Published in final edited form as:

Annu Rev Clin Psychol. 2019 May 07; 15: 257–284. doi:10.1146/annurev-clinpsy-050718-095634.

Augmentation of Extinction and Inhibitory Learning in Anxiety and Trauma-Related Disorders

Lauren A.M. Lebois, **Antonia V. Seligowski**, **Jonathan D. Wolff**, **Sarah B. Hill**, and **Kerry J. Ressler**

Division of Depression and Anxiety Disorders, Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, Massachusetts 02478, USA

Abstract

Although the fear response is an adaptive response to threatening situations, a number of psychiatric disorders feature prominent fear-related symptoms caused, in part, by failures of extinction and inhibitory learning. The translational nature of fear conditioning paradigms has enabled us to develop a nuanced understanding of extinction and inhibitory learning based on the molecular substrates to systems neural circuitry and psychological mechanisms. This knowledge has facilitated the development of novel interventions that may augment extinction and inhibitory learning. These interventions include nonpharmacological techniques, such as behavioral methods to implement during psychotherapy, as well as device-based stimulation techniques that enhance or reduce activity in different regions of the brain. There is also emerging support for a number of psychopharmacological interventions that may augment extinction and inhibitory learning specifically if administered in conjunction with exposure-based psychotherapy. This growing body of research may offer promising novel techniques to address debilitating transdiagnostic fear-related symptoms.

Keywords

amygdala; exposure; extinction; fear conditioning; inhibitory learning; PTSD

EXTINCTION AND INHIBITORY LEARNING

Fear is central to our survival. It is part of a response to cope with threatening circumstances. We are predisposed to pay attention to things that evoke such a response, and we also rapidly learn fear associations to stay safe. In this way the fear response is very adaptable. Problems

kressler@mclean.harvard.edu.

DISCLOSURE STATEMENT

K.J.R. is on the scientific advisory boards of Resilience Therapeutics, the Sheppard Pratt-Lieber Research Institute, the Laureate Institute for Brain Research, the Army Study to Assess Risk and Resilience in Servicemembers (STARRS) project, the University of California San Diego VA Center of Excellence for Stress and Mental Health (CESAMH), and the Anxiety and Depression Association of America. He provides fee-for-service consultation for Biogen and Resilience Therapeutics. He holds patents for the use of D-cycloserine and psychotherapy, targeting the pituitary adenylate cyclase-activating polypeptide (PACAP) type 1 receptor for extinction, targeting tachykinin 2 for prevention of fear and targeting angiotensin to improve extinction of fear. L.A.M.L., A.V.S., J.D.W., and S.B.H. declare no competing interests.

can arise, however, when fear persists after the threat is no longer present. This persistent, pervasive fear is an example of a failure to learn extinction or inhibitory signals. Extinction is the process whereby fear responses no longer occur after one is repeatedly exposed to the feared entity and nothing aversive happens, signaling that there is no longer a reason to be afraid (Bouton et al. 2006). Inhibitory learning is central to the process of extinction and involves learning that the aversive events do not always occur when the stimulus is encountered (Bouton 1993, Craske et al. 2014). This new learning serves to reduce the fear response to allow for other behavioral responses (Bouton 1993, Craske et al. 2014). For example, an individual who is attacked by a dog may have subsequent experiences with dogs that are positive. Although fear might be the initial response, this response decreases with repeated exposures (extinction). In concert with a reduction in fear, the individual learns that dogs are not always dangerous, and this helps to reduce fear when facing dogs in new situations (inhibitory learning).

Failures of Extinction and Inhibitory Learning in Psychiatric Disorders

A number of psychiatric disorders involve a failure of these learning processes as they relate to fear and will be the focus of this review: panic disorder, phobias, social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD). Although these disorders involve disparate symptom clusters, they all share failures of extinction and inhibitory learning as central elements of their dysfunction; in this realm, they differ primarily in the type of cues that trigger the fear response (Cannistraro & Rauch 2003). Individuals with phobias may fear a specific object or situation (e.g., insects, heights, blood), whereas those with panic disorder tend to fear physiological symptoms (e.g., rapid heartbeat, muscle tension) and sometimes stimuli that were previously paired with these symptoms. Those with SAD may fear certain social situations (e.g., public speaking, eating in public), whereas those with PTSD fear stimuli that remind them of specific traumatizing events. In all of these cases, individuals have difficulty inhibiting their fear response when there is no longer any direct threat. This is especially problematic because the feared stimuli often generalize, which can lead to greater functional impairment. For example, individuals who have been robbed in a supermarket parking lot will likely exhibit fear when they return to the same location, but eventually they may be fearful of all parking lots and may no longer be willing to engage in a range of activities (e.g., shopping, going to work), affecting their personal, social, and/or occupational functioning. Given the detrimental effects of these learning deficits, researchers have strived to understand fear learning processes to improve extinction and inhibitory learning.

Translational Behavioral Methods of Testing Extinction and Inhibitory Learning

Fear conditioning paradigms are the primary translational method used to study extinction and inhibitory learning (e.g., Myers & Davis 2002, Phelps et al. 2004). These paradigms are based on Pavlovian classical conditioning principles, whereby an aversive unconditioned stimulus (US) like a shock or air blast is paired with one or more danger signals (conditioned stimuli, or CS+; e.g., a blue triangle) and results in a conditioned response such as feelings of fear, increased heart rate, and a potentiated startle response. A stimulus that is never paired with the aversive stimulus may also be used and can be referred to as a safety signal (CS-; e.g., a red square).

In fear conditioning paradigms, the acquisition phase consists of learning these safety and danger associations by experiencing the danger signal paired with the aversive stimulus, whereas the extinction phase consists of repeated danger signal trials that are no longer paired with the aversive stimulus (Myers & Davis 2002). In typically functioning humans and other animals, the extinction phase results in decreased fear (conditioned response, or CR). Fear inhibition is characterized by the reduction of the conditioned response to the danger signal in the extinction phase and to the safety signal during both acquisition and extinction phases.

It is important to note that extinction is not simply erasing the knowledge that the danger signal precedes the aversive stimulus. The processes of spontaneous recovery of the fear memory over time, renewal of the fear memory in a different context from the one where it was extinguished, and reinstatement of the fear memory following a new stressor all demonstrate the fact that the original fear memory trace is still present but is inhibited through extinction learning (LaBar & Phelps 2005). Rather than erasure, an inhibitory learning process takes place during extinction, and a new competing extinction memory is acquired in addition to the original fear memory (Bouton 1993). During extinction, the individual learns that the danger signal is not always followed by the aversive stimulus, not that the two will never be paired again. Returning to our dog attack example, individuals may have the original aversive association with dogs but may have subsequent experiences with dogs that are positive (i.e., they may form a new association that dogs can be safe, perhaps in a different context). The conditioned stimulus therefore has two simultaneous meanings: its original danger signal meaning (dogs attack) and its new inhibitory meaning (dogs can be safe) (Bouton 1993; see also Craske et al. 2014). Both associations still exist for the individual.

In addition to illuminating the processes of extinction and inhibitory learning more generally, fear conditioning paradigms have improved our understanding of the deficits in these processes in psychiatric disorders. Using these paradigms, researchers have demonstrated that, in general, individuals with fear-related symptoms exhibit deficits in extinction, such that they have higher startle responses to danger signals during the extinction phase and take longer to extinguish these responses (see Duits et al. 2015 for a review). Similar deficits in inhibition have also been observed with the use of safety signals that are never paired with an aversive stimulus, indicating overgeneralization of the fear response (Jovanovic et al. 2012, Lissek et al. 2009). For example, individuals with panic disorder exhibit poor discrimination between danger and safety signals, and this appears to be driven by heightened startle responding to safety signals specifically (Lissek et al. 2009). Subsequent research has demonstrated that this effect is present only among those with panic disorder coupled with a high intolerance of uncertainty (Gorka et al. 2014) and that deficits in cognitive flexibility may be the driving mechanism (Lieberman et al. 2016). Similar patterns have been observed among individuals with various phobias and SAD, such that extinction is delayed or impaired (de Jong & Merckelbach 1993, Hermann et al. 2002, Rabinak et al. 2017) and inhibition of fear to safety signals is poor (Hermann et al. 2002, Rabinak et al. 2017).

PTSD is characterized by these alterations as well, and deficits in extinction and inhibitory learning have been replicated across multiple trauma types in both military and civilian populations (e.g., Jovanovic et al. 2012, Sijbrandij et al. 2013). The repeated finding that individuals with different fear-related symptoms demonstrate altered fear extinction and inhibitory learning highlights the transdiagnostic significance of these processes and the need for a better understanding of their underlying neurobiological pathways.

NEUROBIOLOGICAL MECHANISMS OF EXTINCTION

Systems Level

Rodent and human work has converged on a number of brain regions involved in fear extinction and inhibitory learning. These include the amygdala, bed nucleus of the stria terminalis (BNST), hippocampus (HP), medial prefrontal cortex (mPFC), periaqueductal gray, inferior colliculus, lateral septum, and striatum (Delgado et al. 2008, Knight et al. 2004, Lin et al. 2003, Phelps et al. 2004). We focus below on the regions with the most convergent evidence.

Amygdala.—The amygdala is involved in the detection of salient or relevant information to basic biological drives and psychological needs (Sander et al. 2003). Fear-related stimuli are a particular type of salient information. Different subnuclei of the amygdala contribute to different aspects of fear responding and also extinction. For example, the central amygdala (CeA) plays a major role in fear responding (Fendt & Fanselow 1999, LeDoux et al. 1988). The basolateral amygdala (BLA), by contrast, is involved in the acquisition, expression, and extinction of fear (Fanselow & LeDoux 1999). Human neuroimaging studies of fear conditioning indicate that amygdala activation is associated with both the strength of the fear response and successful extinction (e.g., Phelps et al. 2004). This is likely because the amygdala subnuclei and specific cell types play differential roles in both fear acquisition and extinction. Furthermore, distinct patterns of activity in the amygdala subnuclei may mediate the generalization of the fear response (Ghosh & Chattarji 2015).

Ventromedial prefrontal cortex.—The mPFC, among other functions, is involved in emotion regulation (Quirk & Beer 2006). In particular, the ventromedial prefrontal cortex (vmPFC) plays an inhibitory role in regulating amygdala activation through bidirectional connections between these two areas (Morgan et al. 1993). Rodent studies have demonstrated that damage to the hypothesized rodent equivalent of human vmPFC (infralimbic cortex) results in worse extinction learning, and that there is a strong correlation between its activation and the level of extinction (Lebrón et al. 2004, Lin et al. 2003). In addition, synchronized firing of BLA and vmPFC has been associated with safety signal recognition and reduced fear (Likhtik et al. 2014). Human studies also support the involvement of vmPFC in successful extinction learning and recall (Milad et al. 2005, Phelps et al. 2004).

Hippocampus.—The HP plays a central role in learning and memory processes. Specifically, it is involved in the rapid initial storage of declarative memory and in integrating different aspects of memory during retrieval—for example, both contextual

(spatial) and nonspatial information (Eldridge et al. 2000, Squire & Zola-Morgan 1991). In the context of fear memories, recent rodent work using optogenetic techniques has demonstrated that activating a specific memory trace in the HP that was active during initial fear learning can initiate freezing, a type of fear response for rodents (Liu et al. 2012). This suggests that activating a specific set of cells in the HP drives recall of that memory (Liu et al. 2012). It is also clear that communication between BLA and the anterior HP facilitates fear learning and extinction, though it is yet unclear whether these areas signal directly to each other (Yang & Wang 2017). Initially, information transmitted from the amygdala to the HP tags a stimulus as fearful. Contextual information transmitted from the HP to the amygdala helps signal whether a fear response should be initiated or not, based on whether the current context is associated with danger or safety (Rudy et al. 2004). Damage to the HP interferes with this process (LaBar & Phelps 2005). In addition, new learning that the previous danger signal is no longer paired with the aversive stimulus is facilitated by HP activation (e.g., Knight et al. 2004). Consistent with the above discussion about vmPFC, HP inhibition of the infralimbic cortex facilitates the reemergence of fear that was previously extinguished (Marek et al. 2018).

