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REVIEW

Neuroimaging of Fear-Associated Learning

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Fear conditioning has been commonly used as a model of emotional learning in animals and, with the introduction of functional neuroimaging techniques, has proven useful in establishing the neurocircuitry of emotional learning in humans. Studies of fear acquisition suggest that regions such as amygdala, insula, anterior cingulate cortex, and hippocampus play an important role in acquisition of fear, whereas studies of fear extinction suggest that the amygdala is also crucial for safety learning. Extinction retention testing points to the ventromedial prefrontal cortex as an essential region in the recall of the safety trace, and explicit learning of fear and safety associations recruits additional cortical and subcortical regions. Importantly, many of these findings have implications in our understanding of the pathophysiology of psychiatric disease. Recent studies using clinical populations have lent insight into the changes in regional activity in specific disorders, and treatment studies have shown how pharmaceutical and other therapeutic interventions modulate brain activation during emotional learning. Finally, research investigating individual differences in neurotransmitter receptor genotypes has highlighted the contribution of these systems in fear-associated learning.

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INTRODUCTION

Fear-associated learning (fear conditioning and extinction) has been used for decades to study the neurocircuitry that underlies emotional learning. Animal studies of fear conditioning have established the regions and systems responsible for emotional processing, and these findings have provided a basis for our understanding of the corresponding neurocircuitry in humans. However, it was with the development of functional neuroimaging techniques in the 1990s that researchers have been able to examine whether the regions found to be involved in emotional learning in rodents are also responsible for similar processes in humans. Fear-associated learning has been used extensively in both animals and humans because it is a convenient, although simplistic, model of the acquisition and maintenance of fear responses, and altered fear learning has been hypothesized to play an important role in the development of anxiety disorders such as posttraumatic stress disorder (PTSD) and specific phobia. The goal of this review is to systematically present the key findings of recent human neuroimaging studies of fear learning and extinction, highlight the emerging neural circuitry involved, and describe the contributions of important modulators of fear-associated learning such as genetic variability and hormones. In addition, the more significant results are highlighted and discussed in light of findings available from animal fear-associated learning studies, as well as other experiments from the human literature.

At its most basic level, fear conditioning involves the association of a neutral conditioned stimulus (CS, often a tone or image) with an aversive unconditioned stimulus (US, often electrical shock or a loud noise). After repetitive presentations of the CS with the US, the CS begins to elicit a conditioned response (CR) that occurs independently of the US. Fear conditioning protocols are similar in animal models and human subjects, and the two paradigms are compared visually in Figure 1. In rats, the CR is typically assessed by measuring freezing or fear-enhanced startle response, and in humans the CR is often assessed via psychophysiological measures such as skin conductance response (SCR), electromyography (EMG), or changes in heart rate. During fear extinction, the previously fear conditioned CS is presented repeatedly without the US, usually in a different environment (context). Over time, the CS is no longer associated with the conditioned response when presented in the extinction context. Fear extinction is thus an effective model of learning, establishing that previously 'dangerous' stimuli are no longer threatening and are rather 'safe'. Furthermore, exposure therapy commonly used in anxiety disorders involves components of fear extinction. Finally, during extinction retention (or recall) and fear renewal, the appropriate, context-specific

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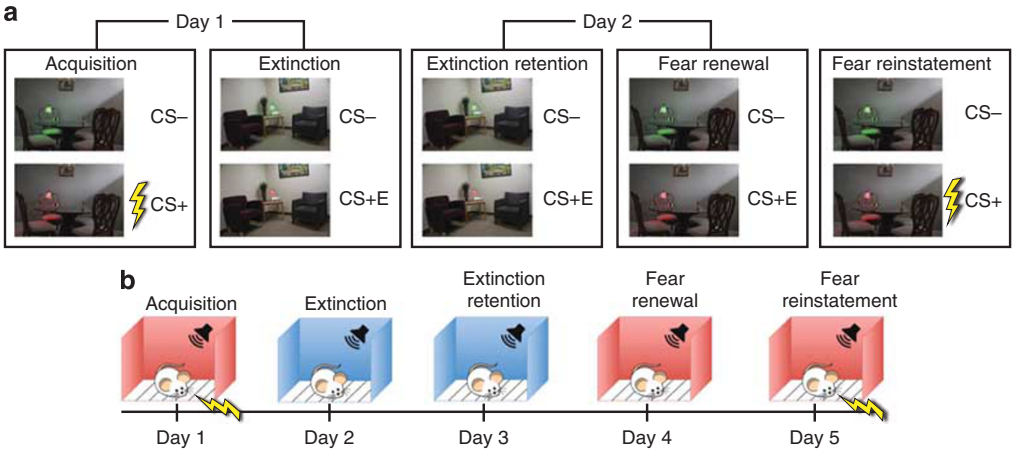

Figure 1. A comparison of typical fear-associated learning paradigms in human neuroimaging (a) and rodents (b).

retrieval of previously acquired fear and safety memory traces is tested. Studying extinction retention and fear renewal in humans elucidates how people use contextual processing to disambiguate how conditioned stimuli indicate threat in the 'danger' context but not in the 'safe' context.

Animal studies of fear-associated learning have provided an understanding of the brain circuits that govern fear conditioning and extinction and, in general, these findings have been corroborated by human neuroimaging studies. Other articles in this issue review findings from animal studies in detail, and describe how these results have shaped our understanding of emotional learning. Briefly, the neurocircuitry conserved across species involves the amygdala as the key region involved in the acquisition of the fear response, receiving inputs from somatosensory cortex, thalamus, and hippocampus that encodes contextual information and compares current contextual cues to previously encoded memories (Maren and Quirk, 2004). Basolateral amygdala (BLA) receives these various sensory and contextual inputs, and the CS–US trace is formed. The centromedial amygdala receives information from BLA, as well as other direct inputs, and projects to the hypothalamus, periaqueductal gray, and other brain stem nuclei, causing the behavioral and physiological changes associated with the CR. Interestingly, it appears that acquisition of the extinction memory also occurs in BLA, whereas hippocampus plays an important role in consolidation of extinction (Quirk and Mueller, 2008), and mPFC seems to be important in the retrieval of the extinction memory (Davis, 1992). In addition, numerous studies suggest that the central amygdala also plays a critical role in fear learning (Li *et al*, 2013; Penzo *et al*, 2014, 2015), and optogenetic studies suggest that different projections to the central amygdala enhance or inhibit fear learning (Tye *et al*, 2011). These complementary pathways could explain how the central amygdala appears to be involved in both fear acquisition and extinction, as separate inputs to this region both increase and decrease the fear response.

