Published in final edited form as:
Horm Behav. 2013 July ; 64(2): 380–389. doi:10.1016/j.yhbeh.2013.01.016.

Fear learning and memory across adolescent development *Hormones and Behavior* Special Issue: Puberty and Adolescence

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Abstract

Throughout the past several decades, studies have uncovered a wealth of information about the neural circuitry underlying fear learning and extinction that has helped to inform treatments for fear-related disorders such as post-traumatic stress and anxiety. Yet, up to 40 percent of people do not respond to such treatments. Adolescence, in particular, is a developmental stage during which anxiety disorders peak, yet little is known about the development of fear-related neural circuitry during this period. Moreover, pharmacological and behavioral therapies that have been developed are based on mature circuitry and function. Here, we review neural circuitry implicated in fear learning and data from adolescent mouse and human fear learning studies. In addition, we propose a developmental model of fear neural circuitry that may optimize current treatments and inform when, during development, specific treatments for anxiety may be most effective.

Keywords

Adolescence; Development; Fear; Extinction; Anxiety; Amygdala; Hippocampus; Prefrontal Cortex; Sensitive Period

Introduction

Throughout the past several decades, advances in psychiatry and neuroscience have shed light on the underlying neural circuitry implicated in anxiety and stress related disorders. The majority of this research has focused on understanding atypical fear responses in the mature adult brain. As a result, pharmacological and behavioral therapies have been developed to target physiologically mature neural circuitry. Although existing therapies and medications offer benefits to adult patients, a comparative lack of knowledge about the development of fear neural circuitry may limit successful treatment outcomes in children and adolescents (Liberman et al., 2006). Many of these disorders have the potential to persist into adulthood (Kim-Cohen et al., 2003; Pine et al., 1998) and become chronic and debilitating when left untreated (Liberman et al., 2006).

Over 75 percent of adults with fear-related disorders met diagnostic criteria as children and adolescents (Kim-Cohen et al., 2003; Pollack et al., 1996). The prevalence of emotional

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disorders and anxiety disorders specifically, is heightened during adolescent years, occurring in as many as one in ten adolescents (Costello et al., 2005; Kessler et al., 2005; Newman et al., 1996). Due to insufficient or inaccurate diagnosis and a dearth of pediatric and adolescent specialized treatments, fewer than one in five anxious children or adolescents are expected to receive treatment for their disorders (Merikangas et al., 2010), leaving a vast number with inadequate or no treatment (Keller et al., 1992; Liberman et al., 2006).

The increased frequency of anxiety disorders in adolescent populations highlights the importance of understanding the neural mechanisms underlying emotion regulation during this developmental phase. This period of development reflects a transition from dependence on parents to relative independence that begins with pubertal onset (Graber and Brooks-Gunn, 1996) and coincides with significant socio-emotional, psychological, and physical changes (Schulz et al., 2009) related to hormonal fluctuations and sexual maturity (Sisk and Zehr, 2005). Pubertal onset involves a surge in gonadal hormone release, which contributes to development of sexual characteristics and sexual interest (Sisk and Zehr, 2005). The effects of puberty and chronological age are often difficult to disentangle due to the wide variability in pubertal onset across individuals (Doremus-Fitzwater et al., 2012; Rah et al., 2009). Relevant to emotional and anxiety research, pubertal maturation has been associated with elevated physiological reactivity to emotional cues (Silk et al., 2009; Spear, 2009) and alterations in limbic circuitry (Schulz et al., 2009). These findings highlight the importance of understanding the development of neural systems associated with the emergent behaviors of adolescence.

The very nature of adolescent development serves to launch an organism toward reproductive success and survival (Insel and Fernald, 2004) and is associated with increased exploratory behavior and emotional reactivity (Spear, 2000). As such, it is probable that within this developmental transition period exist neural and behavioral characteristics divergent from those of dependent children and independent adults. We present examples of divergent behavior in adolescents in the context of changes in plasticity of neural systems. Plasticity refers to activity-dependent changes in synaptic strength with functional organization of neuronal circuits that enable an organism to adapt its behavior in the face of changing environmental demands. Age-related differences in plasticity may be apparent during transition periods (e.g. adolescence), when previously adaptive behaviors may gradually become incompatible with a new range of experiences that arise across the lifespan. These differences may arise due to maturational constraints of developing brain regions and their connectivity and due to hormonal changes that can alter plasticity, especially under stressful situations (Foy, 2011).

In this review, we outline neural circuitry implicated in fear learning and memory, highlight developmental findings from both human and mouse model studies, and suggest a developmental model of adolescent fear neural circuitry. Specifically, we examine changes in fear learning and memory during the transition into and out of adolescence, a time when anxiety disorders have been shown to peak. We use a neurodevelopmental approach to understand how behavior is translated across species. This approach requires the use of behavioral paradigms that can be used both across development and species. Fear learning paradigms are advantageous in this regard, as they can be used to assess fear responses equivalently in humans and mice and across development. Strong cross-species preservation of the neural circuitry implicated in fear learning is supported by human and nonhuman animal studies, further bolstering the translational credibility of rodent models for studying fear regulation and extinction (Gottfried and Dolan, 2004). Although fear learning and extinction have been examined during infancy and adulthood (Milad and Quirk, 2012; Moriceau and Sullivan, 2006), only recently have they been examined during adolescence. We present evidence from two forms of fear conditioning - cued fear and contextual fear

learning. These studies highlight nonlinear changes in fear regulation and extinction and their neural correlates across development.

Neural circuitry involved in fear learning and memory

Acquisition and expression of conditioned fear

During the late 1800's, it was observed that monkeys with damage to their temporal lobes exhibited aberrations in their emotional reactivity (Brown and Schafer, 1888) and in 1937, Kluver and Bucy demonstrated that monkeys with temporal lobe resections displayed many preternatural behaviors, including complete loss of fear (Kluver and Bucy, 1937). In the late 1950's, it was discovered that nuclei buried within the temporal lobe were responsible for these changes in fear behavior (Maren, 2001; Phelps and LeDoux, 2005; Weiskrantz, 1956).