Circuit alterations with fear-related psychiatric symptoms.—Human studies have demonstrated that individuals with fear-related symptoms tend to have altered activation of the amygdala, vmPFC, and HP (e.g., Ottaviani et al. 2012, Shin et al. 2004), with the most common finding being increased amygdala (and cingulate cortex) activation and decreased vmPFC activation to fearful cues. Notably, few studies have examined these alterations in fear conditioning paradigms while measuring brain activity. Work that attempts to measure both has typically been conducted with PTSD samples. For example, recent research suggests that PTSD symptoms are associated with more HP, amygdala, and insula activation during the extinction phase of fear conditioning, which is perhaps indicative of impaired safety learning (Sripada et al. 2013). A recent study used both a neutral functional magnetic resonance imaging (fMRI) inhibition task and a classic fear conditioning paradigm completed outside the MRI scanner to probe the neural correlates of inhibition learning (Jovanovic et al. 2013). The authors found that traumatized individuals with PTSD symptoms demonstrated decreased activation of the vmPFC compared to those without PTSD in the fMRI inhibition task. Participants who showed less activation of the vmPFC during the fMRI scan also showed greater levels of fear to safety signals (i.e., poor inhibitory learning) in the fear conditioning paradigm completed outside the scanner.

It is important to note, however, that individuals with co-occurring dissociative symptoms and PTSD may exhibit the opposite pattern of activation. Dissociation includes a range of symptoms; however, the DSM-5 describes the dissociative subtype of PTSD as individuals who experience feelings of detachment from their body, thoughts, and environment (i.e., depersonalization and derealization). Research has found that individuals who report these feelings on standardized clinician-administered dissociative symptom assessments instead have increased mPFC activation during paradigms designed to elicit PTSD symptoms (e.g., Lanius et al. 2002). Therefore, extinction and inhibitory learning among those with prominent dissociative symptoms may have unique neurobiological correlates that have yet to be explored.

Molecular Level

From the molecular standpoint, there are two overarching ways to attenuate the power of fear memories over an individual: (*a*) creating a new competing memory trace and (*b*) altering the existing fear memory. We review each and their basic molecular mechanisms in turn.

New memory trace.—As discussed earlier, after extinction the memory associating the aversive stimulus with the danger signal still exists, but an additional memory trace is formed in which the aversive stimulus is not paired with the conditioned stimulus and may inhibit the fear response (Craske et al. 2014). Following inhibitory learning, the new extinction memories are stored through the process of consolidation (Tronson & Taylor 2007). Consolidation occurs both at the level of neural networks (systems consolidation) and within the neurons that make up the networks (synaptic consolidation; McGaugh 2000, Squire & Alvarez 1995).

Long-term potentiation (LTP) is a cellular model for understanding synaptic consolidation mechanisms of learning and memory (Lamprecht & LeDoux 2004, McGaugh 2000). At a basic level, LTP is an enduring increase in synaptic strength between neurons (Collingridge et al. 2010)—a plasticity-dependent increase in the amplitude of excitatory postsynaptic potentials (Lamprecht & LeDoux 2004). Because of this change, these connected neurons are more likely to signal to each other in the future.

LTP is initiated when intracellular calcium levels reach a certain level in the postsynaptic neuron, activating additional signaling pathways (Lamprecht & LeDoux 2004). This produces both rapid structural changes (e.g., reorganization of the cytoskeleton, adhesion remodeling) and slower changes in protein synthesis and gene expression (Lamprecht & LeDoux 2004). LTP may produce different signaling and gene expression changes related to extinction depending on the area of the brain in which it occurs (Singewald et al. 2015).

Changes to existing memory trace.—One can also alter the existing fear memory trace to attenuate fear by taking advantage of a process called reconsolidation. During memory retrieval, the activated memory trace goes back to an unstable state. While in this labile state, it can be augmented or disrupted in various ways to change the original memory (e.g., Nader et al. 2000). The process of reconsolidation involves restabilizing the previously consolidated memory, but now incorporating the changes made while it was labile (Tronson & Taylor 2007).

Although disruption of reconsolidation in humans remains unclear, it is now supported by a robust animal literature. The existing fear memory may be affected in the labile state by engaging synaptic plasticity mechanisms that either (*a*) weaken the fearful associations with the original memory trace or (*b*) strengthen the safety associations formed in the new extinction memory trace. Fearful associations can be weakened through long-term depression (LTD) mechanisms to facilitate synaptic plasticity. LTD is an enduring decrease in synaptic strength (Collingridge et al. 2010). Because of this change, the affected neurons are less likely to signal to each other in the future. One can also pharmacologically block protein synthesis that occurs during reconsolidation, effectively precluding the successful

restabilization of the memory (e.g., Nader et al. 2000). Alternatively, one may be able to strengthen the connections comprising the safety association of the new extinction memory. The preferential reactivation of the extinction memory trace can strengthen the new memory through the process of reconsolidation and LTP mechanisms that facilitate synaptic plasticity (Haubrich et al. 2017).

Note that reconsolidation and extinction of an existing memory trace appear to involve different mechanisms with opposite effects, and the boundary conditions of the prevailing process following memory reactivation may be difficult to determine. That being said, brief reactivation generally supports reconsolidation, and long, repeated reactivation supports extinction. Successful extinction and inhibitory learning likely involve both creating new safety memory traces and altering existing fear memories at various stages of recovery. The involvement of one process over another may depend on various factors, such as the timing of extinction after acquisition (Myers & Davis 2007).

Neurotransmitter and Neuromodulatory Systems Overview

A number of different neurotransmitter and neuromodulatory systems in the brain are involved in extinction and inhibitory learning and thus are promising targets for pharmacologically enhancing these processes to help with recovery from fear-related ailments. As discussed earlier, most work on extinction and inhibitory learning focuses on the amygdala (BLA in particular) and mPFC; thus, we focus here on key neurotransmitter and neuromodulators in these areas. We overview these key systems, and specifically how they may be involved in extinction, to support our later discussion of extinction/inhibitory learning pharmacological augmentation.

Glutamatergic system.—Glutamate is the principal excitatory neurotransmitter of the brain, acting throughout the brain as the general “on” switch. It is involved most generally in synaptic plasticity, learning, and memory, and its signaling occurs through ionotropic AMPA, NMDA, and kainite receptors, as well as through metabotropic glutamate receptors (Singewald et al. 2015). Ionotropic receptors enact fast change because they are ion channels: The information transferred is electrical, and binding to these receptors fundamentally alters electrical gradients (Engelman & MacDermott 2004). In contrast, metabotropic receptors are not ion channels, and they are slow acting because their effects must be mediated through intracellular signaling and transcriptional activation rather than through direct electrical activity (Conn & Pin 1997). Because glutamate can bind to both types of receptors, its influence can be either fast or slow acting.

Although glutamatergic receptors serve a ubiquitous excitatory role in the brain, it is important to point out that each receptor can have a different composition that can affect its functioning. That is, each receptor can be made up of a different combination of subunits, and individual subunits can influence how likely glutamate is to occupy the receptor and also the exact signaling cascade that ensues once the receptor is occupied—in essence, conferring functional heterogeneity (Bleakman & Lodge 1998). Furthermore, subunit composition can show brain region–specific expression profiles (Singewald et al. 2015). For all these reasons, drugs that activate the glutamatergic system, or any system with these intricacies, could have

very different consequences depending on whether they target specific receptor subunit compositions that occur in a particular region of the brain or are instead less selective.

In turn, the unique composition of receptor subunits likely influences the role of glutamate in extinction. For example, NMDA receptors containing GluN2A subunits may be specifically involved in fear memory consolidation; in contrast, GluN2B and GluN2C are particularly important for extinction learning (Baker et al. 2017). Furthermore, because of glutamate's excitatory function, glutamatergic signaling can facilitate extinction when it occurs in regions associated with fear inhibition or extinction learning. For example, extinction learning and retrieval are enhanced when AMPA receptors are potentiated through pharmacological means, particularly in the mPFC (e.g., Yamada et al. 2009); in contrast, blocking NMDA receptors in the BLA or mPFC impairs extinction (Myers et al. 2011, Singewald et al. 2015).

Gabaergic system.—GABA is the principal inhibitory neurotransmitter of the brain, acting throughout the brain as the general "off" switch. GABA signals through both ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors. $GABA_A$ is permeable to chloride, and it is generally composed of five subunits (Bormann 2000). $GABA_B$ influences calcium and potassium channels through G protein–coupled receptor mechanisms (Bormann 2000).

Because of GABA's inhibitory function, GABAergic signaling facilitates extinction when it occurs in regions associated with fear acquisition and responding, and it impedes extinction when it occurs in regions associated with extinction learning. For example, injection of a GABA agonist into areas involved in extinction learning and memory (e.g., BLA, mPFC, HP) has a negative impact on extinction (Singewald et al. 2015). In addition, amygdala-based increases in GABAergic signaling are linked to extinction learning. However, there is opposing evidence suggesting that blocking GABAergic signaling with $GABA_A$ receptor antagonists in the BLA and mPFC can also facilitate extinction, depending on timing and pharmacology (e.g., Berlau & McGaugh 2006). The broad functions of the GABA system and the general nonselectivity of these agents make these findings difficult to interpret.

Serotonin.—Serotonergic signaling has been implicated in a wide array of processing, including cognitive, affective, appetitive, motoric, and autonomic (Frazer & Hensler 1999). It is hypothesized that serotonin may be more generally implicated in gating one's level of arousal and behavioral activity (Frazer & Hensler 1999). Serotonin is a monoamine neurotransmitter, and it signals mostly through metabotropic G protein–coupled 5-HT receptors ($5\text{-}HT_1$, $5\text{-}HT_2$, $5\text{-}HT_{4–7}$), with the exception of ionotropic $5\text{-}HT_3$ receptors (Singewald et al. 2015).

Evidence suggests that serotonergic signaling may be more involved in fear acquisition and expression and less involved in extinction learning. For example, levels of serotonin increase in the BLA, mPFC, and dorsal periaqueductal gray during fear acquisition and responding (e.g., Kawahara et al. 1993, Zanoveli et al. 2009), whereas to date no changes in serotonin levels have been reported during extinction learning and memory (Singewald et al. 2015). However, work suggests that some serotonergic antidepressants may impair extinction (Burghardt et al. 2013).

Norepinephrine.—Norepinephrine is involved in regulating mood, sleep, and arousal, and it is key to the manifestation of aggression (Southwick et al. 1999). Norepinephrine also regulates the endocrine system and autonomic nervous system (Southwick et al. 1999). As a monoamine neurotransmitter, it signals through metabotropic G protein–coupled alpha and beta adrenergic receptors (Mueller & Cahill 2010).

Norepinephrine likely plays a role in both fear and extinction memory acquisition, depending on the timing and region of the brain it is acting upon (Mueller & Cahill 2010). For example, norepinephrine increases excitability in the infralimbic cortex, which is involved in extinction (Mueller et al. 2008). Increased norepinephrine levels in mPFC are also associated with extinction learning in humans (Hugues et al. 2007), and higher norepinephrine levels appear to aid extinction (e.g., Abraham et al. 2012).

Dopamine.—Dopamine is involved in learning, especially reward-related learning (Steinberg et al. 2013), and motivation (Salamone & Correa 2012). Recent theories suggest that the overarching role of dopamine is to signal an estimate of whether one should expend limited energy, attention, or time on a particular action (Berke 2018). Dopamine is a monoamine neurotransmitter, and it signals through metabotropic G protein–coupled D1–5 receptors (Abraham et al. 2014).

Evidence suggests that dopamine can both regulate fear expression and affect the consolidation of extinction memories (Singewald et al. 2015). For example, after extinction training, rats exhibit increased dopamine levels in the hypothesized rodent equivalent of human mPFC (Hugues et al. 2007). Administration of L-DOPA, a precursor to dopamine, appears to reduce the context dependence of extinction memories in both mice and humans (Haaker et al. 2013). This makes it less likely that the fear response will return when the conditioned stimulus is experienced outside the original extinction learning context. Converging evidence from mice also suggests that substances used to promote dopamine signaling can augment extinction learning (e.g., Abraham et al. 2012).