NEUROCIRCUITRY OF FEAR CONDITIONING AND EXTINCTION IN HUMANS

To date, the majority of human neuroimaging studies of fear conditioning and extinction have been performed using functional magnetic resonance imaging (fMRI). The fMRI allows researchers to identify the neuronal circuitry involved in performing various tasks by measuring blood oxygen-level dependent (BOLD) effects. More recent work has used functional connectivity measures that analyze the time courses from the BOLD fMRI signal to glean information about how various regions in the brain communicate with one another. A number of studies have used positron emission tomography (PET)-based methodology to assess local changes in metabolism in association with fear conditioning and extinction, and electroencephalography (EEG) and magnetoencephalography (MEG) have occasionally been used to examine changes in cortical electrical activity, both directly and indirectly. These various imaging modalities are usually combined with psychophysiological measures such as skin conductance response (SCR), fear-potentiated startle response, or changes in heart rate in order to assess the CR in humans.

NEUROIMAGING OF FEAR ACQUISITION IN HUMANS

A variety of stimuli have been used in human studies of fear conditioning, with the CS+ typically a distinct visual cue or sound, and the US a mild electrical shock, an aversive loud noise or, less frequently, an unpleasant smell or an uncomfortable visceral stimulus (Gramsch *et al*, 2014; Kattoor *et al*, 2013, 2014). Human fear conditioning studies typically include a second cue (CS−) that is not associated with the US, allowing for a comparison of the CS+ and CS−

responses to isolate the CR using psychophysiological measures and the neural correlates of fear conditioning using neuroimaging techniques.

Early studies using fMRI found differential responses (to CS+ *versus* CS−) in ACC, anterior insula, hippocampus, and amygdala using both trace and delay conditioning paradigms (Buchel *et al*, 1998, 1999; LaBar *et al*, 1998). These findings have been consistently replicated by other research using fMRI (Andreatta *et al*, 2012; Armony and Dolan, 2002; Bach *et al*, 2011; Critchley *et al*, 2002; Knight *et al*, 2005, 2009; Marschner *et al*, 2008; Pohlack *et al*, 2012; Reinhardt *et al*, 2010; van Well *et al*, 2012), PET (Furmark *et al*, 1997), and MEG (Balderston *et al*, 2014; Moses *et al*, 2007). Activation in amygdala, anterior insula, ACC, and left PFC have also been observed while subjects viewed a movie of someone else undergoing fear conditioning (Ma *et al*, 2013; Olsson *et al*, 2007), suggesting similar processes of fear learning can be elicited without directly experiencing the US. Over the course of fear conditioning, amygdala activation typically decreases, as does hippocampal activation during trace conditioning (Buchel *et al*, 1998, 1999; LaBar *et al*, 1998; Reinhardt *et al*, 2010). Meanwhile, ACC and insula activation remain more consistent (Buchel *et al*, 1999), suggesting that amygdala and hippocampus may play a key role during acquisition of the CR, whereas ACC and insula are more involved in CR expression. Furthermore, these results closely resemble findings observed in animal models of fear conditioning (Maren *et al*, 2013) with additional cortical regions implicated mainly in human neuroimaging experiments. One recent large meta-analysis of fear conditioning experiments (Fullana *et al*, 2015) involving 677 subjects further confirmed large-scale activations in ACC/mPFC and the anterior insula, as well as additional cortical regions (supplementary motor area, dorsolateral PFC, and precuneus), ventral striatum, and midbrain. These were interpreted as representing a 'central autonomic-interoceptive' network. Interestingly, amygdala signal was not found in this analysis, and the authors interpret these negative findings (and the strong ACC and anterior insula signals) in light of the fact that human studies primarily involve conscious fear processing. However, the authors also acknowledge that the meta-analytical approach is subject to false negative errors, as well as specific technical difficulties in imaging small structures.

Among the regions implicated by neuroimaging studies of fear-associated learning, the roles of mPFC and, to some degree, the dACC in fear conditioning have been debated, with some studies suggesting that these regions are involved specifically in instructed fear learning. However, a meta-analysis of previous work (Mechias *et al*, 2010), as well as a study that used both instructed fear and Pavlovian conditioning (Maier *et al*, 2012), demonstrated that these regions are activated across a variety of different fear conditioning paradigms. DACC thickness also directly correlates with SCR during conditioning (Milad *et al*, 2007). Thus, dACC and dmPFC appear to play a role in general threat appraisal across a variety of fear conditioning paradigms. The mPFC also appears to be involved in fear acquisition in rodents, but it is not required for fear learning (Burgos-Robles *et al*, 2009; Herry *et al*, 1999; Morgan and LeDoux, 1995). Ventral infralimbic (IL) and dorsal prelimbic (PL) regions that are analogous to the mPFC in humans project to neurons in both central (Quirk *et al*, 2003) and basolateral (Rosenkranz *et al*, 2003) amygdala, with IL seemingly more important in inhibitory innervation to central amygdala (Vertes, 2004). These findings, and in particular the direct connections between mPFC and amygdala, support the notion that mPFC might play a modulatory or supportive role during fear acquisition. In addition, human studies that varied the contingency rate between the CS and US have implicated additional cortical regions in fear conditioning. Studies using high contingency rates show that dlPFC is commonly activated when the threat is highly predictable (Eippert *et al*, 2012; Wheelock *et al*, 2014). This raises the possibility that working memory processes in dlPFC become involved once the CS–US pairing has been explicitly learned. The use of partial reinforcement schedule eliminates this cognitive expectancy effect and limits the role of explicit, declarative memory in the process. Amygdala activation has been observed independent of contingency awareness (Tabbert *et al*, 2011), whereas interestingly, increased CS–US contingency and US expectancy have been associated with lower activation in regions implicated in fear learning, including amygdala, insula, ACC, and vmPFC (Dunsmoor *et al*, 2008; Knight *et al*, 2010; Wood *et al*, 2012, 2013). The aforementioned meta-analysis (Fullana *et al*, 2015) also found that higher reinforcement rates were associated with lower activation in rostral dACC/dmPFC, ventral anterior insula, and right secondary somatosensory cortex. This potentially suggests that when implicit learning has taken place, there is less robust activation of the basic fear-associated learning circuitry described above.

Striatum has also been consistently implicated in fear conditioning studies in humans (Fullana *et al*, 2015). Specifically, one meta-analysis reported that ventral striatum was activated more in subjects who consciously learned the CS–US contingency during conditioning (Klucken *et al*, 2009). These results, as well as results from other neuroimaging studies of decision making (Balleine *et al*, 2007; Hsu *et al*, 2005; Tom *et al*, 2007), are consistent with the hypothesis that the striatum plays a role in assessing the probability of various outcomes. In addition, striatal–amygdala interactions have been observed in avoidance learning during fear conditioning (Delgado *et al*, 2009), suggesting that the striatum accesses information from the amygdala when conscious decision making is occurring in a fearful environment. Furthermore, increased differential ventral striatum activation has also been observed in late acquisition, after explicit representation of the CS–US link had likely been formed (Pohlack *et al*, 2012). Finally, striatal activation has been observed in a study using monetary loss as a US (Delgado *et al*, 2011). All of these results are in line with previous findings and suggest that the striatum's role in

emotional learning might be to assess the probabilities of experiencing the US once the CS–US contingency has been established.