As interest in the study of emotion regulation grew, it was observed that humans with sustained damage to the amygdala and hippocampus, resulting from unilateral anteromedial temporal lobe resection, experienced impaired fear acquisition compared to control subjects (LaBar et al., 1995). Healthy subjects elicit a fear response as evidenced by increased skin conductance response to a neutral stimulus previously paired with an aversive one. Temporal lobectomy patients are unable to elicit a similar fear response, despite the fact that their verbal description of the conditioned stimulus (CS)–unconditioned Stimulus (US) connection is intact (LaBar et al., 1995).

Non-human animal studies have validated structural-functional relationships observed in patient populations. These studies show that unilateral amygdala damage in fear-conditioned rats results in attenuated fear expression, as evidenced by decreased levels of freezing behavior (LaBar and LeDoux, 1996). Lesion, inactivation, electrophysiological, molecular, and pharmacological studies have further confirmed a key role of the amygdala in fear acquisition (Fanselow and Kim, 1994; Maren et al., 1996; Quirk et al., 1997; Rogan et al., 1997; Sigurdsson et al., 2007).

Figure 1 provides a schematic representation of limbic circuitry implicated in fear learning and memory. During standard cued fear conditioning paradigms, both sensory and auditory thalamic inputs converge on the lateral nucleus of the amygdala simultaneously or in close temporal proximity (Collins and Pare, 2000; Quirk et al., 1995; Sotres-Bayon et al., 2006). After repeated pairings, the conditioned stimulus presentations alone are capable of eliciting activity within the lateral nucleus. The basal and lateral nuclei make up the primary sensory interface involved in fear learning and acquisition, while the central nucleus is the amygdala's interface to fear expression systems (Maren, 2001).

Detailed characterization of limbic circuitry in rodents, has demonstrated that once integrated by the basolateral amygdala, relevant sensory information responsible for eliciting a behavioral or autonomic response is relayed to the central nucleus both directly and indirectly (Pitkanen et al., 2000; Sotres-Bayon et al., 2006). After the intra-amygdaloid message has been conveyed from the basal lateral nuclei to the central nucleus, the central nucleus elicits various responses via its divergent projections to downstream efferent structures. These projections target hypothalamic and brainstem nuclei responsible for engaging autonomic responses such as heart rate variability, alterations in blood pressure, respiration, freezing behavior, acoustic startle, and glucocorticoid release (Maren, 2011).

Importantly, context has a profound effect on the acquisition of conditioned fear and the resulting fear memory. Projections from the hippocampus, specifically the CA1 region, to the basal nucleus of the amygdala are implicated in contextual information processing during fear acquisition (Bouton et al., 2006; Phelps and LeDoux, 2005) and lesions to dorsal

hippocampus disrupt both acquisition and expression of contextual fear (Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Selden et al., 1991). By detecting environmentally relevant cues, the hippocampus can alter contextual fear directly and also indirectly influence amygdala-specific cued fear, as animals are capable of using contextual cues to retrieve the meaning of a CS appropriate to a given context (Fanselow and Dong, 2010; Maren, 2001). Via its projections to the basal nucleus of the amygdala, the hippocampus plays an important role in determining the emotional salience of an isolated cue. Whether a cue is experienced in a safe or threatening context, the hippocampal-basal amygdala network can influence subseuent fear responses via projections to the amygdala's central nucleus, by either enhancing or dampening fear behavior.

Whereas patients with selective amygdala damage lack the prototypical autonomic response associated with fear-conditioning (LaBar et al., 1995), patients with selective damage to the hippocampus are unable to verbally describe any CS-US association, despite being able to elicit appropriate autonomic responses to the CS (Bechara et al., 1995). This double dissociation of fear conditioning and declarative knowledge involving the hippocampus and amygdala in humans parallels findings observed in non-human animal models which show impaired performance on fear conditioning tasks after amygdala and hippocampal lesions (LeDoux, 2000).

Detailed molecular, biochemical, and electrophysiological studies in the rodent have uncovered a wealth of knowledge about the underlying neural mechanisms for fear learning. Increased spike-firing in amygdala neurons (Quirk et al., 1995), and long-term potentiation (LTP), or enduring synaptic plasticity, have been shown to occur at synapses in the hippocampus and amygdala during fear conditioning and expression (McKernan and Shinnick-Gallagher, 1997; Rogan and LeDoux, 1995; Rogan et al., 1997; Tsvetkov et al., 2002). Glutamate receptor signaling in the amygdala and hippocampus, through both NMDA and AMPA receptors, has also been shown to be crucial for fear acquisition and expression (Kiyama et al., 1998; Maren et al., 1996; Milad and Quirk, 2012; Miserendino et al., 1990; Tsien et al., 1996), further confirming the role of these two structures in fear acquisition and expression. Disruption of downstream signaling cascades, including protein kinase A (PKA) (Bourtchouladze et al., 1998), mitogen activated protein kinase (MAPK), and phosphatidylinositol 3 kinase (PI3K) in the amygdala and hippocampus has also been shown to disrupt learning in both contextual and auditory fear conditioning paradigms (Chen et al., 2005; Mahan and Ressler, 2011; Schafe et al., 1999). The vast knowledge base of physiological, molecular, and electrophysiological correlates of fear acquisition provide researchers with a foundation to examine underlying mechanims of typical fear learning, and also to study potential abberations in these mechanims during atypical fear learning as seen in anxiety and stress disorders. Understanding typical as well as atypical fear learning, from a systems level view to the fine molecular details, may help uncover not only how abnormal fears are formed but also how they may be ameliorated or extinguished.

