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REVIEW

Sensitive Periods in Affective Development: Nonlinear Maturation of Fear Learning

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At specific maturational stages, neural circuits enter sensitive periods of heightened plasticity, during which the development of both brain and behavior are highly receptive to particular experiential information. A relatively advanced understanding of the regulatory mechanisms governing the initiation, closure, and reinstatement of sensitive period plasticity has emerged from extensive research examining the development of the visual system. In this article, we discuss a large body of work characterizing the pronounced nonlinear changes in fear learning and extinction that occur from childhood through adulthood, and their underlying neural substrates. We draw upon the model of sensitive period regulation within the visual system, and present burgeoning evidence suggesting that parallel mechanisms may regulate the qualitative changes in fear learning across development.

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INTRODUCTION

Across development, both the brain circuits and behavioral capabilities of an organism undergo pronounced maturational changes. Two distinct types of developmental adaptation occur simultaneously. An evolutionarily refined genetic program of development coordinates the emergence of the array of behaviors typically present at a given life stage. Alongside this species-typical course of development, a simultaneous process of specialization occurs in response to the unique experiences of the individual. This experience-dependent plasticity enables the refinement of brain and behavior in accordance with the specific informational landscape and functional demands of a given individual's environment. This tailoring of brain development to the needs of the individual occurs in a sequential and hierarchically organized manner, with the maturation of lower level functions preceding that of higher-order processes. Each functional process, and its underlying brain circuit, undergoes a temporally limited 'sensitive period' of heightened plasticity during which neural development is especially receptive to particular types of experience.

Such sensitive periods have been identified across species in the development of perceptual and motor systems, as well as in cognitive, affective, and social capabilities. As a sensitive period closes, the organization of neural circuits becomes increasingly stable, yielding a corresponding stability in the behavioral functions they implement. Atypical experience during a sensitive developmental window can lead to persistent functional abnormalities. The term 'critical period' has been used to refer to windows of extreme interdependence between experience and development, after which a decrease in neural plasticity typically renders the behavioral outcome irreversible. However, recent research has identified mechanisms through which plasticity can be reinstated beyond the closure of a critical period, suggesting that aberrant neurodevelopmental outcomes may not necessarily be immutable. A provisional model of the regulatory mechanisms governing the initiation of sensitive period plasticity, its closure, and more recently, its reinstatement has emerged through extensive research examining the development of the visual, auditory, and motor systems. This model also appears to generalize to developmental plasticity in neural circuits within other modalities (Nabel and Morishita, 2013).

Although our understanding of mechanisms governing sensitive period changes in plasticity stems primarily from research in sensory and motor systems, there is also abundant evidence for sensitive periods in affective development. In contrast to the development of sensory and motor systems, structural and functional changes within affective neural circuits continue well into young adulthood. The neurocircuitry supporting affective learning and regulation comprises a network of cortical and subcortical

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regions that exhibit extended maturational trajectories (Gogtay *et al*, 2004; Raznahan *et al*, 2014). Variation in early-life experience can persistently alter the development and function of these circuits (Lupien *et al*, 2009), highlighting the important role of experience-dependent plasticity in determining adult affective outcomes. Many psychiatric and behavioral disorders that are thought to involve dysregulated affective learning typically exhibit adolescent onsets, including anxiety and substance abuse (Kessler *et al*, 2005; Wagner and Anthony, 2002). An improved understanding of the factors that regulate affective plasticity may ultimately provide a foundation for potential interventions that might alter such maladaptive neurodevelopmental outcomes through the reinstatement of sensitive period plasticity.

