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Nonlinear Developmental trajectory of fear learning and memory

Elizabeth C. King^{1,2}, Siobhan S. Pattwell², Alice Sun², Charles E. Glatt², and Francis S. Lee^{1,2}

¹Department of Pharmacology, Weill Cornell Medical College of Cornell University, New York, New York.

²Department of Psychiatry, Weill Cornell Medical College of Cornell University, New York, New York.

Abstract

The transition into and out of adolescence represents a unique developmental period during which neuronal circuits are particularly susceptible to modification by experience. Adolescence is associated with an increased incidence of anxiety disorders in humans,^{1–3} and an estimated 75% of adults with fear-related disorders met diagnostic criteria as children and adolescents.^{4,5} Conserved neural circuitry between rodents and humans has facilitated neurodevelopmental studies of behavioral and molecular processes associated with fear learning and memory, which lie at the heart of many anxiety disorders. Here, we review the non-linear developmental aspects of fear learning and memory during a transition period into and out of adolescence and provide a discussion of the molecular mechanisms that may underlie these alterations in behavior. We provide a model that may help to inform novel treatment strategies for children and adolescents with fear-related disorders.

Keywords

adolescence; anxiety; fear; memory; extinction; retrieval

Introduction

Recent advances have fostered the discovery of a wealth of knowledge about the neural circuitry involved in anxiety and stress-related disorders. Substantial research efforts have focused on characterizing exaggerated or inappropriate fear responses in the mature adult brain, resulting in clinical treatments that have been implemented based on their efficacy in mature neural frameworks. Recent studies have begun to delineate the complex nature of fear conditioning and extinction in children and adolescent human patients.^{6,7} Studies of fear acquisition in healthy children and adolescents find that adolescents demonstrate greater fear-potentiated startle responses relative to children.⁷ Similarly, adolescents display patterns of fear generalization more similar to adults than to children.⁷ These results suggest

Address for correspondence: Elizabeth King, Weill Cornell Medical College of Cornell University, 1300 York Ave, Box 244, New York, New York 10065. elk2019@med.cornell.edu.

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that there are dramatic developmental changes in fear learning that occur in the transition from childhood to adolescence that warrant further investigation. Despite these recent advances in adolescent fear research, there remains a relative dearth of knowledge surrounding the developmental trajectory of fear circuitry, which may hinder similarly successful treatment outcomes in children and adolescents.⁸ Early life environmental and physiological stressors are also capable of altering the development of this circuitry, which further highlights the necessity for a more complete understanding of fear circuitry dynamics from childhood through adolescence and on to adulthood.⁹ This review will present recent findings demonstrating that the circuitry implicated in fear regulation has a nonlinear developmental trajectory, particularly surrounding the transitional phase of adolescence. Through a close examination of the various behavioral and physiological aspects of fear regulation in adolescence, we suggest that more effective age-tailored treatment strategies for children and adolescents with anxiety and stress-related disorders can be developed.

The developmental transition from parental dependence to the relative independence and sexual maturity of adolescence is highly conserved across mammalian species.¹⁰ Adolescent animals differ markedly from younger and older animals in various aspects of behavior,¹¹ and many of the behavioral changes that occur during this period are associated with the maturation of multiple central nervous system (CNS) components. Gray matter density changes markedly in adolescence, reflecting pruning or elimination of the redundant synapses of early childhood, while simultaneous increases in myelination reflect alterations in white matter.^{12–18} Excitatory synapses and inhibitory circuits also undergo major refinements in adolescence, reflecting the pruning of excitatory glutamatergic synapses and the proliferation of inhibitory GABAergic circuits.^{13,19–21} Adolescence is also a sensitive period, where adverse events are capable of altering normative developmental trajectories, potentially predisposing an adolescent to develop subsequent behavioral and psychological disorders.⁹ The abundant changes that occur during this sensitive developmental transition are associated with an increased prevalence of psychopathology involving emotional perturbation.^{1,3,22–25}

