data indicates that the instrumental wheel-turn controlling response engages the dorsomedial striatum and that its activation is necessary for control-induced protection (Amat et al., 2014).

Activation of the mPFC is critical for the stress-buffering effects of behavioral control as well. The DRN is one of the major brainstem targets of the mPFC, which provides robust top-down inhibition over DRN 5-HT activity (Hajos et al., 1998; Varga et al., 2001, 2003), presumably through preferential targeting of DRN GABA interneurons (Jankowski and Sesack, 2004). Converging evidence suggests that the presence of control blunts the impact of tailshock through mPFC top-down inhibition over DRN 5-HT. Notably, (1) the presence of control selectively activates mPFC neurons that project to the DRN (Baratta et al., 2009); (2) pharmacological inactivation of the mPFC during control blocks the behavioral and neurochemical protection afforded by ES, even though ES subjects still perform the wheel-turn controlling response (Amat et al., 2005, 2006); and (3) pharmacological activation of the mPFC during IS protects against the aforementioned behavioral and neurochemical consequences of tailshock (Amat et al., 2008). A striking feature of behavioral control, and one of potential clinical importance, is that a prior experience with ES blunts the typical neural and behavioral impact of later exposure to uncontrollable adverse events that occur in very different environments (transsituational) and do not necessarily rely on shock (e.g., social defeat; transstimulus). In addition, the stress-buffering effects of ES are long-lasting as the experience of ES during adolescence (PND35) prevents the neurochemical and behavioral outcomes of IS exposure during adulthood (PND70), an effect that relies on mPFC activation (Kubala et al., 2012). Taken together, ES confers a very generalized protection to the impact of subsequent adversity (Amat et al., 2010). The enduring protection afforded by behavioral control requires mPFC activity both at the time of the initial control experience and at the time of the subsequent challenge (Amat et al., 2006). Thus, as a result of ES exposure, the mPFC becomes activated upon exposure to future adverse events that typically don't activate the mPFC.

To date, several studies suggest that the mPFC is also a critical site of plasticity for generalized stress resistance following ES. ES leads to the production of plasticity-related proteins in the mPFC (Christianson et al., 2014) and increases the intrinsic excitability of layer 5/6 pyramidal neurons in the mPFC as measured by whole-cell patch-clamp recordings (Varela et al., 2012). In addition, intra-mPFC microinjection of the protein synthesis inhibitor anisomycin immediately after the ES experience blocks the ability of prior ES to prevent the neurochemical and behavioral consequences of subsequent inescapable shock (Amat et al., 2006). Other mPFC manipulations during ES, such as blockade of NMDAR activity or inhibition of its downstream effector pathway (ERK/MAPK), also prevent the enduring protection otherwise afforded by control (Christianson et al., 2014). Although these pharmacological manipulations were not conducted in a pathway-specific manner, a recent study by Shansky et al. (2019) showed that ES, but not physically identical IS, selectively increased structural changes to dendritic spines on DRN-projecting pyramidal neurons in the mPFC (Baratta et al., 2019). Increases in spine size have been associated with larger post-synaptic densities and increased synaptic efficacy (Bourne and Harris, 2007; Kasai et al., 2003; Matsuzaki et al., 2004). Thus, these latter findings may implicate a mechanism whereby ES enhances mPFC–DRN circuit function through structural modifications at axo-spinous synapses afferent to this circuit that enable future increases in activity to promote stress resistance. Nevertheless, it remains to be determined whether dendritic prefrontal spine changes are causally linked to the generalized resistance produced by control, and the emergence of new genetic tools such as photoactivatable Rac1 may allow for the direct testing of this idea (Hayashi-Takagi et al., 2015; Moda-Sava et al., 2019).

While behavioral control leads to stress resistance/resilience by engaging top-down mPFC inhibitory control over the DRN, not all stress-

protective factors operate through a similar mechanism (Christianson and Greenwood, 2014). For instance, the predictability of stressor occurrence has been argued as key in modifying an organism's response to stressors (Minor, 1990; Weiss, 1970) and indeed, the provision of safety cues that predict a shock-free period prevents a number of IS-induced behaviors. That is, providing rats with a cessation signal at the termination of each of a series of uncontrollable tailshocks recapitulates the acute protection afforded by ES (Christianson et al., 2012; Jackson and Minor, 1988; Maier and Keith, 1987; Weiss, 1971). As discussed above, mPFC activation is required for behavioral control to prevent the exaggerated threat responding and social avoidance produced by tailshock. It follows then that the threat-reducing effects of a safety cue that signals the absence of the US (tailshock) might also depend on the mPFC. Despite the similarity in behavioral outcomes, inactivation of the mPFC does not alter the ability of safety cues to blunt the impact of IS (Christianson et al., 2008a). Even more surprising, safety cues do not inhibit IS-induced DRN 5-HT activity. Thus behavioral control and safety cues involve separate distinct neural substrates for buffering against IS-induced outcomes. Subsequent studies directed at understanding safety cue operation have identified the posterior insula and extended amygdala as critical (Christianson et al., 2008a, 2011). An open question, and one of clinical significance, is whether safety learning during inescapable stress produces plasticity within the insula-extended amygdala circuit and whether an experience with safety learning provides a similar long-term protection against future adverse events (transsituational, transstimulus) that is observed with behavioral control.

4.3. Behavioral control provides resistance against threat-related processes

Another unresolved issue is identifying what, if any, functional dimensions tether the initial coping experience with future adversity. As mentioned, behavioral control not only buffers against later inescapable tailshock, but also against other stressors that don't involve the use of tailshock (e.g., social defeat). It may be the case that mPFC activity during behavioral control becomes associated with something common to adverse experiences, such that later exposure to adversity now biases the mPFC towards activation. Situations that individuals appraise as threatening are often accompanied by the emotions of fear and/or anxiety. Thus, controllable stress may provide general protection because it alters how the mPFC responds to circumstances that induce these states. If this were true, then controllable stress should impact later fear conditioning and/or extinction.

To examine the impact of stressor controllability, ES, yoked IS, and No Stress control rats were exposed one week later to fear conditioning, followed by testing 24 h later (Baratta et al., 2007). Freezing was measured both to the conditioning context and to the tone (presented in a novel context) that had been paired with shock. As expected, prior IS potentiated fear conditioning to both the context and tone. This is similar to prior reports in which stressor exposure (always uncontrollable) before fear conditioning enhances the level of conditioning that occurs (Baratta et al., 2016; Rau et al., 2005). However, the pattern of freezing behavior was the opposite in ES subjects. Providing a controlling response over the stressor (ES) not only prevented the stress-induced facilitation of fear conditioning, but rather it actually reduced conditioned responding to both the context and the tone. That is, ES freezing levels were significantly lower than No Stress controls, suggesting an active process present in ES, but not IS or No Stress groups. Moreover, in a subsequent study, ES accelerated the later extinction of conditioned responding. In this case, stress treatment was given *after* fear conditioning to ensure that the initial level of conditioning to a given context was similar between all three groups (ES, IS, and No Stress). Therefore, any group differences in the rate of between-session extinction can only be attributed to a difference in extinction/expression and not the acquisition of the fear association. Dramatically, exposure to ES between fear conditioning and extinction also *reduced* spontaneous recovery assessed two weeks after extinction (or 24 days after the initial ES experience). A number of pharmacotherapies have been developed with the goal of reducing fear learning or promoting extinction (Davis, 2002; Mataix-Cols et al., 2017; Rodriguez-Romaguera et al., 2009), but little effort has been directed at understanding whether experiential factors might do this, and if so what their mechanisms of operation would be. Thus, these findings are important, as they define an adverse event, behavioral control over a potent stressor, which produces long-lasting acceleration and permanence of extinction.

Although ES reduced the number of sessions required to reach the extinction criterion, this effect did not result from an acceleration of the learning that occurs during the extinction process. Rather, freezing levels of the ES group were already significantly reduced by the second minute of the first extinction session, a time point that would be too soon for the animal to learn that the context no longer predicted footshock. One interpretation is that ES simply impacts the expression of the conditional response instead of accelerating new inhibitory learning. Thus, the strength of the context-footshock association may not differ in ES subjects, rather the level of behavioral expression (freezing) that such an association would normally produce is blunted.

Neurobiological evidence suggests that ES may alter future responses to stimuli that elicit amygdala-dependent conditioned responses via engagement of the IL (Baratta et al., 2008). This was tested by selective pharmacological inactivation of the IL during each of the experimental phases in which subjects first received ES, IS, or No Stress (Time A), followed by contextual fear conditioning one week later (Time B), and then tested for the level of conditioning to the context 24 h later (Time C). Intra-IL muscimol ($GABA_A$ agonist) prior to ES (Time A) blocked the reduction of later conditional responding that is produced by an experience of ES. Interestingly, intra-IL muscimol administered before fear conditioning (Time B) did not prevent the ES-induced reduction in freezing, nor did it have an impact in IS or No Stress subjects. However, IL inactivation during re-exposure to the conditioned context (Time C) eliminated the reduction in freezing in ES subjects and now ES subjects exhibited a level of responding similar to IS subjects. Together this suggests that the experience of control reduces the expression of conditioned fear rather than the development of the CS-US association. Thus, it would appear that experiencing control over an aversive stimulus alters the IL in such a way that it is later activated under conditions that produce fear, leading to top-down inhibition of its expression. The data also suggest that experiential factors may impact threat-related processes through modulation of mechanisms central to the expression rather than acquisition of fear associations.

In conclusion, the experience of control over tailshock produces a type of stress resilience that generalizes beyond the ES context (transsituational) and beyond protection of outcomes that follow tailshock (transstimulus). With regard to coping, behavioral control alters how the mPFC responds to future threat, thus changing the behavioral response of the organism to adversity, perhaps biasing engagement of more active than passive behaviors. The experiments involving controllability suggest resilience recruits unique mechanisms that are not simply the opposite of the mechanisms that promote vulnerability (Box 1).

5. Conclusions and future directions

In this review we have provided an overview of the neural systems regulating responses to threat and stress, through the lens of how predictability and controllability differentially recruit and modulate activity in these systems. Much of our review hones in on extinction and safety conditioning, two strong processes for suppressing threat responding that act through distinct (yet overlapping) mechanisms. Notably, extinction and safety conditioning differ in the means by which they come to predict the relative absence of threat. Extinction occurs through repeated non-reinforced presentations of a previously conditioned threat cue. As a result, a single CS can strongly predict both the

Box 1
Key terms and abbreviations:

Threat: An aversive outcome.

Threat-associated cue: A stimulus that has come to predict a threat through associative learning processes.

Threat responding: Behavior elicited in anticipation of encountering a threat. Often elicited in the presence of a threat-associated cue.

Threat response regulation: The process of calibrating a threat response based on calculations of the likelihood of encountering a threat in the present environment.

Predictability: The strength of the relationship between a stimulus and a threat (i.e. an aversive outcome).

Controllability: An individual's ability to perceive or exert actual control over some aspect of an adverse event.

5-HT, serotonin; 5-HT1A, serotonin 1A receptor; AMPAR, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors; AP5, 2-amino-5-phosphonovaleric acid; BA, basal nucleus of the amygdala; BLA, basolateral nucleus of the amygdala; BMA, basomedial nucleus of the amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CS, conditional stimulus; DRN, dorsal raphe nucleus; ERK, extracellular signal-regulated kinase; ES, escapable tailshock; GABA, γ-aminobutryic acid; HPA, hypothalamic–pituitary–adrenal; IL, infralimbic cortex; IS, inescapable tailshock; ITC, intercalated cells of the amygdala; LA, lateral nucleus of the amygdala; MAPK, mitogen-activated protein kinase; mPFC, medial prefrontal cortex; NMDAR, N-methyl-D-aspartate receptor; PAG, periaqueductal gray; PFC, prefrontal cortex; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PL, prelimbic cortex; PND, postnatal day; PTSD, post-traumatic stress disorder; PVT, paraventricular nucleus of the thalamus; SEFL, stress-enhanced fear learning; US, unconditional stimulus; vlPAG, ventrolateral periaqueductal gray.

presence or absence of threat. Previous research has considered context and time (Bouton, 1993; Goode and Maren, 2014) as two factors with large roles in determining which predictive relationship will be at the forefront. On the other hand, many instances of safety conditioning occur when two distinct stimuli are encountered at the same time, one strongly predicting threat, and the other strongly predicting the absence of threat. The predictability of threat in this case comes from contrasting the two cues during discriminative conditioning. As an important note, safety conditioning can also occur following discriminative conditioning between a safety cue and an aversive context rather than a cue. Unlike an extinguished CS, the ability of a safety cue to suppress behavior should not be influenced by context, and some researchers have seen an extension of the response-suppressing properties to include a reduction in depressive- and anxiety-like phenotypes (Pollak et al., 2008). However, few studies to date have directly investigated the impact of context or the passage of time for safety conditioning in the realm of threat response regulation.