Extinction of conditioned fear

Once a given CS-US fear association has been acquired, it can be consolidated from an initial short-term association to a more permanent long-term memory. The fear expression of this initial CS-US association can be modified through various manipulations. One such manipulation is to present repeated presentations of the CS alone, in the absence of any US. These unpaired CS presentations lead to the formation of a new memory trace, residing in parallel with the initial memory. When strong enough, this new memory trace, serves to suppress fear expression. This new learning requires a reappraisal of the once-threatening CS, shifting the cue from one of danger to one of safety. The previously fearful behavioral response becomes extinguished after multiple presentations without the US resulting in a diminished conditioned response. This extinction process requires top-down prefrontal

control and interactions between both cortical and subcortical limbic regions (LeDoux, 2000; Maren and Quirk, 2004; Morgan et al., 1993).

Cortical regions implicated in extinction of conditioned fear include areas within prefrontal cortex that are important for appropriately adjusting behaviors when the emotional significance of a given cue changes (Sotres-Bayon et al., 2006). The ventromedial prefrontal cortex (vmPFC), in particular, has been shown to be important for making the switch from fear expression to fear suppression during fear extinction learning and retention (Milad and Quirk, 2002; Pare et al., 2004; Santini et al., 2004). Distinct subregions within the vmPFC have been differentially implicated in the expression and extinction of conditioned fear (Santini et al., 2008; Sierra-Mercado et al., 2011; Sotres-Bayon and Quirk, 2010). Specifically, the dorsally located prelimbic cortex (PL) is associated with production of conditioned fear responses and expression of conditioned fear behaviors (Corcoran and Quirk, 2007), whereas the more ventrally located infralimbic cortex (IL) is associated with suppression of conditioned fear responses (Burgos-Robles et al., 2009; Hefner et al., 2008; Knapska and Maren, 2009; Milad and Quirk, 2012; Milad et al., 2004). The infralimbic cortex can dampen fear responses via projections to a cluster of inhibitory intercalated cells located within the amygdala. These inhibitory intercalated cells modulate activity in the central nucleus, thereby effecting the central nucleus's projections to downstream brainstem targets and their resulting autonomic responses (Milad and Quirk, 2012).

During extinction learning, threat cues are rarely experienced in isolation and are often presented in an environment that can either enhance or reduce a cue's potential threat. Depending on previous experience with a context, whether safe or dangerous, the aversive nature of a potential threat cue can be modulated. Importantly, the ventromedial prefrontal-hippocampal network can modulate extinction learning by detecting contextual cues present in the surrounding environment, and therefore, priming the extinction positively or negatively (Hugues and Garcia, 2007; Kalisch et al., 2006; Laurent and Westbrook, 2009). With continued presentations of a given CS in the absence of a US during extinction, the vmPFC suppresses amygdala circuitry, particularly through its excitatory glutamatergic projections to intra-amygdala inhibitory GABAergic interneurons (Pare et al., 2004). These inhibitory interneurons can be activated by PL or LA neurons during fear conditioning to ultimately lead to decreased fear expression and associated autonomic responses. During extinction learning, however, a subset of intercalated cells can be activated by inputs from infralimbic cortex which is modulated by the hippocampus, and lead to downstream active inhibition of output neurons in the central nucleus, thus eliminating fear expression and the associated physiological responses.

This hippocampally-mediated prefrontal control of amygdala responses increases an organism's flexibility to respond appropriately to danger cues across different environments as measured by context dependent fear conditioning. Responses to potential threat cues in the amygdala and medial prefrontal cortex are inversely related (Hare et al., 2008; Kim et al., 2003) and decreased connectivity between the two regions has been associated with anxiety in adults (Pezawas et al., 2005; Shin et al., 2004). Post-traumatic stress disorder (PTSD) populations, with persistently generalized and inappropriate fear responses, tend to show reduced mPFC and hippocampal volume and activity and exaggerated amygdala reactivity (Bremner, 1999; Milad et al., 2009; Rauch et al., 2006). The complex interactions between the vmPFC, amygdala, and hippocampus during extinction of previously conditioned fear memories is necessary for adjusting behavioral and autonomic responses in rapidly changing environments. Impaired distinction between a danger versus safety cue, or generalization of both, can result in inappropriate fear responses often observed in psychiatric disorders such as PTSD or anxiety (Mahan and Ressler, 2011).

In adult PTSD patients, the failure to consolidate extinction memory has been correlated with a reduction in vmPFC volume and vmPFC activity, as well as hyperactivity in the amygdala (Liberzon and Sripada, 2008; Shin et al., 2004). Importantly, vmPFC-hippocampal connections are bidirectional and alterations in one region likely result in improper feedback and regulation of the other regions, highlighting the importance of employing integrated treatment approaches that equally utilize vmPFC and hippocampal inputs to the amygdala. Re-exposing an individual to specific threat cues during extinction training, while also incorporating hippocampal-dependent contextual elements may be one way to better target the vmPFC-hippocampal-amygdala circuit.

Adolescent fear – behavioral and molecular findings in mice and humans

Advances in the developmental neurobiology of emotion regulation have yielded substantial evidence of protracted development of prefrontal regions relative to phylogenetically older regions (Casey et al., 2005; Giedd et al., 1999; Giedd et al., 1996; Gogtay et al., 2004). Consistent with developmental changes in structural maturation, immature prefrontal functioning and top down control of subcortical regions has been observed in adolescents relative to adults during emotional contexts (Eshel et al., 2007; Hare et al., 2008; Monk et al., 2003). Healthy adolescents exhibit increased generalization of threat cues during fear conditioning tasks (Lau et al., 2011) and enhanced amygdala reactivity to threat occurs in adolescent populations with anxiety disorders compared to non-anxious individuals (Guyer et al., 2008; Lau et al., 2008; Monk et al., 2008).