Fear learning

Under normal conditions, fear learning is a highly adaptive and conserved process that allows organisms to respond appropriately to cues associated with danger. In the case of psychiatric disorders, fear responses may persist long after the danger has passed. This persistent form of fear is a core component of many anxiety disorders, including post-traumatic stress disorder (PTSD). Due to highly conserved neural circuitry in rodents and humans, in-depth characterizations of the behavioral and molecular processes associated with fear learning and memory can be explored using Pavlovian-based fear conditioning paradigms in parallel, species-specific experimental studies.^{26,27} Applying Pavlovian principles, it has been shown that an initially emotionally neutral conditioned stimulus (CS) can acquire negative affective properties on repeated pairings with an adverse unconditioned stimulus (US).²⁶ The relationship between the CS and US is quickly learned and consolidated such that innate behavioral and physiological fear responses will subsequently occur upon presentations of the CS alone.²⁶ For the CS to acquire the aversive properties of

the US and elicit fear responses, a series of events must occur. Firstly, the CS–US association must be learned through the process of acquisition. The paired association is then consolidated, so that it may be later accessed. Upon later presentations of the CS, the associated memory is retrieved and a fear response is produced.^{28,29} When a tone CS is repeatedly paired with an aversive US, such as a foot shock, a rodent will engage in defensive responses such as freezing behavior upon being presented with the tone alone. To assess prototypical fear responses in humans in an experimental setting, an aversive US, such as a loud noise, is often paired with a visual CS cue and skin conductance responses (SCR) are typically measured as a proxy for behavioral fear response.^{22,30}

If cues previously associated with danger are repeatedly presented in the absence of the initial aversive event, threat cues are then reassessed as safe and fear responses are reduced through the process known as extinction learning. Clinical exposure therapies apply fear extinction learning principles in the treatment of patients with exaggerated and inappropriate fear responses.³¹ Extinction learning, far from an erasure of the original fear association, is an active process through which the newly learned safety association of the CS competes with the initial CS–US memory.³²

The amygdala is the core structure involved in fear acquisition and expression of learned fear memories.^{33–35} In-depth anatomical, electrophysiological, and neuroimaging studies have detailed the various components of the amygdala and their roles in fear learning and memory.³⁶ In standard auditory-cued fear conditioning, projections from the cortex and thalamic nuclei receiving sensory inputs converge on the lateral nucleus of the amygdala (LA) simultaneously. The LA, along with the basal nucleus of the amygdala (BA), serves as the primary fear learning interface, and collectively integrates the relevant sensory information and relays it to the central nucleus (CE). Serving as the amygdala's secondary interface, the CE elicits fear responses through downstream projections to hypothalamic and brainstem nuclei to engage autonomic responses.³⁷ The cytoarchitecture of the amygdala is complex: the BLA contains primarily glutamatergic projection neurons, while the medial CE contains primarily GABAergic neurons with medium spiny neuronal morphology.³⁸ There is also a specialized cluster of GABAergic interneurons within the BLA known as intercalated cells (ITC) that mediate interactions between BLA and CE. ITCs integrate input from glutamatergic projections from the ventromedial prefrontal cortex (vmPFC).^{39,40} The vmPFC can be further divided into the dorsally located prelimbic (PL) and ventrally located infralimbic (IL) cortices. The PL is associated with production and expression of conditioned fear responses while the IL is associated with suppression of conditioned fear responses during extinction learning and upon extinction memory recall.^{41–46} During fear extinction learning, IL projections are activated by the repeated CS-only presentations, leading to reduced responses in the CE and ultimately decreased fear-related behavior.^{47,48} During fear acquisition, projections from the hippocampus (specifically the CA1 region) also provide information to the BA about the surrounding environment.^{29,49} Hippocampal–BA integration of contextual information about the surrounding environment has a major influence on downstream CE activity and subsequent fear responses.^{27,46}