A variety of factors in an organism's experience, including context, relative recency of the associative learning, and environmental points of comparison (e.g., other conditioned stimuli) likely mediate when and to what extent distinct neural circuits are engaged. Across our discussion of threat response regulation in naive animals, as well as the impacts of stress exposure and its controllability on threat responding, the mPFC emerged as a key player in each area. It may be that recruitment of the mPFC, and particularly the IL, requires a degree of *certainty* with regard to the probability of encountering a threat. This is in line with findings linking hypoactivity within the mPFC with emotion dysregulation in both animal (reviewed in Gilmartin et al., 2014) and human (reviewed in Mochcovitch et al., 2014) studies. More efforts are needed, though, to tease apart the role of mPFC activity to various stages of threat response regulation in both predictable and unpredictable conditions.

Individual variability in threat prediction and coping capacity are common endophenotypes of psychopathologies including anxiety and PTSD. Furthermore, training in threat response regulation is a key feature of exposure therapy, a component of cognitive-behavioral therapy commonly used for treating both anxiety and PTSD. Cognitive therapy aims to provide the individual with tools to buffer against negative thoughts and affect and to evaluate their accuracy. Thus, a precise understanding of the mechanisms of cognitive therapy could potentially guide treatment selection and lead to improved outcomes and protection against relapse. In this review we discussed evidence that control over a stressful experience (escapable shock) may actually confer resilience during later stressful experiences (e.g., Baratta et al., 2007). Additional work of this kind will be critical to optimizing treatments for psychiatric disease, particularly through behavioral intervention.

Furthermore, understanding the circumstances under which extinction, safety conditioning, or other methods of threat response regulation are most efficacious could inform different clinical situations in which each may show the greatest benefit. Greater insight into this issue will be gained from identifying the neural circuitry underlying extinction or safety conditioning, as different individuals may exhibit elevated or reduced baseline functional activity in some circuits relative to others. Recent work has also considered development as a key determinant of the relative efficacy of extinction or safety conditioning. For example, whereas limitations with extinction learning and later recall have been found during adolescence (Baker et al., 2014; Gerhard et al., 2020; Pattwell et al., 2013), safety conditioning may provide an opportunity to circumvent these limitations and provide an effective means of threat response regulation (Odriozola and Gee, 2020). Work in this area has highlighted the idea that neural systems contributing to safety conditioning develop on a more rapid trajectory than systems contributing to extinction (Odriozola and Gee, 2020). Moreover, there appear to be potential sex differences between extinction and safety conditioning, although substantial additional work is needed in this area (Shansky, 2015).

In sum, calibrating threat responding is adaptive. It allows an organism to walk the line between complete protection from harm and the acceptance of a small amount of risk in the execution of goal-directed behaviors. Any disruption to an organism's ability to calibrate appropriately can have detrimental consequences. In line with this, the relationship between perturbations in threat and stress response regulation and psychiatric disease is an area of immense focus. Understanding the circuitry that mediates threat responding in different situations is critical to understanding the causes and course of psychiatric disease, as well as developing circuit-informed treatments (e.g., Morrison and Ressler, 2014).

Funding

This work was supported by the National Institutes of Health (NIMH) Pathway to Independence Award K99 MH119320 to H.C.M., R01

MH110425 to S.S., R01 MH050479 and R21 MH116353 to M.V.B., R01 MH119106 and R21 MH115673 to J.J.R., and R01 MH104384 to R.T.L.

References

Abelson, J.L., Khan, S., Liberzon, I., Erickson, T.M., Young, E.A., 2008. Effects of perceived control and cognitive coping on endocrine stress responses to pharmacological activation. Biol. Psychiatry 64 (8), 701–707. https://doi.org/10.1016/j.biopsych.2008.05.007.

Adhikari, A., Lerner, T.N., Finkelstein, J., Pak, S., Jennings, J.H., Davidson, T.J., Ferenczi, E., Gunaydin, L.A., Mirzabekov, J.J., Ye, L., Kim, S.Y., Lei, A., Deisseroth, K., 2015. Basomedial amygdala mediates top-down control of anxiety and fear. Nature 527 (7577), 179–185. https://doi.org/10.1038/nature15698.

Agaibi, C.E., Wilson, J.P., 2005. Trauma, PTSD, and resilience: a review of the literature. Trauma Violence Abuse 6 (3), 195–216. https://doi.org/10.1177/1524838005277438.

Amat, J., Matus-Amat, P., Watkins, L.R., Maier, S.F., 1998. Escapable and inescapable stress differentially alter extracellular levels of 5-HT in the basolateral amygdala of the rat. Brain Res. 812 (1–2), 113–120.

Amat, J., Baratta, M.V., Paul, E., Bland, S.T., Watkins, L.R., Maier, S.F., 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat. Neurosci. 8 (3), 365–371. https://doi.org/10.1038/nn1399.

Amat, J., Paul, E., Zarza, C., Watkins, L.R., Maier, S.F., 2006. Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex. J. Neurosci. 26 (51), 13264–13272. https://doi.org/10.1523/jneurosci.3630-06.2006.

Amat, J., Paul, E., Watkins, L.R., Maier, S.F., 2008. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. Neuroscience 154 (4), 1178–1186. https://doi.org/10.1016/j.neuroscience.2008.04.005.

Amat, J., Aleksejev, R.M., Paul, E., Watkins, L.R., Maier, S.F., 2010. Behavioral control over shock blocks behavioral and neurochemical effects of later social defeat. Neuroscience 165 (4), 1031–1038. https://doi.org/10.1016/j.neuroscience.2009.11.005.

Amat, J., Christianson, J.P., Aleksejev, R.M., Kim, J., Richeson, K.R., Watkins, L.R., Maier, S.F., 2014. Control over a stressor involves the posterior dorsal striatum and the act/outcome circuit. Eur. J. Neurosci. 40 (2), 2352–2358. https://doi.org/10.1111/ejn.12609.

Anderson, R.M., Glanz, R.M., Johnson, S.B., Miller, M.M., Romig-Martin, S.A., Radley, J. J., 2016. Prolonged corticosterone exposure induces dendritic spine remodeling and attrition in the rat medial prefrontal cortex. J. Comp. Neurol. 524 (18), 3729–3746. https://doi.org/10.1002/cne.24027.

Anisman, H., Matheson, K., 2005. Stress, depression, and anhedonia: caveats concerning animal models. Neurosci. Biobehav. Rev. 29 (4–5), 525–546. https://doi.org/10.1016/j.neubiorev.2005.03.007.

Arico, C., Bagley, E.E., Carrive, P., Assareh, N., McNally, G.P., 2017. Effects of chemogenetic excitation or inhibition of the ventrolateral periaqueductal gray on the acquisition and extinction of Pavlovian fear conditioning. Neurobiol. Learn. Mem. 144, 186–197. https://doi.org/10.1016/j.nlm.2017.07.006.

Assareh, N., Bagley, E.E., Carrive, P., McNally, G.P., 2017. Brief optogenetic inhibition of rat lateral or ventrolateral periaqueductal gray augments the acquisition of Pavlovian fear conditioning. Behav. Neurosci. 131 (6), 454–459. https://doi.org/10.1037/bne0000217.

Baker, K.D., Den, M.L., Graham, B.M., Richardson, R., 2014. A window of vulnerability: impaired fear extinction in adolescence. Neurobiol. Learn. Mem. 113, 90–100. https://doi.org/10.1016/j.nlm.2013.10.009.

Balleine, B.W., O'Doherty, J.P., 2010. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology 35 (1), 48–69.

Baran, S.E., Armstrong, C.E., Niren, D.C., Hanna, J.J., Conrad, C.D., 2009. Chronic stress and sex differences on the recall of fear conditioning and extinction. Neurobiol. Learn. Mem. 91 (3), 323–332. https://doi.org/10.1016/j.nlm.2008.11.005.

Baratta, M.V., Christianson, J.P., Gomez, D.M., Zarza, C.M., Amat, J., Masini, C.V., Watkins, L.R., Maier, S.F., 2007. Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. Neuroscience 146 (4), 1495–1503. https://doi.org/10.1016/j.neuroscience.2007.03.042.

Baratta, M.V., Lucero, T.R., Amat, J., Watkins, L.R., Maier, S.F., 2008. Role of the ventral medial prefrontal cortex in mediating behavioral control-induced reduction of later conditioned fear. Learn. Mem. 15 (2), 84–87. https://doi.org/10.1101/lm.800308.

Baratta, M.V., Zarza, C.M., Gomez, D.M., Campeau, S., Watkins, L.R., Maier, S.F., 2009. Selective activation of dorsal raphe nucleus-projecting neurons in the ventral medial prefrontal cortex by controllable stress. Eur. J. Neurosci. 30 (6), 1111–1116. https://doi.org/10.1111/j.1460-9568.2009.06867.x.

Baratta, M.V., Kodandaramaiah, S.B., Monahan, P.E., Yao, J., Weber, M.D., Lin, P.A., Gisabella, B., Petrossian, N., Amat, J., Kim, K., Yang, A., Forest, C.R., Boyden, E.S., Goosens, K.A., 2016. Stress enables reinforcement-elicited serotonergic consolidation of fear memory. Biol. Psychiatry 79 (10), 814–822. https://doi.org/10.1016/j.biopsych.2015.06.025.

Baratta, M.V., Gruene, T.M., Dolzani, S.D., Chun, L.E., Maier, S.F., Shansky, R.M., 2019. Controllable stress elicits circuit-specific patterns of prefrontal plasticity in males, but not females. Brain Struct. Funct. 224 (5), 1831–1843. https://doi.org/10.1007/s00429-019-01875-z.

Barrett, D., Gonzalez-Lima, F., 2004. Behavioral effects of metyrapone on Pavlovian extinction. Neurosci. Lett. 371 (2–3), 91–96. https://doi.org/10.1016/j.neulet.2004.08.046.

Barrett, B.A., Caza, P., Spear, N.E., Spear, L.P., 1982. Wall climbing, odors from the home nest and catecholaminergic activity in rat pups. Physiol. Behav. 29 (3), 501–507. https://doi.org/10.1016/0031-9384(82)90273-6.

Bath, K.G., 2020. Synthesizing views to understand sex differences in response to early life adversity. Trends Neurosci. 43 (5), 300–310. https://doi.org/10.1016/j.tins.2020.02.004.

Berlau, D.J., McGaugh, J.L., 2006. Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. Neurobiol. Learn. Mem. 86 (2), 123–132. https://doi.org/10.1016/j.nlm.2005.12.008.

Berretta, S., Pantazopoulos, H., Caldera, M., Pantazopoulos, P., Pare, D., 2005. Infralimbic cortex activation increases c-Fos expression in intercalated neurons of the amygdala. Neuroscience 132 (4), 943–953. https://doi.org/10.1016/j.neuroscience.2005.01.020.

Beyeler, A., Namburi, P., Glober, G.F., Simonnet, C., Calhoon, G.G., Conyers, G.F., Luck, R., Wildes, C.P., Tye, K.M., 2016. Divergent routing of positive and negative information from the amygdala during memory retrieval. Neuron 90 (2), 348–361. https://doi.org/10.1016/j.neuron.2016.03.004.

Bhatnagar, S., Huber, R., Nowak, N., Trotter, P., 2002. Lesions of the posterior paraventricular thalamus block habituation of hypothalamic-pituitary-adrenal responses to repeated restraint. J. Neuroendocrinol. 14 (5), 403–410. https://doi.org/10.1046/j.0007-1331.2002.00792.x.

Bloodgood, D.W., Sugam, J.A., Holmes, A., Kash, T.L., 2018. Fear extinction requires infralimbic cortex projections to the basolateral amygdala. Transl. Psychiatry 8. https://doi.org/10.1038/s41398-018-0106-x.