In addition to the ACC, amygdala, insula, hippocampus, mPFC, and striatum that consistently appear in human fear conditioning studies, another region occasionally implicated by neuroimaging studies of conditioning in healthy humans is lateral orbitofrontal cortex (lOFC). Differential lOFC activation has been observed during both instructed and uninstructed fear conditioning tasks (Armony and Dolan, 2002; Gottfried *et al*, 2002; Tabbert *et al*, 2011). The increased activation in lOFC following the CS+ matches findings in various other neuroimaging studies using aversive stimuli that suggest that lOFC responds specifically to negatively valenced stimuli (Milad and Rauch, 2007). Thus, lOFC may play a role in identifying stimuli as negative, but the region's role has not been replicated reliably in fear learning specifically, and in fact deactivations in lOFC have been found in the meta-analysis performed by Fullana *et al* (2015).

Structural studies have also linked increased SCR during fear acquisition to some of the same key regions implicated by functional neuroimaging studies, particularly amygdala (Cacciaglia *et al*, 2014; Winkelmann *et al*, 2015). One study also found that greater posterior insula thickness was associated with a greater CR during conditioning (Hartley *et al*, 2011). However, positive correlations between CR to CS+ during conditioning and regional thickness found in the amygdala and insula have not been universally observed when the association between hippocampal volume and fear acquisition has been examined. Larger hippocampal volumes have been associated with greater ability to discriminate between contexts (Pohlack *et al*, 2012), and smaller hippocampal volumes have been associated with lower conscious cue discrimination but not differences in SCR (Cacciaglia *et al*, 2014).

In agreement with animal studies, contextual fear conditioning studies in humans have also implicated the amygdala, hippocampus, and mPFC as key regions in this process, although the number of studies that have used contextual conditioning in humans is quite limited. One study analyzing differential responses during contextual conditioning found that activation in medial amygdala was coupled with activation in several important fear learning regions, including hippocampus, anterior insula, parahippocampal gyrus, subgenual ACC, and OFC (Alvarez *et al*, 2008). This analysis fits with findings from cued conditioning that identified these regions as areas involved in either fear learning or the recognition of fearful stimuli. Importantly, the hippocampus plays a central role during contextual conditioning, as several studies have established (Alvarez *et al*, 2008; Andreatta *et al*, 2015). One recent study also reported that initial activity in contextual conditioning was found in dorsomedial PFC, dorsolateral PFC, and OFC (Andreatta *et al*, 2015). These results corroborate the current understanding of prefrontal–hippocampal circuitry and connectivity as the key network responsible for contextual processing (Maren *et al*, 2013; Preston and Eichenbaum, 2013).

Functional connectivity analyses have been used more recently to examine the connectivity between brain regions during fear conditioning tasks. Analyzing the time courses of data collected with BOLD fMRI allows for the identification of regions that are activated and deactivated simultaneously, suggesting that these areas are functionally connected. In addition, resting-state fMRI has been used before and after fear conditioning in an attempt to measure the connections between brain regions at rest and how differences in this connectivity might correlate with changes in fear conditioning (Feng *et al*, 2014; Schultz *et al*, 2012; Tzschoppe *et al*, 2014). Studies during or immediately following fear acquisition have found that several regions implicated by neuroimaging studies of cued fear conditioning also show functional connectivity with each other. During conditioning, greater connectivity between amygdala and regions, including hippocampus, vmPFC, dlPFC, and ACC, was associated with higher conditionability (Tzschoppe *et al*, 2014). Immediately following fear acquisition, subjects have shown enhanced amygdala–dACC and hippocampus–insula functional connectivity, as well as less amygdala–mPFC functional coupling (Feng *et al*, 2014), although a different study reported greater amygdala–dmPFC functional connectivity (Schultz *et al*, 2012). In another study, resting dACC metabolism positively predicted differential SCR response and SCR performance was positively correlated with the amygdala–ACC connectivity (Linnman *et al*, 2012). These results support the hypothesis that fear conditioning involves communication and modification of the connections between the same regions implicated in previous neuroimaging studies and studies using rodent models, but the specific mechanism and the exact changes have to be further elucidated.

NEUROIMAGING OF FEAR EXTINCTION IN HUMANS

Neuroimaging studies of fear extinction have provided insight into how humans associate previously aversive stimuli with safety. In concert with the animal literature, amygdala activation has also been observed during extinction learning in humans, and similarly to the observation in the amygdala during fear acquisition, this effect is often graded through the course of extinction (Gottfried and Dolan, 2004; LaBar *et al*, 1998; Phelps *et al*, 2004). BLA is activated when CS–US associations become more predictable (Boll *et al*, 2013), suggesting that BLA encodes information about the relationship between the CS and the US. This is in concert with our understanding of the role of BLA in extinction learning from animal studies (Quirk and Mueller, 2008). Interestingly, a meta-analysis that combined fear extinction with additional emotional regulation experiments confirmed amygdala activation across these types of studies (Diekhof

et al, 2011) with the vmPFC activated specifically in fear extinction studies.

The role of vmPFC in extinction learning has been discussed extensively in recent years. Although these findings have been reported by fewer studies than findings in the amygdala, several studies have replicated findings in rodents suggesting that vmPFC plays a role in extinction learning (Gottfried and Dolan, 2004; Phelps *et al*, 2004). vmPFC activation is also observed in fear reversal tasks (a modified acquisition task that flips the CS+ and CS− halfway through the run) when a CS that used to be associated with fear is now safe (Schiller *et al*, 2008). However, as more neuroimaging studies have included the fear extinction retention phase, evidence is accumulating that vmPFC is particularly important to consolidation of the extinction memory, and the region is especially involved in the recall of extinction in subsequent testing. Evidence from the animal literature (Quirk and Mueller, 2008) also points toward a similar role of vmPFC in extinction. Nonetheless, it is also possible that vmPFC might have an important role in inhibiting the conditioned fear response at the beginning of the extinction phase (Gottfried and Dolan, 2004; Phelps *et al*, 2004).

One commonly studied aspect of fear extinction is prediction error (PE) that occurs when a subject expects a CS–US pairing that does not occur, or expects a CS without US, when they are actually paired. As confirmed by meta-analysis (Garrison *et al*, 2013), PEs are commonly associated with striatal activation (Robinson *et al*, 2013; Schiller *et al*, 2008), and greater striatal activation is seen following PEs that occur in a threatening context *versus* a safe context (Robinson *et al*, 2013). These results are in line with our understanding of the role of striatum in assessing probabilities of aversive outcomes during fear conditioning. SCR response to an omitted US is also associated with striatal activation, as well as activation in ACC, parietal cortex, and insula (Dunsmoor and LaBar, 2012). As extinction consists of repeated CS trials without the US, and the initial omissions of the US are clearly unexpected, it is not surprising that PE-associated regions are activated at least transiently at the beginning of extinction. One study has also reported greater differential activation in amygdala and midbrain while subjects committed PEs (Boll *et al*, 2013) that may represent activation of the expected fear response.