The investigation of fear acquisition and extinction across development in humans has been limited due to the nature of aversive conditioning paradigms. These paradigms typically use electric shock as the US, which are not deemed appropriate for use with pediatric populations. As such, investigators have used loud tones (Craske et al., 2008), aversive air puffs to the larynx (Grillon et al., 1998), or air puffs paired with loud screams and aversive faces (Schmitz et al., 2011). The use of a naturalistic cue, that has come to be associated with the presence of a threat with experience (e.g., a frightened face, a scream), for a US may confound developmental studies as our experiences over a lifetime are not equivalent but rather limited by age and opportunity for such experiences. For example, a child may have fewer experiences of dangerous situations or threats than an adult, and an anxious child may have many more experiences of threat than a non-anxious child. These experiences will differentially impact fear-related circuitry (Casey et al., 2013). Because variations with US delivery and behavioral assessment in humans may yield variability in results (Glenn et al., 2011), animal models have been helpful in studying developmental effects of fear learning.

Studies examining the mechanisms of hippocampal-dependent contextual fear and amygdala-dependent cued fear acquisition and extinction in rodent models have traditionally focused on early developmental stages (Moriceau and Sullivan, 2006; Rudy, 1993; Rudy and Morledge, 1994) using pre-weaned or pre-adolescent rodents and adult rodents. Recently, developmentally intermediate ages have been investigated due to the translational relevance of studying fear during adolescent development, when increased prevalence of fear related disorders typically emerges.

Development of Cued Fear Learning and Extinction

A number of studies have begun to examine amygdala-dependent, cued fear extinction in rats across development taking advantage of what is known about developmental differences in brain maturation in humans. These studies show that inactivation of the mPFC fails to disrupt long-term extinction in pre-adolescent, postnatal day 17 (P17) rats, yet inactivation of mPFC does disrupt this memory in P24 rats (Kim et al., 2009). Extinction training in these young age groups leads to increased levels of pMAPK in both the prelimbic and

infralimbic cortices, suggestive of non-specific, global mPFC activity, as opposed to the inverse pattern of IL/PL activity typically seen with successful adult extinction retention. In both postnatal day 24 fear-conditioned rats, a single block of CS presentations leads to robust freezing, but does not lead to increased pMAPK in either the IL or PL, contrary to the expected enhancement of PL activity typically seen in fear memory recall (Kim et al., 2009).

Developmental studies of innate fear regulation in rodents demonstrate that during expression of innate, or unconditioned, fear, the mPFC of infant rats is neither active nor responsive while the PL becomes active in pre-adolescence but does not yet regulate freezing behavior. In contrast, the PL in adolescents becomes functionally connected with the amygdala and its downstream brainstem targets, as shown by its ability to begin regulating fear expression and freezing behavior (Chan et al., 2011). These developmentally altered patterns in the mPFC activation are independent of amygdala activity, which suggest that mPFC neural circuitry develops enhanced capacities for fear regulation as an animal matures (Chan et al., 2011). In addition, injections of anterograde tracers placed into the BLA of developing rats show that amygdalo-cortical connectivity is late maturing, with fiber density reaching a plateau circa P45, thus confirming that maturation of this circuit continues into adolescence (Cunningham et al., 2002).

In classical conditioning experiments, adolescent mice have been shown to exhibit increased acquisition of cued fear compared to pre-adolescent and adult mice, despite having equal levels of anxiety-like behavior, as assessed by open field (Hefner and Holmes, 2007). Fear responses during adolescence, typically defined in the rodent as the phase surrounding the 10 days prior to sexual maturation at postnatal day P40, (Adriani et al., 1998; Laviola et al., 1999; Spear, 2000), have been found to be resistant to extinction (McCallum et al., 2010; Pattwell et al., 2012). Adolescent rats require either twice as many extinction trials or a pharmacological intervention, such as the NMDA-agonist D-cycloserine, to achieve reductions in fear expression comparable to younger or older rats (McCallum et al., 2010). This blunted fear extinction during adolescence is associated with a lack of activity in prefrontal cortex, specifically IL, as assessed by pMAPK immunohistochemistry (Kim et al., 2011) or c-Fos immunohistochemistry (Pattwell et al., 2012) compared to younger and older ages. Electrophysiological recordings at IL and PL synapses across development reveal that a fear-conditioning induced potentiation of PL synapses present in adult mice is absent in adolescent mice, Furthermore, extinction-induced enhancement of IL synaptic plasticity in adult mice, is lacking in adolescent mice (Pattwell et al., 2012).

Studies with human subjects also show age-dependent differences in fear reactivity across adolescent development. Tasks using fearful or screaming faces result in heightened amygdala activity (Hare et al., 2008) and fear learning (Glenn et al., 2011) in human adolescents compared to younger children. Diminished fear extinction, relative to children and adults, has been shown in human adolescents, during a task of cued fear conditioning involving aversive sounds (Pattwell et al., 2012) and parallels rodent findings as shown in Figure 2. Taken together, these studies reveal a non-linear pattern in fear extinction learning with blunted regulation of amygdala-dependent fear responses during fear extinction in adolescents.

These findings of diminished fear extinction may help provide insight into the heightened prevalence of anxiety disorders during adolescence. Furthermore, this adolescent extinction data may help inform current treatment approaches, as the major non-pharmacologic therapy for anxiety disorders, cognitive-behavioral therapy (CBT) relies on extinction principles. If the capacity for successful extinction learning is attenuated during specific developmental period, therapies relying primarily on extinction techniques may prove ineffective for treating anxiety disorders in adolescent populations.