Bohus, B., Benus, R.F., Fokkema, D.S., Koolhaas, J.M., Nyakas, C., van Oortmerssen, G.A., Prins, A.J., de Ruiter, A.J., Scheurink, A.J., Steffens, A.B., 1987. Neuroendocrine states and behavioral and physiological stress responses. Prog. Brain Res. 72, 57–70. https://doi.org/10.1016/s0079-6123(08)60196-x.

Bonanno, G.A., Westphal, M., Mancini, A.D., 2011. Resilience to loss and potential trauma. Annu. Rev. Clin. Psychol. 7 (1), 511–535. https://doi.org/10.1146/annurev-clinpsy-032210-104526.

Bourne, J., Harris, K.M., 2007. Do thin spines learn to be mushroom spines that remember? Curr. Opin. Neurobiol. 17 (3), 381–386. https://doi.org/10.1016/j.conb.2007.04.009.

Bouton, M.E., 1993. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychol. Bull. 114 (1), 80–99. https://doi.org/10.1037/0033-2909.114.1.80.

Bouton, M.E., Maren, S., McNally, G.P., 2021. Behavioral and neurobiological mechanisms of pavlovian and instrumental extinction learning. Physiol. Rev. 101 (2), 611–681. https://doi.org/10.1152/physrev.00016.2020.

Brown, S.M., Henning, S., Wellman, C.L., 2005. Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. Cereb. Cortex 15 (11), 1714–1722. https://doi.org/10.1093/cercor/bhi048.

Bukalo, O., Pinard, C.R., Silverstein, S., Brehm, C., Hartley, N.D., Whittle, N., Colacicco, G., Busch, E., Patel, S., Singewald, N., Holmes, A., 2015. Prefrontal inputs to the amygdala instruct fear extinction memory formation. Sci. Adv. 1 (6), e1500251 https://doi.org/10.1126/sciadv.1500251.

Burgos-Robles, A., Vidal-Gonzalez, I., Quirk, G.J., 2009. Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. J. Neurosci. 29 (26), 8474–8482. https://doi.org/10.1523/JNEUROSCI.0378-09.2009.

Cai, W.-H., Blundell, J., Han, J., Greene, R.W., Powell, C.M., 2006. Postreactivation glucocorticoids impair recall of established fear memory. J. Neurosci. 26 (37), 9560–9566. https://doi.org/10.1523/JNEUROSCI.2397-06.2006.

Callaghan, B.L., Richardson, R., 2011. Maternal separation results in early emergence of adult-like fear and extinction learning in infant rats. Behav. Neurosci. 125 (1), 20–28. https://doi.org/10.1037/a0022008.

Callaghan, B.L., Richardson, R., 2012. The effect of adverse rearing environments on persistent memories in young rats: removing the brakes on infant fear memories. Transl. Psychiatry 2 (7), e138. https://doi.org/10.1038/tp.2012.65.

Callaghan, B.L., Tottenham, N., 2016. The Stress Acceleration Hypothesis: effects of early-life adversity on emotion circuits and behavior. Curr. Opin. Behav. Sci. 7, 76–81. https://doi.org/10.1016/j.cobeha.2015.11.018.

Callaghan, B.L., Meyer, H., Opendak, M., Van Tieghem, M., Harmon, C., Li, A., Lee, F.S., Sullivan, R.M., Tottenham, N., 2019. Using a developmental ecology framework to align fear neurobiology across species. Annu. Rev. Clin. Psychol. 15 (1) https://doi.org/10.1146/annurev-clinpsy-050718-095727 null.

Carrive, P., Leung, P., Harris, J., Paxinos, G., 1997. Conditioned fear to context is associated with increased Fos expression in the caudal ventrolateral region of the midbrain periaqueductal gray. Neuroscience 78 (1), 165–177. https://doi.org/10.1016/s0306-4522(97)83047-3.

Carter, C.S., Altemus, M., Pchrousos, G., 2001. Chapter 17 neuroendocrine and emotional changes in the post-partum period. In: Progress in Brain Research, Vol. 133. Elsevier, pp. 241–249. https://doi.org/10.1016/S0079-6123(01)33018-2.

Charney, D.S., Deutch, A.Y., Krystal, J.H., Southwick, S.M., Davis, M., 1993. Psychobiologic mechanisms of posttraumatic stress disorder. Arch. Gen. Psychiatry 50 (4), 294–305. https://doi.org/10.1001/archpsyc.1993.01820160064008.

Chauveau, F., Lange, M.D., Jüngling, K., Lesting, J., Seidenbecher, T., Pape, H.-C., 2012. Prevention of stress-impaired fear extinction through neuropeptide s action in the lateral amygdala. Neuropsychopharmacology 37 (7), 1588–1599. https://doi.org/10.1038/npp.2012.3.

Chen, Y., Baram, T.Z., 2016. Toward understanding how early-life stress reprograms cognitive and emotional brain networks. Neuropsychopharmacology 41 (1), 197–206. https://doi.org/10.1038/npp.2015.181.
Christianson, J.P., Greenwood, B.N., 2014. Stress-protective neural circuits: not all roads lead through the prefrontal cortex. Stress 17 (1), 1–12. https://doi.org/10.3109/10253890.2013.794450.
Christianson, J.P., Benison, A.M., Jennings, J., Sandsmark, E.K., Amat, J., Kaufman, R.D., Baratta, M.V., Paul, E.D., Campeau, S., Watkins, L.R., Barth, D.S., Maier, S.F., 2008a. The sensory insular cortex mediates the stress-buffering effects of safety signals but not behavioral control. J. Neurosci. 28 (50), 13703–13711. https://doi.org/10.1523/JNEUROSCI.4270-08.2008.
Christianson, J.P., Paul, E.D., Irani, M., Thompson, B.M., Kubala, K.H., Yirmiya, R., Watkins, L.R., Maier, S.F., 2008b. The role of prior stressor controllability and the dorsal raphé nucleus in sucrose preference and social exploration. Behav. Brain Res. 193 (1), 87–93. https://doi.org/10.1016/j.bbr.2008.04.024.
Christianson, J.P., Jennings, J.H., Ragole, T., Flyer, J.G.N., Benison, A.M., Barth, D.S., Watkins, L.R., Maier, S.F., 2011. Safety signals mitigate the consequences of uncontrollable stress via a circuit involving the sensory insular cortex and bed nucleus of the stria terminalis. Biol. Psychiatry 70 (5), 458–464. https://doi.org/10.1016/j.biopsych.2011.04.004.
Christianson, J.P., Fernando, A.B.P., Kazama, A.M., Jovanovic, T., Ostroff, L.E., Sangha, S., 2012. Inhibition of fear by learned safety signals: a mini-symposium review. J. Neurosci. 32 (41), 14118–14124. https://doi.org/10.1523/JNEUROSCI.3340-12.2012.
Christianson, J.P., Flyer-Adams, J.G., Drugan, R.C., Amat, J., Daut, R.A., Foilb, A.R., Watkins, L.R., Maier, S.F., 2014. Learned stressor resistance requires extracellular signal-regulated kinase in the prefrontal cortex. Front. Behav. Neurosci. 8, 348. https://doi.org/10.3389/fnbeh.2014.00348.
Christoffel, D.J., Golden, S.A., Russo, S.J., 2011. Structural and synaptic plasticity in stress-related disorders. Rev. Neurosci. 22 (5), 535–549. https://doi.org/10.1515/RNS.2011.044.
Ciocchi, S., Herry, C., Grenier, F., Wolff, S.B.E., Letzkus, J.J., Vlachos, I., Ehrlich, I., Sprengel, R., Deisseroth, K., Stadler, M.B., Müller, C., Lüthi, A., 2010. Encoding of conditioned fear in central amygdala inhibitory circuits. Nature 468 (7321), 277–282. https://doi.org/10.1038/nature09559.
Clay, R., Hebert, M., Gill, G., Stapleton, L.A., Pridham, A., Coady, M., Bishop, J., Adamec, R.E., Blundell, J.J., 2011. Glucocorticoids are required for extinction of predator stress-induced hyperarousal. Neurobiol. Learn. Mem. 96 (2), 367–377. https://doi.org/10.1016/j.nlm.2011.06.012.
Clem, R.L., Huganir, R.L., 2010. Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. Science (New York, N.Y.) 330 (6007), 1108–1112. https://doi.org/10.1126/science.1195298.
Cole, S., McNally, G.P., 2009. Complementary roles for amygdala and periaqueductal gray in temporal-difference fear learning. Learning & Memory (Cold Spring Harbor, N.Y.) 16 (1), 1–7. https://doi.org/10.1101/lm.1120509.
Cook, S.C., Wellman, C.L., 2004. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J. Neurobiol. 60 (2), 236–248. https://doi.org/10.1002/neu.20025.
Corbit, L.H., Balleine, B.W., 2003. The role of prelimbic cortex in instrumental conditioning. Behav. Brain Res. 146 (1–2), 145–157. https://doi.org/10.1016/j.bbr.2003.09.023.
Cordero, M.I., Merino, J.J., Sandi, C., 1998. Correlational relationship between shock intensity and corticosterone secretion on the establishment and subsequent expression of contextual fear conditioning. Behav. Neurosci. 112 (4), 885–891. https://doi.org/10.1037//0735-7044.112.4.885.
Cowan, C.S.M., Callaghan, B.L., Richardson, R., 2013. Acute early-life stress results in premature emergence of adult-like fear retention and extinction relapse in infant rats. Behav. Neurosci. 127 (5), 703–711. https://doi.org/10.1037/a0034118.
Cruz, E., López, A.V., Porter, J.T., 2014. Spontaneous recovery of fear reverses extinction-induced excitability of infralimbic neurons. PLoS One 9 (8), e103596. https://doi.org/10.1371/journal.pone.0103596.
Dallman, M.F., Akana, S.F., Scribner, K.A., Bradbury, M.J., Walker, C.D., Strack, A.M., Cascio, C.S., 1992. Stress, feedback and facilitation in the hypothalamo-pituitary-adrenal axis. J. Neuroendocrinol. 4 (5), 517–526. https://doi.org/10.1111/j.1365-2826.1992.tb00200.x.
Davis, M., 2002. Role of NMDA receptors and MAP kinase in the amygdala in extinction of fear: clinical implications for exposure therapy. Eur. J. Neurosci. 16 (3), 395–398. https://doi.org/10.1046/j.1460-9568.2002.02138.x.
de Boer, S.F., Buwalda, B., Koolhaas, J.M., 2017. Untangling the neurobiology of coping styles in rodents: towards neural mechanisms underlying individual differences in disease susceptibility. Neurosci. Biobehav. Rev. 74 (Pt B), 401–422. https://doi.org/10.1016/j.neubiorev.2016.07.008.
de Quervain, D., Schwabe, L., Roozendaal, B., 2017. Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. 18 (1), 7–19. https://doi.org/10.1038/nrn.2016.155.
Dejean, C., Courtin, J., Rozeske, R.R., Bonnet, M.C., Dousset, V., Michelet, T., Herry, C., 2015. Neuronal circuits for fear expression and recovery: recent advances and potential therapeutic strategies. Biol. Psychiatry 78 (5), 298–306. https://doi.org/10.1016/j.biopsych.2015.03.017.
Dejean, C., Courtin, J., Karalis, N., Chaudun, F., Wurtz, H., Bienvenu, T.C.M., Herry, C., 2016. Prefrontal neuronal assemblies temporally control fear behaviour. Nature 535 (7612), 420. https://doi.org/10.1038/nature18630.
Deschaux, O., Zheng, X., Lavigne, J., Nachon, O., Cleren, C., Moreau, J.-L., Garcia, R., 2013. Post-extinction fluoxetine treatment prevents stress-induced reemergence of extinguished fear. Psychopharmacology 225 (1), 209–216. https://doi.org/10.1007/s00213-012-2806-x.
Deslauriers, J., Toth, M., Der-Avakian, A., Risbrough, V.B., 2018. Current status of animal models of posttraumatic stress disorder: behavioral and biological phenotypes, and future challenges in improving translation. Biol. Psychiatry 83 (10), 895–907. https://doi.org/10.1016/j.biopsych.2017.11.019.
Diehl, M.M., Bravo-Rivera, C., Quirk, G.J., 2019. The study of active avoidance: a platform for discussion. Neurosci. Biobehav. Rev. 107, 229–237. https://doi.org/10.1016/j.neubiorev.2019.09.010.
Do-Monte, F.H., Manzano-Nieves, G., Quiñones-Laracuente, K., Ramos-Medina, L., Quirk, G.J., 2015. Revisiting the role of infralimbic cortex in fear extinction with optogenetics. J. Neurosci. 35 (8), 3607–3615. https://doi.org/10.1523/JNEUROSCI.3137-14.2015.
Eliot, L., Ahmed, A., Khan, H., Patel, J., 2021. Dump the "dimorphism": comprehensive synthesis of human brain studies reveals few male-female differences beyond size. Neurosci. Biobehav. Rev. 125, 667–697. https://doi.org/10.1016/j.neubiorev.2021.02.026.
Falls, W.A., Miserendino, M.J., Davis, M., 1992. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. J. Neurosci. 12 (3), 854–863. https://doi.org/10.1523/JNEUROSCI.12-03-00854.1992.
Fanselow, M.S., 1994. Neural organization of the defensive behavior system responsible for fear. Psychon. Bull. Rev. 1 (4), 429–438. https://doi.org/10.3758/BF03210947.
Ferrara, N.C., Trask, S., Pullins, S.E., Helmstetter, F.J., 2021. Regulation of learned fear expression through the MgN-amygdala pathway. Neurobiol. Learn. Mem. 185, 107526 https://doi.org/10.1016/j.nlm.2021.107526.
Fitzgerald, P.J., Whittle, N., Flynn, S.M., Graybeal, C., Pinard, C.R., Gunduz-Cinar, O., Kravitz, A.V., Singewald, N., Holmes, A., 2014. Prefrontal single-unit firing associated with deficient extinction in mice. Neurobiol. Learn. Mem. 113, 69–81. https://doi.org/10.1016/j.nlm.2013.11.002.
Foilb, A.R., Christianson, J.P., 2018. 11—Brain mechanisms for learning and using safety signals. In: Sangha, S., Foti, D. (Eds.), Neurobiology of Abnormal Emotion and Motivated Behaviors. Academic Press, pp. 204–222. https://doi.org/10.1016/B978-0-12-813693-5.00011-3.
Foilb, A.R., Flyer-Adams, J.G., Maier, S.F., Christianson, J.P., 2016. Posterior insular cortex is necessary for conditioned inhibition of fear. Neurobiol. Learn. Mem. 134, 317–327. https://doi.org/10.1016/j.nlm.2016.08.004.
Foilb, A.R., Bals, J., Sarlitto, M.C., Christianson, J.P., 2018. Sex differences in fear discrimination do not manifest as differences in conditioned inhibition. Learn. Mem. 25 (1), 49–53. https://doi.org/10.1101/lm.045500.117.
Foilb, A.R., Sansaricq, G.N., Zona, E.E., Fernando, K., Christianson, J.P., 2021. Neural correlates of safety learning. Behav. Brain Res. 396, 112884 https://doi.org/10.1016/j.bbr.2020.112884.
Ganon-Elazar, E., Akirav, I., 2013. Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal-prefrontal circuit. Psychoneuroendocrinology 38 (9), 1675–1687. https://doi.org/10.1016/j.psyneuen.2013.01.014.
Garcia, R., Spennato, G., Nilsson-Todd, L., Moreau, J.-L., Deschaux, O., 2008. Hippocampal low-frequency stimulation and chronic mild stress similarly disrupt fear extinction memory in rats. Neurobiol. Learn. Mem. 89 (4), 560–566. https://doi.org/10.1016/j.nlm.2007.10.005.
Gee, D.G., Bath, K.G., Johnson, C.M., Meyer, H.C., Murty, V.P., Bos, Wvanden, Hartley, C.A., 2018. Neurocognitive development of motivated behavior: dynamic changes across childhood and adolescence. J. Neurosci. 38 (44), 9433–9445. https://doi.org/10.1523/JNEUROSCI.1674-18.2018.
Genud-Gabai, R., Klavir, O., Paz, R., 2013. Safety signals in the primate amygdala. J. Neurosci. 33 (46), 17986–17994. https://doi.org/10.1523/JNEUROSCI.1539-13.2013.
Gerhard, D.M., Meyer, H.C., Lee, F.S., 2020. An adolescent sensitive period for threat responding: impacts of stress and sex. Biol. Psychiatry 0 (0). https://doi.org/10.1016/j.biopsych.2020.10.003.
Gilmartin, M.R., Balderston, N.L., Helmstetter, F.J., 2014. Prefrontal cortical regulation of fear learning. Trends Neurosci. 37 (8), 455–464. https://doi.org/10.1016/j.tins.2014.05.004.
Giustino, T.F., Maren, S., 2015. The role of the medial prefrontal cortex in the conditioning and extinction of fear. Front. Behav. Neurosci. 9 https://doi.org/10.3389/fnbeh.2015.00298.
Giustino, T.F., Fitzgerald, P.J., Maren, S., 2016. Fear expression suppresses medial prefrontal cortical firing in rats. PLoS One 11 (10), e0165256. https://doi.org/10.1371/journal.pone.0165256.
Goode, T.D., Maren, S., 2014. Animal models of fear relapse. ILAR J. 55 (2), 246–258. https://doi.org/10.1093/ilar/ilu008.
Goode, T.D., Ressler, R.L., Acca, G.M., Miles, O.W., Maren, S., 2019. Bed nucleus of the stria terminalis regulates fear to unpredictable threat signals. ELife 8. https://doi.org/10.7554/eLife.46525.
Goode, T.D., Acca, G.M., Maren, S., 2020. Threat imminence dictates the role of the bed nucleus of the stria terminalis in contextual fear. Neurobiol. Learn. Mem. 167, 107116 https://doi.org/10.1016/j.nlm.2019.107116.
Gourley, S.L., Kedves, A.T., Olausson, P., Taylor, J.R., 2009. A history of corticosterone exposure regulates fear extinction and cortical NR2B, GluR2/3, and BDNF. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 34 (3), 707–716. https://doi.org/10.1038/npp.2008.123.
Gourley, S.L., Swanson, A.M., Koleske, A.J., 2013. Corticosteroid-induced neural remodeling predicts behavioral vulnerability and resilience. J. Neurosci. 33 (7), 3107–3112. https://doi.org/10.1523/JNEUROSCI.2138-12.2013.
Graham, B.M., Milad, M.R., 2013. Blockade of estrogen by hormonal contraceptives impairs fear extinction in female rats and women. Biol. Psychiatry 73 (4), 371–378. https://doi.org/10.1016/j.biopsych.2012.09.018.