Extinction of trace conditioning appears to also involve dorsolateral PFC (dlPFC), possibly due to the extra time that the trace interval must be held in short-term memory (Ewald *et al*, 2014). Safety learning in humans, a task that associates cue with sense of safety (no US is delivered) rather than with the sense of danger, also seems to involve the dlPFC, and DTI suggests that there may be a connection between dlPFC and amygdala (Pollak *et al*, 2010). These limited studies further support our interpretation of the role of dlPFC as the site of explicit working memory processes in humans that maintain the trace interval, in concert with results from studies of fear acquisition.

NEUROIMAGING OF EXTINCTION RETENTION, FEAR REINSTATEMENT, AND RENEWAL IN HUMANS

More recently, studies have started to examine the extinction retention (or recall) and the fear renewal phases that are usually tested 24 h following the extinction phase. Both examine responses to the extinguished cue (CS+E); however, in extinction retention this cue is presented in the extinction (safe) context, and in fear renewal it is presented in the original fear acquisition (danger) context or a novel context. It has been reported that vmPFC plays an important role in extinction retention (Kalisch *et al*, 2006), corroborating animal work implicating the region in the retrieval of the extinction memory. Studies have also found that the degree of fear extinction retention is positively correlated with vmPFC thickness (Hartley *et al*, 2011; Milad *et al*, 2005; Winkelmann *et al*, 2015). The role of vmPFC in modulating response during extinction retention has also been observed using EEG (Mueller *et al*, 2014), although the limited spatial resolution of EEG makes it difficult to pinpoint activity specifically to the vmPFC. The hypothesis that vmPFC modulates amygdala activation during this process has been recently supported by fMRI findings in patients with vmPFC damage (Motzkin *et al*, 2015), although studies of Vietnam veterans with penetrating brain injuries found that mPFC lesions were associated with decreased prevalence of PTSD (Koenigs *et al*, 2008). Yet, baseline amygdala metabolism has been negatively correlated with activation in vmPFC during extinction retention (Linnman *et al*, 2012). Sleep seems to play an important role in extinction retention, both in terms of SCR and activation of specific brain regions. Subjects who had REM sleep between extinction and extinction retention showed reduced SCR during extinction retention, as well as greater activation of left vmPFC and bilateral lingual gyrus (Spoormaker *et al*, 2010). Deprivation of REM sleep leads to increased SCR during early extinction retention, as well as changes in activation in left middle temporal gyrus (Spoormaker *et al*, 2012).

During fear renewal, a previously extinguished CS is presented either in the fear context (the context that was used for fear acquisition) or a novel context, and no US is presented. Similar to extinction retention testing, the context triggers recall of CS memory; however, here it triggers the fear trace rather than the safety trace. Fear renewal has not been studied using neuroimaging until very recently; however, our lab recently reported greater differential activation of bilateral insula, as well as the cingulate gyrus and precuneus, during fear renewal, suggesting that renewal may recruit this key region of fear acquisition (Garfinkel *et al*, 2014). In an associative learning task, renewal of extinguished associations was correlated with activation in hippocampus and parahippocampal gyrus (Lissek *et al*,

2013), affirming the role of these regions in contextual processing. As expected from the difference in context, these results suggest that in comparison with extinction retention, fear renewal activates more regions in the fear acquisition circuitry.

Fear reinstatement is a process where a previously extinguished CS is reassociated with a US in the same context as conditioning (danger context). Like renewal, reinstatement is not studied as often as acquisition and extinction, but a number of experiments have been reported in the literature. During reinstatement using visceral stimuli, greater differential activation was observed in parahippocampal cortex and posterior cingulate cortex (Gramsch *et al*, 2014; Kattoor *et al*, 2013). In addition, greater activation in response to the CS+ has been observed in hippocampus and thalamus for females *versus* males (Benson *et al*, 2014). Research in patients with hippocampal atrophy (LaBar and Phelps, 2005) corroborates these limited results from neuroimaging studies suggesting that hippocampus might be involved in human fear reinstatement, most likely when subjects are accessing the previously consolidated fear memory trace.

NEUROIMAGING STUDIES OF FEAR CONDITIONING AND EXTINCTION IN PTSD AND ANXIETY DISORDERS

Posttraumatic Stress Disorder

Among various psychiatric disorders, fear conditioning and extinction research has been particularly salient to our understanding of PTSD, phobias, and other anxiety disorders. The major findings from neuroimaging studies of fear-associated learning in patients with psychiatric disorders are outlined in Table 1. With respect to PTSD, fear-associated learning has been utilized both in studies of PTSD patients and in studies using animal models of PTSD with remarkably converging findings. Although alterations during fear acquisition (Linnman *et al*, 2011) or extinction (Fani *et al*, 2012, 2015; Sripada *et al*, 2013) in PTSD patients have been occasionally reported, in general the preponderance of the findings suggest that fear acquisition and extinction are overall preserved in PTSD patients (Garfinkel *et al*, 2014; Milad *et al*, 2009; Shvil *et al*, 2014) as well as in animal models of PTSD (Knox *et al*, 2012).

In contrast, abnormalities in extinction retention and fear renewal have been consistently demonstrated, both in an animal model of PTSD (Knox *et al*, 2012) and in PTSD patients, with associated changes in regional brain activation and volume. PTSD patients have demonstrated lower activation in hippocampus and vmPFC, and greater activation in dACC during extinction recall (Milad *et al*, 2009; Rougemont-Bucking *et al*, 2011), changes that have also been associated with higher SCR to CS+E, signifying impaired recall (Milad *et al*, 2009). Our laboratory demonstrated higher SCR and greater amygdala activity to the CS+E during extinction recall in PTSD patients (Garfinkel *et al*, 2014). We also observed altered fear renewal in PTSD patients, with lower SCR to the CS+E, and lower activity in amygdala and vmPFC as compared with combat controls (Garfinkel *et al*, 2014). As both extinction recall and fear renewal are dependent on contextual disambiguation of the CS, the deficits in both processes strongly implicate abnormalities in contextual processing during fear-associated learning in PTSD. This is also very consistent with the abnormalities observed in hippocampal–mPFC circuitry, as these structures play a key role in the contextualization of memory (Maren *et al*, 2013; Preston and Eichenbaum, 2013). In concert, in an animal model of PTSD, single prolonged stress (Liberzon *et al*, 1997), both abnormal fear renewal (Knox *et al*, 2012), and changes in hippocampus and mPFC (Knox *et al*, 2012) have been consistently demonstrated. Volumetric findings of reduced hippocampal volume, reduced vmPFC volume, and reduced gray matter density in dACC are also associated with PTSD symptomology (Bonne *et al*, 2008; Gilbertson *et al*, 2007; Kuhn and Gallinat, 2013; Rogers *et al*, 2009), further implicating hippocampal–prefrontal involvement. It should be noted that one study of men and women with PTSD found that only men showed deficient extinction recall, and men also showed greater activation in rACC compared with women during recall (Shvil *et al*, 2014). These results reflect findings in studies performed in healthy subjects that demonstrate gender differences in fear-associated learning. In sum, patients with PTSD consistently show impairments in the contextual modulation of both fear extinction and enhancement, and vmPFC seems to be particularly deficient.