Impact of Early-life Stress on fear learning and extinction—Early-life stress, as induced by maternal separation in young rat pups, causes a shift in the typically attenuated adolescent extinction curve (Callaghan and Richardson, 2012). Specifically, rats that were previously subjected to early life stress show typical extinction learning during adulthood, yet exhibit attenuated extinction learning earlier in development, during pre-adolescent ages. These findings suggest fine-tuning of the circuitry with these early experiences may map onto human forms of childhood anxiety. In the rodent experiments, a shift in the developmental window of extinction failure, typically observed during adolescence, can occur in younger, pre-adolescent rats subjected to early-life stress. These data suggest that maladaptive experiences, such as early-life stress, may have the potential to increase susceptibility for anxiety by shifting a developmental window associated with increased fear reactivity

Role of the Hippocampus and mPFC in Cued Extinction Learning—The importance of the mPFC in cued extinction learning and extinction retention is widely accepted and inactivation of the mPFC alone is enough to impair the retrieval of cued extinction memory (Sierra-Mercado et al., 2006). Importantly, and often disregarded, however, is that inactivation of the hippocampus alone before extinction training also leads to impaired retrieval of cued extinction memory the following day (Corcoran et al., 2005) suggesting that mPFC may be an important target of the hippocampus for modulating extinction learning and recalling extinction memory in rodents and humans (Kalisch et al., 2006; Quirk and Mueller, 2008). Furthermore, contextual modulation of amygdala activity requires the hippocampus (Maren and Hobin, 2007). It is important to note that in cases where cued extinction retention and the degree of successful extinction are assessed in the same context as where conditioning took place, it may be difficult, even impossible, to claim that poor extinction learning solely results from insufficient vmPFC regulation.

Many of the extinction paradigms in the existing literature fail to account for important hippocampal contributions associated with contextual information. Distinct populations of neurons exist in the BA for triggering the activation of neuronal circuits responsible for integrating sensory and contextual information (Herry et al., 2008). These populations of “fear neurons,” and “extinction neurons,” as they are called, are differentially connected with the hippocampus and mPFC. Particularly, hippocampal inputs to BA preferentially target the “fear neurons,” over the “extinction neurons,” suggesting that hippocampal input to these neurons may override the retrieval of cued or contextual extinction memory, a likely contributor to the phenomenon of fear renewal (Hobin et al., 2006).

Fear renewal, or the fear that returns upon experiencing a reminder outside of the extinction context, remains a major obstacle for clinical treatment of anxiety disorder in humans (Milad et al., 2005; Rodriguez et al., 1999) and may be the result of tipping the balance between activation between specific neuronal circuits in the hippocampus and amygdala (Herry et al., 2008). This clinical observation lends support for finding better treatment methods, perhaps through further investigation of hippocampally-mediated techniques, such as contextual-based extinction.

Development of Contextual Fear Learning and Extinction

From a developmental perspective, the notion of hippocampal involvement in mediating both contextual and cued fear processing is a promising one. While the hippocampal cytoarchitecture is well established by 34 weeks in utero in the human, (Arnold and Trojanowski, 1996), development of the structure has been shown to continue through adolescence in both rodents and non-human primates (Benes et al., 1994; Kornack and Rakic, 1999).

Longitudinal scans of children and adolescents, between the ages of four and twenty-five years, reveal that postnatal hippocampal maturation is not homogenous and that distinct maturational profiles exist for specific subregions (Gogtay et al., 2006). While overall hippocampal volume remains constant throughout these ages, posterior subregions of the hippocampus show volumetric enlargement over time while anterior regions undergo substantial volumetric reductions. The cause of these heterogeneous volume changes remains unknown, but it is hypothesized that they may be due to differences in neuronal proliferation, synaptic production and/or pruning, myelination, or glial alterations and may parallel differences in functional development (Gogtay et al., 2006). Of note, the anterior region of the hippocampus, which exhibits decreases in volume as a function of age, is reciprocally connected to the prefrontal cortex (Cavada et al., 2000), amygdala (Petrovich et al., 2001; Pitkanen et al., 2000), and hypothalamic-pituitary-adrenal axis (Bannerman et al., 2004) - regions implicated in fear and anxiety.

This heterogeneous postnatal development of hippocampal subregions, specifically the volumetric decreases observed in the anterior region, correlates with contextual fear data showing that contextual fear expression during pre-adolescent ages is intact, temporarily suppressed during adolescence, and then reemerges again during adulthood (Pattwell et al., 2011) (Figure 3), supporting the notion that development is not a linear process in which neural maturation occurs uniformly in one direction or another. Rather, an intricate reciprocal balance between neural development in one brain region may lead to alterations in another region. Convergent adolescent and adult rodent contextual fear data further highlight the importance of the developing hippocampus in mediating fear responses. The aforementioned literature on human and non-human primate hippocampal development suggests a developmentally sensitive fear circuitry model, depicted in Figure 4.

A proposed model of adolescent neural circuitry in fear learning and memory—Crosstalk between CA1 and CA3 regions of the hippocampus is required for contextual fear expression and cued fear extinction in the adult brain. The adult brain integrates specific hippocampally-mediated contextual inputs, thalamic sensory inputs, and prefrontal cortical inputs within intra-amygdalar circuits to produce an appropriate behavioral response. As shown in Figure 4C and Figure 4D, the successful retrieval of cued fear memories across pre-adolescence, adolescence, and adulthood (McCallum et al., 2010; Pattwell et al., 2011; Pattwell et al., 2012), suggests that sensory inputs to the lateral amygdala (LA) are functional across postnatal development. As younger, pre-adolescent mice are unimpaired on contextual fear tasks, one possibility is that pre-adolescent mice rely more heavily on available sensory inputs, and are relying solely on elemental cues of odor, texture, etc., to retrieve the contextual memory rather than its more complex configural elements. The successful retrieval of contextual fear memories during early, pre-adolescent ages, as previously shown in Pattwell et al., 2011, suggests that aforementioned age-dependent volumetric decreases in CA1 region of the hippocampus have yet to occur. In pre-adolescence mice, a potential over-abundance of active synapses between CA1-PL and CA1-BA allow for successful retrieval and expression of contextual fear. As the mice transition to adolescence, and reorganization of CA1 connection, combined with developmental synaptic pruning may interfere with ability of the adolescent mouse's ability to retrieve contextual fear memories.