Acetylcholine.—Acetylcholine signaling is integral to attentional processes, which in turn makes it integral to learning and memory (Sarter & Parikh 2005). In particular, acetylcholine plays a role in increasing the likelihood that a particular sensory input to the brain will be detected and processed (e.g., Nelson et al. 2005). Acetylcholine signals through both ionotropic nicotinic receptors and metabotropic muscarinic receptors (Sarter & Parikh 2005). The nicotinic receptors are made up of five subunits and are permeable to sodium, potassium, and calcium depending on the particular subunit composition (Changeux 2010).

In general, blocking acetylcholine signaling cascades through muscarinic antagonists or lesions impairs conditioning (Han et al. 1999), whereas increasing acetylcholine facilitates conditioning (Weinberger 1998). With specific regard to fear extinction, muscarinic antagonists appear to impair fear extinction retention (Prado-Alcalá et al. 1993, Roldán et al. 2001).

HOW CAN WE AUGMENT EXTINCTION AND INHIBITORY LEARNING TO TREAT PSYCHIATRIC DISORDERS?

Given the devastating effects of impaired extinction and inhibitory learning, research has been dedicated to finding ways to repair and augment these functions in individuals with panic disorder, phobias, SAD, and PTSD. Here we review psychological, device-based brain stimulation, and pharmacological interventions designed to facilitate extinction and inhibitory learning.

Psychological Interventions

The clinical proxy of translational fear extinction paradigms is exposure therapy (Craske et al. 2014). Through various techniques, therapies that incorporate an exposure element have individuals approach internal and external feared stimuli rather than avoid them (Craske et al. 2018). Various forms of cognitive behavioral therapy, cognitive therapy, mindfulness-based therapy, and psychodynamic psychotherapy include elements of exposure. Here we review therapies that implement explicit exposure exercises as well as other approaches that encourage individuals to experience feared feelings and memories more generally. We also review techniques for enhancing the efficacy of exposure.

Exposure therapies are common treatment approaches for several anxiety- and trauma-related disorders, sometimes with and sometimes without other cognitive therapy components (Dep. Veteran Aft. & Dep. Def. 2017). Exposures in these treatments can include (*a*) in vivo exposure, in which a patient gradually approaches feared places, objects, people, or situations (e.g., spiders); (*b*) imaginal exposure, in which the patient vividly imagines the feared place, object, people, or situation and outcome but does not avoid their ensuing anxiety (e.g., trauma memory); and (*c*) interoceptive exposure, which involves inducing the physical sensations that the patient worries are indicative of a panic attack (e.g., breathing through a straw to induce hyperventilation; Kaczkurkin & Foa 2015).

The treatment protocol for each psychiatric disorder with fear-related dysfunction has a favored form of exposure. For specific phobias, in vivo exposure is the preferred treatment, with a number of studies demonstrating its effectiveness (Kaczkurkin & Foa 2015, Olatunji et al. 2010). In panic disorder, interoceptive exposure is the primary form of treatment, and it has proven to be effective compared to no treatment or placebo controls (Kaczkurkin & Foa 2015, Olatunji et al. 2010). For SAD, in vivo exposure is often used and is highly effective, performing better than applied relaxation or waitlist control conditions (Kaczkurkin & Foa 2015, Olatunji et al. 2010).

PTSD is often treated with prolonged exposure (PE) therapy. PE aims to engage individuals emotionally with trauma-related stimuli in a safe space using both imaginal and in vivo techniques (Foa 2011). Through this process, extinction occurs, and individuals learn that trauma reminders and memories are not dangerous, which leads to inhibition of the fear response in safe situations. Additionally, other forms of psychotherapy often used to treat PTSD, such as cognitive processing therapy (CPT; Resick et al. 2016), can involve an element of exposure. For example, individuals in CPT write and read aloud a narrative

account of their worst traumatic experience to the therapist (Resick et al. 2016). A significant amount of research indicates that PE and CPT result in noteworthy improvements in PTSD and other symptoms (Cusack et al. 2016, Kaczkurkin & Foa 2015, Olatunji et al. 2010, Powers et al. 2010).

Importantly, however, recent work suggests that dissociative symptoms may impede the learning necessary for recovery from PTSD via exposure-based therapies, given that immersion and attention to the traumatic memory are required for extinction. Notably, two studies have demonstrated that state dissociation impairs emotional amygdala-related learning and fear extinction (Ebner-Priemer et al. 2009, Kleindienst et al. 2016). Furthermore, a handful of studies have examined how dissociation interacts with treatment outcomes. Current evidence is mixed: Some studies suggest dissociation does not affect treatment efficacy (Hagenaars et al. 2010, Halvorsen et al. 2014, Jaycox et al. 1998), whereas others show that dissociation predicts treatment non-response, dropout, differences in short- and long-term symptom reductions, and differences in which treatment approach may be most effective (Bae et al. 2016; Cloitre et al. 2012; Kleindienst et al. 2011, 2016; Price et al. 2014; Resick et al. 2012; Wolf et al. 2016).

In addition to exposure techniques, a number of other therapeutic approaches in these protocols include features that are consistent with exposure. For example, central tenets of psychodynamic psychotherapy include exploring affect, emotional expression, and efforts to avoid difficult thoughts or feelings, as well as discussing past experiences that may be contributing to present problems (Blagys & Hilsenroth 2000, Shedler 2010). Discussing these topics, and thereby exposing oneself to these past experiences and difficult emotions in a safe environment, is likely to facilitate extinction and inhibitory learning. In addition, dialectical behavior therapy (DBT; Linehan 1993) and mindfulness- or acceptance-based therapies encourage individuals to observe their thoughts and emotions without judgment and without attempting to stop or change them (for acceptance and commitment therapy, or ACT, see Hayes et al. 1999; for mindfulness- and acceptance-based behavioral therapy, see Roemer et al. 2008). More traditional cognitive and cognitive behavioral therapies may also facilitate exposure, given that they ask individuals to identify thoughts and emotions that are unpleasant and/or distressing. The identification, observation, and acceptance of difficult thoughts and emotions practiced in these therapies are likely to facilitate extinction and inhibitory learning.

Techniques to Enhance Extinction When Using Exposure

Although the aforementioned treatments successfully improve symptoms for those with various anxiety- and trauma-related disorders, these treatments are by no means effective for all patients. Olatunji et al. (2010) note in their meta-analytic review of the literature that one study reported that 27% of patients who were panic free after cognitive behavioral therapy that included exposure returned for additional treatment over a two-year follow-up period. Similarly, studies of exposure therapies indicate that a number of patients fail to achieve clinically significant symptom relief or experience a return of fear after exposure therapy (Craske et al. 2014). In an effort to more effectively administer exposure therapy, a number of studies have discussed behavioral strategies and best practices that may potentially

enhance and augment extinction learning (Craske et al. 2014, 2018; Pittig et al. 2016; Weisman & Rodebaugh 2018). Next, we review a number of these techniques along with illustrative clinical examples.

Expectancy violation.—Part of the problem in many disorders with fear-related symptoms is that people expect aversive things to happen even when they are unlikely. Violating those expectations can promote extinction (Craske et al. 2018). Designing exposures to maximally violate aversive expectations and maintaining the exposure until expectations change may be especially helpful (Craske et al. 2018; Craske et al. 2014; Pittig et al. 2016; Weisman & Rodebaugh 2018). For example, individuals with a dog-related phobia may experience reduced fear after repeated exposures to dogs that do not attack them (the feared outcome). However, fear reduction may be enhanced if they not only are safe from attack but also engage with the dogs playfully and receive affection from them.

In a study of imaginal exposure for panic disorder, researchers continued exposure therapy until patients reached less than 5% expectancy of an aversive outcome (Deacon et al. 2013). They found this method to be significantly more effective than standard interoceptive exposure, where the number of sessions is set for all participants and is not determined based on expectancy predictions.

Deepened extinction.—Another potential mechanism for enhancing extinction is the use of deepened extinction, in which multiple fear stimuli are first extinguished separately and then combined during extinction (Craske et al. 2014, 2018; Pittig et al. 2016; Weisman & Rodebaugh 2018). Among individuals with performance-related SAD, this could begin with separate exposures to reading a book aloud, reading to a small group, standing in front of a group, standing on a stage, and being placed under a spotlight. These could then be combined in an exposure where the individual reads a monologue on stage to a group of people while under a spotlight. Weisman & Rodebaugh (2018) note that there is a strong theoretical foundation for the effectiveness of this technique in enhancing exposure treatment, but to date there has been limited research investigating it in the context of human clinical treatment.

Stimulus variability.—A common problem in disorders with fear-related symptoms is that extinction can be specific to the context in which it was learned, which may be only moderately helpful for functioning given the variability and unpredictability of daily experience. Extinction may generalize more broadly if the clinician introduces variation in the duration or spacing of exposure trials, type or number of stimuli, and context of exposure (Craske et al. 2014, 2018; Pittig et al. 2016; Weisman & Rodebaugh 2018). For example, individuals with panic disorder may be asked to increase their heart rate through exercise, small amounts of caffeine, or stress-inducing activities such as giving a speech or simulating an argument. The clinician may ask the individual to engage in these exposures at first while in session, and subsequently at home or at work.

Prevent safety signals and behaviors.—Safety signals and behaviors are cues or actions that temporarily decrease anxiety in the moment of exposure—for example, having a loved one present during the exposure. However, these factors prevent someone from fully

engaging in the emotion elicited by the feared stimulus, hindering or blocking extinction learning (Foa & Kozak 1986). Individuals also misattribute the feeling of safety to the safety behavior or signal, rather than realizing that these signals/behaviors are not necessary for safety (Craske et al. 2014, Pittig et al. 2016, Weisman & Rodebaugh 2018). Thus, eliminating safety signals and behaviors is important to augment exposure therapy (Craske et al. 2014, 2018).

Positive affect.—Another augmentation strategy for exposure therapy that has gained support in recent years is the induction of positive affect during extinction training. Zbozinek & Craske (2017a) note that positive affect can influence memory and learning by enhancing encoding, rehearsal, and retrieval (e.g., Kiefer et al. 2008). Positive affect can also influence attention and make the stimulus that is the focus of attention seem more positive (Zbozinek & Craske 2017a). These factors, in addition to the increased dopaminergic tone induced by positive affect, may facilitate long-term extinction in exposure therapy. For example, a study of university students showed that higher positive affect prior to and after extinction training was associated with less reacquisition of fear (Zbozinek & Craske 2017b).

Device-Based Brain Stimulation Interventions

Device-based brain stimulation techniques may also augment extinction and inhibitory learning processes. The potential ability of these devices to modulate extinction and inhibitory processes and their efficacy as treatments for anxiety- and trauma-related disorders are still in relatively early stages of investigation. Here, we review investigations of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS).

Transcranial direct current stimulation.—tDCS is a noninvasive technique involving a small portable stimulator connected to electrodes that are placed on the head and deliver electrical stimulation (Marin et al. 2014). It is designed to modulate brain excitability through depolarization and hyperpolarization of cortical membranes (Nitsche & Paulus 2000). Anodal tDCS depolarizes neurons and enhances brain excitability whereas cathodal tDCS hyperpolarizes neurons and reduces excitability (Nitsche & Paulus 2000, Nitsche et al. 2003). The majority of tDCS investigations have focused on pain and depression, though investigations have also been conducted for tinnitus, substance abuse, schizophrenia, dementia, and PTSD (Kuo et al. 2014, van’t Wout et al. 2017).

