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REVIEW

Mechanisms to medicines: elucidating neural and molecular substrates of fear extinction to identify novel treatments for anxiety disorders

Olena Bukalo*, Courtney R Pinard* and Andrew Holmes

Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA

Correspondence
Olena Bukalo or Courtney Pinard, 5625 Fishers Ln, Room 2N-09, Rockville, MD 20852, USA. E-mail: bukalool@mail.nih.gov or courtney.pinard@nih.gov

*Equal contribution.

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The burden of anxiety disorders is growing, but the efficacy of available anxiolytic treatments remains inadequate. Cognitive behavioural therapy for anxiety disorders focuses on identifying and modifying maladaptive patterns of thinking and behaving, and has a testable analogue in rodents in the form of fear extinction. A large preclinical literature has amassed in recent years describing the neural and molecular basis of fear extinction in rodents. In this review, we discuss how this work is being harnessed to foster translational research on anxiety disorders and facilitate the search for new anxiolytic treatments. We begin by summarizing the anatomical and functional connectivity of a medial prefrontal cortex (mPFC)–amygdala circuit that subserves fear extinction, including new insights from optogenetics. We then cover some of the approaches that have been taken to model impaired fear extinction and associated impairments with mPFC–amygdala dysfunction. The principal goal of the review is to evaluate evidence that various neurotransmitter and neuromodulator systems mediate fear extinction by modulating the mPFC–amygdala circuitry. To that end, we describe studies that have tested how fear extinction is impaired or facilitated by pharmacological manipulations of dopamine, noradrenaline, 5-HT, GABA, glutamate, neuropeptides, endocannabinoids and various other systems, which either directly target the mPFC–amygdala circuit, or produce behavioural effects that are coincident with functional changes in the circuit. We conclude that there are good grounds to be optimistic that the progress in defining the molecular substrates of mPFC–amygdala circuit function can be effectively leveraged to identify plausible candidates for extinction-promoting therapies for anxiety disorders.

LINKED ARTICLES

This article is part of a themed section on Animal Models in Psychiatry Research. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-20

Abbreviations

ACC, anterior cingulate cortex; BA, basal nucleus of the amygdala; BLA, basolateral amygdala; CBT, cognitive behavioural therapy; CCK, cholecystokinin; CeA, central nucleus of amygdala; CeL, lateral nucleus of the central amygdala; CeM, medial nucleus of the central amygdala; CITZ, capsular infralimbic subregion target zone; CRF, corticotropin-releasing factor; FAAH, fatty acid amide hydrolase; GluA1, AMPA receptor subunit 1; GluA2, AMPA receptor subunit 2; GluN2B, NMDA receptor subtype 2B; GluN2C/D, NMDA receptor subtype 2C/D; GRP, gastrin-releasing peptide; HDAC, histone deacetylase; HAT, histone acetyltransferase ICN, intercalated cell nuclei; IN, main intercalated nucleus; KOP, κ-opioid; LA, lateral amygdala; mGlu, metabotropic glutamate receptor; mImp, medial paracapsular intercalated nucleus; MOP, μ-opioid; mPFC, medial prefrontal cortex; NPS, neuropeptide S; NPY, neuropeptide Y; PD, panic disorder; PEPA, 2-[2,6-difluoro-4-[[2-[(phenylsulfonyl)amino]ethyl]thio]phenoxy]acetamide; PTSD, post-traumatic stress disorder; SERT, serotonin transporter; SSRIs, selective serotonin re-uptake inhibitors

Introduction

Prevalence and treatment of anxiety disorders

Anxiety disorders constitute some of the most widely known and commonly diagnosed neuropsychiatric problems, affecting a significant number of people around the world (Kessler *et al.*, 2011; Wittchen *et al.*, 2011). The broad diagnostic category of anxiety disorders encompasses a range of conditions, including generalized anxiety disorder, panic disorder (PD), various types of phobias and post-traumatic stress disorder (PTSD) (DSM-5, 2013; World Health Organisation, 1994). This categorization has been revised somewhat in the most recent revision of the Diagnostic and Statistical Manual of Mental Disorders, which now separates anxiety disorders into three main subcategories: anxiety disorders, obsessive–compulsive and related disorders, and trauma- and stressor-related disorders (DSM-5, 2013).

Despite modifications in the way anxiety disorders are diagnosed, which is based primarily on symptomatology, there remains considerable overlap in the medications used to treat the different disorders. The main Food and Drug Administration-approved anxiolytic treatments are the benzodiazepines (e.g. clonazepam, lorazepam) and β-blockers (e.g. propranolol), and the tricyclic (e.g. imipramine, clomipramine), MAO A inhibitor (e.g. phenelzine, isocarboxazid) and 5-HT and noradrenaline re-uptake inhibitors (e.g. fluoxetine, escitalopram, venlafaxine) classes of antidepressants. It is noteworthy that none of these drugs were developed for anxiety based on a biological hypothesis of their mechanism of action, but are in use today largely because of serendipitous discoveries of their beneficial clinical effects.

Anxiety disorders are also often treated with various forms of psychotherapy. One commonly employed psychological approach is cognitive behavioural therapy (CBT), which focuses on identifying and modifying maladaptive patterns of thinking and behaving. Recent meta-analysis shows that CBT has efficacy across anxiety disorders, including PTSD, PD and generalized anxiety disorder (Stewart and Chambless, 2009). With the goal of improving long-term therapeutic outcome, patients are often treated with a combination of CBT, or some other psychotherapy, and a regimen of chronic drug treatment. Compelling evidence that such combinations are more effective than either approach alone is, however, lacking (Barlow *et al.*, 2000; Otto *et al.*, 2010; Rodrigues *et al.*, 2011). Indeed, the notion that the combination of drugs and CBT should work to enhance therapeutic efficacy is predicated on the idea that the two interventions will act in an additive or synergistic manner. While intuitively appealing, this view is not often grounded in an understanding of the brain processes by which CBT acts to alleviate anxiety. Nor does it account for how adjunctive drug treatments might affect these processes, either beneficially or deleteriously, to determine the net therapeutic impact of a combination of treatments.

Towards mechanism-based treatments

A number of authors have argued that the development of successful pharmacological adjuncts to CBT must stem from a 'mechanism-up' approach built on a deep understanding of the neural circuit underlying anxiety, and the identification of drugs that target these circuits (Myers and Davis, 2007; Ressler and Mayberg, 2007; Holmes and Quirk, 2010; Graham *et al.*, 2011; Steckler and Risbrough, 2012). Particularly amenable to this approach are those anxiety disorders, such as PTSD and phobias, that typically result from identifiable traumatic events and that are triggered by clear, definable environmental reminders of the trauma. CBT often focuses on severing the cognitive link between environmental cues and trauma by repeated exposure to these cues. The generation and maintenance of trauma-like memories can be readily modelled in rodents using well-established paradigms based on classical conditioning, in which discrete cues or contexts are paired with an aversive outcome (e.g. footshock) to generate a 'fear' memory that is measurable by expression of defensive behaviour (e.g. freezing). Once formed, the capacity to extinguish a fear memory can also be assayed, by measuring the degree to which fear is reduced as a result of repeated presentation of a conditioned stimulus without concomitant footshock. Fear extinction has been employed by a growing number of preclinical anxiety studies, and strongly benefits from having a strong clinical parallel in the form of exposure-based CBT.

Recent years have seen significant progress in elucidating the neural basis of conditioned fear and extinction in rodents. A goal of the current review was to discuss how work is being harnessed to foster translational research on anxiety disorders and facilitate the search for new anxiolytic treatments. To keep the review manageable, we limit our focus to fear extinction and largely avoid studies on fear conditioning, even though those studies would sometimes be informative to the discussion. We first offer an overview of the anatomical and functional connectivity of a medial prefrontal cortex (mPFC)–amygdala circuit that is most strongly implicated in learned fear and extinction – given this is the foundation for mechanism-based modelling and drug discovery. A growing number of rodent models of impaired extinction have been developed. We review the general approaches that have been taken to model extinction and discuss evidence linking some models to mPFC–amygdala dysfunction. We then turn to the chief focus of the review – a summary of studies that have examined how various neurotransmitter and neuromodulator systems might mediate fear extinction via modulation of the mPFC–amygdala circuit. Finally, we consider the potential for moving preclinical targets forward into eventual therapeutic use and the challenges that would need to be overcome.

Functional circuitry of fear and extinction

Anatomical connections between the mPFC and amygdala

Our understanding of the neural circuitry mediating fear and extinction in rodents rests on an increasingly detailed description of the anatomical connections between the PFC and the amygdala. Glutamatergic afferents to the amygdala, arising from cortical pyramidal cell layers 2 and 5 (Gabbott *et al.*, 2005; Little and Carter, 2012; 2013), course ventrally through the striatum or stria terminalis. Tract-tracing studies

in the rat show that axons originating in the infralimbic cortex of the mPFC terminate most densely in the ventromedial lateral nucleus, the rostral part of the accessory basal amygdala, lateral capsular subdivision of the central nucleus and the superficial nuclei (lateral olfactory tract, periamygdaloid cortex and cortical nuclei) (Cassell and Wright, 1986; McDonald *et al.*, 1996; McDonald, 1998; Pinard *et al.*, 2012). Neurons in the more caudal areas of the infralimbic subregion also project to the medial and intermediate subdivisions of the central nucleus (Hurley *et al.*, 1991; McDonald, 1998).

The prelimbic cortex of the mPFC is located dorsally adjacent to the infralimbic subregion and it has a different pattern of connectivity with the amygdala. Prelimbic cortex neurons target the basal nucleus of the amygdala (BA), primarily the dorsomedial portion (McDonald, 1991; 1998; McDonald *et al.*, 1996; Vertes, 2004), while caudal prelimbic cortex neurons concentrate inputs in the medial parvicellular basal nucleus (Sesack *et al.*, 1989). In turn, baso-lateral amygdala (BLA) neurons project back to both the prelimbic cortex and infralimbic subregion, creating a feedback loop (Krettek and Price, 1977; Shinonaga *et al.*, 1994; Conde *et al.*, 1995; Gabbott *et al.*, 2006; Hoover and Vertes, 2007). These BLA inputs to the mPFC exert an inhibitory influence over cortical pyramidal cells, probably via engagement of local interneurons, although excitatory modulation (at least in the prelimbic cortex) is also reported (Perez-Jaranay and Vives, 1991; Ishikawa and Nakamura, 2003; Sotres-Bayon *et al.*, 2012; Sun and Laviolette, 2012; Dilgen *et al.*, 2013).

Anatomical tracing studies show that the infralimbic subregion and prelimbic cortex only sparsely innervate the main, fear-generating, output nucleus of amygdala – the medial nucleus of the central amygdala (CeM) – raising the question of how mPFC neurons modulate fear. One influential model posits that this connection is bridged by infralimbic subregion inputs to the intercalated cell nuclei (ICN) of the amygdala (Royer *et al.*, 1999; Quirk *et al.*, 2003; Pare *et al.*, 2004; Amano *et al.*, 2010; Amir *et al.*, 2011; Li *et al.*, 2011). The ICNs comprise narrow clusters of densely packed, mainly GABAergic, neurons associated with the fibre bundles that lie between the BA/lateral amygdala (LA) and the central lateral (CeL)/central medial (CeM) nuclei, but have a molecular phenotype more akin to striatal neurons (Millhouse, 1986; Nitecka and Ben-Ari, 1987; McDonald and Augustine, 1993; McDonald, 1998; Kaoru *et al.*, 2010; Manko *et al.*, 2011). This model has recently been refined to emphasize the heterogeneity of different ICNs. The medial paracapsular and main ICN nucleus (IN) show a high degree of interconnectivity, but also exhibit diverse electrophysiological and molecular profiles and are differentially activated by fear and fear extinction (Geracitano *et al.*, 2007; Kaoru *et al.*, 2010; Busti *et al.*, 2011).