In this article, we attempt to synthesize a body of work characterizing pronounced nonlinear changes in fear learning and its underlying neural substrates from birth until adulthood. We draw upon the relatively sophisticated understanding of the mechanisms governing critical period regulation within the visual system and discuss how similar neuroplastic changes might underlie qualitative maturational changes in fear learning. We begin by reviewing the molecular mechanisms that govern the opening, closure, and reinstatement of critical periods for the development of ocular dominance in visual cortex. We then turn our attention to affective development, first describing the well-characterized neurocircuitry underlying fear learning and regulation in adulthood, and then presenting the qualitative behavioral and neural changes in this functional system from infancy through adulthood. We then discuss the mechanisms known to regulate plasticity in the fear neurocircuitry, highlighting the clear parallels between regulators of plasticity within the visual system and those influencing juvenile maturation of fear learning. We present burgeoning evidence suggesting that similar mechanisms may contribute to nonlinear behavioral changes in fear expression during adolescence. We conclude with a discussion of how multiple interventions that have been shown to reintroduce neural plasticity beyond the closing of a critical period may similarly be able to alter the function of fear-learning neurocircuitry. The potential to promote plastic changes in the function of affective circuits beyond normal sensitive periods holds promise for the treatment of anxiety, as well as other behavioral and psychiatric disorders in which atypical early affective experience might play a central etiological role.

REGULATION OF CRITICAL PERIOD PLASTICITY WITHIN THE VISUAL SYSTEM: ONSET, CLOSURE, AND REINSTATEMENT

Our understanding of critical periods in brain plasticity stems largely from research on the development of sensory systems (Hensch, 2004; Knudsen, 2004). The organization of the visual systems is established early in development. Work by Hubel and Wiesel demonstrated that binocular visual experience during early life is critical for the development of normal vision. They found that temporarily obstructing visual input to one eye during a time window early in life results in altered organization of primary visual cortex. When occlusion of one eye occurred during a temporally limited period early in development, cortical columns within the occipital cortex representing information from the affected eye decreased in size, ceding their cortical area to neurons encoding information from the functional eye. As a result, vision in the occluded eye is impaired, a condition termed amblyopia. Restoration of input to the eye following the critical period fails to normalize vision. Monocular deprivation in adulthood fails to engender these neural and functional alterations, providing evidence of a critical period for experience-dependent plasticity in the visual system. Deprivation of visual experience early in life in rodents has served as a model for probing the molecular mechanisms that govern the opening and closing of critical periods.

Neuronal signaling in the neonatal brain is predominantly excitatory, with inhibitory neurotransmission increasing as the organism matures. Within the visual system, this increase in inhibitory signaling initiates the opening of a critical period for ocular dominance (Bavelier *et al*, 2010; Hensch, 2004). The balance between excitatory and inhibitory signaling appears to be a primary regulator of the onset of critical period plasticity. Gamma aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the vertebrate brain. The normal developmental increase in GABA neurotransmission can be prevented by genetically disrupting GABA synthesis in the rodent. This manipulation prevents the onset of the critical period for ocular dominance. Administration of benzodiazepines, which enhance GABA signaling, induced critical period plasticity in these genetically altered mice, such that monocular deprivation produced the typical neural and functional alterations in ocular dominance (Hensch *et al*, 1998). This restoration of plasticity occurred even in adult animals. Similarly, administration of benzodiazepine, or other manipulations that increase GABAergic inhibitory neurotransmission, prematurely advances the onset of critical periods in typically developing animals (Di Cristo *et al*, 2007; Fagiolini and Hensch, 2000; Sugiyama *et al*, 2008). Benzodiazepine administration subsequent to the closure of a critical period fails to reintroduce neuroplasticity (Fagiolini and Hensch, 2000), suggesting that the initial maturation of inhibitory signaling exerts a unique influence on the wiring of neural circuits.

The closure of critical period plasticity in visual cortex is accompanied by maturational changes in the extracellular matrix surrounding a class of GABAergic neurons that express parvalbumin (PV). The formation of perineuronal nets, an organized form of chondroitin sulfate proteoglycan-containing extracellular matrix, coincides with the end of the critical period for ocular dominance (Galtrey and Fawcett, 2007; Pizzorusso *et al*, 2002). The organization of perineuronal nets is delayed by dark-rearing, an environmental condition that extends the duration of the critical period, and degradation of PNNs in the adult rodent

reinstates critical period plasticity in visual cortex (Pizzorusso *et al*, 2002). This work suggests that the formation of perineuronal nets is a molecular mechanism that functions as a 'brake' on critical period plasticity (Bavelier *et al*, 2010).