Sensitive periods for fear learning and memory

Development of cued extinction learning

Parallel behavioral experiments in humans and mice demonstrate that cued fear acquisition is intact throughout development.^{50,51} While cued-fear learning is known to emerge during early infancy,⁵² adult-like extinction fails to develop until much later. In pre-adolescent P17 rats, inactivation of the medial prefrontal cortex (mPFC) fails to disrupt long-term extinction, suggesting that pre-adolescent rats undergo process more similar to forgetting rather than active extinction learning. While no disruption is seen in P17 rats, mPFC inactivation does disrupt extinction memory in P24 rats, suggesting that adult-like mechanisms of extinction begin around weaning.⁵³ Extinction training in pre-adolescent groups leads to increased levels of phosphorylated MAPK (pMAPK) in both the PL and IL of the mPFC, suggestive of non-specific mPFC activity, rather than inverse IL/PL activity typically seen with successful adult extinction retention.⁵³ Developmental studies of innate fear regulation in rodents found that the mPFC is neither active nor responsive in infant rats, the PL becomes active but does not yet regulate freezing behavior in pre-adolescence, and the PL becomes functional and its activity corresponds to an appropriately expressed cued-fear response in adolescence.⁵⁴ The non-linear developmental role of the mPFC is independent of amygdala activity, which suggests that mPFC neural circuitry develops enhanced capacities for fear regulation as an animal matures. Injections of anterograde tracers into developing rat BLA show that amygdalocortical connectivity matures well into adolescence, with fiber density reaching a plateau at approximately P45.⁵⁵ Recent investigations of fear extinction–learning circuitry suggest that hippocampal and amygdalar inputs to PL play principal roles in the gating of conditioned fear responses after extinction. The hippocampus modulates fear expression through projections to inhibitory interneurons in the PL, while the amygdala modulates fear through projections to excitatory pyramidal neurons in the PL.⁵⁶ While the PFC is known to develop throughout adolescence and undergo a shift in connectivity within the PL, along with projections from other brain regions, more precise understanding of this shift in connectivity remains to be investigated and may shed light on dynamic developmental learning processes.

Anatomical studies of human cortical development have also shown delayed maturation of the PFC relative to other lower-order sensorimotor regions, as measured by local decreases in gray matter density and increases in the myelination of fibers.^{16,57} Evidence from both human and rodent studies suggest that immature top-down PFC regulation of subcortical structures such as the amygdala resulting from incomplete circuit maturation within the PFC⁵⁷ may coincide with diminished fear-extinction learning during adolescence.⁵¹ In parallel human and rodent behavioral studies of fear-extinction learning, no difference in extinction learning was observed between preadolescents and adults; however, adolescents showed markedly attenuated fear-extinction learning compared to both preadolescents and adults, for both mice and humans (Fig. 1A and B).⁵¹

Studies of fear-extinction learning in rats have also shown that adolescents exhibit impaired extinction retention compared to their younger and older counterparts.⁵⁰ The adolescents in this study displayed normal within-session fear extinction, suggesting that short-term

extinction memory relying on L-type voltage-gated calcium channel activation was intact, while extinction consolidation depending on *N*-methyl-D-aspartate receptor (NMDAR) activation in the mPFC and in the BLA was not.⁵⁸ Supporting the role of normal mPFC activation in extinction consolidation, rats with PFC lesions display normal learned fear expression and within-session extinction but impaired expression of extinction memory at later time points.^{59,60}

Immunohistochemical detection of the immediate early gene *c-Fos* is used to predictably measure successful fear-extinction learning in the IL of adult rodents.⁶¹ The vmPFC in P23 and adult mice revealed markedly higher density *c-Fos*-labeled cells in the IL of fear-extinguished mice compared to nonextinguished fear conditioned controls. *c-Fos* labeling of IL in adolescent mice did not change detectably, suggesting that neural activity in the vmPFC of adolescent mice differs from neural activity observed in adults during fear extinction.⁵¹