Infralimbic subregion axons also project to a network of local ICN dendrites located in a region termed the capsular infralimbic subregion target zone (CITZ) (Cassell and Wright, 1986; McDonald *et al.*, 1996; Vertes, 2004; Marowsky *et al.*, 2005; Pinto and Sesack, 2008; Busti *et al.*, 2011; Pinard *et al.*, 2012). It is worth noting, however, that although the densest mPFC projections to the CITZ arise from the infralimbic subregion, there are also some projections from the prelimbic cortex to the CITZ (McDonald *et al.*, 1996). A final point to bear in mind is, in contrast to the mPFC and major amygdala nuclei, which have analogues in the human brain (note, for an excellent recent review of putatively analogous circuits in humans, see Vanelzakker *et al.*, 2014), the literature on the CITZ and ICNs is largely based on rodents and it remains to be shown whether these structures are similarly integral to the corticoamygdala circuitry in the primate and human brain. In this context, at least one study has reported mPFC (subgenual cortex/area 25) projections to the ICNs in non-human primates (Freedman *et al.*, 2000).

Functional mPFC–amygdala interactions – new insights from optogenetics

Delineating the functional contribution of these mPFC–amygdala circuits to fear in rodents has been the subject of intense recent study using techniques including lesioning and transient inactivation, analysis of patterns of gene expression, and *in vivo* and *ex vivo* neural recordings. This extensive literature has been covered in many excellent reviews (see following citations) and we will not overburden the current paper by retreading this ground. To distill some of the principal conclusions – the infralimbic subregion clearly plays a role in fear inhibition and fear extinction (Milad and Quirk, 2002; Berretta *et al.*, 2005; Likhtik *et al.*, 2005; Sierra-Mercado *et al.*, 2006; Knapska and Maren, 2009; Busti *et al.*, 2011; Knapska *et al.*, 2012), whereas the prelimbic cortex has been implicated in the generation and maintenance of fear (Burgos-Robles *et al.*, 2009; Laurent and Westbrook, 2009a; Sierra-Mercado *et al.*, 2011; Knapska *et al.*, 2012; Li *et al.*, 2012; Sotres-Bayon *et al.*, 2012; Courtin *et al.*, 2014a; Fenton *et al.*, 2014). With regard to the amygdala, the LA, BA, CeL and CeM have all been found to be critical to the formation and/or expression of fear memories (Herry *et al.*, 2010; Pape and Pare, 2010; Orsini and Maren, 2012), while the BA, basomedial amygdala and ICNs are important for extinction (Repa *et al.*, 2001; Anglada-Figueroa and Quirk, 2005; Herry *et al.*, 2008; Likhtik *et al.*, 2008; Knapska and Maren, 2009; Amano *et al.*, 2011; Busti *et al.*, 2011; Lesting *et al.*, 2011; Sierra-Mercado *et al.*, 2011; Livneh and Paz, 2012; Courtin *et al.*, 2014b; Trouche *et al.*, 2013). It should be borne in mind throughout this review that the acquisition, consolidation and retrieval of extinction are separable processes that are under the control of different brain regions and neural systems (Plendl and Wotjak, 2010). However, for the sake of readability, we will refer to studies of extinction without detailing whether the focus was on one or more of these processes.

As in other areas of neuroscience, studies aimed at delineating the neural basis of fear and extinction have begun to take advantage of some powerful optogenetic tools, that allow for precise temporal, and in some instances, molecularly defined, control of specific circuits (Johansen *et al.*, 2012; Lammel *et al.*, 2014). By replacing footshock with optogenetic stimulation of LA pyramidal neurons during cue presentations in a pseudo-conditioning session, Johansen and colleagues were able to generate a mild auditory fear memory (Johansen *et al.*, 2010). Conversely, optogenetic inhibition of the LA/BA during conditioning leads to severe impairments in cued and context fear learning (Goshen *et al.*, 2011). Interestingly, stimulating a subpopulation of pyramidal neurons in the BA expressing Thy1 also produced impaired fear learning, but actually strengthened fear

extinction – demonstrating how the effects of optogenetic manipulations in this region will depend on the cell type targeted (Jasnow *et al.*, 2013). With regards to the central nucleus of the amygdala (CeA), optogenetically stimulating neurons in CeM evoked unconditioned fear, consistent with this nuclei's function as the system's major output station (Ciocchi *et al.*, 2010). The activity of the CeM is regulated by distinct subpopulations of CeL neurons that are either excited or inhibited by conditioned fear stimuli (Haubensak *et al.*, 2010; Duvarci *et al.*, 2011). Optogenetic control of these different subpopulations bi-directionally regulates conditioned fear, revealing an intricate microcircuit in which 'CeL on' cells inhibit 'CeL off' cells to disinhibit CeM output and increase conditioned fear (Haubensak *et al.*, 2010). It will be interesting to extend these observations to the analysis of extinction.

Optogenetics has been employed in a number of fear studies focusing on the mPFC and the region's links to the amygdala. One example examined the effects of optogenetic inhibition of the anterior cingulate cortex (ACC) on time-dependent fear memory recall, and confirming the findings of lesion/inactivation studies (Bontempi *et al.*, 1999), showed that the ACC was necessary for remotely, but not recently, retrieved contextual fear memory (Goshen *et al.*, 2011). Another study applied sustained optogenetic activation of infralimbic subregion/prelimbic cortex pyramidal cells, but not parvalbumin-positive interneurons, during fear conditioning and found that this produced reductions in later fear expression (Yizhar *et al.*, 2011). More in-depth analysis of the mPFC parvalbumin-positive interneurons finds that these cells do exert a major influence on fear extinction. Courtin and colleagues identified a subpopulation of parvalbumin interneurons in the mPFC (primarily prelimbic cortex) that showed high firing during low fear states, suggestive of a fear-inhibiting function (Courtin *et al.*, 2014a). Supporting this suggestion, optogenetically inhibiting these cells produced increased fear and reversed the fear suppressing effects of extinction, likely by disinhibiting the activity of prelimbic cortex pyramidal neurons innervating the BLA (Courtin *et al.*, 2014a).

Complimenting these findings, another recent study sought to elucidate how the functional connections between the mPFC and amygdala changed with extinction. Here, mPFC-originating (infralimbic subregion or prelimbic cortex) fibres in the BLA were optogenetically stimulated to reveal how extinction decreased the strength of excitatory mPFC projections to pyramidal neurons in the BLA (Cho *et al.*, 2013), an effect analogous to the decreased excitability of electrically mPFC-activated BLA neurons after extinction (Vouimba and Maroun, 2011). The authors suggest the decrease in the excitatory influence of the mPFC over the BLA may lessen BLA drive of CeM output and rebalance the circuitry in favour of mPFC inputs to CeM-inhibiting ICNs, thereby enabling extinction (Cho *et al.*, 2013). In an illustration of how extinction leads to bidirectional changes in the mPFC–amygdala circuit, Senn *et al.* used an elegant combination of viral tools to electrophysiologically record from and optogenetically manipulate neurons projecting from the BA to the subregions of the mPFC (Senn *et al.*, 2014). Using this approach, they found not only that BA neurons projecting to prelimbic cortex and infralimbic subregion are activated during fear and extinction, respectively, but that optogenetically inhibiting BA-prelimbic cortex neurons promoted extinction, whereas silencing BA-infralimbic subregion projections impaired extinction (Senn *et al.*, 2014).

These early studies have already highlighted how optogenetics can prove very useful for establishing the diverse roles of components of the mPFC–amygdala circuit to fear and extinction. The technique even has the power to isolate the contributions of specific neural ensembles within the mPFC–amygdala circuitry. This is illustrated by recent work in which optogenetically reactivating only those cells in the dentate gyrus region of the hippocampus recruited during contextual fear conditioning was able to elicit an 'artificial' fear response without context re-exposure (Liu *et al.*, 2012; Ramirez *et al.*, 2013). Using optogenetic techniques such as these, it is likely that the field will soon gain some new important insights into the neural circuitry mediating extinction.

Rodent models of impaired extinction and mPFC–amygdala dysfunction

Various rodent models of impaired extinction have been developed and tested for abnormalities in the structure and function of mPFC–amygdala circuitry. These models generally fall into one of three broad conceptual categories. One set of models exploits differences in extinction that emerge within a rodent population or between different rodent strains, while another is based around explicit exposure to environmental insults such as stress or a drug of abuse (Holmes and Singewald, 2013). The third encompasses models of engineered mutations in specific genes, and we will consider these later, within the context of the relevant neurotransmitter systems.

In an early illustration of the utility of segregating a population of C57BL/6 mice based on extinction performance as a means to reveal underlying mechanisms, deficient extinction associated with reduced neuronal activation in mPFC (note, throughout the review, we will refer to 'mPFC' in most cases where infralimbic subregion and prelimbic cortex were not specified) and BLA as well as abnormal mPFC synaptic plasticity (Herry and Mons, 2004). Along similar lines, sorting Sprague Dawley rats into good and poor extinguishers showed that poor extinction is related to increased firing of neurons in the prelimbic cortex and attenuated burst firing of infralimbic subregion neurons (Burgos-Robles *et al.*, 2007; 2009). This approach has also revealed how rats with relatively poor extinction exhibit less activation of infralimbic subregion inputs to the LA, but hyperactivation of prelimbic cortex inputs to this same region of the amygdala (Knapska *et al.*, 2012).

An alternative to the *post hoc* sorting of subjects based on extinction performance is to select mice, *a priori*, for anxiety-related traits and breed these traits into phenotypically divergent subpopulations. In this manner, rats bred for stable high anxiety-like behaviour exhibit deficient extinction associated with the hypoactivation of neurons in the infralimbic subregion and BLA and the hyperactivation of cells in the CeM (Muigg *et al.*, 2008). Functional variation in the mPFC–amygdala circuit also underpins differences in fear extinction

found across different genetically inbred mouse strains (for an in-depth discussion, see Holmes and Singewald, 2013). For instance, deficient extinction in the 129S1/SvImJ mouse strain is coupled to a range of mPFC–amygdala abnormalities, including infralimbic subregion hypoactivation, prelimbic cortex hyperactivation and neuronal hyperactivity, and at the level of the amygdala, hypoactivation and dendritic hypertrophy in the BLA and CeL, as well as CeM hyperactivation (Hefner *et al.*, 2008; Whittle *et al.*, 2010; Camp *et al.*, 2012; Fitzgerald *et al.*, 2014).

Disturbances to the mPFC–amygdala circuitry are also related to the impaired extinction produced by certain environmental insults. For instance, chronic exposure to alcohol causes extinction deficits tied to the down-regulation of NMDA receptors (for nomenclature see Alexander *et al.*, 2013a) in the mPFC and the loss of infralimbic subregion neuronal firing (Bertotto *et al.*, 2006; Holmes *et al.*, 2012). An even larger body of literature demonstrates marked effects of stress on fear extinction and brain function. Early work found that extinction is highly sensitive to deleterious effects of exposure to stressors including forced swim and restraint (Izquierdo *et al.*, 2006; Miracle *et al.*, 2006). The observation of a deleterious effect on extinction has since been extended to a wide range of stressors, both acute and chronic. These range from maternal separation to social defeat to elevated platform exposure (Matsumoto *et al.*, 2008; 2013; Yamamoto *et al.*, 2008; 2009; Goswami *et al.*, 2010; Judo *et al.*, 2010; Andero *et al.*, 2011; Green *et al.*, 2011; Wilber *et al.*, 2011; Chauveau *et al.*, 2012; Dubreucq *et al.*, 2012; Ishikawa *et al.*, 2012; Knox *et al.*, 2012a; Long and Fanselow, 2012; Toledo-Rodriguez *et al.*, 2012; Deschaux *et al.*, 2013; Ganon-Elazar and Akirav, 2013; Saito *et al.*, 2012; 2013; Segev *et al.*, 2014; Wilson *et al.*, 2013; Zhang and Rosenkranz, 2013; Zheng *et al.*, 2013). Manipulation of stress-related signalling by exogenous corticosterone administration (Gourley *et al.*, 2009; Bingham *et al.*, 2013), blockade of corticosterone synthesis (via metyrapone) (Blundell *et al.*, 2011) or forebrain deletion of the mineralocorticoid receptor (Ter Horst *et al.*, 2012), also impair extinction – although there are other examples in which corticosterone administration can facilitate extinction (Cai *et al.*, 2006; Brinks *et al.*, 2009).