Other structural mechanisms such as myelination and synaptic pruning may also act as structural regulators of critical period plasticity. In the human brain, myelination begins in the brainstem at approximately 6 months of age, with a regional progression from posterior to anterior and inferior to superior (Lenroot and Giedd, 2006). White matter tracts throughout the majority of the brain are myelinated by early childhood; however, myelination of axons in several cortical areas continues into young adulthood, suggesting an extended period of neuroplasticity in these circuits (Yakovlev and Lecours, 1967). With the closing of the visual critical period, cortical myelin matures and myelin associated inhibitors including NogoA, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelinglycopretein (OMgp) are expressed and act upon a common Nogo receptor NgR, which is involved in limiting plasticity (Akbik *et al*, 2012). NgR knockout mice display prolonged visual plasticity, suggesting its requirement for closure of the critical period (McGee *et al*, 2005).

The term critical period was introduced to capture the strong temporal limitation on experience-dependent neurodevelopmental outcomes. However, subsequent to the delineation of the molecular mechanisms governing critical period plasticity, continued research has identified a range of manipulations that can reintroduce plasticity in the visual beyond the critical developmental period (Bavelier *et al*, 2010). In general, these interventions work by removing structural barriers to plasticity, including perineuronal nets and myelin-associated inhibitory proteins or by altering the balance between local excitatory and inhibitory neurotransmission. Directly reducing GABA transmission in adulthood can partially reactivate ocular dominance plasticity (Harauzov *et al*, 2010). In addition, neuromodulators of excitatory-inhibitory circuit balance such as serotonin can also reset this balance and promote the recovery of visual functions in adult amblyopic animals (Vetencourt *et al*, 2008). Acetylcholine transmission also modulates plasticity within the visual system. A novel membrane-associated protein, Lynx1, binds to the nicotinic acetylcholine receptor (nAChR) and attenuates nicotinic cholinergic transmission and has been shown to have increased expression as the visual critical period closes (Morishita *et al*, 2010). Genetic deletion of Lynx1 led to increases in nicotinic transmission and allows the critical period to remain open into adulthood (Morishita *et al*, 2010).

A key question is whether these mechanisms governing the opening and closing of critical period plasticity in the visual system also apply to developmental periods of plasticity in affective function, most notably fear regulation, which exhibits marked functional changes well into young adulthood (Casey *et al*, 2012; Shechner *et al*, 2014).

PAVLOVIAN FEAR LEARNING AND EXTINCTION

The ability to recognize and respond appropriately to threats in the environment is critical to an organism's survival. This adaptive function relies on the ability to rapidly and persistently learn associations between previously experienced negative events and the cues and contexts that predicted their occurrence. Experimental studies typically model this real-world associative learning using Pavlovian conditioning paradigms, in which a neutral cue is paired with an intrinsically aversive stimulus. This pairing produces a learned association between the previously neutral cue, now the conditioned stimulus (CS), and the aversive unconditioned stimulus (US), which enables the CS to elicit a range of physiological and behavioral conditioned responses (CRs) to the anticipated threat. In experimental studies of rodents, the most typical CR assessed is freezing. In humans, common CRs include changes in skin conductance, startle responses, and pupil dilation. Fear learning is rapid and long-lasting, typically requiring only a few pairings of the CS and US and persisting for long periods after the initial association is formed. Learned fear often extends to the broader context in which an aversive experience occurs. Contextual fear is assessed by measuring conditioned responses to the original fear-learning context, in the absence of the conditioned cue.

Although learned fear memories are persistent, their expression can be inhibited through new learning that a once threatening stimulus is now safe. Experimentally, this process of extinction learning is modeled by repeatedly presenting the CS without the aversive US, which is typically accompanied by a gradual decrease in the expression of the CR. This mitigation in fear responding does not reflect unlearning of the original fear association, but instead appears to reflect the formation of a new competing association between the CS and safety. The persistence of the original fear memory is evidenced by the fact that extinguished fear often returns under a number of circumstances including a change in context (renewal), exposure to an aversive stimulus (reinstatement), or the mere passage of time (spontaneous recovery) (Bouton, 2004).