Graham, B.M., Milad, M.R., 2014. Inhibition of estradiol synthesis impairs fear extinction in male rats. Learn. Mem. 21 (7), 347–350. https://doi.org/10.1101/lm.034926.114.

Grahn, R.E., Will, M.J., Hammack, S.E., Maswood, S., McQueen, M.B., Watkins, L.R., Maier, S.F., 1999. Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. Brain Res. 826 (1), 35–43.

Green, M.K., Rani, C.S.S., Joshi, A., Soto-Piña, A.E., Martinez, P.A., Frazer, A., Strong, R., Morilak, D.A., 2011. Prenatal stress induces long term stress vulnerability, compromising stress response systems in the brain and impairing extinction of conditioned fear after adult stress. Neuroscience 192, 438–451. https://doi.org/10.1016/j.neuroscience.2011.06.041.

Greenwood, B.N., Fleshner, M., 2008. Exercise, learned helplessness, and the stress-resistant brain. Neuromolecular Med. 10 (2), 81–98. https://doi.org/10.1007/s12017-008-8029-y.

Greenwood, B.N., Strong, P.V., Fleshner, M., 2010. Lesions of the basolateral amygdala reverse the long-lasting interference with shuttle box escape produced by uncontrollable stress. Behav. Brain Res. 211 (1), 71–76. https://doi.org/10.1016/j.bbr.2010.03.012.

Greiner, E.M., Müller, I., Norris, M.R., Ng, K.H., Sangha, S., 2019. Sex differences in fear regulation and reward-seeking behaviors in a fear-safety-reward discrimination task. Behav. Brain Res. 368, 111903 https://doi.org/10.1016/j.bbr.2019.111903.

Gross, C.T., Canteras, N.S., 2012. The many paths to fear. Nat. Rev. Neurosci. 13 (9), 651–658. https://doi.org/10.1038/nrn3301.

Gruene, T.M., Flick, K., Stefano, A., Shea, S.D., Shansky, R.M., 2015. Sexually divergent expression of active and passive conditioned fear responses in rats. ELife 4, e11352. https://doi.org/10.7554/eLife.11352.

Hagihara, K.M., Bukalo, O., Zeller, M., Aksoy-Aksel, A., Karalis, N., Limoges, A., Rigg, T., Campbell, T., Mendez, A., Weinholtz, C., Mahn, M., Zweifel, L.S., Palmiter, R.D., Ehrlich, I., Lüthi, A., Holmes, A., 2021. Intercalated amygdala clusters orchestrate a switch in fear state. Nature 594 (7863), 403–407. https://doi.org/10.1038/s41586-021-03593-1.

Hajos, M., Richards, C.D., Szekely, A.D., Sharp, T., 1998. An electrophysiological and neuroanatomical study of the medial prefrontal cortical projection to the midbrain raphe nuclei in the rat. Neuroscience 87 (1), 95–108.

Hammack, S.E., Cooper, M.A., Lezak, K.R., 2012. Overlapping neurobiology of learned helplessness and conditioned defeat: implications for PTSD and mood disorders. Neuropharmacology 62 (2), 565–575. https://doi.org/10.1016/j.neuropharm.2011.02.024.

Hassien, A.M., Shue, F., Bernier, B.E., Drew, M.R., 2020. A mouse model of stress-enhanced fear learning demonstrates extinction-sensitive and extinction-resistant effects of footshock stress. Behav. Brain Res. 379, 112391 https://doi.org/10.1016/j.bbr.2019.112391.

Haubensak, W., Kunwar, P.S., Cai, H., Ciocchi, S., Wall, N.R., Ponnusamy, R., Biag, J., Dong, H.-W., Deisseroth, K., Callaway, E.M., Fanselow, M.S., Lüthi, A., Anderson, D. J., 2010. Genetic dissection of an amygdala microcircuit that gates conditioned fear. Nature 468 (7321), 270–276. https://doi.org/10.1038/nature09553.

Hayashi-Takagi, A., Yagishita, S., Nakamura, M., Shirai, F., Wu, Y.I., Loshbaugh, A.L., Kuhlman, B., Hahn, K.M., Kasai, H., 2015. Labelling and optical erasure of synaptic memory traces in the motor cortex. Nature 525 (7569), 333–338. https://doi.org/10.1038/nature15257.

Hefner, K., Whittle, N., Juhasz, J., Norcross, M., Karlsson, R.-M., Saksida, L.M., Bussey, T. J., Singewald, N., Holmes, A., 2008. Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain. J. Neurosci. 28 (32), 8074–8085. https://doi.org/10.1523/JNEUROSCI.4904-07.2008.

Henry, J.P., Stephens, P.M., 1977. Stress, Health, and the Social Environment: A Sociobiologic Approach to Medicine. Springer-Verlag. https://doi.org/10.1007/978-1-4612-6363-0.

Herman, J.P., Adams, D., Prewitt, C., 1995. Regulatory changes in neuroendocrine stress-integrative circuitry produced by a variable stress paradigm. Neuroendocrinology 61 (2), 180–190. https://doi.org/10.1159/000126839.

Herry, C., Ciocchi, S., Senn, V., Demmou, L., Müller, C., Lüthi, A., 2008. Switching on and off fear by distinct neuronal circuits. Nature 454 (7204), 600–606. https://doi.org/10.1038/nature07166.

Hobin, J.A., Ji, J., Maren, S., 2006. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. Hippocampus 16 (2), 174–182. https://doi.org/10.1002/hipo.20144.

Hofer, M.A., Shair, H.N., 1987. Isolation distress in two-week-old rats: influence of home cage, social companions, and prior experience with littermates. Dev. Psychobiol. 20 (4), 465–476. https://doi.org/10.1002/dev.420200410.

Hoffman, A.N., Lorson, N.G., Sanabria, F., Foster Olive, M., Conrad, C.D., 2014. Chronic stress disrupts fear extinction and enhances amygdala and hippocampal Fos expression in an animal model of post-traumatic stress disorder. Neurobiol. Learn. Mem. 112, 139–147. https://doi.org/10.1016/j.nlm.2014.01.018.

Iacoviello, B.M., Charney, D.S., 2014. Psychosocial facets of resilience: Implications for preventing posttrauma psychopathology, treating trauma survivors, and enhancing community resilience. Eur. J. Psychotraumatol. 5.