The stress-impairing effects on extinction can be traced to an array of functional alterations in the mPFC–amygdala circuit. These include infralimbic subregion dendritic hypotrophy, prelimbic cortex neuronal hyperactivity, increased BLA synaptic excitability and neuronal spine density, mPFC glucocorticoid receptor up-regulation and NMDA receptor, L-α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ionotropic (AMPA) receptor and ERK down-regulation, and impaired synaptic plasticity both in the mPFC and reciprocal pathways interconnecting the mPFC and the amygdala (Maroun and Richter-Levin, 2003; Izquierdo *et al.*, 2006; Maroun, 2006; Gourley *et al.*, 2009; Wilber *et al.*, 2009; 2011; Judo *et al.*, 2010; Chauveau *et al.*, 2012; Ishikawa *et al.*, 2012; Knox *et al.*, 2012b; Toledo-Rodriguez *et al.*, 2012; Bingham *et al.*, 2013; Maroun *et al.*, 2013). The role of the infralimbic subregion is further demonstrated by the finding that infralimbic subregion lesions occlude stress-induced impairments of extinction (Farrell *et al.*, 2010). Also of note, performing extinction training soon after conditioning impairs extinction (the 'immediate extinction effect') (Maren and Chang, 2006; Myers *et al.*, 2006; Macpherson *et al.*, 2013; Maren, 2014). Although the immediate extinction procedure was not explicitly designed as a stressor, the effect could possibly reflect the stress of fear conditioning temporarily impairing mPFC function and thereby hampering extinction (Maren, 2014). Indeed, immediate extinction deficits are linked to functional correlates in the mPFC that are reminiscent of those produced by various stressors, including reductions in mPFC neuronal bursting and hyperactivation of the prelimbic cortex (Chang *et al.*, 2010; Kim *et al.*, 2010; Stafford *et al.*, 2013).

Stress effects on extinction are strongly influenced by the age of subjects. Extinction in younger rodents at pre-weaning age produces more robust reductions in fear than seen in adults (Callaghan *et al.*, 2013). This form of juvenile extinction parallels the stage of development at which extracellular matrix structures known as perineuronal nets have not yet fully developed around parvalbumin-positive interneurons in the BLA (Gogolla *et al.*, 2009; Karpova *et al.*, 2012). It is also related to the loss of synaptic plasticity and dendritic spine density in mPFC caused by haploinsufficiency of the extracellular matrix protein, reelin (Ammassari-Teule *et al.*, 2009; Iafrati *et al.*, 2013).

Post-natal stress has recently been shown to expedite the development of the adult-like form of extinction in pre-weaning rats, and may do so by catalysing the development of BLA perineuronal nets or mPFC–amygdala connectivity into the adult form, although this remains to be formally tested (Callaghan and Richardson, 2012; Cowan *et al.*, 2013). In contrast to pre-weaning rodents, adolescent rats and mice show a resistance to extinction (as compared with adults) that is associated with a lack of neuronal activation and synaptic plasticity in the infralimbic subregion (McCallum *et al.*, 2010; Kim *et al.*, 2011; Pattwell *et al.*, 2012), and may reflect the immaturity of the infralimbic subregion and a functional bias towards the fear-promoting prelimbic cortex at this ontogenic time point (Chan *et al.*, 2011; Li *et al.*, 2012).

These findings clearly show how age is an important factor moderating mPFC–amygdala mediation of fear extinction. More generally, the consistent finding to emerge from a diverse set of rodent models is that impaired extinction is closely linked with the functional deficiencies at certain nodes in the mPFC circuit (particularly the infralimbic subregion, BLA and CeL), and a corresponding over-engagement of other areas (notably the prelimbic cortex and CeM).

Neurotransmitters and neuromodulators in mPFC–amygdala-mediated extinction

Our growing understanding of the mPFC–amygdala circuitry subserving extinction, together with the availability of models of deficient extinction linked to circuit dysfunction, offers rich opportunities for identifying novel anxiety treatments. A reasonable and potentially tractable route is to develop anxiolytic drugs that target 'druggable' neurotransmitter and molecular systems known to modulate the

functions of the mPFC–amygdala circuit. In the present section, we review some of the major systems studied to date that may have offered such candidates.

Dopamine

There are prominent dopamine projections arising from the ventral midbrain to both the mPFC and amygdala (Pinard *et al.*, 2008; Pinto and Sesack, 2008), and a number of authors have suggested this neurotransmitter could exert a major influence on fear extinction (for an excellent recent review, see Abraham *et al.*, 2014). *In vitro*, the activation of dopamine receptors (via apomorphine), or stimulation of D_1-like receptors (for nomenclature see Alexander *et al.*, 2013a) specifically (via SKF3892 or SKF81297), attenuates mPFC-evoked inhibition of BLA pyramidal neuronal firing, possibly by stimulating local inhibitory interneurons (Rosenkranz and Grace, 1999; 2002). Another source of BLA modulation by dopamine comes from the midbrain dopaminergic neurons that synapse onto BLA pyramidal, and predominantly parvalbumin-positive interneurons (Brinley-Reed and McDonald, 1999; Pinard *et al.*, 2008; Pinto and Sesack, 2008; Muller *et al.*, 2009). These inputs probably underlie the increases in LA neuronal oscillatory inhibitory network activity that can be produced by dopamine, mimicked by D_1-like agonists (dihydrexidine, SK81297) and blocked by D_1-like (using SCH23390), but not the D_2-like (via sulpiride) antagonists (Bissiere *et al.*, 2003; Loretan *et al.*, 2004; Kroner *et al.*, 2005). These effects of dopamine could potentially exert strong effects on extinction in view of the importance of amygdala network activity for fear (Rainnie *et al.*, 2006; Pape and Pare, 2010).

Dopamine's effects on extinction circuitry are not limited to the BLA. The CeA and ICNs are also innervated by dopamine, with D_1-like receptors showing particularly rich expression on the ICNs (Asan, 1998; Fuxe *et al.*, 2003; Marowsky *et al.*, 2005; Jacobsen *et al.*, 2006; Pinto and Sesack, 2008; Pinard *et al.*, 2012). Dopamine suppresses the excitability of ICNs in a manner that is mimicked by D_1-like (dihydrexidine), but not D_2-like (quinpirole), receptor agonism, and prevented by D_1-like (SCH23390), but not D_2-like (sulpiride), receptor antagonism (Marowsky *et al.*, 2005; Manko *et al.*, 2011). Acting through D_1 receptors in this way, dopamine could depress ICN activity and augment amygdala output, especially under conditions of high dopamine release, such as fear and stress (Marowsky *et al.*, 2005). In turn, the actions of D_1 receptors will be influenced by various factors regulating dopamine availability, such as the dopamine-clearing organic cation transporter 3, which is expressed on the ICNs and is linked to the regulation of stress (Baganz *et al.*, 2011; Hill and Gasser, 2013). Collectively, these anatomical and electrophysiological data suggest that dopamine is well positioned to regulate amygdala-mediated fear extinction at any one of a number of levels. Although most of these data implicate D_1-like receptors in these effects, a contribution of D_2-like receptors should not be discounted. *In vitro* application of a D_2-like agonist (quinpirole), but not a D_1-like agonist (SKF38393) results in the amplification of LA neuronal excitability (Rosenkranz and Grace, 1999), suppression of LA interneuronal feedforward inhibition and the release of synaptic plasticity at pyramidal neurons (Bissiere *et al.*, 2003). Moreover, *in vivo*, systemic activation of D_2-like receptors (again using quinpirole) attenuates BLA-driven suppression of neuron firing in the mPFC (Floresco and Tse, 2007). Thus, D_2-like receptors can excite both the BLA and mPFC and it would be unlikely that this would not translate into changes in fear extinction under at least some conditions.

Given dopamine has such profound effects on the mPFC–amygdala circuitry, how do genetic and pharmacological manipulations of dopamine and its receptors influence extinction? Constitutive gene deletion of the D_1 receptor produces impaired extinction (El-Ghundi *et al.*, 2001), and systemic administration of drugs that increase dopamine (using the dopamine re-uptake inhibitors methamphetamine, d-amphetamine or cocaine), or activate D_1-like receptors (via SKF38393), also either impair extinction or have no effect on the behaviour (Miczek and Luttinger, 1978; Borowski and Kokkinidis, 1998; Mueller *et al.*, 2009; Carmack *et al.*, 2010). The effects of systemically targeting D_2-like receptors are also somewhat mixed. Systemic D_2-like agonism (with quinpirole) disrupts extinction (Nader and LeDoux, 1999), whereas blockade of D_2-like receptors (with haloperidol, sulpiride or raclopride) can either facilitate or impair extinction (Nader and LeDoux, 1999; Ponnusamy *et al.*, 2005; Holtzman-Assif *et al.*, 2010; Mueller *et al.*, 2010). In part, these discrepancies may be attributable to the lack of selectivity for specific subtypes within the D_1-like (comprising the D_1 and D_5 subtypes) and D_2-like (made up of the D_2, D_3 and D_4 subtypes) receptor families, given the roles of individual subtypes are only now being uncovered (Holmes *et al.*, 2004). Of note in this context, studies using selective D_4 receptor agonists (PD-168,077) and antagonists (L-741,741) suggest that D_4 receptors promote BLA-driven mPFC neuronal excitation (Laviolette *et al.*, 2005; Floresco and Tse, 2007), and that mPFC D_4 receptor inhibition (via L-741,741) is sufficient to impair extinction (Pfeiffer and Fendt, 2006). Further studies that make use of selective pharmacological probes at other dopamine receptor subtypes, once these become available, will be essential to refining our understanding of dopamine's role in extinction.

Another issue that could contribute to the apparent variability in effects produced by systemic dopamine manipulations is the potential for complex and even opposing actions of dopamine at different regions within the broader mPFC–amygdala circuitry. Site-specific infusions and electrophysiological recordings have been one way to broach this issue. Infusing either a D_1-like (SCH23390) or D_2-like (raclopride) receptor antagonist directly into the infralimbic subregion impairs fear extinction, whereas systemic D_2-like inactivation (also using raclopride) reduces the firing of infralimbic subregion neurons during extinction (Hikind and Maroun, 2008; Mueller *et al.*, 2010; Fiorenza *et al.*, 2012). Similar, extinction impairing, effects are produced by blocking D_1 receptors in the BLA, as demonstrated by intra-BLA infusion of a D_1-like antagonist (SCH23390) (Hikind and Maroun, 2008; Fiorenza *et al.*, 2012). Thus, the effect of inactivating D_1 receptors is actually quite consistent across these two brain regions. This then poses the questions of whether augmenting dopamine availability at D_1 receptors would exert a pro-extinction profile.

As already noted, there are examples of 'dopamine boosters,' including psychostimulant drugs, that have detrimental or few effects on extinction. More positively, however, a

recent study reported the facilitation of extinction in humans and mice following systemic administration of the dopamine precursor L-DOPA or a dopamine (and noradrenaline) re-uptake inhibitor (methylphenidate) (Abraham *et al.*, 2012; Haaker *et al.*, 2013). These pro-extinction effects of L-DOPA are associated with increased neuronal activation in the mPFC and a depression of CeM amygdala output in mice, as well as increased midbrain–mPFC functional coupling in human volunteers (Haaker *et al.*, 2013). This pattern of activation tentatively suggests that the behavioural effect of L-DOPA may occur by promoting dopamine activity in the mPFC. In support of this scheme, mPFC dopamine levels are found to rise during extinction, while depleting dopamine in the mPFC (via locally applied 6-hydroxdopamine) impairs extinction (Morrow *et al.*, 1999; Fernandez Espejo, 2003; Hugues *et al.*, 2007; Saito *et al.*, 2013). However, further work will be needed to clarify the precise mechanisms underlying L-DOPA's effects on extinction. These include elucidating the contribution of dopamine from that of noradrenaline, a neurotransmitter we consider in the next section.