In recent years, several studies have examined the relationship among tDCS and extinction processes in healthy participants who underwent fear conditioning. Investigating how different tDCS protocols affect fear circuitry and expression is a necessary step toward the therapeutic application of tDCS for anxiety-related disorders (Marin et al. 2014). An early study (Asthana et al. 2013) demonstrated that the administration of inhibitory cathodal tDCS targeting the left dorsolateral prefrontal cortex (dlPFC) following fear conditioning reduced fear expression the following day when participants were presented with the conditioned stimulus. Conversely, the administration of excitatory anodal tDCS targeting the right dlPFC following a reminder of the conditioned stimulus enhanced fear expression (Feeser et al. 2014). van’t Wout et al. (2016) demonstrated that excitatory anodal tDCS targeting the

vmPFC during the first extinction learning block enhanced fear extinction during a second block of extinction learning. Inhibitory cathodal tDCS targeting the right dlPFC during reconsolidation did not affect fear expression (Mungee et al. 2016). A recent animal study by Nasehi et al. (2017) revealed that the timing of administration of propranolol and right prefrontal tDCS modulated contextual and auditory fear learning. In the first study to our knowledge of the effects of tDCS on fear extinction in veterans with PTSD, van't Wout et al. (2017) demonstrated that those who received excitatory anodal tDCS to the vmPFC during extinction consolidation had moderately reduced fear expression compared to those who received it during extinction learning. However, the ability of tDCS to specifically target deep brain structures, such as vmPFC, remains unclear.

The varying results—enhanced, diminished, and no effect on fear extinction—of these studies underscore the complexity of emotional and fear processes, and of their corresponding neural circuitry, as well as the differences in the studies' designs. The studies discussed differ in their fear conditioning paradigms and in the timing, duration, intensity, and location of stimulation. To move toward tDCS treatments for anxiety- and trauma-related disorders, we need to further investigate the effects of tDCS on fear circuitry, refine our stimulation parameters, and conduct multisite double-blind trials along with studies targeting specific symptoms.

Transcranial magnetic stimulation.—TMS is a noninvasive technique that stimulates cortical neurons and their processes via electromagnetic pulses (see Diana et al. 2017 for a recent review). Magnetic coils connected to a stimulator are placed on the scalp and deliver pulses that penetrate the skull and reach brain tissues. Whether these pulses facilitate or impede neuronal excitability depends on several factors, including the location and parameters of stimulation. PTSD and extinction-related studies investigating TMS typically use repetitive TMS (rTMS) techniques, which involve prolonged pulse sequences and long-term neuronal alterations. Prior research suggests that low-frequency (~1 Hz) rTMS impedes neuronal excitability, whereas high-frequency rTMS (~5–25 Hz) facilitates neuronal excitability. Research on TMS has predominantly focused on its potential to treat depression, and in 2008, rTMS was approved for depression by the Food and Drug Administration (FDA). Given the central roles that the vmPFC and dlPFC play in fear learning and extinction processes, and their accessible locations, these regions have been the focus of research examining the effects of rTMS on extinction and PTSD.

Studies of rTMS and PTSD began in 1998 with two small-sample studies that suggested rTMS significantly reduces PTSD symptoms, though in both studies the improvements were short lived (Grisaru et al. 1998, McCann et al. 1998). Research that followed has found that low- and sometimes also high-frequency dlPFC rTMS can reduce PTSD symptoms (Boggio et al. 2010, Cohen et al. 2004, Nam et al. 2013, Oznur et al. 2014, Watts et al. 2012). Some studies have also found evidence that the effects persist two to three months later (Boggio et al. 2010, Watts et al. 2012).

Three investigations have been conducted on the effects of TMS combined with manualized treatments for PTSD or with components of the treatments. A team of researchers compared nine participants with PTSD who received both rTMS and imaginal exposure with a group

who received sham TMS and imaginal exposure, and they did not report significant differences (Osuch et al. 2009). Isserles et al. (2013) conducted a double-blind study of 30 people with PTSD who were assigned to one of three group receiving, respectively: exposure to script of a personally traumatizing event followed by deep TMS (dTMS), exposure to script of a nontraumatizing event followed by dTMS, and exposure to script of a traumatizing event followed by sham TMS. Their data show that dTMS following exposure resulted in significantly decreased scores on interview-based intrusion symptoms and heart rate, with a trend toward improvement in overall PTSD symptoms score. A recent larger study (103 participants) examined the use of low-frequency rTMS in the right dlPFC prior to weekly CPT for 12–15 sessions, and it found that both active and sham groups showed significant reductions in PTSD symptoms, though the active rTMS group had a greater reduction in symptom scores (Kozel et al. 2018).

Another recent investigation sought to translate an animal TMS fear extinction study to humans. Twenty-eight healthy participants were first fear conditioned to two danger cues; then, the following day, during extinction learning, they had brief high-frequency rTMS in the left PFC paired with one of the conditioned cues. The results indicated that the group that received rTMS in the left PFC had significantly lower skin conductance responses to the conditioned cue during extinction recall (Raij et al. 2018). TMS has also been recently used to investigate brain functions that may predict the efficacy of prolonged exposure at the individual level (Fonzo et al. 2017). Taken together, these studies (though generally underpowered) as well as several meta-analyses (Berlim & Van Den Eynde 2014, Clark et al. 2015, Karsen et al. 2014, Trevizol et al. 2016, Yan et al. 2017) suggest that TMS may enhance fear extinction and reduce PTSD symptoms without cognitive impairments or significant side effects. Larger study samples, optimization of stimulation parameters, long-term protocols, mechanistic studies, and studies that measure extinction and inhibitory learning outcomes in addition to overall symptom change are necessary to advance toward clinical implementation.

Vagus nerve stimulation.—VNS is a minimally invasive technique that involves the placement of a stimulation device in the upper-left chest that connects to electrodes on the left vagus nerve in the neck (Marin et al. 2014). The signal from the vagus nerve reaches several brain regions, including the amygdala and the hypothalamus, through stimulation of the solitary tract nucleus (George et al. 2000), altering brain norepinephrine regulation. VNS has been widely investigated and used as a treatment for epilepsy and depression, and it is approved by the FDA for these conditions. A few preclinical studies and one clinical study have demonstrated that VNS can enhance both fear memory consolidation and extinction.

In two studies, rats were subjected to an auditory fear conditioning task, a retention test, and extinction training (Peña et al. 2013, 2014). Following extinction training paired with VNS, rats that received VNS demonstrated enhanced fear extinction, which was also more rapid the longer the extinction protocols. Notably, even when the conditioned fear was based on a distant memory, VNS improved extinction. These studies and others indicate that VNS may promote synaptic plasticity in circuitry associated with extinction memory (Alvarez-Dieppa et al. 2016; Childs et al. 2015; Peña et al. 2013, 2014).

Recently, Noble et al. (2017) extended the investigation of VNS by testing rats in a single prolonged stress (SPS) model of PTSD. The SPS model consists of sequential restraining, forced swimming, loss of consciousness, and a week of social isolation (Liberzon et al. 1997). Rats that received extinction training paired with VNS demonstrated improved extinction and a reduction in behaviors associated with all PTSD clusters. When they were subsequently reexposed to the unconditioned stimulus, as well as to tasks unrelated to the original conditioned stimulus, the VNS-treated SPS rats did not relapse and exhibited both reduced anxiety and reduced avoidance behaviors. These finding suggest that VNS may be helpful for specific traumatic stimuli as well as for broader PTSD- and anxiety-related symptoms.

The nonhuman animal studies above provide hope for the use of VNS to promote extinction processes in humans, though investigations of VNS and extinction in humans, to our knowledge, have yet to be conducted. Exposure therapy may often be hindered by impaired extinction, relapse, or co-occurring symptoms such as anxiety. The potential for VNS to enhance extinction, hinder relapse, and reduce anxiety makes it particularly appealing to investigate as an adjunct to exposure therapy (Fanselow 2013, Marin & Milad 2015).

Deep-brain stimulation.—DBS is an invasive technique that involves implanting electrodes that deliver chronic high-frequency electric stimulation to specific brain regions (Marin et al. 2014). DBS has been predominantly used to treat movement disorders such as Parkinson's disease, but promising preclinical and clinical results have been demonstrated for depression (Mayberg et al. 2005) and obsessive-compulsive disorder (Greenberg et al. 2006). Animal models investigating the effects of DBS, or DBS-like stimulation, on fear extinction and PTSD suggest that targeting the human PFC, amygdala, ventral striatum, and HP with DBS may improve fear extinction and reduce anxiety (Lavano et al. 2018).

Langevin et al. (2010) investigated the effects of DBS in the right amygdala on anxiety-related behaviors in fear conditioned rats. Compared to the sham group, rats that received BLA DBS treatment showed evidence of reduced amygdala hyperactivity and anxiety-like symptoms. A study on the effects of striatal DBS on fear extinction in rats found that DBS targeting the dorsal aspect of the ventral striatum facilitates extinction, whereas DBS of the ventral aspect of the ventral striatum impairs extinction (Rodriguez-Romaguera et al. 2012). In addition, they demonstrated that to be effective, DBS must be administered along with extinction training, and that the more time spent on extinction training, the more DBS facilitates extinction, and vice versa. They later replicated these effects and extended their findings to show plasticity signatures in regions critical for extinction learning (Do-Monte et al. 2013).

Recently, Reznikov et al. (2018) demonstrated that chronic DBS delivered to the infralimbic cortex of rats with persistent extinction deficits and long-term anxiety enhanced extinction learning, improved anxiety-like behavior, and reduced BLA cell firing. Studies translating these preclinical DBS extinction investigations to humans have yet to be published to our knowledge, though a DBS study protocol has been proposed and a study in veterans with refractory PTSD is currently underway (Koek et al. 2014). A case study from this group has been published, and the results indicate that chronic BLA DBS significantly reduced a

veterans interview-based PTSD symptom scores without any serious adverse effects (Langevin et al. 2016).

Although these preclinical and clinical studies are promising, it is important to recognize their limitations. A nonexhaustive list of limitations includes (*a*) the different time frame of studies in rats and in humans (short term versus long term), (*b*) the absence of similar PTSD refractory characteristics in humans and rats, (*c*) the persistence of symptoms in humans compared to an acute response in rats, and (*d*) the presence of nonextinction-related PTSD symptoms in humans. Moving forward, animal studies should aim to bridge these modeling gaps, refine stimulation parameters and targets, and continue to investigate how DBS works, along with its plasticity effects. Human studies should be pursued in a cautious manner given the invasive nature of DBS.

Psychopharmacological Interventions

Psychopharmacological treatments can also be used to facilitate extinction and inhibitory learning. We focus here on psychopharmacological treatments designed to work within a psychotherapeutic treatment session or over the course of a specific anxiety- or trauma-related treatment. We discuss in particular D-cycloserine, scopolamine, losartan, ketamine, and 3,4-methylenedioxymethamphetamine (MDMA). There are a number of other drugs at various stages of testing and with different levels of pharmacological and neurobiological support, but space limits our ability to discuss them in detail here (see Singewald et al. 2015 for a recent comprehensive review).

D-cycloserine.—D-cycloserine is an antibiotic originally used to treat tuberculosis (Rodrigues et al. 2014). It acts as a superagonist at GluN2C-containing NMDA receptors, but as a partial agonist at GluN2A-, GluN2B-, and GluN2D-containing NMDA receptors (Dravid et al. 2010). Promising evidence from rodent models suggests D-cycloserine promotes extinction learning (e.g., Ledgerwood et al. 2003). Initial human trials were very positive (e.g., Difede et al. 2014, Ressler et al. 2004); however, more recent studies and reviews have been mixed (e.g., Rodrigues et al. 2014). The authors of these reviews, however, acknowledge that the limited number of studies, the heterogeneity in the study samples, and the small sample sizes do not permit drawing strong conclusions at this time, especially given the positive findings at the single-study level.

Importantly, the timing of drug administration, the region of the brain influenced by D-cycloserine, the subunit composition it binds to, and the behaviors exhibited during extinction training could facilitate either fear or extinction learning, as evidenced by recent rodent and human work (Baker et al. 2017, Bolkan & Lattal 2014). Importantly, D-cycloserine tends to reach maximal concentrations in the cerebral spinal fluid two hours after consumption (Baron et al. 1955), and this timing can be slowed by fatty food intake (Zhu et al. 2001). A recent study demonstrating augmentation of extinction with D-cycloserine had participants take the drug 90 minutes before exposure therapy, so that peak concentration would likely occur in the middle of the therapy session (Difede et al. 2014). This timing may be optimal for beneficial effects. Furthermore, D-cycloserine binds to a range of NMDA receptors. As discussed above, these different subunit compositions can

play a role in promoting either fear or extinction learning (Baker et al. 2017). Thus, D-cycloserine could simultaneously promote both extinction learning and reconsolidation of fear memory. A logical conclusion is that a drug specific for GluN2B- and/or GluN2C-containing NMDA receptors may be more effective in promoting extinction, especially when administered to reach peak concentration during actual exposure. Additional work on precise targeting of NMDA enhancement to improve extinction over reconsolidation processes, or on exposure therapy mechanisms to reduce reconsolidation during extinction, will be needed for these types of plasticity-enhancing approaches to be most effective.