Ishikawa, S., Saito, Y., Yanagawa, Y., Otani, S., Hiraide, S., Shimamura, K., Matsumoto, M., Togashi, H., 2012. Early postnatal stress alters extracellular signal-regulated kinase signaling in the corticolimbic system modulating emotional circuitry in adult rats. Eur. J. Neurosci. 35 (1), 135–145. https://doi.org/10.1111/j.1460-9568.2011.07921.x.

Izquierdo, A., Wellman, C.L., Holmes, A., 2006. Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J. Neurosci. 26 (21), 5733–5738. https://doi.org/10.1523/JNEUROSCI.0474-06.2006.

Jackson, R.L., Minor, T.R., 1988. Effects of signaling inescapable shock on subsequent escape learning: Implications for theories of coping and "learned helplessness.". J. Exp. Psychol. Anim. Behav. Process. 14 (4), 390–400.

Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517 (7534), 284–292. https://doi.org/10.1038/nature14188.

Jankowski, M.P., Sesack, S.R., 2004. Prefrontal cortical projections to the rat dorsal raphe nucleus: ultrastructural features and associations with serotonin and gamma-aminobutyric acid neurons. J. Comp. Neurol. 468 (4), 518–529. https://doi.org/10.1002/cne.10976.

Jin, J., Maren, S., 2015. Fear renewal preferentially activates ventral hippocampal neurons projecting to both amygdala and prefrontal cortex in rats. Sci. Rep. 5, 8388. https://doi.org/10.1038/srep08388.

Johansen, J.P., Tarpley, J.W., LeDoux, J.E., Blair, H.T., 2010. Neural substrates for expectation-modulated fear learning in the amygdala and periaqueductal gray. Nat. Neurosci. 13 (8), 979–986. https://doi.org/10.1038/nn.2594.

Judo, C., Matsumoto, M., Yamazaki, D., Hiraide, S., Yanagawa, Y., Kimura, S., Shimamura, K., Togashi, H., 2010. Early stress exposure impairs synaptic potentiation in the rat medial prefrontal cortex underlying contextual fear extinction. Neuroscience 169 (4), 1705–1714. https://doi.org/10.1016/j.neuroscience.2010.06.035.

Karalis, N., Dejean, C., Chaudun, F., Khoder, S., Rozeske, R.R., Wurtz, H., Bagur, S., Benchenane, K., Sirota, A., Courtin, J., Herry, C., 2016. 4-Hz oscillations synchronize prefrontal-amygdala circuits during fear behavior. Nat. Neurosci. 19 (4), 605–612. https://doi.org/10.1038/nn.4251.

Karstoft, K.-I., Galatzer-Levy, I.R., Statnikov, A., Li, Z., Shalev, A.Y., members of Jerusalem Trauma Outreach and Prevention Study (J-TOPS) group, 2015. Bridging a translational gap: Using machine learning to improve the prediction of PTSD. BMC Psychiatry 15, 30. https://doi.org/10.1186/s12888-015-0399-8.

Kasai, H., Matsuzaki, M., Noguchi, J., Yasumatsu, N., Nakahara, H., 2003. Structure-stability-function relationships of dendritic spines. Trends Neurosci. 26 (7), 360–368. https://doi.org/10.1016/s0166-2236(03)00162-0.

Kazama, A.M., Heuer, E., Davis, M., Bachevalier, J., 2012. Effects of neonatal amygdala lesions on fear learning, conditioned inhibition, and extinction in adult macaques. Behav. Neurosci. 126 (3), 392–403. https://doi.org/10.1037/a0028241.

Keay, K.A., Bandler, R., 2001. Parallel circuits mediating distinct emotional coping reactions to different types of stress. Neurosci. Biobehav. Rev. 25 (7–8), 669–678. https://doi.org/10.1016/s0149-7634(01)00049-5.

Keiser, A.A., Turnbull, L.M., Darian, M.A., Feldman, D.E., Song, I., Tronson, N.C., 2017. Sex differences in context fear generalization and recruitment of Hippocampus and amygdala during retrieval. Neuropsychopharmacology 42 (2), 397–407. https://doi.org/10.1038/npp.2016.174.

Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B., Zaslavsky, A.M., 2005. US prevalence and treatment of mental disorders: 1990–2003. N. Engl. J. Med. 352 (24), 2515–2523. https://doi.org/10.1056/NEJMsa043266.

Knapska, E., Maren, S., 2009. Reciprocal patterns of c-Fos expression in the medial prefrontal cortex and amygdala after extinction and renewal of conditioned fear. Learn. Mem. 16 (8), 486–493. https://doi.org/10.1101/lm.1463909.

Knapska, E., Macias, M., Mikosz, M., Nowak, A., Owczarek, D., Wawrzyniak, M., Pieprzyk, M., Cymerman, I.A., Werka, T., Sheng, M., Maren, S., Jaworski, J., Kaczmarek, L., 2012. Functional anatomy of neural circuits regulating fear and extinction. Proc. Natl. Acad. Sci. U.S.A. 109 (42), 17093–17098. https://doi.org/10.1073/pnas.1202087109.

Knox, D., Perrine, S.A., George, S.A., Galloway, M.P., Liberzon, I., 2010. Single prolonged stress decreases glutamate, glutamine, and creatine concentrations in the rat medial prefrontal cortex. Neurosci. Lett. 480 (1), 16–20. https://doi.org/10.1016/j.neulet.2010.05.052.

Knox, D., George, S.A., Fitzpatrick, C.J., Rabinak, C.A., Maren, S., Liberzon, I., 2012. Single prolonged stress disrupts retention of extinguished fear in rats. Learn. Mem. 19 (2), 43–49. https://doi.org/10.1101/lm.024356.111.

Knox, D., Stanfield, B.R., Staib, J.M., David, N.P., Keller, S.M., DePietro, T., 2016. Neural circuits via which single prolonged stress exposure leads to fear extinction retention deficits. Learn. Mem. 23 (12), 689–698. https://doi.org/10.1101/lm.043141.116.

Kong, E., Monje, F.J., Hirsch, J., Pollak, D.D., 2014. Learning not to fear: neural correlates of learned safety. Neuropsychopharmacology 39 (3), 515–527.

Konorski, J., 1967. Integrative Activity of the Brain: An Interdisciplinary Approach. University of Chicago Press.

Koolhaas, J.M., Korte, S.M., De Boer, S.F., Van Der Vegt, B.J., Van Reenen, C.G., Hopster, H., De Jong, I.C., Ruis, M.A., Blokhuis, H.J., 1999. Coping styles in animals: current status in behavior and stress-physiology. Neurosci. Biobehav. Rev. 23 (7), 925–935. https://doi.org/10.1016/s0149-7634(99)00026-3.

Koolhaas, J.M., de Boer, S.F., Coppens, C.M., Buwalda, B., 2010. Neuroendocrinology of coping styles: towards understanding the biology of individual variation. Front. Neuroendocrinol. 31 (3), 307–321. https://doi.org/10.1016/j.yfrne.2010.04.001.

Krueger, J.N., Sangha, S., 2021. On the Basis of Sex: Differences in Safety Discrimination vs. Conditioned Inhibition. Behav. Brain Res., 113024 https://doi.org/10.1016/j.bbr.2020.113024.

Kubala, K.H., Christianson, J.P., Kaufman, R.D., Watkins, L.R., Maier, S.F., 2012. Short- and long-term consequences of stressor controllability in adolescent rats. Behav. Brain Res. 234 (2), 278–284. https://doi.org/10.1016/j.bbr.2012.06.027.

Lacagnina, A.F., Brockway, E.T., Crovetti, C.R., Shue, F., McCarty, M.J., Sattler, K.P., Lim, S.C., Santos, S.L., Denny, C.A., Drew, M.R., 2019. Distinct hippocampal engrams control extinction and relapse of fear memory. Nat. Neurosci. 22 (5), 753–761. https://doi.org/10.1038/s41593-019-0361-z.

Lazarus, R.S., Folkman, S., 1984. Stress, Appraisal, and Coping. Springer Publishing Company.