Noradrenaline

Various lines of evidence implicate the ascending noradrenaline system in extinction, with indications that both the mPFC and BLA may be involved. For instance, extinction produces increases in endogenous levels of noradrenaline in the mPFC (Hugues *et al.*, 2007), where it may produce neuronal excitement (Mueller *et al.*, 2008). Furthermore, infusing noradrenaline into the infralimbic subregion or BLA leads to an enhancement or impairment of extinction respectively (Berlau and McGaugh, 2006; Fiorenza *et al.*, 2012). Improvements in extinction can also be produced by systemic administration of drugs (e.g. methylphenidate) that increase levels of noradrenaline (as well as dopamine), presumably in both the mPFC and amygdala (and elsewhere) (Abraham *et al.*, 2012). Much of the research aimed at extending these observations has focused on delineating the specific noradrenaline receptors involved.

There is accumulating support for both α- and β-adrenoceptors in extinction. Systemic blockade of α_2-adrenoceptors (using yohimbine) facilitates extinction (Cain *et al.*, 2004; Morris and Bouton, 2007), although it is unclear whether this drug's effects can be attributable solely to the α_2-adrenoceptor because the behavioural effect is not mimicked by a more selective antagonist (atipamezole) (Davis *et al.*, 2008) (for further discussion, see Holmes and Quirk, 2010). Systemic treatment with a β-adrenoceptor agonist (isoprenaline) (Do Monte *et al.*, 2010) also facilitates extinction, whereas an antagonist at this receptor (propranolol) disrupts extinction in some studies, but only in other studies if given repeatedly or used to oppose the pro-extinction effects of a NMDA receptor partial agonist (D-cycloserine) (Cain *et al.*, 2004; Ouyang and Thomas, 2005; Rodriguez-Romaguera *et al.*, 2009; Do Monte *et al.*, 2010; Yamada *et al.*, 2011; Archbold *et al.*, 2013). These findings indicate that targeting β-adrenoceptors can affect extinction, but not always in a straightforward manner. A similar inference can be made from studies that have examined the consequences of regional infusions of drugs acting on β-adrenoceptors.

On the one hand, stimulating β-adrenoceptors (using isoprenaline) specifically within the infralimbic subregion facilitates extinction, but on the other hand, infusions given into the BLA after fear is reactivated lead to impairments in extinction (Do Monte *et al.*, 2010; Debiec *et al.*, 2011). Conversely, blocking β-adrenoceptors (with propranolol) in the infralimbic subregion impairs extinction, while intra-BLA infusion of another β-adrenoceptor blocker (timolol) enhances extinction (Mueller *et al.*, 2008; Fiorenza *et al.*, 2012). Taken together, these findings generally fit a scheme in which increasing noradrenaline signalling through β-adrenoceptors in the infralimbic subregion favours extinction, whereas promoting such signalling in the BLA opposes extinction. Contrary to this scheme, there is one report of enhanced extinction after intra-mPFC β-adrenoceptor antagonist (timolol) administration, the mPFC-wide nature of this infusion would have encompassed regions outside of the infralimbic subregion (Fiorenza *et al.*, 2012). Nonetheless, additional studies are warranted before any firm conclusions can be made and noradrenaline-acting drugs considered for possible clinical development as adjuncts to exposure therapy. Of note in this regard, treatment with propranolol has been proposed as a potential exposure-adjunct and prophylactic treatment for PTSD when given soon after trauma, but has received limited or discouraging clinical support (Orr *et al.*, 2006; Bos *et al.*, 2012; Hoge *et al.*, 2012; Soeter and Kindt, 2012). Preliminary results using yohimbine as an adjunct to exposure therapy have been somewhat more promising (Powers *et al.*, 2009), but as noted, it remains questionable whether its effects can be solely attributable to actions on the noradrenaline system.

5-HT

The 5-hydroxytryptaminergic system is of special interest as a target for extinction-modulating drugs in view of the use of 5-hydroxytryptaminergic-acting drugs, such as the selective 5-HT re-uptake inhibitors (SSRIs), to treat anxiety disorders, sometimes in combination with exposure therapy (Schneier *et al.*, 2012; Yang *et al.*, 2012; Bui *et al.*, 2013). A number of studies have examined the extinction-related effects of genetically ablating or pharmacologically inhibiting the primary target of SSRIs, the 5-HT transporter (SERT, see Alexander *et al.*, 2013b). This has shown that mutant mice and rats lacking SERT are extinction impaired and exhibit abnormalities in the dendritic morphology and spine density of pyramidal neurons in the infralimbic subregion and BLA (Wellman *et al.*, 2007; Nietzer *et al.*, 2011; Hartley *et al.*, 2012; Nonkes *et al.*, 2012; Riddle *et al.*, 2013). Electrophysiological recordings find that SERT-deficient mutants also show increased synchronization of θ wave activity between the LA and mPFC during extinction (Narayanan *et al.*, 2011), which is reminiscent of the altered functional mPFC–amygdala coupling reported in humans with a loss-of-function mutation in the SERT gene (Heinz *et al.*, 2005; Pezawas *et al.*, 2005). Thus, genetic loss of the SERT may cause a functional rebalancing of the mPFC–amygdala circuitry that favours fear over extinction.

While the SERT is blocked by SSRIs, it is clear that the effects of pharmacological inhibition are not synonymous with those produced by genetic disturbances, probably because of lasting genetic influences on brain development (for discussion, see Caspi *et al.*, 2010). Indeed, fear and extinction are sensitive to disruptions of the developing

5-hydroxytryptaminergic system, for example by deleting Pet-1, a transcription factor critically involved in 5-hydroxytryptaminergic neuron development (Wellman *et al.*, 2013). In contrast to the extinction-impairing effects of SERT gene mutation, a number of studies find that systemic chronic fluoxetine treatment facilitates extinction under most experimental conditions (c.f., caloric restriction) (Norcross *et al.*, 2008; Spennato *et al.*, 2008; Deschaux *et al.*, 2011; 2013; Camp *et al.*, 2012; Karpova *et al.*, 2012; Fitzgerald *et al.*, 2014; Riddle *et al.*, 2013). Systemic treatment with a non-selective MAO inhibitor, methylene blue, also improves extinction and increases cytochrome oxidase activity in the mPFC (Gonzalez-Lima and Bruchey, 2004; Wrubel *et al.*, 2007). However, while a similar extinction-facilitating effect is seen with certain other monoaminergic antidepressants (e.g. venlafaxine) (Yang *et al.*, 2012), the opposite (i.e. extinction impairing) effect is seen after treatment with the SERT citalopram (Burghardt and Bauer, 2013).

One culprit for these discrepancies may be the differences in the pharmacological profiles and downstream actions of SSRIs. The 5-hydroxytryptaminergic system is notoriously complex and has a high number (over 14) of receptor subtypes, many expressed in the mPFC and amygdala (Holmes, 2008). Citalopram is a relatively specific inhibitor of SERT, but down-regulates BLA expression of the NMDA receptor subtype 2B (GluN2B) subunit, which as discussed later, would be predicted to impair extinction (Burghardt and Bauer, 2013; Burghardt *et al.*, 2013). Fluoxetine has a number of 'off-target' effects, that include antagonist actions at the 5-HT_{2C} receptor subtype, but it remains unclear whether these direct pharmacological actions or certain downstream changes underlie the drug's facilitatory effects on extinction. Of relevance here, fluoxetine decreases the number of perineuronal nets around parvalbumin-positive interneurons in the BLA, which as discussed earlier, is linked to the superior extinction shown by juvenile rodents (Karpova *et al.*, 2012). This suggests at least one potential mechanism for the drug's extinction effects, although it would be valuable to show that citalopram, for example, failed to affect a change in BLA perineuronal nets. It would also be useful to have a clearer picture of the contribution of specific 5-HT receptors to fear extinction. Unfortunately, there remains a paucity of literature on this topic. One recent study shows that systemic administration of a 5-HT_{1A} receptor partial agonist (tandospirone) ameliorated extinction deficits and associated deficits in mPFC synaptic plasticity generated in a model of juvenile stress (Saito *et al.*, 2013), although the effects are attributed to increases in mPFC dopamine levels, rather than changes in 5-hydroxytryptaminergic transmission *per se*.

Various 5-HT receptors, including the 5-HT_{1A}, 5-HT_{2A} and 5-HT_{3A} subtypes, are well expressed in the BLA, suggesting another possible site whereby 5-HT could affect extinction (Mascagni and McDonald, 2007; McDonald and Mascagni, 2007). *In vitro* recordings show that 5-HT inhibits glutamate-induced excitation of BLA pyramidal neurons possibly, via activation of GABAergic interneurons, in a manner that is mimicked by a 5-HT_2 receptor agonist (α-methyl-5-HT), but not a 5-HT_{1A} receptor agonist (8-OH-DPAT) (Rainnie, 1999; Stutzmann and LeDoux, 1999). 5-HT_2 modulation of BLA neuronal activity could account for the pro-extinction effects recently reported after systemic administration of a 5-HT_{2A} receptor agonist (TCB-2), but this remains speculative in lieu of more directed experiments (Zhang and Rosenkranz, 2013; Zhang *et al.*, 2013). Also intriguing, but preliminary, is the finding that systemic blockade of 5-HT_3 receptors (using granisetron) improves extinction, while constitutively deleting the *5-HT3A* gene impairs extinction (Park and Williams, 2012; Kondo *et al.*, 2013). Establishing a potential link with the amygdala and the GABA system, the pro-extinction effects of 5-HT_3 receptor blockade were paralleled by increases in the amygdala expression of gephyrin, a $GABA_A$ receptor clustering protein (Park and Williams, 2012). The GABA system will be the focus in the next section.

In summary, there currently is a surprising dearth of research on 5-HT's role in extinction, given the dominance of 5-HT-acting drugs in anxiolytic drug market. A priority for the field going forward will be both to elucidate the extinction-related effects of targeting specific 5-HT receptor subtypes and clarify the mechanisms of action by which first-line anxiolytic treatments, such as fluoxetine, promote extinction in preclinical assays.

GABA

By providing the major source of inhibitory neurotransmission in the mPFC and amygdala, GABA exerts a powerful influence on a range of fear- and anxiety-related behaviours, including fear extinction (for a detailed discussion, see Ehrlich *et al.*, 2009; Makkar *et al.*, 2010; Pape and Pare, 2010; Courtin *et al.*, 2013). The effect of stimulating $GABA_A$ receptors can be so robust that $GABA_A$ receptor agonists (such as muscimol) are often used an experimental tool to temporally inactivate a specific brain region and thereby probe its contribution to extinction (for receptor nomenclature see Alexander *et al.*, 2013c). Temporary inactivations have been used to help establish necessary contribution of the infralimbic subregion or BLA (but not prelimbic cortex) to extinction (Sierra-Mercado *et al.*, 2006; 2011; Laurent and Westbrook, 2008; 2009a; 2010; Laurent *et al.*, 2008; Parkes and Westbrook, 2010; Sotres-Bayon *et al.*, 2012; Holmes and Singewald, 2013; Holmes *et al.*, 2013). Disruptions to extinction (possibly involving effects on memory reconsolidation) after augmenting $GABA_A$ receptor signalling is also achieved by delivering benzodiazepine agonists (diazepam, chlordiazepoxide, midazolam) systemically or directly into the BLA (Kamano, 1972; Goldman, 1977; Pereira *et al.*, 1989; Bouton *et al.*, 1990; Bustos *et al.*, 2009; Hart *et al.*, 2009; 2010).

$GABA_A$ receptor drug manipulations have bidirectional effects on extinction. For example, delivering a $GABA_A$ receptor antagonist (picrotoxin) either systemically or directly into the infralimbic subregion facilitates extinction (McGaugh *et al.*, 1990; Thompson *et al.*, 2010; Chang and Maren, 2011; Fitzgerald *et al.*, 2014). This behavioural effect could stem from the disinhibition of infralimbic subregion projections to the amygdala, which would be in line with the observation that the ICNs and LA neurons are activated by intra-infralimbic subregion $GABA_A$ receptor blockade (using picrotoxin) (Berretta *et al.*, 2005). Disinhibition of amygdala neuronal activity could also possibly explain the improvement in extinction produced by infusion of a $GABA_A$ receptor antagonist (bicuculline) directly into the BLA (Berlau and McGaugh, 2006). Another route by which $GABA_A$ receptors in the amygdala might modulate extinction is at the level of the

ICNs. $GABA_A$ receptors containing the α2/α3 subunits are expressed on ICNs projecting to the CeA and are physiologically sensitive to application of a benzodiazepine agonist (diazepam), GABA potentiator (zolpidem) and specific α3 subunit agonist (TP003) (Marowsky *et al.*, 2005; Geracitano *et al.*, 2012). The behavioural consequence of pharmacologically targeting these receptors is an interesting question that has not been addressed at the current time.