Rodent data has also shown that bidirectional PL-amygdala synapses mature earlier than IL-amygdala synapses (Chan et al., 2011). This delayed maturation of IL-amygdala connectivity may also account developmental differences in ability to express contextual fear. If the amygdala has not yet received any inhibition from IL inputs during pre-adolescence, PL-amygdala synaptic activation is dominant, allows for expression of fear during contextual tasks. During adolescent development in both rodents and humans,

however, vmPFC maturation can be observed (Cunningham et al., 2002; Gogtay et al., 2004) and as IL-amygdala synapses are refined, activity in PL-amygdala circuits must override IL-amygdala inputs, allowing for fear expression. Because CA1-PL connectivity is necessary for this interaction, and because CA1 undergoes volumetric decreases throughout adolescent development (Gogtay et al., 2006), which may be indicative of changes in synaptic pruning or myelination, CA1 inputs to BA and PL are not sufficient for fear expression in adolescent mice (as shown by the shading out of CA1 and the resulting dotted arrows in Figure 4C and Figure 4D). This hypothesis is also supported by blunted responses in synaptic neurotransmission in BA of P29 mice upon contextual fear tests, as shown via electrophysiological experiments (Pattwell et al., 2011) and preliminary data in which there is little c-Fos activity in CA1, PL, and BA in P29 fear-conditioned mice upon contextual fear retrieval compared to control mice (Pattwell et al., unpublished data).

Importantly, CA1 is responsible for retrieval of fear memories, while CA3 is responsible for fear acquisition and encoding of fear memories. Consistent with behavioral findings, adolescent mice acquire and consolidate contextual fear memories, despite exhibiting a lack of fear retrieval and expression. Preliminary c-Fos data suggest that CA3 is active during retrieval in adolescent fear-conditioned mice (Pattwell et al., unpublished data), supporting the notion that the fear memory has been encoded and retrieved, allowing for retrieval at later, post-adolescent ages when the neural circuitry underlying fear learning and memory has reached stabilized, adult-like structural and functional maturation. Further, it has been shown that inactivation of CA1 can interfere with CA3 communication with extra-hippocampal regions (Lee and Kesner, 2004), such as the amygdala. With little or no fear expression and corresponding CA1-PL or CA1-BA inputs, contextual extinction and contextual reconsolidation update appear to work remarkably well in adolescent mice to persistently attenuate fear memories, possibly due to a lack of CA1 inputs, allowing for intra-amygdalar activation of ITC cells with little or no competing input from CA1 or PL. CA1-vmPFC connectivity has also been shown to be important for retrieval of cued fear extinction in and it is possible that the lack of extinction learning and retention of extinction memory in adolescent mice (as described in (McCallum et al., 2010; Pattwell et al., 2012)) may result from a similar mechanism, consistent with the developmental role of CA1 maturation in fear learning and integration with IL/PL circuits.

Concluding Remarks

In this review, we outlined the neural circuitry implicated in fear learning, discussed developmental differences in fear learning during the transitions into and out of adolescence, and suggested a plausible developmental model of fear neural circuitry that may underlie adolescent fear behaviors. In particular, contextual fear is expressed during early, juvenile ages, suppressed during adolescence, and re-emerges during adulthood (Pattwell et al., 2011). Additionally, cued fear extinction learning is intact during early ages in both mice and humans, blunted during adolescence, and intact again in adulthood (McCallum et al., 2010; Pattwell et al., 2012). These findings suggest a nonlinear pattern in the development of fear learning during which adolescent behaviors differ from prototypical fear responses associated with both younger and older ages (Casey et al., 2008).

An evolutionary hypothesis for the suppression of contextual fear is consistent with the demands associated with adolescent development. Adolescence is a time of exploration when one must leave the safety and stability of their environment in search of reproductive success, thus, a suppression of contextual fear may contribute to the fearlessness required for exploring new environments that is typically seen with this age group (Spear, 2000). As specific danger cues remain relevant during this novelty-seeking period, cued fear expression remains intact and is resistant to extinction during adolescence. Combined, these

behaviors allow the adolescent to remain both exploratory and cautious, thus optimizing chances for survival and success.

As we have outlined throughout this review, the brain of an adolescent is developmentally distinct from that of a child or an adult. As such, the adolescent brain experiences and interprets associations differently than children and adults during daily life. In the event of traumatic situations, it should be noted that the same features of adolescent brain development designed for survival and evolutionary success may contribute to a vulnerability for anxiety disorders that are treatment resistant such as PTSD or anxiety. The lack of fear extinction associated with adolescent development, may hinder responses to traditional psychotherapy, such as CBT. Because CBT desensitizes an individual to anxiogenic stimuli through repeated exposures (i.e. extinction learning), future studies aimed at examining whether this technique is effective during adolescence, when extinction learning is attenuated, may provide insight into optimal treatment strategies for anxious individuals. Clinical studies of youth rarely extend into adulthood or examine age-effects in non-linear terms, so additional research is needed to explore whether anxious adolescents will benefit similarly to children and adults during CBT.