Levine, S., 2000. Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. Eur. J. Pharmacol. 405 (1–3), 149–160. https://doi.org/10.1016/s0014-2999(00)00548-3.
Li, X.B., Inoue, T., Nakagawa, S., Koyama, T., 2004. Effect of mediodorsal thalamic nucleus lesion on contextual fear conditioning in rats. Brain Res. 1008 (2), 261–272. https://doi.org/10.1016/j.brainres.2004.02.038.
Li, Y., Dong, X., Li, S., Kirouac, G.J., 2014. Lesions of the posterior paraventricular nucleus of the thalamus attenuate fear expression. Front. Behav. Neurosci. 8, 94. https://doi.org/10.3389/fnbeh.2014.00094.
Liberzon, I., Krstov, M., Young, E.A., 1997. Stress-restress: effects on ACTH and fast feedback. Psychoneuroendocrinology 22 (6), 443–453. https://doi.org/10.1016/s0306-4530(97)00044-9.
Lin, C.-H., Yeh, S.-H., Lu, H.-Y., Gean, P.-W., 2003. The similarities and diversities of signal pathways leading to consolidation of conditioning and consolidation of extinction of fear memory. J. Neurosci. 23 (23), 8310–8317. https://doi.org/10.1523/JNEUROSCI.23-23-08310.2003.
Liston, C., Gan, W.-B., 2011. Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. Proc. Natl. Acad. Sci. 108 (38), 16074–16079. https://doi.org/10.1073/pnas.1110444108.
Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., Hof, P.R., Morrison, J.H., McEwen, B.S., 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. 26 (30), 7870–7874. https://doi.org/10.1523/JNEUROSCI.1184-06.2006.
Liston, C., Cichon, J.M., Jeanneteau, F., Jia, Z., Chao, M.V., Gan, W.-B., 2013. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. Nat. Neurosci. 16 (6), 698–705. https://doi.org/10.1038/nn.3387.
Long, V.A., Fanselow, M.S., 2012. Stress-enhanced fear learning in rats is resistant to the effects of immediate massed extinction. Stress 15 (6), 627–636. https://doi.org/10.3109/10253890.2011.650251.
Lopez, J., Bagot, R.C., 2021. Defining valid chronic stress models for depression with female rodents. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2021.03.010.
Lowry, C.A., Johnson, P.L., Hay-Schmidt, A., Mikkelsen, J., Shekhar, A., 2005. Modulation of anxiety circuits by serotonergic systems. Stress 8 (4), 233–246. https://doi.org/10.1080/10253890500492787.
Magariños, A.M., McEwen, B.S., 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors. Neuroscience 69 (1), 83–88. https://doi.org/10.1016/0306-4522(95)00256-I.
Maier, S.F., Keith, J.R., 1987. Shock signals and the development of stress-induced analgesia. J. Exp. Psychol. Anim. Behav. Process. 13 (3), 226–238.
Maier, S.F., Seligman, M.E.P., 2016. Learned helplessness at fifty: insights from neuroscience. Psychol. Rev. 123 (4), 349–367. https://doi.org/10.1037/rev0000033.
Maier, S.F., Watkins, L.R., 1998. Stressor controllability, anxiety, and serotonin. Cognit. Ther. Res. 22 (6), 595–613.
Maier, S.F., Watkins, L.R., 2005. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci. Biobehav. Rev. 29 (4–5), 829–841. https://doi.org/10.1016/j.neubiorev.2005.03.021.
Maier, S.F., Seligman, M.E.P., Solomon, R.L., 1969. Pavlovian fear conditioning and learned helplessness: effects on escape and avoidance behavior of (a) the CS-US contingency, and (b) the independence of the US and voluntary responding. In: Campbell, B.A., Church, R.M. (Eds.), Punishment and Aversive Behavior. Appleton-Century-Crofts, pp. 299–342.
Maier, S.F., Busch, C.R., Maswood, S., Grahn, R.E., Watkins, L.R., 1995a. The dorsal raphe nucleus is a site of action mediating the behavioral effects of the benzodiazepine receptor inverse agonist DMCM. Behav. Neurosci. 109 (4), 759–766. https://doi.org/10.1037//0735-7044.109.4.759.
Maier, S.F., Grahn, R.E., Watkins, L.R., 1995b. 8-OH-DPAT microinjected in the region of the dorsal raphe nucleus blocks and reverses the enhancement of fear conditioning and interference with escape produced by exposure to inescapable shock. Behav. Neurosci. 109 (3), 404–412. https://doi.org/10.1037//0735-7044.109.3.404.
Maras, P.M., Molet, J., Chen, Y., Rice, C., Ji, S.G., Solodkin, A., Baram, T.Z., 2014. Preferential loss of dorsal-hippocampus synapses underlies memory impairments provoked by short, multimodal stress. Mol. Psychiatry 19 (7), 811–822. https://doi.org/10.1038/mp.2014.12.
Marek, R., Jin, J., Goode, T.D., Giustino, T.F., Wang, Q., Acca, G.M., Holehonnur, R., Ploski, J.E., Fitzgerald, P.J., Lynagh, T., Lynch, J.W., Maren, S., Sah, P., 2018. Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. Nat. Neurosci. 21 (3), 384–392. https://doi.org/10.1038/s41593-018-0073-9.
Maren, S., Holmes, A., 2016. Stress and fear extinction. Neuropsychopharmacology 41 (1), 58–79. https://doi.org/10.1038/npp.2015.180.
Maren, S., Holt, W., 2000. The hippocampus and contextual memory retrieval in Pavlovian conditioning. Behav. Brain Res. 110 (1–2), 97–108. https://doi.org/10.1016/s0166-4328(99)00188-6.
Maren, S., Phan, K.L., Liberzon, I., 2013. The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat. Rev. Neurosci. 14 (6), 417–428. https://doi.org/10.1038/nrn3492.
Maroun, M., 2006. Stress reverses plasticity in the pathway projecting from the ventromedial prefrontal cortex to the basolateral amygdala. Eur. J. Neurosci. 24 (10), 2917–2922. https://doi.org/10.1111/j.1460-9568.2006.05169.x.
Maroun, M., Ioannides, P.J., Bergman, K.L., Kavushansky, A., Holmes, A., Wellman, C.L., 2013. Fear extinction deficits following acute stress associate with increased spine density and dendritic retraction in basolateral amygdala neurons. Eur. J. Neurosci. 38 (4), 2611–2620. https://doi.org/10.1111/ejn.12259.
Maswood, S., Barter, J.E., Watkins, L.R., Maier, S.F., 1998. Exposure to inescapable but not escapable shock increases extracellular levels of 5-HT in the dorsal raphe nucleus of the rat. Brain Res. 783 (1), 115–120.
Mataix-Cols, D., Fernandez de la Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., Frumento, P., de Kleine, R., Difede, J., Dunlop, B.W., Farrell, L.J., Geller, D., Gerardi, M., Guastella, A.J., Hofmann, S.G., Hendriks, G.-J., Kushner, M. G., Lee, F.S., Lenze, E.J., et al., 2017. D-Cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis of individual participant data. JAMA Psychiatry 74 (5), 501–510. https://doi.org/10.1001/jamapsychiatry.2016.3955.
Matsuzaki, M., Honkura, N., Ellis-Davies, G.C.R., Kasai, H., 2004. Structural basis of long-term potentiation in single dendritic spines. Nature 429 (6993), 761–766. https://doi.org/10.1038/nature02617.
Mcewen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann. N. Y. Acad. Sci. 1032 (1), 1–7. https://doi.org/10.1196/annals.1314.001.
McEwen, B.S., Morrison, J.H., 2013. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79 (1), 16–29. https://doi.org/10.1016/j.neuron.2013.06.028.
McGaugh, J.L., 2000. Memory—a century of consolidation. Science 287 (5451), 248–251. https://doi.org/10.1126/science.287.5451.248.
McGaugh, J.L., Roozendaal, B., 2002. Role of adrenal stress hormones in forming lasting memories in the brain. Curr. Opin. Neurobiol. 12 (2), 205–210. https://doi.org/10.1016/s0959-4388(02)00306-9.
McNally, G.P., Cole, S., 2006. Opioid receptors in the midbrain periaqueductal gray regulate prediction errors during pavlovian fear conditioning. Behav. Neurosci. 120 (2), 313–323. https://doi.org/10.1037/0735-7044.120.2.313.
McNally, G.P., Westbrook, R.F., 2006. Predicting danger: the nature, consequences, and neural mechanisms of predictive fear learning. Learn. Mem. 13 (3), 245–253. https://doi.org/10.1101/lm.196606.
McNally, G.P., Johansen, J.P., Blair, H.T., 2011. Placing prediction into the fear circuit. Trends Neurosci. 34 (6), 283–292. https://doi.org/10.1016/j.tins.2011.03.005.
Meyer, H.C., Lee, F.S., 2019. Translating developmental neuroscience to understand risk for psychiatric disorders. Am. J. Psychiatry 176 (3), 179–185. https://doi.org/10.1176/appi.ajp.2019.19010091.
Meyer, E.M., Long, V., Fanselow, M.S., Spigelman, I., 2013. Stress increases voluntary alcohol intake, but does not alter established drinking habits in a rat model of posttraumatic stress disorder. Alcohol. Clin. Exp. Res. 37 (4), 566–574. https://doi.org/10.1111/acer.12012.
Meyer, H.C., Odriozola, P., Cohodes, E.M., Mandell, J.D., Li, A., Yang, R., Hall, B.S., Haberman, J.T., Zacharek, S.J., Liston, C., Lee, F.S., Gee, D.G., 2019. Ventral hippocampus interacts with prelimbic cortex during inhibition of threat response via learned safety in both mice and humans. Proc. Natl. Acad. Sci. 116 (52), 26970–26979. https://doi.org/10.1073/pnas.1910481116.
Meyer, H.C., Gerhard, D.M., Amelio, P.A., Lee, F.S., 2021. Pre-adolescent stress disrupts adult, but not adolescent, safety learning. Behav. Brain Res. 400, 113005 https://doi.org/10.1016/j.bbr.2020.113005.
Milad, M.R., Quirk, G.J., 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420 (6911), 70–74. https://doi.org/10.1038/nature01138.
Milad, M.R., Vidal-Gonzalez, I., Quirk, G.J., 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav. Neurosci. 118 (2), 389–394. https://doi.org/10.1037/0735-7044.118.2.389.
Minor, T.R., 1990. Conditioned fear and neophobia following inescapable shock. Anim. Learn. Behav. 18 (2), 212–226. https://doi.org/10.3758/Bf03205261.
Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A., Chattarji, S., 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc. Natl. Acad. Sci. U.S.A. 102 (26), 9371–9376. https://doi.org/10.1073/pnas.0504011102.
Mochcovitch, M.D., da Rocha Freire, R.C., Garcia, R.F., Nardi, A.E., 2014. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J. Affect. Disord. 167, 336–342. https://doi.org/10.1016/j.jad.2014.06.041.
Moda-Sava, R.N., Murdock, M.H., Parekh, P.K., Fetcho, R.N., Huang, B.S., Huynh, T.N., Witztum, J., Shaver, D.C., Rosenthal, D.L., Alway, E.J., Lopez, K., Meng, Y., Nellissen, L., Grosenick, L., Milner, T.A., Deisseroth, K., Bito, H., Kasai, H., Liston, C., 2019. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 364 (6436), eaat8078. https://doi.org/10.1126/science.aat8078.
Morgan, M.A., LeDoux, J.E., 1995. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav. Neurosci. 109 (4), 681–688. https://doi.org/10.1037//0735-7044.109.4.681.
Moriceau, S., Sullivan, R.M., 2006. Maternal presence serves as a switch between learning fear and attraction in infancy. Nat. Neurosci. 9 (8), 1004–1006. https://doi.org/10.1038/nn1733.
Morrison, F.G., Ressler, K.J., 2014. From the neurobiology of extinction to improved clinical treatments. Depress. Anxiety 31 (4), 279–290. https://doi.org/10.1002/da.22214.
Muigg, P., Hetzenauer, A., Hauer, G., Hauschild, M., Gaburro, S., Frank, E., Landgraf, R., Singewald, N., 2008. Impaired extinction of learned fear in rats selectively bred for high anxiety—evidence of altered neuronal processing in prefrontal-amygdala pathways. Eur. J. Neurosci. 28 (11), 2299–2309. https://doi.org/10.1111/j.1460-9568.2008.06511.x.
Müller, I., Brinkman, A.L., Sowinski, E.M., Sangha, S., 2018. Adolescent conditioning affects rate of adult fear, safety and reward learning during discriminative conditioning. Sci. Rep. 8 (1), 17315 https://doi.org/10.1038/s41598-018-35678-9.