As the complex pattern of receptor expression suggests, the role of GABA in extinction is more nuanced than simply turning a brain region on or off with a $GABA_A$ receptor agonist or antagonist. Extinction testing up-regulates the infralimbic subregion and BLA expression of glutamic acid decarboxylase isoform (GAD67), an enzyme that controls the synthesis of GABA in the brain (Heldt and Ressler, 2007; Sangha *et al.*, 2012) and promotes the binding and clustering of $GABA_A$ receptors in the BLA (Chhatwal *et al.*, 2005b; Heldt and Ressler, 2007; Lin *et al.*, 2009a). Extinction is impaired either by BLA viral knockdown of GAD67 or by constitutive deletion of the other GAD isoform, GAD65 (Sangha *et al.*, 2009; Heldt *et al.*, 2012). Thus, effective extinction appears to recruit and require GABAergic signalling in the mPFC–amygdala circuitry, perhaps to shape the plastic changes in circuitry that underlies extinction. This may go some way to explain ostensibly paradoxical cases whereby infusion of a $GABA_A$ receptor agonist (muscimol) into either the infralimbic subregion or BLA facilitates extinction (Akirav *et al.*, 2006), and where systemic administration of a GABA signalling-reducing benzodiazepine partial inverse agonist (FG 7142) impairs extinction (Harris and Westbrook, 1998; Kim and Richardson, 2007; 2009).

These behavioural findings beg the question of how GABAergic neurotransmission contributes, mechanistically, to extinction. Some authors emphasize a role for GABA in decreasing BLA pyramidal neuronal activity and actively reversing some of the plastic changes produced by fear learning (Lin *et al.*, 2003a,b). In addition, a number of recent studies provide compelling evidence for the integral role played by GABAergic parvalbumin interneurons in the BLA and mPFC. First is the aforementioned study by Courtin *et al.* showing that parvalbumin interneurons exert an outsized influence in controlling the activity of prelimbic cortex/ACC pyramidal neurons and maintain reduced fear after extinction by suppressing prelimbic cortex excitatory inputs to the amygdala (Courtin *et al.*, 2014a). The dysregulation of prelimbic cortex pyramidal cells could explain why extinction is impaired in mutants with genetically induced loss of parvalbumin-positive interneurons in the mPFC, although this genetic insult was not restricted to the prelimbic cortex in these models (Pitts *et al.*, 2012; Bissonette *et al.*, 2014). Second, Cho *et al.* have found that excitatory mPFC input to parvalbumin interneurons in the BLA decreases with extinction, which they posit results in the disinhibition of a population of BLA pyramidal neurons and a net shift in favour of the amygdala output-inhibiting mPFC connections to the ICNs, which appear functionally unaltered after extinction (Cho *et al.*, 2013). Cho *et al.* also observed that fear extinction led to an increase in the inhibition auditory cortical inputs to the BLA that was reversed by a $GABA_B$ receptor blocker (CGP52432) (Cho *et al.*, 2013). A contribution of $GABA_B$ receptors to extinction-induced amygdala plasticity echoes the observation that extinction increases amygdala expression of the $GABA_{B2}$ receptor subunit (Heaney *et al.*, 2012). It is also noteworthy, in light of behavioural studies, that systemic delivery of a $GABA_B$ receptor antagonist (baclofen) or gene deletion of the $GABA_{B1}$ receptor subunit lead to impaired extinction, although other studies report no effect of other systemically delivered $GABA_B$ receptor antagonists (phaclofen or CGP52432) or positive allosteric modulators (GS39783) (Jacobson *et al.*, 2006; Heaney *et al.*, 2012; Sweeney *et al.*, 2013).

In summary, the available evidence indicates that GABA signalling has important, but nuanced role in extinction. On the one hand, GABA system is recruited during extinction, probably in the service of plasticity mechanisms that reshaping neuronal networks underlying extinction. On the other hand, commonly prescribed drugs such as benzodiazepines, which increase GABAergic tone and effectively alleviate many of the acute symptoms of anxiety, would be expected to limit the efficacy of extinction-based therapies by interfering with the activation of the mPFC–amygdala circuitry. It would appear, therefore, that GABA-targeting pharmacological adjuncts to exposure therapy would need to strike a delicate balance between maintaining GABA activity without overactivating the system.

Glutamate

The involvement of glutamatergic neurotransmission in extinction has been demonstrating by experimental manipulations of the AMPA, metabotropic glutamate (mGlu) and NMDA receptors.

In terms of AMPA receptors, a handful of studies have found that pharmacologically blocking the receptors (via 6-cyano-7-nitroquinoxaline-2,3-dione) in the BLA does not alter extinction (Falls *et al.*, 1992; Lin *et al.*, 2003c; Zimmerman and Maren, 2010). However, activating AMPA receptors, via systemic treatment with an AMPA receptor agonist 2-[2,6-difluoro-4-[[2-[(phenylsulfonyl)amino]ethyl] thio]phenoxy]acetamide (PEPA) facilitates extinction in various rodent models (Zushida *et al.*, 2007; Yamada *et al.*, 2009; 2011), although not in severely extinction-impaired animals (Whittle *et al.*, 2013). Data obtained from combining direct drug infusions (of PEPA) into the mPFC or BLA, with *ex vivo* electrophysiological analysis of changes in neuronal activity, has identified the mPFC as a possible locus of these drug effects (Zushida *et al.*, 2007).

The precise mechanistic basis for pro-extinction effects of AMPA receptor stimulation is not wholly clear, but may involve alterations in synaptic plasticity, AMPA receptor internalization and intracellular signalling, given evidence that extinction leads to alterations in the phosphorylation and cell-surface expression of AMPA receptors, as well as decoupling from synaptic scaffolding proteins including post-synaptic density 95 (Lin *et al.*, 2003c; Mao *et al.*, 2006; 2008; 2013; Kim *et al.*, 2007b; Lee *et al.*, 2013). In this context, systemic or intra-BLA infusion of a synthetic peptide that blocks activity-dependent internalization of the AMPA receptor subunit, GluA2, impairs extinction (Kim *et al.*, 2007b; Dalton *et al.*, 2008; Lin *et al.*, 2010), while interference with phosphorylation of the AMPA receptor subunit 1 (GluA1) bolsters at least some measures of extinction (Lee *et al.*, 2013). The behavioural actions of AMPA receptor

manipulations are also linked to the effects of two signalling molecules downstream of AMPA: calcineurin and PKA. Transgenic or pharmacological inhibition of calcineurin facilitates extinction (Lin *et al.*, 2003a,b; Havekes *et al.*, 2008), whereas mutant or drug-independent inhibition of PKA has the opposite effect (Isiegas *et al.*, 2006; Nijholt *et al.*, 2008). Targeting these downstream molecules could potentially offer alternative approaches to modulating AMPA receptors to affect changes in extinction.

Another route to modifying extinction through glutamate-targeting drugs is through mGlu receptors. Blocking the $mGlu_1$ receptor subtype (using CPCCOEt) disrupts AMPA receptor-mediated synaptic depotentiation in the BLA and produces impairments in extinction (Kim *et al.*, 2007a,b). The $mGlu_1$ receptor is also notable for its expression on neurons innervating in some ICNs, although the possible role of this population of receptors in extinction is unknown (Busti *et al.*, 2011). Of the various other mGlu subtypes, $mGlu_5$ and $mGlu_7$ have been quite well studied for their effects on extinction. Gene deletion of either of these subtypes results in deficits in extinction (Callaerts-Vegh *et al.*, 2006; Goddyn *et al.*, 2008; Xu *et al.*, 2009), suggesting that augmenting function at these subunits could promote extinction. Indeed, pro-extinction effects have been reported with a $mGlu_7$ receptor agonist (AMN082) given either systemically or directly into the BLA, not mPFC (Fendt *et al.*, 2008; Morawska and Fendt, 2012; Toth *et al.*, 2012a; Dobi *et al.*, 2013; Whittle *et al.*, 2013). These effects have been traced to the localization of $mGlu_7$ receptors in the proximity of the ICNs and on local and thalamic glutamatergic inputs in the BLA (Dobi *et al.*, 2013). In terms of $mGlu_5$, results to date show that extinction is disrupted by systemic, intra- infralimbic subregion or intra-BLA blockade of the subtype [via 2-methyl-6-(phenylethynyl)pyridine], but in some instances, only if extinction training is sufficiently deepened with prolonged training (Fontanez-Nuin *et al.*, 2011; Toth *et al.*, 2012a; Mao *et al.*, 2013). These extinction-impairing effects of mGluA5 antagonists have been tied to reduced infralimbic subregion neuronal bursting and the disruption of synaptic plasticity and synaptic insertion of the AMPA GluA2 subunit (Fontanez-Nuin *et al.*, 2011; Sepulveda-Orengo *et al.*, 2013).

In comparison with AMPA and mGlu receptors, NMDA receptors have been extensively studied for their role in fear extinction. Systemic, intra-BLA or intra-mPFC delivery of NMDA receptor blockers (e.g. via MK-801 or AP5) reliably produce deficits in extinction (Falls *et al.*, 1992; Baker and Azorlosa, 1996; Lee and Kim, 1998; Santini *et al.*, 2001; Lin *et al.*, 2003c; Lee *et al.*, 2006; Burgos-Robles *et al.*, 2007; Laurent and Westbrook, 2008; 2009b; Laurent *et al.*, 2008; Chan and McNally, 2009; Parsons *et al.*, 2010; Zimmerman and Maren, 2010; Parkes and Westbrook, 2011; Fiorenza *et al.*, 2012; Holmes *et al.*, 2012). Moreover, NMDA receptors in the BLA are permissive for the extinction-related effects of drugs targeting other systems, such as glucocorticoids. Systemic administration or intra-BLA delivery of a synthetic glucocorticoid (dexamethasone) or glucocorticoid agonist (RU28362) enhances extinction, whereas systemic inhibition of glucocorticoid synthesis (using metyrapone) or intra-BLA glucocorticoid receptor blockade (with mifepristone) impairs extinction (Yang *et al.*, 2006; 2007). The pro-extinction effects of systemic glucocorticoid receptor agonism (using dexamethasone) are occluded by blocking NMDA receptors in the BLA (using MK-801 or DL-AP5), whereas the deficiency in extinction caused by the glucocorticoid synthesis inhibitor (via metyrapone) are reversed by systemic NMDA receptor partial agonist (D-cycloserine) administration (Yang *et al.*, 2007). Achieving a better understanding of these interactions may have clinical implications down the line. A randomized, double-blind, placebo-controlled study of acrophobics found that adjunctive cortisol treatment increased the efficacy of exposure therapy (de Quervain *et al.*, 2011), echoing earlier support for hydrocortisone augmentation of exposure therapy in PTSD (Yehuda and LeDoux, 2007; Surís *et al.*, 2010). The preclinical literature would suggest that consideration should be given to augmenting the effectiveness of such treatment with NMDA receptor-acting drugs.