NEURAL CIRCUITS UNDERLYING FEAR LEARNING AND REGULATION IN ADULTHOOD

Studies in animal models employing Pavlovian fear conditioning and extinction paradigms have elucidated a detailed model of the brain circuitry underlying fear learning and regulation in adulthood. The amygdala plays a central role in the acquisition, storage, and expression of fear learning. The amygdala is a heterogeneous structure consisting of multiple functionally distinct subnuclei. The lateral nucleus of the amygdala (LA) receives convergent sensory and somatosensory input carrying information about CS and US presentation (Amaral, 1986; McDonald *et al*, 1996; Price, 2003). Plasticity within the LA following

the paring of these stimuli results in the formation of the learned fear memory (Quirk *et al*, 1997; Quirk *et al*, 1995). Upon subsequent CS presentations, stimulus-evoked firing within the LA activates the central nucleus of the amygdala (CE), triggering the expression of the fear response *via* descending to brainstem and hypothalamic regions (Davis, 2000). The LA maintains a long-term representation of this fear memory (Repa *et al*, 2001), regardless of whether or not the behavioral fear response is expressed. This persistent fear encoding within the LA likely enables the return of fear, even when fear expression has been inhibited through extinction learning (Bouton, 2004). Although the LA exhibits transient responses to CS presentation, involvement of the prelimbic region of the medial prefrontal cortex (PL) appears to be necessary for the sustained expression of fear (Corcoran and Quirk, 2007). Neurons in the PL exhibited sustained firing in response to CS presentation that mirrors the duration of the freezing response itself (Burgos-Robles *et al*, 2009). The PL receives afferent input from the LA (McDonald, 1991) and projects to CE, *via* the basal nucleus of the amygdala. Following CS presentation, phasic signals from the LA may initiate sustained prelimbic firing that directly influences fear expression through its CE projections.

The contextual learning that occurs during fear conditioning depends upon interaction between the amygdala and the hippocampus (Fanselow, 2000; Maren *et al*, 2013). Whereas amygdala damage subsequent to conditioning abolishes both cued and contextual fear, a lesion localized to the hippocampus selectively impairs fear expression to the context (Kim and Fanselow, 1992). The hippocampus is thought to support the construction of a contextual representation, which becomes associated with the aversive stimulus through synaptic plasticity in the amygdala (Maren and Fanselow, 1995; Maren *et al*, 2013). Expression of contextual fear is also dependent on the PL (Corcoran and Quirk, 2007), which receives afferent projections from the hippocampus (Condé *et al*, 1995). This network of regions, with the amygdala at its center, interacts to support the acquisition of fear learning during adulthood.

The acquisition, consolidation, and retrieval of initial extinction learning involve a dynamic interaction between the amygdala and the infralimbic subregion of the medial prefrontal cortex (IL) (Quirk and Mueller, 2007). The amygdala is necessary for the initial acquisition of extinction learning (Herry *et al*, 2006; Kim *et al*, 2007a; Sotres-Bayon *et al*, 2007). During extinction learning, a population of cells within the basal nucleus (BA) of the amygdala increases in firing rate in response to unreinforced CS presentations (Herry *et al*, 2008). These neurons have reciprocal connections with the IL, which plays a critical role in extinction learning, consolidation, and retrieval (Burgos-Robles *et al*, 2007; Morgan and LeDoux, 1995; Morgan *et al*, 1993; Quirk *et al*, 2000). Following extinction training, presentation of the CS evokes activity within IL neurons that is associated with reduced conditioned fear expression (Milad and Quirk, 2002). This cortical activity is thought to modulate fear expression *via* the intercalated cell masses (ITC). The ITC is a population of inhibitory cells interposed between the BA/LA and CE. Activation of these cells *via* increased firing in IL inhibits the LA signals to the CE, decreasing the expression of conditioned fear responses (Berretta, 2005; Likhtik *et al*, 2008). In contrast to the IL, the neighboring PL opposes extinction recall, driving the expression of fear responses (Corcoran and Quirk, 2007; Sierra-Mercado *et al*, 2011; Sotres-Bayon *et al*, 2012). During extinction training, CS-evoked activity within PL predicts the subsequent failure of extinction retrieval (Burgos-Robles *et al*, 2009), suggesting that the dynamic interaction between the amygdala and IL and PL cortical regions determines the success or failure of extinction learning. Projections from the hippocampus to both the IL and PL, as well as the amygdala, appear to mediate the context-dependent expression of extinction (Ji and Maren, 2005; Sotres-Bayon *et al*, 2012), providing contextual information that influences whether extinction learning is retrieved, or the original fear memory returns (Bouton, 2004; Fanselow, 2000; Maren *et al*, 2013).