Studies investigating the effect of treatment on fear learning and extinction in PTSD patients have been limited thus far, but represent a field with a great opportunity to advance our understanding of the disorder and how to effectively treat patients. Repeated exposure to traumatic memory (RETM) is a commonly used therapy for PTSD based upon fear extinction. One study using functional connectivity measures showed that RETM is associated with strengthened connectivity of the amygdala with regions such as hippocampus and insula, as well as mPFC with insula, and hippocampus with striatum, dorsal cingulate cortex, and OFC (Cisler *et al*, 2014). These results suggest that exposure therapy may change the way that several key regions involved in fear learning communicate with one another, helping to establish the proper associations between cues, context, and the fear response.

Specific Phobia

Generally, functional imaging studies of patients with specific phobia suggest that phobic patients have greater activation in response to phobia-related stimuli in regions such as amygdala, insula, and thalamus (Ipser *et al*, 2013). Specifically, fear conditioning using aversive pictures as unconditioned stimuli has been used to assess differences in emotional learning in patients with specific phobia. One such study found that patients with spider phobia showed

TABLE 1 Summary of Results from Studies of Fear-Associative Learning in Patients with Psychiatric Disorders

Disorder	Phase of fear learning	Reference	Subjects	Key brain regions implicated
Posttraumatic stress disorder (PTSD)	Acquisition	Linnman *et al* (2011)	19 PTSD patients, 24 trauma-exposed controls	Amygdala, dACC, HC, insula
	Acquisition and extinction	Sripada *et al* (2013)	15 PTSD patients	Amygdala, HC, insula, OFG, superior MFG
	Acquisition and extinction[a]	Fani *et al* (2015)	48 African-American females	ACC, cingulum, HC
	Acquisition, extinction, recall	Milad *et al* (2009)	16 PTSD patients, 15 trauma-exposed controls	Amygdala, cerebellum, dACC, HC, vmPFC
	Acquisition, extinction, recall	Rougemont-Bucking *et al* (2011)	18 PTSD patients, 16 trauma-exposed controls	dACC, MFG, PCC, vmPFC
	Acquisition, extinction, recall[b]	Shvil *et al* (2014)	31 PTSD patients, 25 trauma-exposed controls	dACC, insula, vmPFC
	Acquisition, extinction, recall, renewal	Garfinkel *et al* (2014)	14 PTSD patients, 14 combat-exposed controls	Amygdala, insula, thalamus, vmPFC
Specific phobia	Acquisition[c]	Schweckendiek *et al* (2011)	15 Spider phobics, 14 healthy controls	ACC, amygdala, insula, mPFC, thalamus
	Acquisition[c]	Wiemer *et al* (2014)	18 Female spider phobics, 18 healthy controls	Amygdala, dlPFC, insula
Panic disorder (PD)	Acquisition	Tuescher *et al* (2011)	8 PD patients, 8 PTSD patients, 8 healthy controls	ACC, amygdala, dlPFC, HC, insula, PAG, thalamus, ventral striatum
Panic disorder with agoraphobia (PD/A)	Acquisition[d]	Kircher *et al* (2013)	42 PD/A patients, 42 healthy controls	ACC, amygdala, IFG, insula, MFG
	Acquisition	Lueken *et al* (2014)	60 PD/A patients, 60 healthy controls	IFG, insula, midbrain
	Acquisition[d]	Straube *et al* (2014a)	42 PD/A patients, 42 healthy controls	Hippocampus, IFG
	Acquisition[d, e]	Straube *et al* (2014b)	42 PD/A patients	ACC, amygdala, hippocampus, insula, MFG
	Acquisition and extinction[d]	Lueken *et al* (2013)	49 PD/A patients	ACC, amygdala, HC
	Acquisition and extinction[d, e]	Lueken *et al* (2015)	41 PD/A patients	ACC, amygdala
Generalized anxiety disorder (GAD)	Acquisition	Britton *et al* (2013)	14 Anxious youth, 15 anxious adults, 25 healthy youth, 28 healthy adults	sgACC, vmPFC
	Acquisition	Greenberg *et al* (2013b)	32 Female GAD patients, 25 healthy controls	ACC, amygdala, insula, SMA, vmPFC
	Acquisition[a]	Cha *et al* (2014)	32 Female GAD patients, 25 healthy controls	Amygdala, dlPFC, PHG, MFG, thalamus, vmPFC
Schizophrenia	Acquisition, extinction, recall, renewal	Holt *et al* (2012)	20 Schizophrenia patients, 17 healthy controls	HC, insula, PCC, thalamus, vmPFC
Obsessive–compulsive disorder (OCD)	Acquisition, extinction, recall	Milad *et al* (2013)	21 OCD patients, 21 healthy controls	Cerebellum, dACC, HC, insula, PAG, PCC, vmPFC
Attention deficit hyperactivity disorder (ADHD)	Acquisition	Maier *et al* (2014)	17 ADHD patients, 17 healthy controls	Amygdala, dACC, dmPFC

Abbreviations: ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; HC, hippocampus; MFG, medial frontal gyrus; OFG, orbital frontal gyrus; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; sgACC, subgenual anterior cingulate cortex; SMA, supplementary motor area; vmPFC, ventromedial prefrontal cortex.
[a]Examined structural connectivity.
[b]Examined sex differences.
[c]Used phobia-related stimuli.
[d]Examined the effect of cognitive behavioral therapy.
[e]Examined genotypes.

enhanced activation in amygdala to phobia-related conditioned stimuli *versus* nonphobia-related conditioned stimuli (Schweckendiek *et al*, 2011). This greater activation in the amygdala most likely suggests that these patients show an exaggerated fear response to the more individually salient phobia-related stimuli. However, spider phobics also overestimate the correlation between CS and US when the CS is a picture of a spider, and this is associated with greater activation in dorsolateral PFC (Wiemer *et al*, 2014). The larger dlPFC signal here might be reflective of various processes like increased access of working memory (Curtis and D'Esposito, 2003) as subjects process the association between the CS and the US, and volitional control of emotional responses to phobic stimuli (MacDonald *et al*, 2000). Although these changes in amygdala and dlPFC are probably not alterations in the fear learning process *per se*,

they may enhance fear acquisition by increasing the reactivity of the fear neurocircuitry. Additional studies of fear conditioning in specific phobia are necessary to replicate these results and further investigate emotional learning differences in this patient population.