There has been initial progress in delineating the contribution of specific NMDA receptor subunits to extinction. Transgenic overexpression of the GluN2B subunit facilitates extinction (Tang *et al.*, 1999), while GluN2B-selective antagonism (using ifenprodil or Ro 25-6981) either systemically or specifically within the mPFC or BLA (but not the hippocampus) disrupts extinction learning or relearning (Sotres-Bayon *et al.*, 2007; 2009; Laurent and Westbrook, 2008; Laurent *et al.*, 2008; Dalton *et al.*, 2012; Leaderbrand *et al.*, 2014). Systemic treatment with a GluN2B-selective antagonist (Ro 25-891) also reverses an enhanced extinction phenotype in reelin haploinsufficient mutants, that is typically only seen in young rodents, to a more adult-like form (Iafrati *et al.*, 2013). The role of other NMDA receptor subunits is an important, but unresolved question. One recent study demonstrated that potentiating the actions of the NMDA receptor subtype 2C/D (GluN2C/D) subunit in the BLA (using CIQ) enhances extinction (Ogden *et al.*, 2014). Another way to achieve nuanced pharmacological modulation of the NMDA receptor is to target the glycine binding site located on the GluN1 subunit. Enhancements in extinction are achieved by intra-BLA inhibition of glycine reuptake (via NFPS) (Mao *et al.*, 2009), or by more direct stimulation of the glycine site by systemic or intra-BLA administration of D-serine or D-cycloserine (Walker *et al.*, 2002; Ledgerwood *et al.*, 2003; 2005; Yang and Lu, 2005; Lee *et al.*, 2006; Mao *et al.*, 2006; 2008; Woods and Bouton, 2006; Weber *et al.*, 2007; Bouton *et al.*, 2008; Matsuda *et al.*, 2010; McCallum *et al.*, 2010; Yamada *et al.*, 2011; Baker *et al.*, 2012; Fiorenza *et al.*, 2012; Toth *et al.*, 2012a). The pro-extinction effects of D-cycloserine extend to models of environmentally induced extinction impairment, including those produced by stress (Matsumoto *et al.*, 2008; Yamamoto *et al.*, 2008; Akirav *et al.*, 2009; Judo *et al.*, 2010), sleep deprivation (Silvestri and Root, 2008) and chronic alcohol exposure (Bertotto *et al.*, 2006). D-cycloserine does not, however, promote extinction under all conditions. For example, systemic D-cycloserine is ineffective when extinction occurs soon after conditioning (Chang and Maren, 2011), is preceded by footshock (Langton and Richardson, 2010) or has to be relearned (Langton and Richardson, 2010). The extinction-related effects of D-cycloserine are also obscured if subjects exhibit poor basal extinction (Tomilenko and Dubrovina, 2007; Weber *et al.*, 2007; Bouton *et al.*, 2008; Hefner *et al.*, 2008; Whittle *et al.*, 2013) or have a history of chronic treatment with D-cycloserine or certain antidepressant (Parnas *et al.*, 2005; Werner-Seidler and Richardson, 2007).

Under conditions where they do manifest, the extinction improving effects of D-cycloserine are probably not solely because of modulation of NMDA receptor function. Rather, these effects can be linked back in part to some of the changes in AMPA receptors and ERK1/2 signalling discussed earlier. D-cycloserine increases BLA AMPA receptor internalization (Mao *et al.*, 2006; 2008) and blocking peptidergically inhibiting the GluA2 subunit occludes the pro-extinction effects produced by intra-BLA D-cycloserine (Lin *et al.*, 2010). Similarly, systemic or intra-BLA administration of ERK1/2 blockers (PD98059, U0-126 or SL327) also reverses the pro-extinction effects of systemic D-cycloserine (Yang and Lu, 2005; Matsuda *et al.*, 2010). Tangentially, ERK1/2 inhibition (via PD98059) also occludes the extinction enhancing effects of Ginkgo biloba extract (EGb761) (Yang *et al.*, 2009) and brain-derived neurotrophic factor (BDNF)-induced phosphorylation of stathmin, a cytoskeleton regulator that, when deleted, promotes extinction and BLA neuronal activation (Shumyatsky *et al.*, 2005; Martel *et al.*, 2012). These findings serve to illustrate the intimate functional interplay between not only different glutamate receptors, but also neurotrophins and intracellular signalling molecules. As such, they underscore how the extinction-related effects of a given compound will typically result from multiple molecular changes that extend beyond the drug's primary pharmacological target.

Neuropeptides

Various neuropeptide systems have long attracted interest as potential anxiolytics, given their modulatory actions on emotional processes (Holmes *et al.*, 2003). Neuropeptides expressed in the mPFC–amygdala circuit represent a number of interesting potential candidates for novel pharmacological approaches to promoting fear extinction. Two good examples are neuropeptide Y (NPY) and neuropeptide S (NPS), which are localized in the BLA on GABAergic (McDonald and Pearson, 1989) and glutamatergic (Xu *et al.*, 2007) neurons respectively. Extinction is facilitated by i.c.v. infusion of NPY, and this effect is blocked by systemic antagonism of the Y_1 receptor subtype (via BIBO3304) (Gutman *et al.*, 2008; Lach and de Lima, 2013). The locus of these effects remains to be precisely established, but might entail the actions of NPY on GABA interneurons in the BLA, given the finding that specifically antagonizing Y_1 receptor (again using BIBO3304) in the BLA, or constitutively deleting the subunit, impairs extinction (Gutman *et al.*, 2008; Verma *et al.*, 2012).

The mechanism underlying the modulation of fear extinction by NPS is somewhat clearer, and involves a key role for the amygdala. Intra-BLA infusion of NPS is sufficient to exert a pro-extinction effect and blocking BLA NPS receptors is enough to disrupt extinction (Jungling *et al.*, 2008; Chauveau *et al.*, 2012). These effects might occur through presynaptic NPS receptors on BLA pyramidal neurons; NPS has been shown to increase glutamatergic inputs to (medial paracapsular) ICNs and could thereby dampen CeA output and augment extinction (Jungling *et al.*, 2008). Although these findings strongly implicate the amygdala, NPS could also affect extinction at the level of the mPFC, given the finding that i.c.v. infusion of the peptide increases extracellular levels of dopamine (not 5-HT) in the mPFC (Si *et al.*, 2010).

A number of recent findings have revealed an interesting, albeit complex, role for opioid peptides in extinction. Systemic blockade of κ-opioid receptors (KOP receptors) [via norbinaltorphimine (nor-BNI)] or gene deletion of dynorphin (but not encephalin or β-endorphin) leads to increased fear and/or poorer extinction, in association with reduced neuronal activity in the BLA and mPFC (Bilkei-Gorzo *et al.*, 2012). However, successful fear extinction correlates with a *reduction* in the mRNA expression of KOP receptors in the BLA (Knoll *et al.*, 2011) and i.c.v. antagonism (via nor-BNI) can reduce fear renewal after extinction (Cole *et al.*, 2011; 2013) [infusion of a KOP receptor agonist (U50,488) into the nucleus accumbens is also without effect Muschamp *et al.*, 2011]. It is unclear, therefore, whether KOP receptors primarily work to promote or disrupt fear extinction.

With respect to other opioid receptor subtypes, systemic treatment with a subtype non-selective opioid receptor antagonist with preferential binding for μ-opioid receptors (MOP receptors) (naloxone) impairs extinction (McNally and Westbrook, 2003). Blocking MOP receptors specifically within the BLA (again via naloxone) failed to affect extinction (Parsons *et al.*, 2010), suggesting the effect of systemic antagonism may be localized to MOP receptors elsewhere in the brain. In this context inhibiting MOP receptors (again via naloxone) in the periaqueductal grey is sufficient to impair extinction (McNally *et al.*, 2004; Parsons *et al.*, 2010), and this effect is recapitulated by a more selective MOP receptor blocker [CTAP (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2)], but not selective KOP (with nor-BNI) or δ-opioid receptor (naltrindole) antagonists (McNally, 2005). These various observations show that both KOP and MOP receptors influence extinction, but the precise locus of these effects remains to be determined. One site of particular interest to future work is the ICNs, which express high levels of MOP receptors and extinction is impaired by ablating ICNs using a MOP receptor agonist (demorphin) conjugated to a toxin (Likhtik *et al.*, 2008; Busti *et al.*, 2011; Geracitano *et al.*, 2012; Pinard *et al.*, 2012).

Somatostatin and oxytocin play prominent roles in fear and extinction that have been convincingly linked to the mPFC–amygdala circuit. Fear learning increases excitatory input to somatostatin-positive neurons in the mouse CeL, which could act to dampen CeL inhibitory control of CeM output and thereby release fear and oppose extinction (Li *et al.*, 2013) (c.f. Amano *et al.*, 2012). Correspondingly, optogenetic stimulation of somatostatin-positive CeL neurons produces increases in conditioned fear (Li *et al.*, 2013) (akin to the 'CeL on' cells discussed earlier Haubensak *et al.*, 2010), and would be predicted to oppose extinction. Another potential link between somatostatin and extinction is through regulation of AC by the somatostatin receptor-3 subtype, given the finding that gene deletion of the type 3 AC produces extinction of impairment (Wang *et al.*, 2011). The pro-fear function of the CeL's somatostatin-positive cells contrasts with neighbouring somatostatin-negative cells, which are also GABAergic, but are defined by PKC-δ expression, and reduce CeA output and fear, consistent with the 'CeL off' cells discussed earlier (Haubensak *et al.*, 2010; Amano *et al.*, 2012).

Another feature of 'CeL off' cells is the expression of oxytocin receptors and modulation by oxytocin (Huber *et al.*, 2005). Local application of oxytocin to the CeL, or optogenetic stimulation of oxytocin-labelled inputs to the CeL from the hypothalamus reduces CeM excitability and attenuates fear (Viviani *et al.*, 2011; Knobloch *et al.*, 2012). This raises

the question of whether a similar mechanism may also be recruited during extinction to suppress CeM-driven fear. However, pre-extinction i.c.v. administration of oxytocin has been found to disrupt, rather than promote, extinction, and to do so in a manner that is occluded by oxytocin receptor antagonism [via desGly-NH2,d(CH2)5[Tyr(Me)2,Thr4]OVT; Toth *et al.*, 2012b]. This might very likely reflect opposing extinction-related effects of oxytocin acting in different brain regions. This hypothesis is borne out by the finding that infusion of oxytocin (but not an agonist, [Thr^4,Gly^7]-oxytocin) into the BLA or dorsal raphe nucleus impairs extinction, whereas infusion into the infralimbic subregion (but not CeA) improves extinction (Kovacs *et al.*, 1979; Lahoud and Maroun, 2013). Such region-based, opposite effects make it difficult to predict with certainty how a systemically delivered oxytocin-acting drug might influence extinction in a clinical setting. Notwithstanding, there is preliminary evidence that oxytocin, given intranasally, can improve extinction in healthy humans (Acheson *et al.*, 2013).

There is nascent support for two functionally related peptides, gastrin and cholecystokinin (CCK), in fear extinction. Deletion of gastrin-releasing peptide (GRP) receptors alters extinction-related neuronal activation in the mPFC (activity is decreased) and BLA (activity is increased) and promotes BLA synaptic plasticity, but appears to have rather mixed effects on extinction, with only one of two studies reporting an impairment (Chaperon *et al.*, 2012; Martel *et al.*, 2012). The endogenous ligand of GRP receptors, GRP, stimulates gastrin, which in turn binds the CCK_2 receptor (previously known as CCK-B) subtype. Infusion of a CCK_2 receptor agonist (pentagastrin), i.c.v., impairs extinction (Chhatwal *et al.*, 2009), an effect that is occluded by systemic or intra-BLA CCK_2 blockade (via CR2945) (Chhatwal *et al.*, 2009). Furthermore, systemic or intra-BLA antagonism of CCK_2 receptors (with CR2945) reverses the fear extinction deficits produced by systemic antagonism of CB_1 cannabinoid receptors (via SR141716) (Chhatwal *et al.*, 2009). Together, these observations demonstrate that activating CCK_2 receptors in the BLA, either through direct agonism or via loss of CB_1 receptor-mediated inhibitory control over CCK release (Mascagni and McDonald, 2003), is deleterious to extinction, and, conversely, that blocking this receptor may enable extinction.

Finally, despite being one of the most widely investigated neuropeptides in stress and anxiety, surprisingly, few studies have examined the contribution of corticotropin-releasing factor (CRF) to fear extinction. Infusion of a CRF antagonist (α-helical CRF9-41), i.c.v., prevents fear recovery after extinction (Waddell *et al.*, 2008). This effect could conceivably stem from the potent modulatory actions of CRF on GABA transmission in the amygdala (Rainnie *et al.*, 2004). In this regard, deleting $GABA_A$-α1 receptors solely on CRF neurons is sufficient to impair extinction in a manner reversible by blocking CRF_1 receptors (via R121919) systemically or in the bed nucleus of the stria terminalis (Gafford *et al.*, 2012). Nonetheless, there remains much still to understand about the role of CRF in fear extinction.