Fear-conditioning studies in adult humans suggest that the neurocircuitry underlying fear learning and extinction is highly evolutionarily conserved (Hartley and Phelps, 2013; Phelps and LeDoux, 2005). Human lesion and neuroimaging studies reveal a central role for the amygdala in fear conditioning (Bechara *et al*, 1995; Büchel *et al*, 1998; Cheng *et al*, 2006; LaBar *et al*, 1998; LaBar *et al*, 1995). In addition to the engagement of the amygdala, functional magnetic resonance imaging (fMRI) studies of fear conditioning commonly report CS-evoked increases in blood oxygen level-dependent (BOLD) activation in the dorsal anterior cingulate cortex (dACC). CS-evoked BOLD activation as well as cortical thickness in this region correlates positively with the magnitude of conditioned fear expression, motivating the suggestion that this region may be a human homologue of the rodent PL (Hartley and Phelps, 2013; Milad *et al*, 2007a; Milad and Quirk, 2012). Human imaging studies that dissociate neural responses to conditioned cues and contexts corroborate the involvement of the hippocampus in contextual fear learning (Alvarez *et al*, 2008; Marschner *et al*, 2008).

Functional imaging studies of extinction report increases in BOLD signal in a subgenual anterior cingulate/vmPFC region during initial extinction learning, as well as a corresponding decrease in amygdala BOLD activation (Kalisch *et al*, 2006; Milad *et al*, 2007b; Phelps *et al*, 2004). Increases in BOLD activation are also observed during extinction recall (Phelps *et al*, 2004). Both the magnitude of vmPFC BOLD signal as well as the thickness of the cortex in this region have been found to correlate with the degree of extinction retrieval (Hartley *et al*, 2011; Milad *et al*, 2005; Milad *et al*, 2007b). On the basis of these findings, the subgenual vmPFC region has been proposed to be a potential human homologue of the rodent IL region (Hartley and Phelps, 2013; Milad *et al*, 2007a; Milad and Quirk, 2012), and may diminish fear expression *via* its projections to the amygdala. Context-dependent retrieval of extinction is associated with increased BOLD activation in

the hippocampus (Kalisch *et al*, 2006; Milad *et al*, 2007b), and hippocampal lesions impair context-dependent fear reinstatement (LaBar and Phelps, 2005), a finding that parallels observations in rodents (Wilson *et al*, 1995).

DEVELOPMENTAL CHANGES IN FEAR-LEARNING CIRCUITS

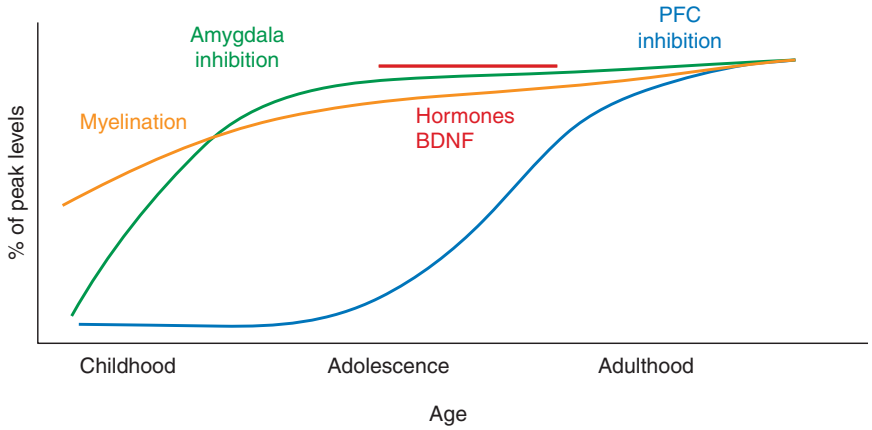
Although research across species has delineated a fairly detailed model of the neurocircuitry supporting fear learning and extinction during adulthood, there has been much less study of the neurocognitive development of these processes. The prefrontal and subcortical circuitry implicated in adult fear learning undergoes substantial developmental change from childhood through adulthood (Gogtay *et al*, 2004; Lenroot and Giedd, 2006; Raznahan *et al*, 2014). Mirroring these pronounced changes in the brain, numerous studies to date suggest that fear learning and regulation exhibit qualitative changes across development (Figure 1).