Müller, I., Adams, D.D., Sangha, S., Chester, J.A., 2021. Juvenile stress facilitates safety learning in male and female high alcohol preferring mice. Behav. Brain Res., 113006 https://doi.org/10.1016/j.bbr.2020.113006.
Myers, K.M., Davis, M., 2002. Behavioral and neural analysis of extinction. Neuron 36 (4), 567–584. https://doi.org/10.1016/S0896-6273(02)01064-4.
Naert, A., Callaerts-Vegh, Z., D'Hooge, R., 2011. Nocturnal hyperactivity, increased social novelty preference and delayed extinction of fear responses in post-weaning socially isolated mice. Brain Res. Bull. 85 (6), 354–362. https://doi.org/10.1016/j.brainresbull.2011.03.027.
Ng, K.H., Pollock, M.W., Urbanczyk, P.J., Sangha, S., 2018. Altering D1 receptor activity in the basolateral amygdala impairs fear suppression during a safety cue. Neurobiol. Learn. Mem. 147 (Supplement C), 26–34. https://doi.org/10.1016/j.nlm.2017.11.011.
Novick, A.M., Mears, M., Forster, G.L., Lei, Y., Tejani-Butt, S.M., Watt, M.J., 2016. Adolescent social defeat alters N-methyl-d-aspartic acid receptor expression and impairs fear learning in adulthood. Behav. Brain Res. 304, 51–59. https://doi.org/10.1016/j.bbr.2016.02.013.
Nyhuis, T.J., Masini, C.V., Day, H.E.W., Campeau, S., 2016. Evidence for the integration of stress-related signals by the rostral posterior hypothalamic nucleus in the regulation of acute and repeated stress-evoked hypothalamo-pituitary-Adrenal response in rat. J. Neurosci. 36 (3), 795–805. https://doi.org/10.1523/JNEUROSCI.3413-15.2016.
Odriozola, P., Gee, D.G., 2020. Learning about safety: conditioned inhibition as a novel approach to fear reduction targeting the developing brain. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2020.20020232 appi.ajp.2020.20020232.
Opendak, M., Sullivan, R.M., 2019. Unique infant neurobiology produces distinctive trauma processing. Dev. Cogn. Neurosci. 36, 100637 https://doi.org/10.1016/j.dcn.2019.100637.
Opendak, M., Robinson-Drummer, P., Blomkvist, A., Zanca, R.M., Wood, K., Jacobs, L., Chan, S., Tan, S., Woo, J., Venkataraman, G., Kirschner, E., Lundström, J.N., Wilson, D.A., Serrano, P.A., Sullivan, R.M., 2019. Neurobiology of maternal regulation of infant fear: the role of mesolimbic dopamine and its disruption by maltreatment. Neuropsychopharmacology 44 (7), 1247–1257. https://doi.org/10.1038/s41386-019-0340-9.
Orsini, C.A., Maren, S., 2012. Neural and cellular mechanisms of fear and extinction memory formation. Neurosci. Biobehav. Rev. 36 (7), 1773–1802. https://doi.org/10.1016/j.neubiorev.2011.12.014.
Orsini, C.A., Kim, J.H., Knapska, E., Maren, S., 2011. Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. J. Neurosci. 31 (47), 17269–17277. https://doi.org/10.1523/JNEUROSCI.4095-11.2011.
Orsini, C.A., Yan, C., Maren, S., 2013. Ensemble coding of context-dependent fear memory in the amygdala. Front. Behav. Neurosci. 7 https://doi.org/10.3389/fnbeh.2013.00199.
Ostroff, L.E., Cain, C.K., Bedont, J., Monfils, M.H., LeDoux, J.E., 2010. Fear and safety learning differentially affect synapse size and dendritic translation in the lateral amygdala. Proc. Natl. Acad. Sci. 107 (20), 9418–9423. https://doi.org/10.1073/pnas.0913384107.
Ozawa, T., Ycu, E.A., Kumar, A., Yeh, L.-F., Ahmed, T., Koivumaa, J., Johansen, J.P., 2017. A feedback neural circuit for calibrating aversive memory strength. Nat. Neurosci. 20 (1), 90–97. https://doi.org/10.1038/nn.4439.
Padilla-Coreano, N., Do-Monte, F.H., Quirk, G.J., 2012. A time-dependent role of midline thalamic nuclei in the retrieval of fear memory. Neuropharmacology 62 (1), 457–463. https://doi.org/10.1016/j.neuropharm.2011.08.037.
Pape, H.-C., Pare, D., 2010. Plastic synaptic networks of the Amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol. Rev. 90 (2), 419–463. https://doi.org/10.1152/physrev.00037.2009.
Pattwell, S.S., Bath, K.G., 2017. Emotional learning, stress, and development: an ever-changing landscape shaped by early-life experience. Neurobiol. Learn. Mem. 143, 36–48. https://doi.org/10.1016/j.nlm.2017.04.014.
Pattwell, S.S., Lee, F.S., Casey, B.J., 2013. Fear learning and memory across adolescent development: hormones and Behavior Special Issue: puberty and Adolescence. Horm. Behav. 64 (2), 380–389. https://doi.org/10.1016/j.yhbeh.2013.01.016.
Pavlov, I.P., 1927. Conditioned Reflexes: an Investigation of the Physiological Activity of the Cerebral Cortex. Oxford Univ. Press.
Perusini, J.N., Meyer, E.M., Long, V.A., Rau, V., Nocera, N., Avershal, J., Maksymetz, J., Spigelman, I., Fanselow, M.S., 2016. Induction and expression of fear sensitization caused by acute traumatic stress. Neuropsychopharmacology 41 (1), 45–57. https://doi.org/10.1038/npp.2015.224.
Polderman, T.J.C., Kreukels, B.P.C., Irwig, M.S., Beach, L., Chan, Y.-M., Derks, E.M., Esteva, I., Ehrenfeld, J., Heijer, M.D., Posthuma, D., Raynor, L., Tishelman, A., Davis, L.K., on behalf of the International Gender Diversity Genomics Consortium, 2018. The biological contributions to gender identity and gender diversity: bringing data to the table. Behav. Genet. 48 (2), 95–108. https://doi.org/10.1007/s10519-018-9889-z.
Pollak, D.D., Monje, F.J., Zuckerman, L., Denny, C.A., Drew, M.R., Kandel, E.R., 2008. An animal model of a behavioral intervention for depression. Neuron 60 (1), 149–161. https://doi.org/10.1016/j.neuron.2008.07.041.
Ponomarev, I., Rau, V., Eger, E.I., Harris, R.A., Fanselow, M.S., 2010. Amygdala transcriptome and cellular mechanisms underlying stress-enhanced fear learning in a rat model of posttraumatic stress disorder. Neuropsychopharmacology 35 (6), 1402–1411. https://doi.org/10.1038/npp.2010.10.
Preston, A.R., Eichenbaum, H., 2013. Interplay of hippocampus and prefrontal cortex in memory. Current Biology: CB 23 (17), R764–773. https://doi.org/10.1016/j.cub.2013.05.041.
Quirk, G.J., Russo, G.K., Barron, J.L., Lebron, K., 2000. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J. Neurosci. 20 (16), 6225–6231.
Radley, J.J., Sawchenko, P.E., 2015. Evidence for involvement of a limbic paraventricular hypothalamic inhibitory network in hypothalamic-pituitary-adrenal axis adaptations to repeated stress. J. Comp. Neurol. 523 (18), 2769–2787. https://doi.org/10.1002/cne.23815.
Radley, J.J., Sisti, H.M., Hao, J., Rocher, A.B., McCall, T., Hof, P.R., McEwen, B.S., Morrison, J.H., 2004. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125 (1), 1–6. https://doi.org/10.1016/j.neuroscience.2004.01.006.
Radley, J.J., Rocher, A.B., Rodriguez, A., Ehlenberger, D.B., Dammann, M., McEwen, B.S., Morrison, J.H., Wearne, S.L., Hof, P.R., 2008. Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. J. Comp. Neurol. 507 (1), 1141–1150. https://doi.org/10.1002/cne.21588.
Radley, J.J., Kabbaj, M., Jacobson, L., Heydendael, W., Yehuda, R., Herman, J.P., 2011. Stress Risk Factors and sTRESS-rELATED pathology: neuroplasticity, EPIGENETICS and ENDOPHENOTYPES. Stress 14 (5), 481–497. https://doi.org/10.3109/10253890.2011.604751.
Raio, C.M., Phelps, E.A., 2015. The influence of acute stress on the regulation of conditioned fear. Neurobiol. Stress 1, 134–146. https://doi.org/10.1016/j.ynstr.2014.11.004.
Ramanathan, K.R., Jin, J., Giustino, T.F., Payne, M.R., Maren, S., 2018. Prefrontal projections to the thalamic nucleus reuniens mediate fear extinction. Nat. Commun. 9 (1), 4527. https://doi.org/10.1038/s41467-018-06970-z.
Rau, V., Fanselow, M.S., 2009. Exposure to a stressor produces a long lasting enhancement of fear learning in rats. Stress 12 (2), 125–133. https://doi.org/10.1080/10253890802137320.
Rau, V., DeCola, J.P., Fanselow, M.S., 2005. Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. Neurosci. Biobehav. Rev. 29 (8), 1207–1223. https://doi.org/10.1016/j.neubiorev.2005.04.010.
Ray, M.H., Russ, A.N., Walker, R.A., McDannald, M.A., 2020. The nucleus accumbens core is necessary to scale fear to degree of threat. J. Neurosci. 40 (24), 4750–4760. https://doi.org/10.1523/JNEUROSCI.0299-20.2020.
Rescorla, R.A., 1969. Conditioned inhibition of fear resulting from negative CS-US contingencies. J. Comp. Physiol. Psychol. 67 (4), 504–509.
Ressler, K.J., Mercer, K.B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., Norrholm, S.D., Kilaru, V., Smith, A.K., Myers, A.J., Ramirez, M., Engel, A., Hammack, S.E., Toufexis, D., Braas, K.M., Binder, E.B., May, V., 2011. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature 470 (7335), 492–497. https://doi.org/10.1038/nature09856.
Ressler, R.L., Goode, T.D., Evemy, C., Maren, S., 2020. NMDA receptors in the CeA and BNST differentially regulate fear conditioning to predictable and unpredictable threats. Neurobiol. Learn. Mem. 174, 107281 https://doi.org/10.1016/j.nlm.2020.107281.
Richardson, R., Siegel, M.A., Campbell, B.A., 1989. Effect of maternal presence on the cardiac and behavioral responses to shock in rats as a function of age. Dev. Psychobiol. 22 (6), 567–583. https://doi.org/10.1002/dev.420220604.
Robinson-Drummer, P.A., Opendak, M., Blomkvist, A., Chan, S., Tan, S., Delmer, C., Wood, K., Sloan, A., Jacobs, L., Fine, E., Chopra, D., Sandler, C., Kamenetzky, G., Sullivan, R.M., 2019. Infant trauma alters social buffering of threat learning: emerging role of prefrontal cortex in preadolescence. Front. Behav. Neurosci. 13 https://doi.org/10.3389/fnbeh.2019.00132.
Rodriguez-Romaguera, J., Quirk, G.J., 2017. Extinction of conditioned fear and avoidance: relevance for OCD. In: Pittenger, C. (Ed.), Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Oxford University Press.
Rodriguez-Romaguera, J., Sotres-Bayon, F., Mueller, D., Quirk, G.J., 2009. Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction. Biol. Psychiatry 65 (10), 887–892. https://doi.org/10.1016/j.biopsych.2009.01.009.
Rogan, M.T., Leon, K.S., Perez, D.L., Kandel, E.R., 2005. Distinct neural signatures for safety and danger in the Amygdala and striatum of the mouse. Neuron 46 (2), 309–320. https://doi.org/10.1016/j.neuron.2005.02.017.
Roozendaal, B., Carmi, O., McGaugh, J.L., 1996. Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. Proc. Natl. Acad. Sci. U.S.A. 93 (4), 1429–1433. https://doi.org/10.1073/pnas.93.4.1429.
Rozeske, R.R., Der-Avakian, A., Bland, S.T., Beckley, J.T., Watkins, L.R., Maier, S.F., 2009. The medial prefrontal cortex regulates the differential expression of morphine-conditioned place preference following a single exposure to controllable or uncontrollable stress. Neuropsychopharmacology 34 (4), 834–843. https://doi.org/10.1038/npp.2008.34.
Rozeske, R.R., Evans, A.K., Frank, M.G., Watkins, L.R., Lowry, C.A., Maier, S.F., 2011. Uncontrollable, But Not Controllable, Stress Desensitizes 5-HT1A Receptors in the Dorsal Raphe Nucleus. J. Neurosci. 31 (40), 14107–14115. https://doi.org/10.1523/JNEUROSCI.3095-11.2011.
Saito, Y., Matsumoto, M., Otani, S., Yanagawa, Y., Hiraide, S., Ishikawa, S., Kimura, S., Shimamura, K., Togashi, H., 2012. Phase-dependent synaptic changes in the hippocampal CA1 field underlying extinction processes in freely moving rats. Neurobiol. Learn. Mem. 97 (4), 361–369. https://doi.org/10.1016/j.nlm.2012.02.006.
Sangha, S., 2015. Plasticity of fear and safety neurons of the amygdala in response to fear extinction. Front. Behav. Neurosci. 9 https://doi.org/10.3389/fnbeh.2015.00354.
Sangha, S., Chadick, J.Z., Janak, P.H., 2013. Safety encoding in the basal amygdala. J. Neurosci. 33 (9), 3744–3751. https://doi.org/10.1523/JNEUROSCI.3302-12.2013.