Exposure therapy, which uses elements of fear extinction, is the most widely used treatment for specific phobia and has been studied often with neuroimaging. Exposure therapy has been shown to increase activation in prefrontal cortex during the presentation of phobia-related images, whereas it decreases activation in amygdala, insula, and cingulate cortex (Hauner *et al*, 2012). At 6 months after completion of exposure therapy, prefrontal cortex activation was lower as well. A small meta-analysis of three neuroimaging studies in patients with specific phobia (Goossens *et al*, 2007; Paquette *et al*, 2003; Straube *et al*, 2006) found that exposure therapy leads to lower activation in right frontal cortex, limbic cortex, and basal ganglia (Ipser *et al*, 2013). This was interpreted to suggest that, over time, exposure therapy reduces the reactivity in several key regions of fear neurocircuitry. These changes are probably not indicative of an alteration in the process of fear learning, but rather a reduction of the salience of fearful stimuli over the course of treatment.

Panic Disorder

A relatively small number of studies have investigated fear conditioning in patients with panic disorder (PD), as well as patients with panic disorder with agoraphobia (PD/A). Interestingly, inferior frontal gyrus (IFG) has been implicated in fear conditioning in PD/A patients. During acquisition, greater differential activation of IFG has been seen in PD/A patients *versus* controls (Lueken *et al*, 2014), and cognitive behavioral therapy (CBT) reduced this activation in PD/A patients (Kircher *et al*, 2013). Further studies found that PD/A patients receiving CBT treatment also showed greater activation of the hippocampus during fear acquisition, and this was positively correlated with treatment outcome (Lueken *et al*, 2013; Straube *et al*, 2014a). These studies also found that CBT treatment is associated with lowered connectivity between the left IFG and the left hippocampus across time. These results are interesting, as previous work in healthy subjects typically does not implicate IFG in fear-associated learning and may suggest that patients with panic disorder recruit additional regions of frontal cortex to modulate fear acquisition. IFG is a crucial region in the ventral attention network and appears to be activated during cue detection (Hampshire *et al*, 2010). Another study in patients with PD demonstrated greater activity to CS− during conditioning in ventral striatum, amygdala, subgenual cingulate, and periaqueductal gray (Tuescher *et al*, 2011). Taken together, these results might indicate that panic disorder may be associated with altered attention to cues, as well as inappropriate fear responses to safe cues, but more research is clearly required, and these interpretations have to be tested directly.

Generalized Anxiety Disorder and Social Anxiety Disorder

Generalization of fear conditioning has been postulated to play a key role in the development of generalized anxiety disorder (GAD), and fear-associated learning has been examined in GAD using neuroimaging. The studies often used a modified conditioning task (generalization of conditioned threat) where subjects were presented with a variety of cues that were similar in various degrees to the CS (ie, rectangles of varying widths), but only the CS was associated with the US. Several studies investigating the generalization of conditioned fear have shown that insula reactivity increases as stimuli become more similar to the US (Dunsmoor *et al*, 2011; Greenberg *et al*, 2013a; Lissek *et al*, 2014). Greater SCR associated with generalized fear has also been correlated with amygdala activity (Dunsmoor *et al*, 2011). In another generalization task, greater differential activation was observed in insula, ACC, and striatum when subjects expected a US that was not delivered (Dunsmoor and LaBar, 2012). These results consistently implicate insula and other key areas of the fear learning circuitry in the generalization process, reinforcing the role of these regions in cue discrimination. On the other hand, it was reported that hippocampus and vmPFC reactivity increases as stimuli become less similar (Lissek *et al*, 2014). Furthermore, connectivity analyses suggest that these changes are modulated by the hippocampus.

Several experiments using the generalization of conditioned threat task have examined potential neural deficits in patients with GAD. Patients with GAD showed less discrimination between the fear and safety cues, especially in vmPFC (Greenberg *et al*, 2013b). This decrement has also been correlated with lower vmPFC thickness as well as with lower connectivity between vmPFC and thalamus and IFG (Cha *et al*, 2014). If vmPFC is indeed involved in discrimination between safe and danger signals, this is consistent with the reports of increased trait anxiety association with lower ventral PFC activation during fear acquisition, as well as lower connectivity between vPFC and hippocampus (Indovina *et al*, 2011). Consistent with this, patients with GAD (and social phobia) showed lower vmPFC and subgenual ACC activation during cognitive appraisal of previously conditioned CS+ as compared with healthy subjects (Britton *et al*, 2013). These results are interesting, as the role of vmPFC in fear responses is generally seen as inhibitory; therefore, these deficits might be indicative of broad deficits in the inhibition of the fear response.

Only one study of fear-associated learning has focused on the effect of social anxiety on fear learning and extinction. In a population of healthy subjects, there was a slight negative correlation between social anxiety and vmPFC activation during extinction recall, similar to deficits observed in other anxiety or fear disorders (Pejic *et al*, 2013). More work needs to be done to understand whether patients with

social anxiety disorder actually show impairments in fear-associated learning, and whether these impairments differ from those observed in other anxiety disorders and PTSD.

Neuroimaging Studies of Fear Learning and Extinction in Other Psychiatric Disorders

Fear conditioning and extinction experiments have also been used to study emotional learning in other psychiatric disorders. Although some findings point toward changes in fear-associated learning and in regions implicated in fear and anxiety regulation like vmPFC, dACC, and amygdala, overall the very small number of studies in these disorders clearly render these findings as preliminary and require replication. Two studies have reported deficiencies in extinction recall, similar to changes observed in PTSD, in patients with schizophrenia, with lower differential vmPFC activation *versus* controls (Holt *et al*, 2009, 2012). Schizophrenic patients also showed less activation in hippocampus, thalamus, and posterior cingulate gyrus during acquisition, but it is unclear whether these differences are indicative of a fear learning deficit or differences in fear reactivity that are associated with schizophrenia symptomatology. Other studies in animal models and human patients suggest that hippocampal deficits play a major role in schizophrenia pathophysiology (Harrison, 2004). These changes in hippocampal functions can clearly affect contextual processing and fear-associated learning downstream. Impaired extinction recall has also been reported recently in a single study of patients with obsessive–compulsive disorder (OCD) (Milad *et al*, 2013). Patients with OCD showed reduced vmPFC activation during recall, but they also exhibited reduced activation in caudate and hippocampus during fear conditioning. However, symptom severity was positively correlated with vmPFC response, and inversely correlated with dACC response. These results are opposite of observations in PTSD, and the experimenters speculate that these findings may be indicative of a coping mechanism that severe OCD patients are using to avoid aversive stimuli. Further studies are needed to ascertain the significance of these differences in regional activations.