Scopolamine.—Scopolamine is an antagonist that blocks muscarinic acetylcholine receptors, and it is used most commonly to prevent nausea, vomiting, and motion sickness (Craske et al. 2018). Work in rodents suggests that scopolamine tips the balance of memory encoding versus retrieval (by the hippocampus) toward retrieval, thereby facilitating the retrieval of inhibitory memories and making extinction learning more context independent (Chang & Liang 2012, Douchamps et al. 2013, Zelikowsky et al. 2013). Although some human studies have demonstrated the rapid antidepressant effects of scopolamine (Navarria et al. 2015), there have yet to be human trials to test its efficacy in treating anxiety- or trauma-related disorders and in augmenting extinction specifically. Future studies must also consider that scopolamine is commonly used to pharmacologically induce amnesia in animals, and it is known to interfere with the ability of the hippocampal memory system to effectively bind sensory, especially spatial, information to episodic memory traces (e.g., Newman et al. 2013).

Losartan.—Losartan is an antagonist of angiotensin II type 1 (AT_1) receptors, and it is widely used as a medication to treat high blood pressure and regulate the cardiovascular system (Marvar et al. 2014). The use of AT_1 blockers to promote fear extinction in PTSD patients is warranted by several lines of preclinical and clinical evidence. First, it is well established that individuals diagnosed with PTSD are more likely to have hypertension as well as an increased risk for heart attack and stroke (e.g., Edmondson & Cohen 2013). Furthermore, stressors have been shown to elicit elevated levels of circulating angiotensin II, which can drive stress-induced hypertension (e.g., Saavedra & Benicky 2007). In response to chronic stress, AT_1 binding can be significantly elevated in the hypothalamus, and this can be countered by angiotensin receptor blockers like losartan (e.g., Armando et al. 2007, Bregonzio et al. 2008). Lastly, clinical studies have shown that angiotensin receptor blockers can protect against stress-induced brain pathology and exert pro-cognitive effects inpatients with vascular disease and hypertension (Amenta et al. 2002, Anderson et al. 2011).

With regard to extinction learning benefits, promising work in rodents has found that losartan facilitated extinction learning but did not affect fear learning, blood pressure, or neuroendocrine stress measures (Marvar et al. 2014). A retrospective observational study of traumatized individuals found that individuals on various angiotensin receptor blockers and angiotensin-converting enzyme inhibitors had fewer PTSD symptoms (Khoury et al. 2012). A randomized controlled clinical trial is currently ongoing in a PTSD sample to further test the efficacy of this drug for augmenting extinction and inhibitory learning.

Ketamine.—Ketamine is traditionally used as an anesthetic at higher doses and an analgesic at lower doses (Hirota & Lambert 1996). It is a noncompetitive NMDA receptor antagonist and acts as an open channel blocker (e.g., Orser et al. 1997). Ketamine stops downstream signaling usually initiated by NMDA receptor activation (McGhee et al. 2008), and cellular homeostatic responses are thought to result in increased AMPA-dependent plasticity (e.g., Autry et al. 2011). In addition to this influence on NMDA receptors, there is evidence that ketamine can also affect opioid and monoaminergic receptors (Hirota & Lambert 1996). Much of the psychiatric work with ketamine is in the field of depression, given its fast-acting antidepressant effects (Browne & Lucki 2013). Ketamine may also be helpful for facilitating extinction learning and/or reducing fear responding in anxiety- and trauma-related disorders, but this remains to be tested. A number of small-sample PTSD studies with retrospective/naturalistic designs have reported mixed results—though none has tested augmentation of extinction specifically. For example, both a retrospective and a prospective naturalistic study of accident victims found that those who received ketamine peri traumatically for medical reasons reported more PTSD symptoms at follow-up (e.g., Schönenberg et al. 2008). These studies suggest that ketamine administered close to trauma exposure may actually lead to worse outcomes, perhaps due to enhanced plasticity related to trauma memory consolidation. A number of other studies, however, have not reported these negative associations. For example, a medical chart review study found that veterans who received ketamine during surgery were less likely to have PTSD despite more severe physical injuries (McGhee et al. 2008). A retrospectively analyzed randomized controlled trial did not find significant differences in anxiety or dissociative symptoms between individuals with depression and trauma/PTSD who were or were not given ketamine, suggesting that ketamine has no enduring impact on these symptoms (Zeng et al. 2013). Finally, a randomized controlled trial with a chronic PTSD sample found that ketamine significantly decreased reported distress caused by traumatizing events (Feder et al. 2014).

Given these mixed findings, and significant concerns that ketamine induces transient psychotic and dissociative states (Krystal et al. 1994), more work is needed to properly examine ketamine’s efficacy for augmenting extinction. Particular concern regarding the use of ketamine remains for individuals with prominent dissociative symptoms (e.g., the dissociative subtype of PTSD).

MDMA.—MDMA has been historically used in a psychotherapeutic context, but in the 1980s the US Drug Enforcement Administration officially labeled ecstasy/Molly an illegal drug. MDMA improves mood and facilitates feelings of well-being, often making individuals feel more extroverted but also inducing perceptual distortion in vision (Peroutka et al. 1988, Vollenweider et al. 1998). MDMA is a monoamine transporter substrate that passes through dopamine, norepinephrine, and serotonin transporters (Verrico et al. 2007). Transporters sit on the presynaptic nerve terminals and recycle neurotransmitters from the synapse. MDMA can enter presynaptic nerve terminals to inhibit the vesicular monoamine transporter 2 (VMAT2) and activate the trace amine-associated receptor 1 (TAARl; e.g., Berry et al. 2017). The consequences of MDMA are therefore twofold. First, due to the blocking of VMAT2, presynaptic nerve terminals fill up with monoamines that can no longer be loaded into synaptic vesicles. Second, TAARl activation leads monoamine transporters to

disseminate monoamines instead of recycling them back into the presynaptic neuron. This floods synapses with monoamines and causes the observed behavioral effects of MDMA. Downstream, this can influence the levels of oxytocin, prolactin, and cortisol in the brain (Dumont et al. 2009, Harris et al. 2002, Mas et al. 1999, Thompson et al. 2007, Wolff et al. 2006).

Recently, research has explored the possible therapeutic benefit of MDMA in controlled settings, as the drug is hypothesized to facilitate emotional engagement while recalling traumatizing events (Mithoefer et al. 2011), which may augment extinction learning. Separate rodent studies have shown a direct effect of MDMA on extinction processing (Young et al. 2015). So far, small-scale human trials have been conducted in PTSD samples with promising preliminary findings. In a randomized controlled pilot study, individuals who received MDMA during two eight-hour experimental psychotherapy sessions on average reported marked decreases in PTSD symptoms up to two months after the sessions (Mithoefer et al. 2011) as well as at long-term follow-ups 17 to 74 months later (Mithoefer et al. 2013). Additional work is necessary to further understand the effectiveness of MDMA for PTSD and other disorders, especially given the abuse potential of this substance.

CONCLUSIONS AND FUTURE DIRECTIONS

A central feature of a number of psychiatric disorders, including phobias, PTSD, SAD, and panic disorder, is dysfunctional fear responding driven by failures of extinction and inhibitory learning. Pavlovian fear conditioning paradigms can be used to study fear responding and extinction/inhibitory learning across different species. These translational paradigms have enabled researchers to draw sophisticated conclusions about the mechanisms of extinction and inhibitory learning based on converging nonhuman animal and human research. In turn, this has bolstered exploration and implementation of psychological, behavioral, device-based, and psychopharmacological interventions that may be utilized to repair or augment extinction and inhibitory learning in psychiatric disorders.

Despite these scientific developments, the aforementioned techniques fail to help a significant number of patients reach normative functioning. For example, a recent review suggests that approximately 55% of individuals attain nonclinical status after various forms of exposure therapy (Loerinc et al. 2015). This underpins the need for further advances in understanding the behavioral and biological mechanisms of extinction that may lead to more targeted pharmacotherapy and neurocircuitry modulation and to improvements in combined psychotherapeutic approaches. For example, moving beyond traditional amygdala- and vmPFC-focused exploration of extinction mechanisms may lead to novel neural targets for neurotherapeutic and pharmacological interventions. Finally, the use of powerful machine learning techniques that combine empirical biological data with clinical results in fear extinction may provide new insights into subgroups of individuals who may benefit the most from particular interventions, taking us one step closer to precision medicine in the realm of disorders with fear-related symptoms (Bzdok & Meyer-Lindenberg 2018).

ACKNOWLEDGMENTS

The authors thank Evan Lebois for his feedback and comments. This work was primarily supported by the National Institutes of Mental Health (F32 MH109274 to L.A.M.L.; MH112956, MH108665, and MH096764 to K.J.R.).

LITERATURE CITED

Abraham AD, Cunningham CL, Lattal KM. 2012 Methylphenidate enhances extinction of contextual fear. Learn. Mem 19(2):67–72 [PubMed: 22251891]

Abraham AD, Neve KA, Lattal KM. 2014 Dopamine and extinction: a convergence of theory with fear and reward circuitry. Neurobiol. Learn. Mem 108:65–77 [PubMed: 24269353]

Alvarez-Dieppa AC, Griffin K, Cavalier S, McIntyre CK. 2016Vagus nerve stimulation enhances extinction of conditioned fear in rats and modulates Arc protein, CaMKII, and GluN2B-containing NMDA receptors in the basolateral amygdala. Neural Plast. 2016:4273280 [PubMed: 27957346]

Amenta F, Mignini F, Rabbia F, Tomassoni D, Veglio F. 2002 Protective effect of anti-hypertensive treatment on cognitive function in essential hypertension: analysis of published clinical data. J. Neurol. Sci 203–4:147–51

Anderson C, Teo K, Gao P, Arima H, Dans A, et al. 2011 ONTARGET and TRANSCEND investigators. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol. 10(1):43–53 [PubMed: 20980201]

Armando I, Volpi S, Aguilera G, Saavedra JM. 2007 Angiotensin II AT1 receptor blockade prevents the hypothalamic corticotropin-releasing factor response to isolation stress. Brain Res. 1142:92–99 [PubMed: 17306778]

Asthana M, Nueckel K, Mühlberger A, Neueder D, Polak T, et al. 2013 Effects of transcranial direct current stimulation on consolidation of fear memory. Front. Psychiatry 4:107 [PubMed: 24069003]

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, et al. 2011 NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475(7354):91–95 [PubMed: 21677641]

Bae H, Kim D, Park YC. 2016 Dissociation predicts treatment response in eye-movement desensitization and reprocessing for posttraumatic stress disorder. J. Trauma Dissociation 17(1): 112–30 [PubMed: 26156867]

Baker JF, Cates ME, Luthin DR. 2017 D-cycloserine in the treatment of posttraumatic stress disorder. Ment. Health Clin 7(2):88–94 [PubMed: 29955504]

Baron H, Epstein IG, Mulinos MG, Nair KG. 1955 Absorption, distribution, and excretion of cycloserine in man. Antibiot. Annu 3:136–40 [PubMed: 13355257]

Berke JD. 2018 What does dopamine mean? Nat. Neurosci 21(6):787–93 [PubMed: 29760524]

Berlau DJ, McGaugh JL. 2006 Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. Neurobiol. Learn. Mem 86(2):123–32 [PubMed: 16458544]

Berlim MT, Van Den Eynde F. 2014 Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials. Can. J. Psychiatry Rev. Can. Psychiatr 59(9): 487–96