If non-linear development of the neural circuitry implicated in fear learning has evolutionarily primed adolescents to exhibit attenuated fear extinction, resistance to classical extinction therapies may put anxious adolescents at a clinical disadvantage. CBT relying on exposure therapy may need to be reconsidered as a treatment option for developing populations, who lack the ability to extinguish previously acquired associations. At the dawn of individualized psychiatric treatment, when treatments are now being tailored for patients with various genetic polymorphisms (Mahan and Ressler, 2011), new avenues in individualized medicine may also need to incorporate the age of the patient to determine when, during development, specific treatments may be most effective.

Acknowledgments

This work was supported by the Sackler Institute (B.J.C., S.S.P.); the DeWitt-Wallace Fund of the New York Community Trust (F.S.L.); National Institutes of Health Grants HD055177 (B.J.C. and S.S.P.) and MH079513 (B.J.C. and F.S.L.).

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Highlights

- Adolescence is a developmental stage when anxiety disorders are peaking.
- Current therapies for anxiety disorders rely on fear extinction principles.
- Development of neural circuitry underlying extinction learning continues through adolescence.
- Parallel human and rodent experiments reveal attenuated extinction during adolescence.

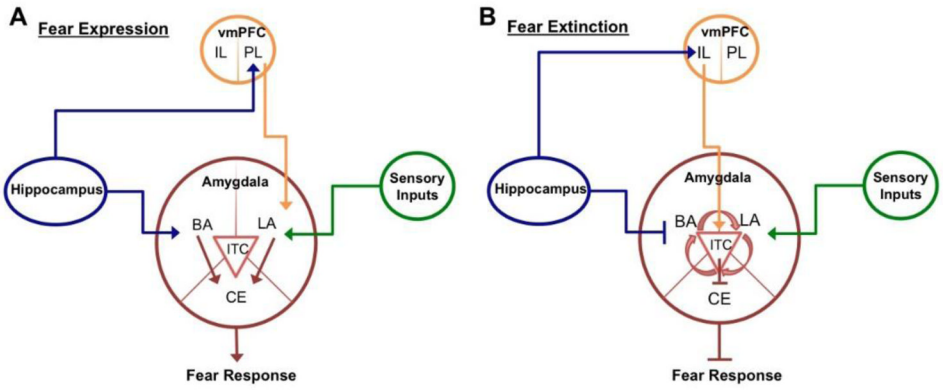

Figure 1. Neural circuitry of fear expression and extinction

(A) During acquisition and expression of conditioned fear, projections from PL and thalamic nuclei (mediating converging sensory information) excite LA neurons, while hippocampal projections (mediating contextual inputs) lead to excitation of BA neurons directly or indirectly via connections with PL. LA and BA neurons activate CE output neurons, which project to downstream brainstem and hypothalamic nuclei responsible for mediating physiological responses, resulting in fear expression. (B) During extinction of conditioned fear, hippocampal projections (mediating contextual inputs) lead to divergent excitation of IL neurons and inhibition of BA neurons. IL projections directly activate GABAergic ITC cells within the amygdala. Integration of ITC, BA, and LA inputs during extinction results in a suppression of CE output neurons, resulting in a lack of physiological response and suppression of fear expression. Arrowheads delineate pathway excitation; straight ends delineate pathway inhibition. (BA, basal amygdala; LA, lateral amygdala; CE, central amygdala; vmPFC, ventromedial prefrontal cortex; PL, prelimbic cortex; IL, infralimbic cortex; ITC, intercalated cells). *For simplicity, connection arrows are delineated as being unidirectional, although bidirectional projections exist.

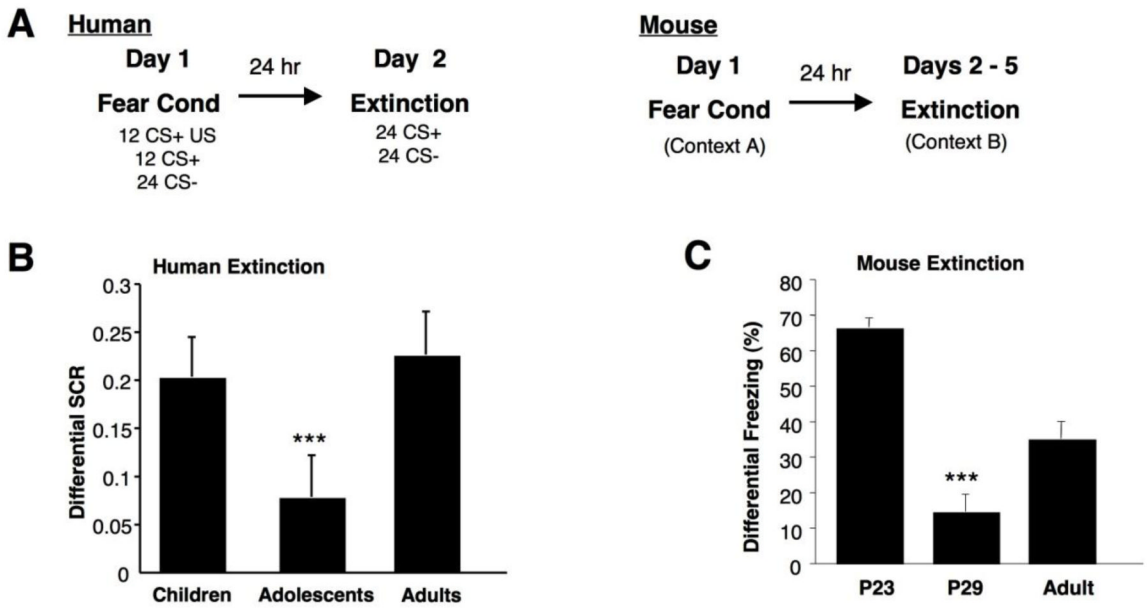

Figure 2. Cued extinction learning and spontaneous recovery across development in mice and humans

(A) Behavioral paradigms for parallel fear conditioning experiments in humans and mice. (B) Analysis of extinction indices [(Averaged first two extinction trials) – (Averaged last two extinction trials)] reveals a main effect of age group for humans, such that adolescents display attenuated fear extinction learning compared to children and adults, [adolescent . 05916 ± 0.06904; children .25435 ± 0.04839; adults 0. 22510 ± 0.05931). (C) A lack of extinction learning and retention of extinction memory in is observed in adolescent mice, as displayed by a significantly decreased differential extinction indices [(Day 1, Tone 1) – (Day 4, Tone 5)] compared to older and younger ages, [(P23 66.5% ± 2.75; P29 14.72% ± 4.79; P70 35.17% ± 4.89). Adapted from Figure 1 of Pattwell et al., 2012.