In rodents, fear learning emerges early in postnatal development and appears to track the functional maturation of the amygdala (Landers and Sullivan, 2012). Prior to postnatal day 10 (P10), infant rats exhibit attenuated amygdala responses to aversive stimuli. Behaviorally, these animals exhibit a paradoxical approach response to an odor stimulus previously paired with shock (Camp and Rudy, 1988; Sullivan *et al*, 2000). This early neonatal period corresponds to a sensitive period for attachment learning, and the suppression of fear responding during this period may functionally promote attachment between the infant and caregiver, even if the quality of care received is poor (Landers and Sullivan, 2012). After P10, the odor-shock conditioning produces a conditioned odor aversion, reflecting the emergence of cued fear learning. This behavioral change coincides with the onset of learning-induced synaptic plasticity within the amygdala (Thompson *et al*, 2008). The timing of the functional maturation of the amygdala appears to be experience-dependent. Through suppression of pup corticosterone levels, maternal presence delays the onset of fear conditioning whereas maternal separation promotes earlier maturation of aversive learning (Moriceau and Sullivan, 2006). Even once animals have developed the ability to learn conditioned aversion, infant fear memories remain qualitatively different from those of adults in that they are not as persistent. Conditioned fear learned at P17 is typically forgotten within 10 days (Callaghan and Richardson, 2012). Notably, this infantile amnesia for fear memories is also experience-dependent, and is attenuated under conditions of early-life stress. Animals that have experienced chronic maternal separation at P17 exhibit full recall of fear 10 days later (Callaghan and Richardson, 2012).

Contextual fear conditioning in rodents emerges later than cued fear learning (Rudy, 1993). Whereas pre-weanling (P17) rats do not appear to extend learned fear associations to the broader surrounding environment, adult-like contextual fear conditioning emerges by P24. The emergence of contextual fear learning may reflect increased maturation of the hippocampus and its connections to the amygdala in the post-weanling animals (Raineki *et al*, 2010). Contextual fear memories in this juvenile, pre-adolescent phase are also labile, and undergo forgetting with the passage of time (Akers *et al*, 2014). This infantile amnesia stems from heightened hippocampal neurogenesis, which is thought to induce reconfiguration of the neural circuits that encode hippocampal-dependent memories (Akers *et al*, 2014). In contrast, during adolescence, once contextual fear learning is acquired, its expression undergoes a temporary suppression (Pattwell *et al*, 2011). In mice, contextual fear memories learned during or prior to adolescence (P29) are not expressed during this developmental stage; however, these memories reemerge during the transition into adulthood ($>$P45). This temporary suppression of contextual fear expression is proposed to foster exploratory behavior that would be necessary to support the typical transition from maternal care into independence during this developmental stage.