Berry MD, Gainetdinov RR, Hoener MC, Shahid M. 2017 Pharmacology of human trace amine-associated receptors: therapeutic opportunities and challenges. Pharmacol. Ther 180:161–80 [PubMed: 28723415]

Blagys MD, Hilsenroth MJ. 2000 Distinctive features of short-term psychodynamic-interpersonal psychotherapy: a review of the comparative psychotherapy process literature. Clin. Psychol.: Sci. Pract 7(2):167–88

Bleakman D, Lodge D. 1998 Neuropharmacology of AMPA and kainate receptors. Neuropharmacology 37(10–11):1187–204 [PubMed: 9849657]

Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, et al. 2010 Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J. Clin. Psychiatry 71(8):992–99 [PubMed: 20051219]

Bolkan SS, Lattal KM. 2014 Opposing effects of D-cycloserine on fear despite a common extinction duration: interactions between brain regions and behavior. Neurobiol. Learn. Mem 113:25–34 [PubMed: 24374132]

Bormann J 2000 The "ABC" of GABA receptors. Trends Pharmacol. Sci 21(1):16–19 [PubMed: 10637650]

Bouton ME. 1993 Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychol. Bull 114(1):80–99 [PubMed: 8346330]

Bouton ME, Westbrook RF, Corcoran KA, Maren S. 2006 Contextual and temporal modulation of extinction: behavioral and biological mechanisms. Biol. Psychiatry 60(4):352–60 [PubMed: 16616731]

Bregonzio C, Seltzer A, Armando I, Pavel J, Saavedra JM. 2008 Angiotensin II AT(1) receptor blockade selectively enhances brain AT(2) receptor expression, and abolishes the cold-restraint stress-induced increase in tyrosine hydroxylase mRNA in the locus coeruleus of spontaneously hypertensive rats. Stress 11(6):457–66 [PubMed: 18609298]

Browne CA, Lucki I. 2013 Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. Front. Pharmacol 4:161 [PubMed: 24409146]

Burghardt NS, Sigurdsson T, Gorman JM, McEwen BS, LeDoux JE. 2013 Chronic antidepressant treatment impairs the acquisition of fear extinction. Biol. Psychiatry 73(11):1078–86 [PubMed: 23260230]

Bzdok D, Meyer-Lindenberg A. 2018 Machine learning for precision psychiatry: opportunities and challenges. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3(3):223–30 [PubMed: 29486863]

Cannistraro PA, Rauch SL. 2003 Neural circuitry of anxiety: evidence from structural and functional neuroimaging studies. Psychopharmacol. Bull 37(4):8–25

Chang S-D, Liang KC. 2012 Roles of hippocampal GABA(A) and muscarinic receptors in consolidation of context memory and context-shock association in contextual fear conditioning: a double dissociation study. Neurobiol. Learn. Mem 98(1):17–24 [PubMed: 22543193]

Changeux J-P. 2010 Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. Nat. Rev. Neurosci 11(6):389–401 [PubMed: 20485364]

Childs JE, Alvarez-Dieppa AC, McIntyre CK, Kroener S. 2015 Vagus nerve stimulation as a tool to induce plasticity in pathways relevant for extinction learning. J. Vis. Exp 102:e53032

Clark C, Cole J, Winter C, Williams K, Grammer G. 2015 A review of transcranial magnetic stimulation as a treatment for post-traumatic stress disorder. Curr. Psychiatry Rep 17(10):83 [PubMed: 26324821]

Cloitre M, Petkova E, Wang J, Lu Lassell F. 2012 An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD related to childhood abuse. Depress. Anxiety 29(8):709–17 [PubMed: 22550033]

Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. 2004 Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. Am. J. Psychiatry 161(3):515–24 [PubMed: 14992978]

Collingridge GL, Peineau S, Howland JG, Wang YT. 2010 Long-term depression in the CNS. Nat. Rev. Neurosci 11(7):459–73 [PubMed: 20559335]

Conn PJ, Pin JP. 1997 Pharmacology and functions of metabotropic glutamate receptors. Annu. Rev. Pharmacol. Toxicol 37:205–37 [PubMed: 9131252]

Craske MG, Hermans D, Vervliet B. 2018 State-of-the-art and future directions for extinction as a translational model for fear and anxiety. Philos. Trans. R. Soc. B 373:20170025. Correction 2018 Philos. Trans. R. Soc. B 373:20180432

Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. 2014 Maximizing exposure therapy: an inhibitory learning approach. Behav. Res. Ther 58:10–23 [PubMed: 24864005]

Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, et al. 2016 Psychological treatments for adults with posttraumatic stress disorder: a systematic review and meta-analysis. Clin. Psychol. Rev 43:128–41 [PubMed: 26574151]

de Jong PJ, Merckelbach H. 1993 Covariation bias, classical conditioning, and phobic fear. Integr. Physiol. Behav. Sci 28(2):167–70 [PubMed: 8318443]

Deacon B, Kemp JJ, Dixon LJ, Sy JT, Farrell NR, Zhang AR. 2013 Maximizing the efficacy of interoceptive exposure by optimizing inhibitory learning: a randomized controlled trial. Behav. Res. Ther 51(9):588–96 [PubMed: 23872701]

Delgado MR, Nearing KI, Ledoux JE, Phelps EA. 2008 Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron 59(5):829–38 [PubMed: 18786365]

Dep.Veteran Aff., Dep. Def. 2017 VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Washington, DC: Gov. Print. Off https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal.pdf

Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. 2017 Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat. Rev. Neurosci 18(11):685–93 [PubMed: 28951609]

Difede J, Cukor J, Wyka K, Olden M, Hoffman H, Lee FS, Altemus M. 2014 D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology 39(5):1052–58 [PubMed: 24217129]

Do-Monte FH, Rodriguez-Romaguera J, Rosas-Vidal LE, Quirk GJ. 2013 Deep brain stimulation of the ventral striatum increases BDNF in the fear extinction circuit. Front. Behav. Neurosci 7:102 [PubMed: 23964215]

Douchamps V, Jeewajee A, Blundell P, Burgess N, Lever C. 2013 Evidence for encoding versus retrieval scheduling in the hippocampus by theta phase and acetylcholine. J. Neurosci 33(20): 8689–704 [PubMed: 23678113]

Dravid SM, Burger PB, Prakash A, Geballe MT, Yadav R, et al. 2010 Structural determinants of D-cycloserine efficacy at the NR1/NR2C NMDA receptors. J. Neurosci 30(7):2741–54 [PubMed: 20164358]

Duits P, Cath DC, Lissek S, Hox JJ. 2015 Updated meta-analysis of classical fear conditioning in the anxiety disorders. Depress. Anxiety 32(4):239–53 [PubMed: 25703487]

Dumont GJH, Sweep FCGJ, van der Steen R, Hermsen R, Donders ART, et al. 2009 Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. Soc. Neurosci 4(4):359–66 [PubMed: 19562632]

Ebner-Priemer UW, Mauchnik J, Kleindienst N, Schmahl C, Peper M, et al. 2009 Emotional learning during dissociative states in borderline personality disorder. J. Psychiatry Neurosci 34(3):214–22 [PubMed: 19448852]

Edmondson D, Cohen BE. 2013 Posttraumatic stress disorder and cardiovascular disease. Prog. Cardiovasc. Dis 55(6):548–56 [PubMed: 23621964]

Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA. 2000 Remembering episodes: a selective role for the hippocampus during retrieval. Nat. Neurosci 3(11):1149–52 [PubMed: 11036273]

Engelman HS, MacDermott AB. 2004 Presynaptic ionotropic receptors and control of transmitter release. Nat. Rev. Neurosci 5(2):135–45 [PubMed: 14735116]

Fanselow MS. 2013 Fear and anxiety take a double hit from vagal nerve stimulation. Biol. Psychiatry 73(11):1043–44 [PubMed: 23647735]

Fanselow MS, LeDoux JE. 1999 Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 23(2):229–32 [PubMed: 10399930]

Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, et al. 2014 Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry 71(6):681–88 [PubMed: 24740528]

Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. 2014 Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimul. 7(1):105–12 [PubMed: 24095257]

Fendt M, Fanselow MS. 1999 The neuroanatomical and neurochemical basis of conditioned fear. Neurosci. Biobehav. Rev 23(5):743–60 [PubMed: 10392663]

Foa EB. 2011 Prolonged exposure therapy: past, present, and future. Depress. Anxiety 28(12):1043–47 [PubMed: 22134957]

Foa EB, Kozak MJ. 1986 Emotional processing of fear: exposure to corrective information. Psychol. Bull 99(1):20–35 [PubMed: 2871574]

Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, et al. 2017 PTSD psychotherapy outcome predicted by brain activation during emotional reactivity and regulation. Am. J. Psychiatry 174(12):1163–74 [PubMed: 28715908]

Frazer A, Hensler JG. 1999 Serotonin involvement in physiological function and behavior In Basic Neurochemistry: Molecular, Cellular and Medical Aspects, ed. GJ Siegel, Agranoff BW, Albers RW, pp. 263–92. Philadelphia: Lippincott-Raven 6th ed.

George MS, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, et al. 2000 Vagus nerve stimulation: a new tool for brain research and therapy. Biol. Psychiatry 47(4):287–95 [PubMed: 10686263]

Ghosh S, Chattarji S. 2015 Neuronal encoding of the switch from specific to generalized fear. Nat. Neurosci 18(1):112–20 [PubMed: 25436666]

Gorka SM, Lieberman L, Nelson BD, Sarapas C, Shankman SA. 2014 Aversive responding to safety signals in panic disorder: the moderating role of intolerance of uncertainty. J. Anxiety Disord 28(7):731–36 [PubMed: 25173980]

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, et al. 2006 Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 31:2384–93 [PubMed: 16855529]

Grisaru N, Amir M, Cohen H, Kaplan Z. 1998 Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. Biol. Psychiatry 44(1):52–55 [PubMed: 9646883]

Haaker J, Gaburro S, Sah A, Gartmann N, Lonsdorf TB, et al. 2013 Single dose of l-dopa makes extinction memories context-independent and prevents the return of fear. PNAS 110(26):E2428–36 [PubMed: 23754384]

Hagenaars MA, van Minnen A, Hoogduin KAL. 2010 The impact of dissociation and depression on the efficacy of prolonged exposure treatment for PTSD. Behav. Res. Ther 48(1):19–27 [PubMed: 19766987]

Halvorsen JØ, Stenmark H, Neuner F, Nordahl HM. 2014 Does dissociation moderate treatment outcomes of narrative exposure therapy for PTSD? A secondary analysis from a randomized controlled clinical trial. Behav. Res. Ther 57:21–28 [PubMed: 24762779]

Han JS, Holland PC, Gallagher M. 1999 Disconnection of the amygdala central nucleus and substantia innominata/nucleus basalis disrupts increments in conditioned stimulus processing in rats. Behav. Neurosci 113(1):143–51 [PubMed: 10197914]

Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. 2002 Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology 162(4):396–405 [PubMed: 12172693]

Haubrich J, Machado A, Boos FZ, Crestani AP, Sierra RO, et al. 2017 Enhancement of extinction memory by pharmacological and behavioral interventions targeted to its reactivation. Sci. Rep 7(1):10960 [PubMed: 28887561]

Hayes SC, Strosahl KD, Wilson KG. 1999 Acceptance and Commitment Therapy. New York: Guilford Press

Hermann C, Ziegler S, Birbaumer N, Flor H. 2002 Psychophysiological and subjective indicators of aversive Pavlovian conditioning in generalized social phobia. Biol. Psychiatry 52(4):328–37 [PubMed: 12208640]

Hirota K, Lambert DG. 1996 Ketamine: its mechanism(s) of action and unusual clinical uses. Br. J. Anaesth 77(4):441–44 [PubMed: 8942324]

Hugues S, Garcia R, Léna I. 2007 Time course of extracellular catecholamine and glutamate levels in the rat medial prefrontal cortex during and after extinction of conditioned fear. Synapse 61(11): 933–37 [PubMed: 17663454]

Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, et al. 2013 Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder—a pilot study. Brain Stimul. 6(3):377–83 [PubMed: 22921765]

Jaycox LH, Foa EB, Morral AR. 1998 Influence of emotional engagement and habituation on exposure therapy for PTSD. J. Consult. Clin. Psychol 66(1):185–92 [PubMed: 9489273]