Endocannabinoids

Already mentioned in the context of a link with CCK system, CB_1 receptors are further implicated by a compelling literature tying endocannabinoids with fear extinction (for more detailed recent reviews, see Riebe *et al.*, 2012; Gunduz-Cinar *et al.*, 2013). Numerous reports have shown that gene knockout or systemic blockade (via SR141716A) of CB_1 receptors impairs extinction (Marsicano *et al.*, 2002), whereas extinction is promoted by systemically activating CB_1 receptors (via WIN55,212-2, arachidonyl-2-chloroethylamide or cannabidiol) or increasing endocannabinoids by blocking re-uptake (via AM404) or inhibiting the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH) (Kathuria *et al.*, 2003) (using AM3506 or URB597) (Marsicano *et al.*, 2002; Cannich *et al.*, 2004; Suzuki *et al.*, 2004; Chhatwal *et al.*, 2005a; Pamplona *et al.*, 2006; 2008; Bitencourt *et al.*, 2008; Kamprath *et al.*, 2009; Gunduz-Cinar *et al.*, 2013; Laricchiuta *et al.*, 2013; Reich *et al.*, 2013; Segev *et al.*, 2014). The mPFC–BLA circuit is implicated as a site of these actions by a number of observations. First, endocannabinoids regulate synaptic plasticity in the BLA and fear extinction increases endocannabinoid levels and recruits various extinction-related intracellular signalling cascades in this region (Marsicano *et al.*, 2002; Cannich *et al.*, 2004; Gunduz-Cinar *et al.*, 2013). Second, CB1 receptor agonism (via WIN55,212-2 or cannabidiol), re-uptake inhibition (using AM404) or FAAH inhibition (with AM3506), either in the BLA, or in at least some studies, the mPFC or infralimbic subregion, promotes fear extinction and prevents stress-induced extinction deficits (Lin *et al.*, 2006; 2009b; Do Monte *et al.*, 2013; Ganon-Elazar and Akirav, 2013; Gunduz-Cinar *et al.*, 2013). Along similar lines, CB_1 receptor antagonism (via AM251) limited to the mPFC also impairs extinction (Kuhnert *et al.*, 2013).

The basis for CB_1 receptor-mediated control of extinction has being further delineated in studies using sophisticated gene mutant techniques. This work has shown that deletion of CB_1 receptors on forebrain or cortical glutamatergic cells or dopamine D_1 receptor-expressing neurons is sufficient to disrupt extinction (Kamprath *et al.*, 2009; Terzian *et al.*, 2011). Extinction is also impaired if CB_1 receptors are absent on all, but a subpopulation of forebrain glutamatergic neurons (Ruehle *et al.*, 2013), although this same population of CB_1 receptors may not mediate stress effects on extinction (Dubreucq *et al.*, 2012). In a more focused examination of CB_1 receptor function acting within the mPFC–amygdala circuit, the pro-extinction actions CB_1 receptors have been localized to a subset of neurons within the BA (Trouche *et al.*, 2013). Trouche and colleagues found that the excitability of fear-activated BA pyramidal neurons is diminished following extinction in association with an increased inhibitory input from parvalbumin- and CCK-positive, CB_1 receptor-expressing, interneurons (Trouche *et al.*, 2013). Taken together, the weight of these and other preclinical findings point to the potential therapeutic benefit of activating CB_1 receptors. Encouragingly, initial clinical data show that stimulating cannabinoid receptors with synthetic constituents of cannabis (cannabidiol, dronabinol) promotes extinction in healthy volunteers in some, although not all studies, and increases (blood oxygen level-dependent fMRI) activity within the human mPFC (Klumpers *et al.*, 2012; Das *et al.*, 2013; Rabinak *et al.*, 2013; 2014).

Miscellaneous: from ACh to epigenetics

The intense interest in fear extinction has led researchers to explore the role of myriad neurotransmitter and molecular

systems in the process. Covering all of these leads is out of the scope of the current review, but we will touch on some of them in this section.

We have concentrated on the major amine, excitatory and inhibitory neurotransmitters, but there is a more nascent body work concerning a number of other transmitters in fear extinction. One example is the histamine system, which has been found to exert bidirectional effects on mPFC–amygdala-mediated extinction. A histamine H_2 receptor antagonist (ranitidine) delivered into the BLA or mPFC impairs extinction, while enhancing histamine in these regions by inhibiting the histamine-metabolizing enzyme, N-methyltransferase (via SKF91488) improves extinction (Fiorenza *et al.*, 2012). Another neurotransmitter, ACh, has a long been established as a mediator of learning is memory, and more recently, identified as a modulator fear extinction. Systemic blockade of muscarinic receptors (scopolamine) enhances extinction by rendering the process context-independent (Zelikowsky *et al.*, 2013). Stimulating muscarinic receptors in the mPFC (via cevimeline) enhances extinction, whereas blocking the receptors systemically or in the mPFC (via scopolamine) impairs extinction (Santini *et al.*, 2012), possibly by attenuating neuronal excitability modulated by the M-type potassium channel (Santini and Porter, 2010). Although there may or may not be a link with muscarinic receptors, or with cholinergic signalling, there is evidence implicating another type of ion channel, the L-type voltage-gated calcium channel ($Ca_V1.x$; for nomenclature see Alexander *et al.*, 2013d), in extinction. Blocking (but not stimulating, with BayK) $Ca_V1.x$ (using nifedipine or verapamil) either systemically or specifically within the BLA (but not i.c.v.) impairs extinction and prevents increases BLA mitogen-activated kinase activation, with the systemic effect being dependent upon the $Ca_V1.2$ channel isoform (Busquet *et al.*, 2008; Waltereit *et al.*, 2008; Davis and Bauer, 2012).

Beyond the major neurotransmitters, neurotrophins are currently a focus in many fields of learning and memory. A particularly well-studied neurotrophic system in the context of fear extinction is BDNF. Extinction is impaired in mice that are haploinsufficient for BDNF or carry a BDNF gene variant that also impairs extinction in human subjects (Soliman *et al.*, 2010; Psotta *et al.*, 2013). Virus-mediated deletion of BDNF or the BDNF trkB receptor (for receptor nomenclature see Alexander *et al.*, 2013e) within BLA (but not prelimbic cortex) also disrupts extinction (Chhatwal *et al.*, 2006; Choi *et al.*, 2010). Conversely, systemic administration of a trkB receptor agonist (7,8-dihydoxyflavone) increases mPFC BDNF expression, BLA trkB activity and facilitates extinction, as does infusion of BDNF into hippocampal inputs to the infralimbic subregion (Peters *et al.*, 2010; Andero *et al.*, 2011; Baker-Andresen *et al.*, 2013). Increasing brain levels of magnesium (via treatment with magnesium-l-threonate) also improves extinction in association with increased mPFC, but in this case not BLA, BDNF expression and related enhancements in mPFC synaptic plasticity (Abumaria *et al.*, 2011). Increases in mPFC BDNF were not, however, related to the enhanced extinction produced by a cute or chronic systemic administration of an angiotensin receptor type 1 antagonist (losartan) (Marvar *et al.*, 2014).

Increased BDNF signalling might promote extinction by increasing the number of parvalbumin-positive synapses around BLA fear neurons and thereby increasing inhibitory control of excitatory, fear-promoting, neurons (Kohara *et al.*, 2007; Gittis *et al.*, 2011) – a mechanism analogous to that discussed earlier involving CCK and CB_1 receptors (Trouche *et al.*, 2013). In addition to BDNF, fibroblast growth factor-2 (FGF-2), a mitogen with assorted effects on neuroplasticity, neurogenesis and various molecular signalling pathways involved in memory, is another neurotrophin acting within the mPFC–amygdala circuit to modify extinction. A series of studies by Graham, Richardson and colleagues found that FGF-2, delivered systemically or directly into the BLA, facilitates extinction (Graham and Richardson, 2009; 2010; 2011a,b).

A connection has emerged between extinction, BDNF and epigenetic changes in the mPFC–amygdala circuit. Systemic treatment with valproic acid, a commonly prescribed anticonvulsant and mood-stabilizing medication, facilitates extinction in association with increases in the mPFC expression of BDNF and an epigenetic change (increased histone H4 acetylation) around the BDNF gene promoter (Bredy *et al.*, 2007; Bredy and Barad, 2008; Heinrichs *et al.*, 2013; Whittle *et al.*, 2013). Extinction-promoting effects are not limited to valproic acid, but extend to other manipulations with histone deacetylase (HDAC)-inhibiting properties, including treatment with sodium butyrate, vorinostat or trichostatin A, and dietary zinc depletion (Lattal *et al.*, 2007; Whittle *et al.*, 2010; Fujita *et al.*, 2012; Matsumoto *et al.*, 2013). Suggesting that at least some of these behavioural effects may work through the mPFC–amygdala circuit, improvements in fear extinction produced by zinc depletion correlated with the normalization of aberrant activation of multiple mPFC and amygdala subregions (Whittle *et al.*, 2010). Of further relevance in this regard, inhibiting the activity of another transcriptional modifier of histone acetylation, the histone acetyltransferase (HAT) p300 in the infralimbic subregion (using C646 or a combined p300/cAMP-responsive element-binding protein-binding protein inhibitor, PCAF) strengthened extinction and enhanced synaptic plasticity within the infralimbic subregion (Marek *et al.*, 2011; Wei *et al.*, 2012).

These findings have fostered the investigation of specific subtypes of class I HDACs in extinction. Infusion of a HDAC1/HDAC3 inhibitor (MS-275) into the hippocampus (but not when given systemically; Whittle *et al.*, 2013) disrupts extinction, while viral-mediated hippocampal overexpression HDAC1 has the opposite effect (Bahari-Javan *et al.*, 2012). Conversely, and more akin to the effects of subtype non-specific HDAC inhibitors, extinction is facilitated by gene knockout of HDAC2 (not HDAC1) on forebrain neurons (Morris *et al.*, 2013). Given HDAC constrains gene expression and synaptic plasticity (Sharma, 2010), the pro-extinction effects of HDAC inhibitors can be framed in terms of the release of extinction-mediating plasticity in the mPFC–amygdala circuitry. However, the finding that inhibition of HDAC or HAT does not uniformly promote extinction suggests that there are additional factors at play that have not yet been adequately illuminated (Marek *et al.*, 2011). Clarifying these mechanisms will be important to inform the clinical potential of this interesting approach to modifying extinction (for an excellent recent review, see Whittle and Singewald, 2014.