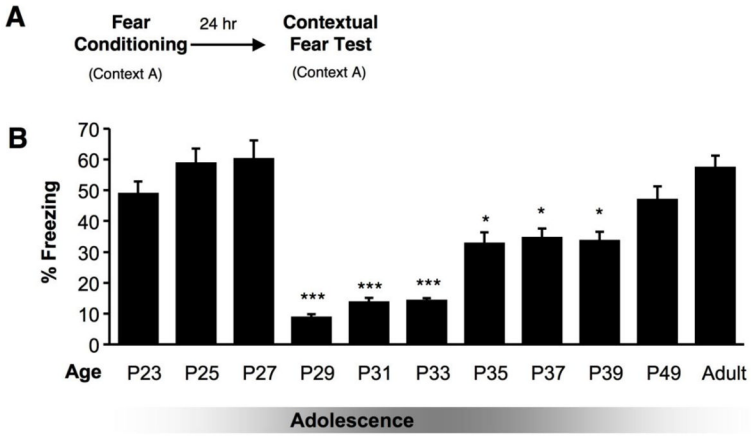

Figure 3. Hippocampal-dependent contextual fear memory across adolescent development

(A) Mice of all ages were fear conditioned (fear cond) with three tone-shock pairings. Twenty-four hr later, they were returned to the conditioning context (Context A) and freezing behavior was scored. (B) Adolescent mice (P29 – P39) froze significantly less than both younger (P23 – P27) and older (P49 – P70) mice. All results are presented as a mean ± SEM. determined from analysis of 7–10 mice per group (fear conditioning) and 28 mice per group (novel object placement), (*$p < 0.05$, ***$p < 0.001$). Adapted from Figure 1, Pattwell et al., 2011.

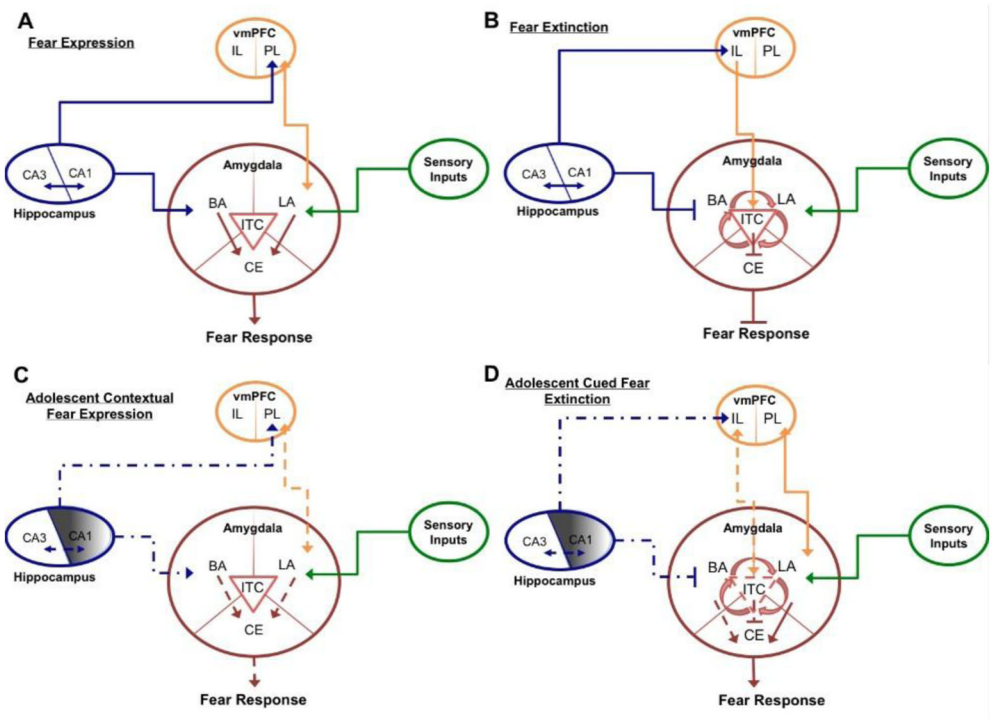

Figure 4. Developmental neural circuitry of fear expression and extinction

Diagrammatic representation of adult neural circuitry implicated in (A) fear expression and (B) fear extinction. (C) A lack of contextual fear expression in adolescent mice can be traced to immature CA1. Without proper CA1-PL and CA1-BA inputs, there is a lack of downstream activation of CE output neurons, resulting in a diminished or suppressed fear response. (Weak signals and low functional connectivity represented by dotted lines). (D) A lack of CA1 excitatory input to IL combined with a lack of CA1 inhibitory input to BA, typical in cued fear extinction, results in reduced inhibition of CE output neurons, resulting in fear expression and a lack of extinction. Arrowheads delineate pathway excitation; straight ends delineate pathway inhibition. (BA, basal amygdala; LA, lateral amygdala; CE, central amygdala; vmPFC, ventromedial prefrontal cortex; PL, prelimbic cortex; IL, infralimbic cortex; ITC, intercalated cells). *For simplicity, connection arrows are delineated as being unidirectional, although bidirectional projections exist.