Jovanovic T, Ely T, Fani N, Glover EM, Gutman D, et al. 2013 Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample. Cortex 49(7):1884–91 [PubMed: 23020899]

Jovanovic T, Kazama A, Bachevalier J, Davis M. 2012 Impaired safety signal learning may be a biomarker of PTSD. Neuropharmacology 62(2):695–704 [PubMed: 21377482]

Kaczkurkin AN, Foa EB. 2015 Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. Dialogues Clin. Neurosci 17(3):337–46 [PubMed: 26487814]

Karsen EF, Watts BV, Holtzheimer PE. 2014 Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. Brain Stimul. 7(2):151–57 [PubMed: 24486424]

Kawahara H, Yoshida M, Yokoo H, Nishi M, Tanaka M. 1993 Psychological stress increases serotonin release in the rat amygdala and prefrontal cortex assessed by in vivo microdialysis. Neurosci. Lett 162(1–2):81–84 [PubMed: 8121642]

Khoury NM, Marvar PJ, Gillespie CF, Wingo A, Schwartz A, et al. 2012 The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. J. Clin. Psychiatry 73(6):849–55 [PubMed: 22687631]

Kiefer M, Schuch S, Schenck W, Fiedler K. 2008 Emotion and memory: Event-related potential indices predictive for subsequent successful memory depend on the emotional mood state. Adv. Cogn. Psychol 3(3):363–73 [PubMed: 20517520]

Kleindienst N, Limberger MF, Ebner-Priemer UW, Keibel-Mauchnik J, Dyer A, et al. 2011 Dissociation predicts poor response to Dialectical Behavioral Therapy in female patients with Borderline Personality Disorder. J. Pers. Disord 25(4):432–47 [PubMed: 21838560]

Kleindienst N, Priebe K, Görg N, Dyer A, Steil R, et al. 2016 State dissociation moderates response to dialectical behavior therapy for posttraumatic stress disorder in women with and without borderline personality disorder. Eur. J. Psychotraumatol 7:30375 [PubMed: 27396380]

Knight DC, Smith CN, Cheng DT, Stein EA, Helmstetter FJ. 2004 Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. Cogn. Affect. Behav. Neurosci 4(3): 317–25 [PubMed: 15535167]

Koek RJ, Langevin J-P, Krahl SE, Kosoyan HJ, Schwartz HN, et al. 2014 Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation. Trials 15(1):356 [PubMed: 25208824]

Kozel FA, Motes MA, Didehbani N, DeLaRosa B, Bass C, et al. 2018 Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: a randomized clinical trial. J. Affect. Disord 229:506–14 [PubMed: 29351885]

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, et al. 1994 Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry 51(3):199–214 [PubMed: 8122957]

Kuo M-F, Paulus W, Nitsche MA. 2014 Induction of cortical plasticity: clinical applications In Replace, Repair, Restore, Relieve—Bridging Clinical and Engineering Solutions in Neurorehabilitation, Vol. 7, ed. Jensen W, Andersen OK, Akay M, pp. 3–7. Cham, UK: Springer

LaBar KS, Phelps EA. 2005 Reinstatement of conditioned fear in humans is context dependent and impaired in amnesia. Behav. Neurosci 119(3):677–86 [PubMed: 15998188]

Lamprecht R, LeDoux J. 2004 Structural plasticity and memory. Nat. Rev. Neurosci 5(1):45–54 [PubMed: 14708003]

Langevin J-P, De Salles AAF, Kosoyan HP, Krahl SE. 2010 Deep brain stimulation of the amygdala alleviates post-traumatic stress disorder symptoms in a rat model. J. Psychiatr. Res 44(16):1241–45 [PubMed: 20537659]

Langevin J-P, Koek RJ, Schwartz HN, Chen JWY, Sultzer DL, et al. 2016 Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. Biol. Psychiatry 79(10):e82–84 [PubMed: 26475671]

Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, et al. 2002 Brain activation during scriptdriven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. Biol. Psychiatry 52(4):305–11 [PubMed: 12208637]

Lavano A, Guzzi G, Della Torre A, Lavano SM, Tiriolo R, Volpentesta G. 2018 DBS in treatment of posttraumatic stress disorder. Brain Sci. 8(1):18

Lebrón K, Milad MR, Quirk GJ. 2004 Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. Learn. Mem 11(5):544–48 [PubMed: 15466306]

Ledgerwood L, Richardson R, Cranney J. 2003 Effects of D-cycloserine on extinction of conditioned freezing. Behav. Neurosci 117(2):341–49 [PubMed: 12708530]

LeDoux JE, Iwata J, Cicchetti P, Reis DJ. 1988 Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J. Neurosci 8(7):2517–29 [PubMed: 2854842]

Liberzon I, Krstov M, Young EA. 1997 Stress-restress: effects on ACTH and fast feedback. Psychoneuroendocrinology 22(6):443–53 [PubMed: 9364622]

Lieberman L, Gorka SM, Sarapas C, Shankman SA. 2016 Cognitive flexibility mediates the relation between intolerance of uncertainty and safety signal responding in those with panic disorder. Cogn. Emot 30(8):1495–503 [PubMed: 26212088]

Likhtik E, Stujenske JM, Topiwala MA, Harris AZ, Gordon JA. 2014 Prefrontal entrainment of amygdala activity signals safety in learned fear and innate anxiety. Nat. Neurosci 17(1):106–13 [PubMed: 24241397]

Lin C-H, Yeh S-H, Lu H-Y, Gean P-W. 2003 The similarities and diversities of signal pathways leading to consolidation of conditioning and consolidation of extinction of fear memory. J. Neurosci 23(23):8310–17 [PubMed: 12967993]

Linehan M 1993 Cognitive-Behavioral Treatment of Borderline Personality Disorder. New York: Guilford Press

Lissek S, Rabin SJ, McDowell DJ, Dvir S, Bradford DE, et al. 2009 Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. Behav. Res. Ther 47(2):111–18 [PubMed: 19027893]

Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, et al. 2012 Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484(7394):381–85 [PubMed: 22441246]

Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG. 2015 Response rates for CBT for anxiety disorders: need for standardized criteria. Clin. Psychol. Rev 42:72–82 [PubMed: 26319194]

Marek R, Jin J, Goode TD, Giustino TF, Wang Q, et al. 2018 Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. Nat. Neurosci 21(3): 384–92 [PubMed: 29403033]

Marin M-F, Camprodon JA, Dougherty DD, Milad MR. 2014 Device-based brain stimulation to augment fear extinction: implications for PTSD treatment and beyond. Depress. Anxiety 31(4): 269–78 [PubMed: 24634247]

Marin M-F, Milad MR. 2015 Neuromodulation approaches for the treatment of post-traumatic stress disorder: stimulating the brain following exposure-based therapy. Curr. Behav. Neurosci. Rep 2(2):67–71

Marvar PJ, Goodman J, Fuchs S, Choi DC, Banerjee S, Ressler KJ. 2014 Angiotensin type 1 receptor inhibition enhances the extinction of fear memory. Biol. Psychiatry 75(11):864–72 [PubMed: 24094510]

Mas M, Farré M, de la Torre R, Roset PN, Ortuño J, et al. 1999 Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. J. Pharmacol. Exp. Ther 290(1):136–45 [PubMed: 10381769]

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, et al. 2005 Deep brain stimulation for treatment-resistant depression. Neuron 45(5):651–60 [PubMed: 15748841]

McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M, et al. 1998 Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Arch. Gen. Psychiatry 55(3):276–79 [PubMed: 9510224]

McGaugh JL. 2000 Memory—a century of consolidation. Science 287(5451):248–51 [PubMed: 10634773]

McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. 2008 The correlation between ketamine and posttraumatic stress disorder in burned service members. J. Trauma 64(2 Suppl.):S195–98 [PubMed: 18376165]

Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL. 2005 Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. PNAS 102(30):10706–11 [PubMed: 16024728]

Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. 2011 The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. J. Psychopharmacol 25(4):439–52 [PubMed: 20643699]

Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, et al. 2013 Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. J. Psychopharmacol 27(1):28–39 [PubMed: 23172889]

Morgan MA, Romanski LM, LeDoux JE. 1993 Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci. Lett 163(1):109–13 [PubMed: 8295722]

Mueller D, Cahill SP. 2010 Noradrenergic modulation of extinction learning and exposure therapy. Behav. Brain Res 208(1):1–11 [PubMed: 19931568]

Mueller D, Porter JT, Quirk GJ. 2008 Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. J. Neurosci 28(2):369–75 [PubMed: 18184779]

Mungee A, Burger M, Bajbouj M. 2016 No effect of cathodal transcranial direct current stimulation on fear memory in healthy human subjects. Brain Sci. 6(4):55

Myers KM, Carlezon WA Jr., Davis M 2011 Glutamate receptors in extinction and extinction-based therapie for psychiatric illness. Neuropsychopharmacology 36(1):274–93 [PubMed: 20631689]

Myers KM, Davis M. 2002 Behavioral and neural analysis of extinction. Neuron 36(4):567–84 [PubMed: 12441048]

Myers KM, Davis M. 2007 Mechanisms of fear extinction. Mol. Psychiatry 12(2):120–50 [PubMed: 17160066]

Nader K, Schafe GE, LeDoux JE. 2000 The labile nature of consolidation theory. Nat. Rev. Neurosci 1(3):216–19 [PubMed: 11257912]

Nam D-H, Pae C-U, Chae J-H. 2013 Low-frequency, repetitive transcranial magnetic stimulation for the treatment of patients with posttraumatic stress disorder: a double-blind, sham-controlled study. Clin. Psychopharmacol. Neurosci 11(2):96–102 [PubMed: 24023554]

Nasehi M, Soltanpour R, Ebrahimi-Ghiri M, Zarrabian S, Zarrindast MR. 2017 Interference effects of transcranial direct current stimulation over the right frontal cortex and adrenergic system on conditioned fear. Psychopharmacology 234(22):3407–16 [PubMed: 28887641]

Navarria A, Wohleb ES, Voleti B, Ota KT, Dutheil S, et al. 2015 Rapid antidepressant actions of scopolamine: role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors. Neurobiol. Dis 82:254–61 [PubMed: 26102021]

Nelson CL, Sarter M, Bruno JP. 2005 Prefrontal cortical modulation of acetylcholine release in posterior parietal cortex. Neuroscience 132(2):347–59 [PubMed: 15802188]

Newman EL, Gillet SN, Climer JR, Hasselmo ME. 2013 Cholinergic blockade reduces theta-gamma phase amplitude coupling and speed modulation of theta frequency consistent with behavioral effects on encoding. J. Neurosci 33(50):19635–46 [PubMed: 24336727]

Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, et al. 2003 Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J. Physiol 553(Pt. 1):293–301 [PubMed: 12949224]

Nitsche MA, Paulus W. 2000 Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol 527(Pt. 3):633–39 [PubMed: 10990547]

Noble LJ, Gonzalez IJ, Meruva VB, Callahan KA, Belfort BD, et al. 2017 Effects of vagus nerve stimulation on extinction of conditioned fear and post-traumatic stress disorder symptoms in rats. Transl. Psychiatry 7(8):e1217 [PubMed: 28892066]

Olatunji BO, Cisler JM, Deacon BJ. 2010 Efficacy of cognitive behavioral therapy for anxiety disorders: a review of meta-analytic findings. Psychiatr. Clin. N. Am 33(3):557–77

Orser BA, Pennefather PS, MacDonald JF. 1997 Multiple mechanisms of ketamine blockade of *N*-methyl-D-aspartate receptors. Anesthesiology 86(4):903–17 [PubMed: 9105235]

Osuch EA, Benson BE, Luckenbaugh DA, Geraci M, Post RM, McCann U. 2009 Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. J. Anxiety Disord 23(1):54–59 [PubMed: 18455908]

Ottaviani C, Cevolani D, Nucifora V, Borlimi R, Agati R, et al. 2012 Amygdala responses to masked and low spatial frequency fearful faces: a preliminary fMRI study in panic disorder. Psychiatry Res. 203(2–3):159–65 [PubMed: 22944369]