Electrophysiological recordings in the vmPFC of P23 and adult mice after fear acquisition and extinction showed potentiation of PL excitatory synapses after fear acquisition and depotentiation upon extinction, suggesting that PL excitatory synapses regulate fear expression. Concurrently, IL excitatory synapses in adult fear-extinguished mice show potentiation, suggesting a role for IL vmPFC excitatory synapses in extinction. The changes in PL and IL synaptic plasticity observed in P23 and adult mice were absent in adolescent mice, suggesting that the vmPFC is not similarly engaged in learned fear regulation during this developmental period.⁵¹

Development of contextual fear memory

A nonlinear pattern of fear expression has also been observed in the acquisition of contextual fear across development. Unlike cued-fear responses, which involve projections between the sensory thalamus, amygdala, and prefrontal cortex, contextual fear responses integrate spatial aspects of the surrounding environment.³⁷ The hippocampus is known to play a central role in contextual fear memory, mediating fear responses based on safe versus threatening environments through its projections to the amygdala and prefrontal cortex.⁶² The developmental trajectory of the hippocampus in adolescent humans has been shown to be highly heterogeneous, with posterior subregions showing enlargement and anterior subregions showing volume loss, reflecting changes in myelination and synaptic pruning.¹⁶ Parallel changes in hippocampal volume may account for significant alterations in fear, anxiety, and conditioned-freezing responses across development in rodents as well.^{63–65}

As recently shown, hippocampal-dependent contextual fear memory undergoes significant suppression during adolescence.²⁸ When pre-adolescent, adolescent, and adult mice were fear conditioned, all groups were found to display similar levels of freezing behavior during fear acquisition. When hippocampal-dependent contextual fear was assessed by returning mice to the conditioning context 24 hours post-conditioning, adolescent mice froze significantly less than younger or older mice indicating absence of contextual fear response (Fig. 1C). Amygdala-dependent cued fear expression was preserved in adolescent mice, suggesting the processing associated with amygdala-dependent cued conditioning lacked the hippocampally-mediated spatial complexity associated with contextual fear

conditioning.^{28,29} In addition, the absence of a contextual fear response after 24 hours post-conditioning was accompanied with blunted response of established retrieval-associated signaling in the PI3 kinase and MAP kinase pathways, suggesting that the suppression of contextual fear in adolescent mice is associated with a lack of memory retrieval– associated signaling in the hippocampus.^{66–68}

The absence of hippocampally-dependent contextual fear in adolescent mice also suggests that either hippocampal immaturity or immature connectivity in the mPFC–amygdala–hippocampal fear circuitry is responsible for the attenuated contextual fear response. In the same study, hippocampal-dependent spatial abilities were found to be intact in a hippocampal-dependent novel object–placement task, ruling out the possibility of hippocampal immaturity in adolescent mice,²⁸ thus an alteration in the integration of the mPFC–amygdala–hippocampal fear circuitry is the most likely explanation for the lack of expression of contextual fear in early adolescent mice.

Despite the absence of contextual fear responses 24 hours post-conditioning, mice that underwent conditioning in adolescence demonstrated significantly higher levels of contextual fear expression 14 days postconditioning²⁸ than 24-hour post-conditioning fear expression. This delay in the onset of contextual fear expression demonstrates that adolescent mice are capable of contextual fear learning but that there is a latent period during which the expression of the prototypical fear response to context is suppressed until early adulthood. Field excitatory postsynaptic potential (fEPSP) slope was recorded by *in vitro* electrophysiology from the BA in fear-conditioned and non-fear–conditioned mice to measure behaviorally induced changes in synaptic strength. Consistent with the observed suppression of contextual fear in adolescent mice, fEPSP slopes from adolescent fear-conditioned and control mice were not significantly different. A significantly higher fEPSP slope was, however, seen in the BA 14 days post-conditioning in mice that underwent fear conditioning in adolescence, suggesting that improvements in contextual fear expression observed 14 days post-conditioning may be due to a delay in the synaptic potentiation of the BA.²⁸ These studies suggest that only memory retrieval is significantly altered in adolescence, while memory acquisition is intact.