Sangha, S., Robinson, P.D., Greba, Q., Davies, D.A., Howland, J.G., 2014. Alterations in reward, fear and safety cue discrimination after inactivation of the rat prelimbic and infralimbic cortices. Neuropsychopharmacology 39 (10), 2405–2413.
Sangha, S., Diehl, M.M., Bergstrom, H.C., Drew, M.R., 2020. Know safety, no fear. Neurosci. Biobehav. Rev. 108, 218–230. https://doi.org/10.1016/j.neubiorev.2019.11.006.
Santini, E., Quirk, G.J., Porter, J.T., 2008. Fear conditioning and extinction differentially modify the intrinsic excitability of infralimbic neurons. J. Neurosci. 28 (15), 4028–4036. https://doi.org/10.1523/JNEUROSCI.2623-07.2008.
Sarlitto, M.C., Foilb, A.R., Christianson, J.P., 2018. Inactivation of the ventrolateral orbitofrontal cortex impairs flexible use of safety signals. Neuroscience. https://doi.org/10.1016/j.neuroscience.2018.03.037.
Schroeder, A., Notaras, M., Du, X., Hill, R.A., 2018. On the developmental timing of stress: delineating sex-specific effects of stress across development on adult behavior. Brain Sci. 8 (7) https://doi.org/10.3390/brainsci8070121.
Senn, V., Wolff, S.B.E., Herry, C., Grenier, F., Ehrlich, I., Gründemann, J., Fadok, J.P., Müller, C., Letzkus, J.J., Lüthi, A., 2014. Long-range connectivity defines behavioral specificity of amygdala neurons. Neuron 81 (2), 428–437. https://doi.org/10.1016/j.neuron.2013.11.006.
Shansky, R.M., 2015. Sex differences in PTSD resilience and susceptibility: challenges for animal models of fear learning. Neurobiol. Stress 1, 60–65. https://doi.org/10.1016/j.ynstr.2014.09.005.
Shpokayte, M., McKissick, O., Yuan, B., Rahsepar, B., Fernandez, F.R., Ruesch, E., Grella, S.L., White, J.A., Liu, X.S., Ramirez, S., 2020. Hippocampal cells multiplex positive and negative engrams. BioRxiv. https://doi.org/10.1101/2020.12.11.419887, 2020.12.11.419887.
Sierra-Mercado, D., Corcoran, K.A., Lebrón-Milad, K., Quirk, G.J., 2006. Inactivation of the ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. Eur. J. Neurosci. 24 (6), 1751–1758. https://doi.org/10.1111/j.1460-9568.2006.05014.x.
Sierra-Mercado, D., Padilla-Coreano, N., Quirk, G.J., 2011. Dissociable roles of prelimbic and infralimbic cortices, ventral Hippocampus, and Basolateral Amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 36 (2), 529–538. https://doi.org/10.1038/npp.2010.184.
Skelly, M.J., Chappell, A.E., Carter, E., Weiner, J.L., 2015. Adolescent social isolation increases anxiety-like behavior and ethanol intake and impairs fear extinction in adulthood: possible role of disrupted noradrenergic signaling. Neuropharmacology 97, 149–159. https://doi.org/10.1016/j.neuropharm.2015.05.025.
Sotres-Bayon, F., Quirk, G.J., 2010. Prefrontal control of fear: more than just extinction. Curr. Opin. Neurobiol. 20 (2), 231–235. https://doi.org/10.1016/j.conb.2010.02.005.
Sotres-Bayon, F., Bush, D.E.A., LeDoux, J.E., 2007. Acquisition of fear extinction requires activation of NR2B-Containing NMDA receptors in the lateral amygdala. Neuropsychopharmacology 32 (9), 1929–1940. https://doi.org/10.1038/sj.npp.1301316.
Stanton, M.E., Wallstrom, J., Levine, S., 1987. Maternal contact inhibits pituitary-adrenal stress responses in preweanling rats. Dev. Psychobiol. 20 (2), 131–145. https://doi.org/10.1002/dev.420200204.
Stockhorst, U., Antov, M.I., 2016. Modulation of fear extinction by stress, stress hormones and estradiol: a review. Front. Behav. Neurosci. 9 https://doi.org/10.3389/fnbeh.2015.00359.
Tao, Y., Cai, C.-Y., Xian, J.-Y., Kou, X.-L., Lin, Y.-H., Qin, C., Wu, H.-Y., Chang, L., Luo, C.-X., Zhu, D.-Y., 2021. Projections from infralimbic cortex to paraventricular thalamus mediate fear extinction retrieval. Neurosci. Bull. 37 (2), 229–241. https://doi.org/10.1007/s12264-020-00603-6.
Toledo-Rodriguez, M., Pitiot, A., Paus, T., Sandi, C., 2012. Stress during puberty boosts metabolic activation associated with fear-extinction learning in hippocampus, basal amygdala and cingulate cortex. Neurobiol. Learn. Mem. 98 (1), 93–101. https://doi.org/10.1016/j.nlm.2012.05.006.
Tovote, P., Fadok, J.P., Lüthi, A., 2015. Neuronal circuits for fear and anxiety. Nat. Rev. Neurosci. 16 (6), 317–331. https://doi.org/10.1038/nrn3945.
Tovote, P., Esposito, M.S., Botta, P., Chaudun, F., Fadok, J.P., Markovic, M., Wolff, S.B.E., Ramakrishnan, C., Fenno, L., Deisseroth, K., Herry, C., Arber, S., Lüthi, A., 2016. Midbrain circuits for defensive behaviour. Nature 534 (7606), 206–212. https://doi.org/10.1038/nature17996.
Upton, K.J., Sullivan, R.M., 2010. Defining age limits of the sensitive period for attachment learning in rat pups. Dev. Psychobiol. 52 (5), 453–464. https://doi.org/10.1002/dev.20448.
Varela, J.A., Wang, J., Christianson, J.P., Maier, S.F., Cooper, D.C., 2012. Control over stress, but not stress per se increases prefrontal cortical pyramidal neuron excitability. J. Neurosci. 32 (37), 12848–12853. https://doi.org/10.1523/jneurosci.2669-12.2012.
Varga, V., Szekely, A.D., Csillag, A., Sharp, T., Hajos, M., 2001. Evidence for a role of GABA interneurones in the cortical modulation of midbrain 5-hydroxytryptamine neurones. Neuroscience 106 (4), 783–792.
Varga, V., Kocsis, B., Sharp, T., 2003. Electrophysiological evidence for convergence of inputs from the medial prefrontal cortex and lateral habenula on single neurons in the dorsal raphe nucleus. Eur. J. Neurosci. 17 (2), 280–286. https://doi.org/10.1046/j.1460-9568.2003.02465.x.
Vianna, D.M., Graeff, F.G., Brandão, M.L., Landeira-Fernandez, J., 2001. Defensive freezing evoked by electrical stimulation of the periaqueductal gray: comparison between dorsolateral and ventrolateral regions. Neuroreport 12 (18), 4109–4112. https://doi.org/10.1097/00001756-200112210-00049.
Viau, V., Sawchenko, P.E., 2002. Hypophysiotropic neurons of the paraventricular nucleus respond in spatially, temporally, and phenotypically differentiated manners to acute vs. repeated restraint stress: rapid publication. J. Comp. Neurol. 445 (4), 293–307. https://doi.org/10.1002/cne.10178.
Wagner, A.R., Rescorla, R.A., 1972. Inhibition in Pavlovian conditioning: application of a theory. Inhibition and Learning. https://scholar.google.com/citations?view_op=view_citation&hl=en&user=7OFub-oAAAAJ&citation_for_view=7OFub-oAAAAJ:d1gkVwhDpl0C.
Walker, D.L., Davis, M., 2002. The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction. Pharmacol. Biochem. Behav. 71 (3), 379–392. https://doi.org/10.1016/S0091-3057(01)00698-0.
Walker, D.L., Cassella, J.V., Lee, Y., De Lima, T.C., Davis, M., 1997. Opposing roles of the amygdala and dorsolateral periaqueductal gray in fear-potentiated startle. Neurosci. Biobehav. Rev. 21 (6), 743–753. https://doi.org/10.1016/s0149-7634(96)00061-9.
Walker, F.R., Masters, L.M., Dielenberg, R.A., Day, T.A., 2009. Coping with defeat: acute glucocorticoid and forebrain responses to social defeat vary with defeat episode behaviour. Neuroscience 162 (2), 244–253. https://doi.org/10.1016/j.neuroscience.2009.04.041.
Walker, C.-D., Bath, K.G., Joels, M., Korosi, A., Larauche, M., Lucassen, P.J., Morris, M.J., Raineki, C., Roth, T.L., Sullivan, R.M., Taché, Y., Baram, T.Z., 2017. Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: Critical considerations of methodology, outcomes and translational potential. Stress 20 (5), 421–448. https://doi.org/10.1080/10253890.2017.1343296.
Walker, R.A., Wright, K.M., Jhou, T.C., McDannald, M.A., 2020. The ventrolateral periaqueductal grey updates fear via positive prediction error. Eur. J. Neurosci. 51 (3), 866–880. https://doi.org/10.1111/ejn.14536.
Wang, Q., Jin, J., Maren, S., 2016. Renewal of extinguished fear activates ventral hippocampal neurons projecting to the prelimbic and infralimbic cortices in rats. Neurobiol. Learn. Mem. 134 (Part A), 38–43. https://doi.org/10.1016/j.nlm.2016.04.002.
Watson, T.C., Cerminara, N.L., Lumb, B.M., Apps, R., 2016. Neural correlates of fear in the Periaqueductal Gray. J. Neurosci. 36 (50), 12707–12719. https://doi.org/10.1523/JNEUROSCI.1100-16.2016.
Weiss, J.M., 1970. Somatic effects of predictable and unpredictable shock. Psychosom. Med. 32 (4), 397–408. https://doi.org/10.1097/00006842-197007000-00008.
Weiss, J.M., 1971. Effects of coping behavior with and without a feedback signal on stress pathology in rats. J. Comp. Physiol. Psychol. 77 (1), 22–30. https://doi.org/10.1037/h0031581.
Weiss, J.M., 1972. Influence of psychological variables on stress-induced pathology. Ciba Found. Symp. 8, 253–265. https://doi.org/10.1002/9780470719916.ch12.
Weiss, J.M., Glazer, H.I., Pohorecky, L.A., Brick, J., Miller, N.E., 1975. Effects of chronic exposure to stressors on avoidance-escape behavior and on brain norepinephrine. Psychosom. Med. 37 (6), 522–534. https://doi.org/10.1097/00006842-197511000-00006.
Wellman, C.L., 2001. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J. Neurobiol. 49 (3), 245–253. https://doi.org/10.1002/neu.1079.
Wellman, C.L., Moench, K.M., 2019. Preclinical studies of stress, extinction, and prefrontal cortex: intriguing leads and pressing questions. Psychopharmacology 236 (1), 59–72. https://doi.org/10.1007/s00213-018-5023-4.
Wilber, A.A., Walker, A.G., Southwood, C.J., Farrell, M.R., Lin, G.L., Rebec, G.V., Wellman, C.L., 2011. Chronic stress alters neural activity in medial prefrontal cortex during retrieval of extinction. Neuroscience 174, 115–131. https://doi.org/10.1016/j.neuroscience.2010.10.070.
Will, M.J., Watkins, L.R., Maier, S.F., 1998. Uncontrollable stress potentiates morphine's rewarding properties. Pharmacol. Biochem. Behav. 60 (3), 655–664.
Willner, P., 2017. The chronic mild stress (CMS) model of depression: History, evaluation and usage. Neurobiol. Stress 6, 78–93. https://doi.org/10.1016/j.ynstr.2016.08.002.
Wilson, C.A., Vazdarjanova, A., Terry, A.V., 2013. Exposure to variable prenatal stress in rats: effects on anxiety-related behaviors, innate and contextual fear, and fear extinction. Behav. Brain Res. 238, 279–288. https://doi.org/10.1016/j.bbr.2012.10.003.
Wood, S.K., 2014. Individual differences in the neurobiology of social stress: implications for depression-cardiovascular disease comorbidity. Curr. Neuropharmacol. 12 (2), 205–211. https://doi.org/10.2174/1570159X11666131120224413.
Woon, E.P., Seibert, T.A., Urbanczyk, P.J., Ng, K.H., Sangha, S., 2020. Differential effects of prior stress on conditioned inhibition of fear and fear extinction. Behav. Brain Res. 381, 112414 https://doi.org/10.1016/j.bbr.2019.112414.
Wright, K.M., McDannald, M.A., 2019. Ventrolateral periaqueductal gray neurons prioritize threat probability over fear output. ELife 8, e45013. https://doi.org/10.7554/eLife.45013.
Yamamoto, S., Morinobu, S., Fuchikami, M., Kurata, A., Kozuru, T., Yamawaki, S., 2008. Effects of single prolonged stress and D-cycloserine on contextual fear extinction and hippocampal NMDA receptor expression in a rat model of PTSD. Neuropsychopharmacology 33 (9), 2108–2116. https://doi.org/10.1038/sj.npp.1301605.
Yang, Y.-L., Chao, P.-K., Lu, K.-T., 2006. Systemic and intra-amygdala administration of glucocorticoid agonist and antagonist modulate extinction of conditioned fear. Neuropsychopharmacology 31 (5), 912–924. https://doi.org/10.1038/sj.npp.1300899.
Yousuf, H., Ehlers, V.L., Sehgal, M., Song, C., Moyer, J.R., 2020. Modulation of intrinsic excitability as a function of learning within the fear conditioning circuit. Neurobiol. Learn. Mem. 167, 107132 https://doi.org/10.1016/j.nlm.2019.107132.
Zeidan, M.A., Igoe, S.A., Linnman, C., Vitalo, A., Levine, J.B., Klibanski, A., Goldstein, J.M., Milad, M.R., 2011. Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. Biol. Psychiatry 70 (10), 920–927. https://doi.org/10.1016/j.biopsych.2011.05.016.

Zhang, W., Rosenkranz, J.A., 2013. Repeated restraint stress enhances cue-elicited conditioned freezing and impairs acquisition of extinction in an age-dependent manner. Behav. Brain Res. 248, 12–24. https://doi.org/10.1016/j.bbr.2013.03.028.

Zheng, X., Deschaux, O., Lavigne, J., Nachon, O., Cleren, C., Moreau, J.-L., Garcia, R., 2013. Prefrontal high-frequency stimulation prevents sub-conditioning procedure-provoked, but not acute stress-provoked, reemergence of extinguished fear. Neurobiol. Learn. Mem. 101, 33–38. https://doi.org/10.1016/j.nlm.2013.01.003.

Zhu, S., Shi, R., Wang, J., Wang, J.-F., Li, X.-M., 2014. Unpredictable chronic mild stress not chronic restraint stress induces depressive behaviours in mice. Neuroreport 25 (14), 1151–1155. https://doi.org/10.1097/WNR.0000000000000243.

Zlotnick, C., Johnson, J., Kohn, R., Vicente, B., Rioseco, P., Saldivia, S., 2008. Childhood trauma, trauma in adulthood, and psychiatric diagnoses. Compr. Psychiatry 49 (2), 163–169. https://doi.org/10.1016/j.comppsych.2007.08.007.