As with fear learning, the acquisition and expression of extinction learning also changes markedly across development. Extinction training in pre-weanling animals (prior to P24) produces the typical decrease in fear expression. However, unlike adult animals, these animals do not exhibit the fear re-emergence phenomena that typically occur following extinction training (Gogolla *et al*, 2009; Kim and Richardson, 2007b; Yap and Richardson, 2007). This resistance of extinction to spontaneous recovery, reinstatement, and renewal suggests that extinction training at this developmental stage may evoke a process akin to unlearning of the original fear memory, as opposed to the formation of a new competing safety memory. Consistent with this interpretation, extinction learning in these pre-weanling animals does not depend upon engagement of the IL, but instead appears to be amygdala-dependent (Kim *et al*, 2009; Kim and Richardson, 2008). This suggests that early-life extinction may effectively yield fear erasure. Paralleling the influence of stress on the maturation of fear learning, separation from the mother advances the onset of adult-like extinction learning, from which fears reemerge (Callaghan and Richardson, 2011). In contrast to the ease with which fears are diminished in these younger animals, both fear extinction learning and retention are attenuated during adolescence (Kim *et al*, 2011; McCallum *et al*, 2010; Pattwell *et al*, 2012). Relative to pre- and post-adolescent animals, adolescents exhibit diminished fear extinction learning that is paralleled by an absence of fear-learning-induced synaptic plasticity within the PL and extinction-learning-induced plasticity within the IL (Pattwell *et al*, 2012).

These studies suggest that the development of both cued fear extinction and contextual fear expression progress in a nonlinear manner, with adolescents showing diminished abilities relative to preadolescents and adults. Adolescence is a time of exploration when one must leave the safety and stability of his or her familial environment in order to attain reproductive success; thus, a suppression of contextual fear



Behavior	Child	Adolescent	Adult
Fear learning	Cue and context learning emerge, prone to forgetting	Mature cue learning, contextual fear expression suppressed	Mature cue and context learning
Fear extinction	Leads to erasure	Attenuated/ recovery	Fear extinguishes but recovers
Reconsolidation	Extinction may yield reconsolidation	?	Reconsolidation yields persistent attenuation

Figure 1. Developmental regulation of fear-related plasticity and behavior. (Top) Inhibitory neurotransmission peaks early within the amygdala, whereas increases in the prefrontal cortex begin during adolescence and do not peak until adulthood. Gonadal hormones and BDNF levels peak during adolescence. Myelination increases gradually from childhood to adulthood. (Bottom) Fear learning, extinction, and reconsolidation exhibit qualitative maturational changes across the lifespan. Cued and contextual fear learning emerge during childhood, but the memories are labile. Contextual fear expression and extinction learning are attenuated during adolescence. In adulthood, extinguished fear recovers, but can be attenuated persistently through reconsolidation.

may contribute to the fearlessness required for exploring new environments that is typically seen with this age group (Casey *et al*, 2010; 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 would enable the adolescent to remain both exploratory and cautious, optimizing chances for survival and reproductive success. The circuit-level changes in the brain underlying these developmental discontinuities in fear expression have yet to be clearly delineated. However, the pronounced structural remodeling of subcortical-prefrontal connections (eg myelination, synaptic pruning) that occurs during adolescence is likely to contribute to these qualitative shifts in fear expression (Somerville and Casey, 2010; Spear, 2000). For example, there is substantial pruning of neurons projecting from the IL to the basal amygdala from adolescence to adulthood (Cressman *et al*, 2010). Changes in connectivity between both the amygdala and the hippocampus, and the IL and PL during adolescence may initiate the shift from the restricted subcortical circuitry governing fear learning in juvenile stages, toward the more flexible and expansive circuit for fear regulation that is evident in adulthood. Clarifying precisely how these transitions in the fear neurocircuitry during adolescence yield pronounced nonlinearity in fear learning and extinction remains an important area for future investigation.

Human studies of fear learning across development have been somewhat limited by the methodological constraints involved in designing effective aversive learning paradigms that are ethical to conduct in children. Typically, these paradigms use unconditioned stimuli such as white noise, unpleasant images, or a combination of the two (Shechner *et al*, 2014). Developmental studies of human fear learning corroborate findings in animals of the early maturation of fear learning. Children as young as 3 years show evidence of fear acquisition (Gao *et al*, 2010), with discrimination between an aversively conditioned and a neutral stimulus (CS+ > CS−) improving with age (Gao *et al*, 2010; Glenn *et al*, 2012). This increased discrimination ability with age continues into adulthood, and is associated with distinct developmental patterns of neural activity during fear learning (Lau *et al*, 2011). Consistent developmental changes in fear extinction learning have been observed across species. As in rodents, fear extinction in humans is also selectively attenuated during adolescence relative to