Fear learning has also been studied in attention deficit hyperactivity disorder (ADHD). No difference in response was exhibited in an uninstructed fear learning paradigm, but ADHD patients showed lower SCR and lower dACC activation in response to the CS+ (Maier *et al*, 2014). In addition, ADHD patients showed higher amygdala activation to the CS− *versus* controls. These differences could indicate reduced attention to aversive stimuli that healthy subjects find more salient, making the response to CS+ and CS− more similar. Finally, recent work has investigated changes in fear conditioning and extinction in irritable bowel syndrome (IBS), a gastrointestinal disorder with psychological factors. Greater activation of prefrontal cortex and amygdala in response to the CS+ (Icenhour *et al*, 2015) was reported in IBS, as well as differential hippocampal activation during reinstatement. These differences may be indicative of the increased salience of specific aversive cues to IBS patients, as this study used rectal distension as the US. Using visceral pain as the US in subjects who typically have increased gastrointestinal discomfort should enhance the response in the fear learning neurocircuitry, but may not signify an actual change in fear learning. As only a single neuroimaging study of fear learning in patients with each of these disorders (OCD, ADHD, and IBS) has been reported, further research is needed to replicate these results.

NEUROBIOLOGICAL FACTORS AND INDIVIDUAL DIFFERENCES IN FEAR-ASSOCIATED LEARNING

The studies described above have examined the contribution of various brain regions and networks to different phases of fear-associated learning in both healthy controls and patients with psychiatric disorders. However, it is also clear from animal studies, work in other emotional tasks, and the neuropathology seen in psychiatric patients that substantial individual differences are present in fear-associated learning. One of the potential contributors to these differences is the individual level of various hormones and neurotransmitters that have an important role in regulating fear-associated learning. Although the formation and consolidation of fear and extinction traces are believed to involve cellular and system plasticity, ie, synaptic reorganization, the relevant hormonal and neurotransmitter level can have a critical role in expression or modulation of this synaptic plasticity. In this context, key molecules involved in the stress response and its regulation have been studied extensively. For example, one study focused on *NR3C1* and *CRHR1* genotypes containing greater numbers of minor alleles that have been previously associated with hypersensitivity to glucocorticoids, decreased cortisol levels, and increased PTSD symptomology (Bachmann *et al*, 2005; Hauer *et al*, 2011). Researchers found that these genotypes controlling expression of the glucocorticoid and corticotropin-releasing hormone receptors, respectively, were associated with greater activation in amygdala during conditioning, reduced activation in prefrontal cortex during extinction, and changes in coupling between the two regions (Ridder *et al*, 2012). Thus, increased sensitivity to glucocorticoids may lead to impairments in fear learning and extinction that manifest in psychiatric disorders.

Cortisol and other LHPA hormones appear to modulate fear learning, but their effect (at least in some regions) may vary based upon gender and differences in levels of sex hormones. Numerous studies suggest that there might be an interaction between stress and sex hormones in fear-associated learning, with hydrocortisone administration enhancing fear acquisition in women and inhibiting fear acquisition in men (Merz *et al*, 2010; Tabbert *et al*, 2010). In men, cortisol has been shown to reduce CS+/CS− differentiation in hippocampus, thalamus, and insula but appears

to enhance this differentiation in women (Tabbert *et al*, 2010). A similar pattern was observed when stress was induced by the Trier Social Stress Test. Across gender, stress enhanced CS+/CS− differentiation in the hippocampus and inhibited activation in the medial frontal cortex (Merz *et al*, 2013). However, stress reduced CS+/CS− differentiation in the amygdala and nucleus accumbens in men but enhanced differentiation in women taking oral contraceptives (low estrogen and progesterone levels) (Merz *et al*, 2013). In men, hydrocortisone administered 45 min before fear extinction also led to greater SCR and diminished differential CS+/CS− activation in amygdala, MFC, and nucleus accumbens (Merz *et al*, 2014), suggesting that cortisol might impair both extinction and conditioning, specifically in men.

Several experiments have examined the direct effects of gender and/or sex hormones on fear learning and extinction. One neuroimaging study of fear learning in women found that women with high levels of estrogen showed greater activation of vmPFC during fear extinction than women with low levels of estrogen, as well as greater activation of vmPFC and amygdala during extinction recall (Zeidan *et al*, 2011). These results are in concert with rodent studies (Chang *et al*, 2009; Zeidan, *et al*, 2011) demonstrating that high levels of estrogen enhance extinction learning and retention. Similarly, human studies have associated low levels of estradiol in women with impaired fear inhibition (Glover *et al*, 2013) and impaired extinction learning (Glover *et al*, 2012; Milad *et al*, 2010; Wegerer *et al*, 2014). However, neuroimaging studies of the differences between genders have not yielded consistent results. One study reported similar SCR responses in men and women during fear acquisition but greater BOLD response in right amygdala, rACC, and dACC in women (Lebron-Milad *et al*, 2012). During extinction recall, on the other hand, men showed greater differential activation in bilateral rACC as compared with women (Lebron-Milad *et al*, 2012). This complexity is further highlighted by findings from a different study that showed that women with low estrogen and progesterone levels have shown greater CS+/CS− differentiation during fear extinction in amygdala, ACC, vmPFC, and thalamus, compared with both women with high estrogen and progesterone levels, and as compared with men (Merz *et al*, 2012). The emerging picture is thus quite complex, with gender differences that cannot simply be understood in terms of circulating levels of gonadal steroids. The preponderance of animal and human findings suggest that, in females, higher levels of estrogen enhance extinction learning and retention and affect activation in brain regions commonly involved in fear-associated learning. Nonetheless, further research is required to address gender differences and the various effects of sex hormones.

Among the neurotransmitter systems, variability in the serotoninergic system has most often been reported to affect fear-associated learning. The short allele 5-HTTLPR (a serotonin transporter) genotype has been associated with greater response to CS+ during fear conditioning in amygdala, insula, thalamus, and occipital cortex (Klucken *et al*, 2013), and subjects with the short allele 5-HTTLPR genotype and history of stressful life events have shown greater reactivity in insula in response to CS+ during fear conditioning (Hermann *et al*, 2012; Klucken *et al*, 2013). 5-HTTLPR polymorphisms have also been shown to affect connections between amygdala and the perigenual ACC (Pezawas *et al*, 2005). Concerns have been raised, however, about the reproducibility of genetic association studies (Munafò *et al*, 2009), and thus further research is necessary to confirm the results from these experiments. However, in support of serotonin's role in fear learning, serotonin-depleted subjects have shown lower activation in amygdala and OFC in response to CS+ during fear acquisition (Hindi Attar *et al*, 2012). Together, these reports raise the possibility that serotoninergic transmission might play an important role in fear learning, such that lower serotonin response impairs activation in critical emotional learning regions, particularly the insula and amygdala.