Oznur T, Akarsu S, Celik C, Bolu A, Ozdemir B, et al. 2014 Is transcranial magnetic stimulation effective in treatment-resistant combat related posttraumatic stress disorder? Neurosciences 19(1):29–32 [PubMed: 24419446]

Peña DF, Childs JE, Willett S, Vital A, McIntyre CK, Kroener S. 2014 Vagus nerve stimulation enhances extinction of conditioned fear and modulates plasticity in the pathway from the ventromedial prefrontal cortex to the amygdala. Front. Behav. Neurosci 8:327 [PubMed: 25278857]

Peña DF, Engineer ND, McIntyre CK. 2013 Rapid remission of conditioned fear expression with extinction training paired with vagus nerve stimulation. Biol. Psychiatry 73(11):1071–77 [PubMed: 23245749]

Peroutka SJ, Newman H, Harris H. 1988 Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. Neuropsychopharmacology 1(4):273–77 [PubMed: 2908020]

Phelps EA, Delgado MR, Nearing KI, LeDoux JE. 2004 Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43(6):897–905 [PubMed: 15363399]

Pittig A, van den Berg L, Vervliet B. 2016 The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments. Curr. Opin. Psychiatry 29(1):39–47 [PubMed: 26575298]

Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. 2010 A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin. Psychol. Rev 30(6):635–41 [PubMed: 20546985]

Prado-Alcalá RA, Fernández-Ruiz J, Quirarte G. 1993 Cholinergic neurons and memory In Aspects of Synaptic Transmission 2, ed. Stone TW, pp. 59–71. London: Taylor & Francis

Price M, Kearns M, Houry D, Rothbaum BO. 2014 Emergency department predictors of posttraumatic stress reduction for trauma-exposed individuals with and without an early intervention. J. Consult. Clin. Psychol 82(2):336–41 [PubMed: 24491070]

Quirk GJ, Beer JS. 2006 Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr. Opin. Neurobiol 16(6):723–27 [PubMed: 17084617]

Rabinak CA, Mori S, Lyons M, Milad MR, Phan KL. 2017 Acquisition of CS-US contingencies during Pavlovian fear conditioning and extinction in social anxiety disorder and posttraumatic stress disorder. J. Affect. Disord 207:76–85 [PubMed: 27716541]

Raij T, Nummenmaa A, Marin M-F, Porter D, Furtak S, et al. 2018 Prefrontal cortex stimulation enhances fear extinction memory in humans. Biol. Psychiatry 84(2):129–37 [PubMed: 29246436]

Resick PA, Monson CM, Chard KM. 2016 Cognitive Processing Therapy for PTSD: A Comprehensive Manual New York: Guilford Press

Resick PA, Suvak MK, Johnides BD, Mitchell KS, Iverson KM. 2012 The impact of dissociation on PTSD treatment with cognitive processing therapy. Depress. Anxiety 29(8):718–30 [PubMed: 22473922]

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, et al. 2004 Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch. Gen. Psychiatry 61(11):1136–44 [PubMed: 15520361]

Reznikov R, Bambico FR, Diwan M, Raymond RJ, Nashed MG, et al. 2018 Prefrontal cortex deep brain stimulation improves fear and anxiety-like behavior and reduces basolateral amygdala

activity in a preclinical model of posttraumatic stress disorder. Neuropsychopharmacology 43(5): 1099–106 [PubMed: 28862251]

Rodrigues H, Figueira I, Lopes A, Gonçalves R, Mendlowicz MV, et al. 2014 Does D-cycloserine enhance exposure therapy for anxiety disorders in humans? A meta-analysis. PLOS ONE 9(7):e93519 [PubMed: 24991926]

Rodriguez-Romaguera J, Do Monte FHM, Quirk GJ. 2012 Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. PNAS 109(22):8764–69 [PubMed: 22586125]

Roemer L, Orsillo SM, Salters-Pedneault K. 2008 Efficacy of an acceptance-based behavior therapy for generalized anxiety disorder: evaluation in a randomized controlled trial. J. Consult. Clin. Psychol 76(6):1083–89 [PubMed: 19045976]

Roldán G, Cobos-Zapiaín G, Quirarte GL, Prado-Alcalá RA. 2001 Dose- and time-dependent scopolamine-induced recovery of an inhibitory avoidance response after its extinction in rats. Behav. Brain Res 121(1–2):173–79 [PubMed: 11275294]

Rudy JW, Huff NC, Matus-Amat P. 2004 Understanding contextual fear conditioning: insights from a two-process model. Neurosci. Biobehav. Rev 28(7):675–85 [PubMed: 15555677]

Saavedra JM, Benicky J. 2007 Brain and peripheral angiotensin II play a major role in stress. Stress 10(2):185–93 [PubMed: 17514587]

Salamone JD, Correa M. 2012 The mysterious motivational functions of mesolimbic dopamine. Neuron 76(3):470–85 [PubMed: 23141060]

Sander D, Grafman J, Zalla T. 2003 The human amygdala: an evolved system for relevance detection. Rev. Neurosci 14(4):303–16 [PubMed: 14640318]

Sarter M, Parikh V. 2005 Choline transporters, cholinergic transmission and cognition. Nat. Rev. Neurosci 6(1):48–56 [PubMed: 15611726]

Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. 2008 Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. J. Psychopharmacol 22(5):493–97 [PubMed: 18208917]

Shedler J 2010 The efficacy of psychodynamic psychotherapy. Am. Psychol 65(2):98–109 [PubMed: 20141265]

Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, et al. 2004 Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch. Gen. Psychiatry 61(2):168–76 [PubMed: 14757593]

Sijbrandij M, Engelhard IM, Lommen MJJ, Leer A, Baas JMP. 2013 Impaired fear inhibition learning predicts the persistence of symptoms of posttraumatic stress disorder (PTSD). J. Psychiatr. Res 47(12):1991–97 [PubMed: 24090716]

Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ. 2015 Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. Pharmacol. Ther 149:150–90 [PubMed: 25550231]

Southwick SM, Bremner JD, Rasmusson A, Morgan CA, Arnsten A, Charney DS. 1999 Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol. Psychiatry 46(9):1192–204 [PubMed: 10560025]

Squire LR, Alvarez P. 1995 Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol 5(2):169–77 [PubMed: 7620304]

Squire LR, Zola-Morgan S. 1991 The medial temporal lobe memory system. Science 253(5026):1380–86 [PubMed: 1896849]

Sripada RK, Garfinkel SN, Liberzon I. 2013 Avoidant symptoms in PTSD predict fear circuit activation during multimodal fear extinction. Front. Hum. Neurosci 7:672 [PubMed: 24146643]

Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. 2013A causal link between prediction errors, dopamine neurons and learning. Nat. Neurosci 16(7):966–73 [PubMed: 23708143]

Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. 2007 A role for oxytocin and 5-HT 1A receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine (“ecstasy”). Neuroscience 146(2):509–14 [PubMed: 17383105]

Trevizol AP, Barros MD, Silva PO, Osuch E, Cordeiro Q, Shiozawa P. 2016 Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis. Trends Psychiatry Psychother. 38(1):50–55 [PubMed: 27074341]

Tronson NC, Taylor JR. 2007 Molecular mechanisms of memory reconsolidation.Nat. Rev. Neurosci 8(4):262–75 [PubMed: 17342174]

van't Wout M, Longo SM, Reddy MK, Philip NS, Bowker MT, Greenberg BD. 2017 Transcranial direct current stimulation may modulate extinction memory in posttraumatic stress disorder. Brain Behav.7(5):e00681 [PubMed: 28523223]

van't Wout M, Mariano TY, Garnaat SL, Reddy MK, Rasmussen SA, Greenberg BD. 2016 Can transcranial direct current stimulation augment extinction of conditioned fear? Brain Stimul. 9(4): 529–36 [PubMed: 27037186]

Verrico CD, Miller GM, Madras BK. 2007 MDMA (ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. Psychopharmacology 189(4):489–503 [PubMed: 16220332]

Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D. 1998 Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. NeuroReport 9(17):3897–902 [PubMed: 9875725]

Watts BV, Landon B, Groft A, Young-Xu Y. 2012 A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimul. 5(1):38–43 [PubMed: 22264669]

Weinberger NM. 1998 Tuning the brain by learning and by stimulation of the nucleus basalis. Trends Cogn. Sci 2(8):271–73 [PubMed: 21227204]

Weisman JS, Rodebaugh TL. 2018 Exposure therapy augmentation: a review and extension of techniques informed by an inhibitory learning approach. Clin. Psychol. Rev 59:41–51 [PubMed: 29128146]

Wolf EJ, Lunney CA, Schnurr PP. 2016 The influence of the dissociative subtype of posttraumatic stress disorder on treatment efficacy in female veterans and active duty service members. J. Consult. Clin. Psychol 84(1):95–100 [PubMed: 26167946]

Wolff K, Tsapakis EM, Winstock AR, Hartley D, Holt D, et al. 2006 Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. J. Psychopharmacol 20(3):400–10 [PubMed: 16574714]

Yamada D, Zushida K, Wada K, Sekiguchi M. 2009 Pharmacological discrimination of extinction and reconsolidation of contextual fear memory by a potentiator of AMPA receptors. Neuropsychopharmacology 34(12):2574–84 [PubMed: 19675539]

Yan T, Xie Q, Zheng Z, Zou K, Wang L. 2017 Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): a systematic review and meta-analysis. J. Psychiatr. Res 89:125–35 [PubMed: 28278422]

Yang Y, Wang J-Z. 2017 From structure to behavior in basolateral amygdala-hippocampus circuits. Front. Neural Circuits 11:86 [PubMed: 29163066]

Young MB, Andero R, Ressler KJ, Howell LL. 2015 3,4-methylenedioxymethamphetamine facilitates fear extinction learning. Transl. Psychiatry 5:e634 [PubMed: 26371762]

Zanoveli JM, Carvalho MC, Cunha JM, Brandão ML. 2009 Extracellular serotonin level in the basolateral nucleus of the amygdala and dorsal periaqueductal gray under unconditioned and conditioned fear states: an in vivo microdialysis study. Brain Res. 1294:106–15 [PubMed: 19646971]

Zbozinek TD, Craske MG. 2017a Positive affect predicts less reacquisition of fear: relevance for long-term outcomes of exposure therapy. Cogn. Emot 31(4):712–25 [PubMed: 26907670]

Zbozinek TD, Craske MG. 2017b The role of positive affect in enhancing extinction learning and exposure therapy for anxiety disorders. J. Exp. Psychopathol 8(1):13–39

Zelikowsky M, Hast TA, Bennett RZ, Merjanian M, Nocera NA, et al. 2013 Cholinergic blockade frees fear extinction from its contextual dependency. Biol. Psychiatry 73(4):345–52 [PubMed: 22981655]

Zeng MC, Niciu MJ, Luckenbaugh DA, Ionescu DF, Mathews DC, et al. 2013 Acute stress symptoms do not worsen in posttraumatic stress disorder and abuse with a single subanesthetic dose of ketamine. Biol. Psychiatry 73(12):e37–38 [PubMed: 23245747]

Zhu M, Nix DE, Adam RD, Childs JM, Peloquin CA. 2001 Pharmacokinetics of cycloserine under fasting conditions and with high-fat meal, orange juice, and antacids. Pharmacotherapy 21(8): 891–97 [PubMed: 11718495]

SUMMARY POINTS

1. Failures of extinction and inhibitory learning are central to several psychiatric disorders including panic disorder, phobias, social anxiety disorder, and posttraumatic stress disorder.
2. Failures of extinction and inhibitory learning can be observed from the molecular to the psychological level of analysis.
3. Successful techniques to augment extinction and inhibitory learning exist and/or are under development at the psychological, device-based brain stimulation, and psychopharmacological level.

FUTURE ISSUES

1. Moving beyond traditional amygdala- and prefrontal cortex-focused exploration of extinction mechanisms may lead to novel neural targets for neurotherapeutic and pharmacological interventions.
2. Machine learning techniques that combine biological data with clinical phenotype data in fear extinction may provide new insights into subgroups of individuals who may benefit the most from particular interventions.