Table 1

Rodent models of impaired fear extinction linked to mPFC–amygdala circuitry abnormalities

Category of model	Link to mPFC–amygdala circuit	Reference
Subpopulation or strain		
Poor extinction C57BL/6 mice	mPFC/BLA hypoactivation, prolonged mPFC long-term depression	Herry and Mons, 2004
Poor extinction Sprague Dawley rats	Increased prelimbic cortex neuronal firing, reduced infralimbic cortex neuronal bursting	Burgos-Robles *et al.*, 2007; 2009
Poor extinction transgenic rats	Hypoactivation of infralimbic cortex inputs to BLA, hyperactivation of prelimbic cortex inputs to BLA	Knapska *et al.*, 2012
129S1/SvImJ inbred strain	Infralimbic cortex/BLA/CeL hypoactivation, prelimbic cortex/CeM hyperactivation, prelimbic cortex/infralimbic cortex neuronal hyperactivity	Hefner *et al.*, 2008; Whittle *et al.*, 2010; Camp *et al.*, 2012; Fitzgerald *et al.*, 2014
High-anxiety behavior rats	Infralimbic cortex/BLA hypoactivity, CeM hyperactivity	Muigg *et al.*, 2008
Adolescent rats and mice	Infralimbic cortex hypoactivation, impaired infralimbic cortex synaptic plasticity	Kim *et al.*, 2011; Pattwell *et al.*, 2012
Environmental insult		
Chronic alcohol	Infralimbic cortex dendritic hypertrophy, reduced infralimbic cortex NMDA receptor function, infralimbic cortex neuronal hypoactivity	Holmes *et al.*, 2012
Forced swim stress	Infralimbic cortex dendritic hypotrophy	Izquierdo *et al.*, 2006
Restraint stress	Infralimbic cortex neuronal hypoactivity, prelimbic cortex neuronal hyperactivity, BLA synaptic hyperactivity	Wilber *et al.*, 2011; Chauveau *et al.*, 2012
Elevated platform stress	BLA dendritic hypotrophy/spinogenesis, infralimbic cortex GR up-regulation	Maroun and Richter-Levin, 2003; Maroun, 2006; Deschaux *et al.*, 2013; Maroun *et al.*, 2013
Social defeat stress	Increased mPFC 2-AG levels	Dubreucq *et al.*, 2012
Chronic corticosterone	mPFC NMDA/AMPA receptor down-regulation	Gourley *et al.*, 2009
Prenatal stress or corticosterone	Infralimbic cortex GR down-regulation	Bingham *et al.*, 2013
Maternal separation	Infralimbic cortex GR up-regulation/NMDA receptor down-regulation	Wilber *et al.*, 2009
Post-natal footshock stress		Ishikawa *et al.*, 2012
Adolescent stress	Prelimbic cortex/BA hyperactivation, impaired mPFC synaptic plasticity	Judo *et al.*, 2010; Toledo-Rodriguez *et al.*, 2012; Saito *et al.*, 2013
'Immediate extinction effect'	Reduced mPFC neuronal bursting, mPFC neuronal hypoactivity, prelimbic cortex hyperactivity	Chang *et al.*, 2010; Kim *et al.*, 2010; Stafford *et al.*, 2013
Genetic manipulation		
Reelin haploinsufficient	Abnormal mPFC synaptic plasticity/spine density	Iafrati *et al.*, 2013
5-HT transporter knockout	Infralimbic cortex dendritic hypertrophy, increased BLA spine density, increased LA-mPFC theta activity	Wellman *et al.*, 2007; Narayanan *et al.*, 2011; Nietzer *et al.*, 2011
Pet-1 knockout	BLA dendritic hypertrophy	Wellman *et al.*, 2013
GAD67 knockdown	BLA specific	Heldt *et al.*, 2012
Plaur knockout	Reduced mPFC interneurons	Bissonette *et al.*, 2014
Dynorphin knockout	Infralimbic cortex/BLA hypoactivation	Bilkei-Gorzo *et al.*, 2012
GRP receptor knockout	mPFC hypoactivation, BLA hyperactivation and increased synaptic plasticity	Martel *et al.*, 2012
TrkB knockdown	BLA specific knockdown	Chhatwal *et al.*, 2006
Stathmin knockout	mPFC hyperactivation, BLA hypoactivation	Martel *et al.*, 2012

Table 1

Continued

Category of model	Link to mPFC–amygdala circuit	Reference
Pharmacological manipulation		
6-hydroxdopamine	mPFC dopamine depletion	Morrow *et al.*, 1999; Fernandez Espejo, 2003; Hugues *et al.*, 2007; Saito *et al.*, 2013
Dopamine D_1 antagonist	Intra-BLA or intra-infralimbic cortex infusion	Hikind and Maroun, 2008; Fiorenza *et al.*, 2012
Dopamine D_2 antagonist	Intra-infralimbic cortex infusion	Mueller *et al.*, 2010
Dopamine D_4 antagonist	Intra-mPFC infusion	Pfeiffer and Fendt, 2006
Noradrenaline	Intra-BLA infusion	Berlau and McGaugh, 2006; Fiorenza *et al.*, 2012
β-adrenoceptor agonist	Intra-mPFC or intra-BLA infusion	Fiorenza *et al.*, 2012
β-adrenoceptor antagonist	Intra-infralimbic cortex infusion	Mueller *et al.*, 2008
$GABA_A$ agonist	Intra-infralimbic cortex or intra-BLA infusion	Sierra-Mercado *et al.*, 2006; 2011; Laurent and Westbrook, 2008; 2009a; 2010; Laurent *et al.*, 2008; Parkes and Westbrook, 2010; Sotres-Bayon *et al.*, 2012; Holmes and Singewald, 2013; Holmes *et al.*, 2013
Benzodiazepine agonist	Intra-BLA infusion	Hart *et al.*, 2009; 2010
AMPA receptor internalization inhibition	Intra-BLA infusion	Kim *et al.*, 2007b; Dalton *et al.*, 2008
mGluA1 antagonist	Intra-BLA infusion	Kim *et al.*, 2007a
mGluA5 antagonist	Intra-BLA infusion	Fontanez-Nuin *et al.*, 2011; Sepulveda-Orengo *et al.*, 2013
NMDA receptor antagonist	Intra-BLA or intra-mPFC infusion	Falls *et al.*, 1992; Lee and Kim, 1998; Lin *et al.*, 2003c; Burgos-Robles *et al.*, 2007; Laurent and Westbrook, 2008; 2009b; Laurent *et al.*, 2008; Zimmerman and Maren, 2010; Parkes and Westbrook, 2011; Fiorenza *et al.*, 2012; Holmes *et al.*, 2012
GluN2B antagonist	Intra-BLA or intra-mPFC infusion	Sotres-Bayon *et al.*, 2007; 2009; Laurent and Westbrook, 2008; Laurent *et al.*, 2008; Dalton *et al.*, 2012
Glucocorticoid receptor antagonist	Intra-BLA	Yang *et al.*, 2006
NPY-Y1 antagonist	Intra-BLA infusion	Gutman *et al.*, 2008
NPS antagonist	Intra-BLA infusion	Jungling *et al.*, 2008
KOP receptor antagonism	mPFC and BLA hypoactivation	Bilkei-Gorzo *et al.*, 2012
MOP receptor ablation	ICN specific	Likhtik *et al.*, 2008
Oxytocin	Intra-BLA infusion	Likhtik *et al.*, 2008
CCK_2 receptor agonist	BLA CCK-B receptor dependent	Chhatwal *et al.*, 2009
CB_1 receptor antagonist	Intra-BLA infusion	Kuhnert *et al.*, 2013
H_2 receptor antagonist	Intra-BLA or mPFC infusion	Fiorenza *et al.*, 2012
$Ca_V1.x$ antagonist	Intra-BLA infusion, BLA MAPK hypoactivation	Davis and Bauer, 2012

Concluding remarks

Our goal here was to provide a comprehensive, although not exhaustive, update on a large and ever-expanding body of preclinical research that connects fear extinction with the function and dysfunction of a neural circuit comprising various regions of the mPFC and amygdala. Fear extinction deficits associated with the mPFC–amygdala circuit abnormalities observed across rodent subpopulation differences or produced by environmental, genetic or pharmacological manipulations, are summarized in Table 1. Table 2 lists pharmacologically induced rescue or facilitation of fear extinction that can be attributed to functional alterations in the mPFC or amygdala. There are good grounds to be optimistic that real progress can be made in further defining the neural basis of fear extinction, and using this knowledge base as a platform to identify plausible candidates for extinction-promoting therapeutics.

Table 2

Pharmacological facilitation or rescue of extinction produced by directly targeting the mPFC–amygdala circuitry or associated with functional changes in the circuitry

Pharmacological manipulation	Relevance to mPFC–amygdala circuit	Reference
L-DOPA	mPFC activation, CeM deactivation	Haaker *et al.*, 2013
Noradrenaline	Intra-BLA infusion	Fiorenza *et al.*, 2012
β-adrenoceptor agonist	Intra-infralimbic cortex infusion	Do Monte *et al.*, 2010
5-HT re-uptake inhibition	Decreased BLA perineuronal nets	Karpova *et al.*, 2012
Methylene blue	Increased mPFC activity	Wrubel *et al.*, 2007
5-HT_{1A} agonism	Increased mPFC dopamine	Saito *et al.*, 2013
$GABA_A$ agonism	Intra-infralimbic cortex or intra-BLA infusion	Akirav *et al.*, 2006
$GABA_A$ antagonism	Intra-infralimbic cortex or intra-BLA infusion	Berlau and McGaugh, 2006; Thompson *et al.*, 2010; Chang and Maren, 2011; Fitzgerald *et al.*, 2014
AMPA receptor agonist	Intra-mPFC or intra-BLA infusion	Zushida *et al.*, 2007
$mGluA_7$ agonism	Intra-BLA infusion	Morawska and Fendt, 2012; Dobi *et al.*, 2013
$mGluA_5$ antagonism	Intra-BLA infusion	Mao *et al.*, 2013
GluN2B antagonism	Normalized mPFC synaptic plasticity	Iafrati *et al.*, 2013
GluN2C/D potentiator	Intra-BLA infusion	Ogden *et al.*, 2014
Glycine re-uptake inhibition	Intra-BLA infusion	Mao *et al.*, 2009
NMDA receptor partial agonism	Intra-BLA infusion	Walker *et al.*, 2002; Ledgerwood *et al.*, 2003; Lee *et al.*, 2006; Akirav *et al.*, 2009; Baker *et al.*, 2012; Toth *et al.*, 2012a
Ginkgo biloba extract	Intra-BLA	Yang *et al.*, 2009
Glucocorticoid agonism	Intra-BLA	Yang *et al.*, 2006
NPS	Intra-BLA infusion, increased ICN inputs	Jungling *et al.*, 2008; Chauveau *et al.*, 2012
Oxytocin	Intra-infralimbic cortex infusion	Likhtik *et al.*, 2008
CB_1 receptor agonism	Intra-BLA or intra-mPFC infusion	Lin *et al.*, 2006; 2009b; Do Monte *et al.*, 2013; Ganon-Elazar and Akirav, 2013
FAAH inhibition	Intra-BLA infusion, enhanced BLA synaptic plasticity	Gunduz-Cinar *et al.*, 2013
TrkB agonism, BDNF	Increased mPFC BDNF expression, BLA TrkB activity, BDNF inputs to infralimbic cortex	Peters *et al.*, 2010; Andero *et al.*, 2011; Baker-Andresen *et al.*, 2013
Brain magnesium increaser	Enhanced mPFC synaptic plasticity	Abumaria *et al.*, 2011
FGF-2	Intra-BLA	Graham and Richardson, 2011b
Dietary zinc deficiency	Normalized infralimbic cortex/BLA/CeL/CeM activation	Whittle *et al.*, 2010
Valproic acid	Increased mPFC BDNF expression	Bredy and Barad, 2008
HAT inhibition	Intra-infralimbic cortex infusion, enhanced mPFC synaptic plasticity	Marek *et al.*, 2011
Histamine metabolism inhibitor	Intra-BLA or mPFC infusion	Fiorenza *et al.*, 2012
Muscarinic agonism	Intra-mPFC infusion	Santini *et al.*, 2012

However, despite the wealth of data that has amassed in recent years and the increasing knowledge base this provides, there remain major challenges to developing anxiolytic medications from preclinical findings in rodents. Some of the issues are common to any psychotropic drug development effort, and include the design of safe, brain-penetrant molecules with limited adverse side effects. Individual differences in treatment tolerability and efficacy, caused by genetic variation, previous medication history or sex/gender, is another concern; in fact, there is now good evidence that fear extinction in rodents and humans is strongly influenced by the oestrus/menstrual cycle and gonadal hormones because of modulation of the mPFC–amygdala circuit (Lebron-Milad and Milad, 2012). The careful dissection of the brain regions mediating fear extinction has also shown that some systems can have both extinction-facilitating and -impairing effects, depending on the region where they are acting. An example is the β-adrenoceptor, blockade of which interferes with

extinction when limited to the infralimbic subregion, but promotes extinction when the BLA is targeted – hence it is difficult to predict the net effect of medicating a patient with a β-adrenceptor blocker or agonist during exposure therapy. A lesson here is that despite the availability of powerful tools for manipulation, the brain in ever more atomized ways, pharmacological studies using simple systemic treatments still have an important place in translational neuroscience. There is also room for developing new behaviour-based interventions, alongside drug treatments, to improve the effectiveness of exposure-based therapies, with promising developments in applying simple behavioural techniques to facilitate extinction (Auber *et al.*, 2013).

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Conflict of interest

None.

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