Conclusions and future directions

The studies presented here review the neural circuitry underlying fear learning and memory and the nonlinear development of behavioral fear responses across development. The transition into and out of adolescence is a unique developmental stage for fear learning and memory, where cued-fear extinction and contextual fear expression is markedly altered relative to earlier and later stages.^{28,50,51} Adolescence represents a unique sensitive or critical period in fear learning. Critical periods in development are specific developmental windows, during which “brain circuits that subserve a given function are particularly receptive to acquiring certain kinds of information or even need that instructive signal for their continued normal development.”⁶⁹ Critical periods thus represent a form of general sensitivity when neuronal properties are particularly primed for modification by experience. The majority of research on critical periods in development has focused on the visual system, where monocular deprivation during a confined postnatal period has been shown to

result in a permanent loss of visual acuity in the deprived eye despite no physical damage to the eye itself,⁷⁰ while monocular deprivation outside of this window does not result in loss of visual acuity. Closure of the critical period for plasticity in the visual system is known to be dependent on the inhibitory neurotransmitter, GABA (γ -aminobutyric acid) which through late-developing GABAergic inhibitory connections impinges on pre-existing excitatory circuits.⁷⁰ The divergence in adolescence from the prototypical fear responses appears to represent a similar critical period warranting a closer look at known critical period regulators. As an example, closure of critical periods in vision is related to maturation of the extracellular matrix surrounding fast-spiking GABAergic interneurons that express parvalbumin (PV). In particular, the formation of perineuronal nets (PNNs), an organized form of chondroitin sulfate proteoglycan (CSPG)-containing extracellular matrix, initiates critical period closure. Thus, maturation of the GABAergic system during peri-adolescence may also be potentially involved in the opening and closing of this sensitive period for fear regulation.

Adolescence is a developmental period marked by the onset of increased exploratory, risk taking, novelty seeking, social interaction, and play behaviors.⁷¹ Consistent with these new developmental perquisites, contextual fear associations are suppressed whereas cued-fear associations are uniquely tenacious, allowing the adolescent to remain both exploratory and cautious. These adaptive social and exploratory behaviors foster the adolescent's transition from parental dependence to relative independence and the search for new sources of food and mates. A failure to venture out of the home environment could result in the depletion of food in the home environment and failure to mate; however, a lack of vigilance to predatory threats in a novel environment is equally likely to hinder procreation. As such, a heightened sensitivity to cues of threat in novel environments may coexist with resilient social and exploratory behaviors as an adaptive evolutionary measure.

The same features of adolescent brain development that foster social and exploratory behaviors may also contribute to increased sensitivity to fear-related disorders such as PTSD or anxiety and subsequent treatment resistance. Considering the possibility that evolutionarily conserved neural circuitry may prime adolescents to exhibit attenuated fear extinction, therapeutic methods relying on traditional exposure therapy techniques may benefit from new avenues of treatment. While it cannot be concluded that the heightened sensitivity to cues of threat in adolescence predisposes the development of all subcategories of anxiety disorders, the proposed model of fear learning and memory does provide a possible explanation for the increased prevalence of some anxiety disorders in adolescence. In light of these findings, it can be concluded that all anxiety treatments that rely on exposure therapies are likely to encounter similar difficulties in treatment effectiveness in adolescent populations.

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Figure 1.

Cued and contextual learning across development in mice and humans. (A) Adolescent humans show attenuated fear-extinction learning compared to younger and older age groups, as demonstrated by cued fear– extinction indices. (B) Adolescent mice (P29) demonstrate a lack of cued extinction learning and retention of cued extinction memory, as demonstrated by a significantly decreased differential extinction indices, compared to older (P70) and younger (P23) ages. *** $P < 0.001$. From Ref. 51 with permission. (C) Adolescent mice (P29) mice freeze significantly less than older (adult) or younger (P23) mice. *** $P < 0.001$. From Ref. 28 with permission.