Limited data have also implicated genetic variability in dopaminergic, glutamatergic, and BDNF systems in fear-associated learning. Subjects with a variant of an NMDA receptor gene (*GRIN2A*) have shown lower amygdala response during fear learning (Cacciaglia *et al*, 2013). In a different study, subjects with the 9R allele of DAT1, a dopamine transporter gene predominantly expressed in the striatum, had significantly higher extinction rates, as well as stronger activation following prediction errors in the ventral striatum (Raczka *et al*, 2011). The Val66Met single-nucleotide polymorphism (SNP) of the brain-derived neurotrophin (BDNF) gene has been associated with impaired fear extinction in mice and humans (Soliman *et al*, 2010), but neuroimaging studies of Val66Met carriers only found activation changes in amygdala and ACC during fear acquisition (Lonsdorf *et al*, 2014). No changes were seen in fear extinction. These studies have not been replicated, and (as stated earlier) results from genetic association experiments are often variable. However, these limited findings do suggest that, like serotonin, individual differences in NMDA and BDNF may affect fear learning processes in regions like the amygdala. Differences in the dopaminergic system, on the other hand, may affect fear learning by altering associated processes in striatum that assess the probability of aversive outcomes, in concert with the role of dopamine transmission in risk and reward assessment.

More recently, evidence of the role of cannabinoids in the modulation of fear-associated learning has been accumulating, particularly with respect to fear extinction. Genetically, variants in the human FAAH gene (that controls expression of an endocannabinoid-degrading enzyme) have been associated with habituation to threat in the human amygdala (Gunduz-Cinar *et al*, 2013), and participants who received synthetic tetrahydrocannibinol (THC) showed greater vmPFC and hippocampal activation during extinction recall (Rabinak *et al*, 2014). In addition, synthetic THC administration has since been associated with enhanced basolateral and superficial amygdala connectivity to rostral ACC and mPFC (Gorka *et al*, 2015). These results, observed in a

number of laboratories, suggest that cannabinoids might serve as interesting modulators of fear learning and extinction, as well as potential therapeutic agents for some disorders involving the same processes.

Studies of individual differences in patients with psychiatric disorders have the potential to elucidate how hormones and neurotransmitter systems contribute to emotional learning deficits. Currently, only a handful of neuroimaging studies have investigated genotype associations with differences in the fear learning neurocircuitry in patient populations. Studies in PD/A patients, for example, reported that inhibitory ACC–amygdala coupling during fear conditioning was seen specifically in CBT responders with the 5-HTTPLR L/L genotype (Lueken *et al*, 2015). In contrast, a serotonin receptor 1A gene (*HTR1A*) 'risk' genotype was associated with reduced effects of CBT on differential activation in ACC and insula during conditioning (Straube *et al*, 2014b). These reports support the idea that individual variance in serotonin signaling modulates fear learning, but more work is needed to elucidate the relationship between serotonin receptor genotypes and psychiatric symptomology. In the same vein, the effects of gender/sex hormones on fear extinction was examined in patients with PTSD, and increased fear-potentiated startle was linked to low estrogen levels (Glover *et al*, 2012). Thus, future research combining neuroimaging, fear learning tasks, and measures of individual differences in hormone levels in patient populations may be useful in uncovering the complex mechanisms responsible for emotional learning deficits in psychiatric disorders.

SUMMARY AND FUTURE RESEARCH DIRECTIONS

Functional neuroimaging studies of fear-associated learning have been very useful in delineating the neural circuits involved in human emotional learning by: (1) confirming the roles of key brain regions identified by prior animal studies in the support of fear and safety learning in humans; (2) further extending our understanding of the neural circuitry involved in explicit emotional learning in humans by delineating the unique role of brain regions involved in processes like anticipation, working memory, probability assessment, and prediction error; and (3) starting to identify the key biological systems (genes, neurotransmitters, and hormones) that modulate emotional learning and contribute to individual differences in conditioning, extinction, and extinction retention. Beyond confirming the key roles of ACC, amygdala, insula, hippocampus, and vmPFC in fear conditioning, extinction, and extinction retention, these studies highlight the contributions of regions like the striatum and dlPFC to specific aspects of cognitive processing of explicit fear-associated learning like interoceptive awareness, probability assessment, working memory, and anticipation. Although only a handful of meta-analytic studies involving fear-associated learning have been reported so far in the literature, the convergence of evidence from different studies provides initial support to the overall picture outlined above. Furthermore, these findings underscore the complexity involved in the emotional learning process in humans and the need to carefully consider future experimental design to allow valid interpretations. As explicit cognitive processing during emotional learning is ubiquitous in humans, we believe that this contribution might be particularly important to the understanding of human emotional learning and human psychopathology. This is especially true considering the (at times) liberal application of insights gained from rodent studies. Moreover, studies of individual differences have also demonstrated that levels of specific neurotransmitters, as well as stress and sex hormones, modulate regional brain activation during fear learning and extinction, both adding levels of complexity and providing a potential link to the abnormalities in fear-associated learning that might be present in various psychiatric conditions. These initial findings are new, exciting, and carry great promise, as they might help in integrating genetic, molecular, cellular, and brain circuitry information in understanding emotional learning, as well as understanding the mechanisms underlying many psychiatric disorders that involve abnormalities in related systems and functions.

Human fear-associated learning studies have also started delineating disorder-specific abnormalities in the brain circuitry of PTSD, GAD, specific phobia, and schizophrenia patients. The majority of published work has naturally involved disorders of fear and anxiety, as abnormal fear-associated learning had been postulated to contribute to their pathophysiology. Interestingly, the converging findings in PTSD patients suggest the presence of abnormalities in brain regions that modulate extinction retention and renewal, potentially implicating altered contextual processing and the hippocampal-prefrontal circuit. Clearly, additional research is needed to replicate existing findings and to extend these findings to additional patient populations. Furthermore, experiments using fear-associated learning tasks also offer a potentially useful model to examine the effect of therapeutic interventions. For example, one recent study of cognitive reappraisal showed that this strategy seems to reduce fear acquisition and enhance fear extinction, based on psychophysiological and regional activation changes in structures like the ACC, insula, hippocampus, and vmPFC (Hermann *et al*, 2014). This type of work, as well as studies described earlier that have examined changes in fear learning following CBT in various patient populations, suggest that fear-associated learning might prove to be a useful and less subjective tool to examine and compare therapeutic effects. Similarly, investigating the effect of pharmacological interventions like cannabinoids and antidepressants on fear-associated learning may provide insight into how modification of neurotransmitter systems involved in emotional learning processes can be potentially harnessed to achieve better therapeutic effects. Finally, the effect of sleep on fear learning and extinction is another exciting and

relatively novel area of research that is currently gaining momentum. One recent study, for example, reported an association between vmPFC activity during conditioning and REM sleep the following night, as well as an association between hippocampal activity during conditioning and stage 2 and stage 4 sleep (Spoormaker *et al*, 2014). Sleep before fear extinction has been shown to enhance extinction learning in spider phobics (Pace-Schott *et al*, 2012) and healthy controls, with accompanying changes in hippocampal and amygdalar activation (Hauner *et al*, 2013). These types of results, together with a growing understanding of sleep physiology and its underlying cellular and molecular processes, might offer an opportunity to understand the key role that sleep plays in healthy and abnormal emotional learning. These studies are particularly relevant given the prevalence of sleep disturbances in psychiatric disorders. Future studies examining sleep architecture, as well as other phases of fear-associated learning (in both healthy subjects and patient populations), should provide valuable insight into these relationships.

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