children and adults (Pattwell *et al*, 2012). Although there have not been functional imaging studies to date of fear extinction across development, a recent fMRI study examining developmental changes in connectivity between the medial prefrontal cortex and the amygdala found that although BOLD activity within the vmPFC and the amygdala are inversely correlated in adolescence and adulthood, activity in these regions is positively correlated during childhood (Gee *et al*, 2013b). Although these functional connectivity measures do not directly reflect the non-linear developmental pattern observed in fear extinction and associated synaptic plasticity (Pattwell *et al*, 2012), they provide an indication of the pronounced maturational changes in the dynamic interaction between these regions. Interestingly, mirroring the early maturation of the fear neurocircuitry induced by maternal separation in the rodent (Callaghan and Richardson, 2011), institutionally-reared children who experienced early maternal deprivation show the more mature pattern of positive vmPFC-amygdala coupling (Gee *et al*, 2013a). This suggests that, as in rodents, the maturational trajectory of human fear neurocircuitry is also highly sensitive to experiential variation during early development (Tottenham, 2013).

DEVELOPMENTAL REGULATION OF FEAR-RELATED PLASTICITY

The molecular mechanisms governing sensitive period plasticity within affective circuits have not been characterized in the same detail as those that influence the development of the visual system. However, burgeoning evidence suggests that changes in the balance between excitatory and inhibitory signaling and structural changes in the brain including the formation of perineuronal nets, synaptic pruning, and myelination of white matter tracts also modulate affective neuroplasticity, regulating the opening and closure of sensitive periods for fear and extinction learning (Figure 1).

Early in development, neuronal communication is predominantly excitatory. The increase in inhibitory signaling that initiates the onset of critical periods is mediated by activity at the $GABA_A$ receptor (Hensch, 2005). At birth, the $GABA_A$ receptor is excitatory, with a shift to inhibitory action occurring early in development (Ben-Ari *et al*, 2012; Le Magueresse and Monyer, 2013). Several elements of the GABAergic system continue to exhibit marked developmental change through adolescence and early adulthood (Kilb, 2012; Le Magueresse and Monyer, 2013). GABAergic synapse proliferation, GABA receptor and transporter distribution, and metabolic enzyme production, all modulate GABAergic tone. Each of these components contribute to the fine tuning of the excitatory/inhibitory balance in the brain and are likely to play important roles in regulating developmental stage-specific alterations in neural plasticity and behavior. Within the amygdala, a number of changes in GABAergic function occur during pre-adolescence, including the emergence and maturation of parvalbumin-expressing GABAergic interneurons, as well as decreases in the density of GABAergic cell bodies and increases in the density of GABAergic fibers (Ehrlich *et al*, 2013). These changes appear to play a critical role in several of the qualitative changes in fear learning that occur during this stage. The switch from approach to avoidance responding to a conditioned stimulus that typically occurs at P10 in the rat is prevented by $GABA_A$ blockade (Sullivan *et al*, 2000; Thompson *et al*, 2008). Similarly, the rapid forgetting of fear learning early in development, referred to as infantile amnesia, is mediated by the $GABA_A$ receptor (Kim *et al*, 2006). Unlike adult fear extinction, extinction learning at P17, when fear recovery is absent, is not GABA-dependent (Kim and Richardson, 2010).

The formation of perineuronal nets surrounding GABAergic interneurons acts as structural brakes that contribute to the closure of sensitive periods in ocular dominance plasticity (Pizzorusso *et al*, 2002). Similarly, PNNs appear to play a critical role in enabling the stability to fear memories. The formation of PNNs within the amygdala appear to support the transition from the infantile extinction that resembles fear erasure, to the more adult-like state in which recovery of extinguished fear typically occurs (Gogolla *et al*, 2009; Gundelfinger *et al*, 2010). Moreover, structural degradation of these PNNs in adulthood reintroduces a juvenile-like state in which extinction results in a persistent attenuation of fear memory (Gogolla *et al*, 2009). There are two possible mechanisms by which degradation of PNNs might enable fear memory erasure. PNNs may stabilize fear memories by rendering potentiated synapses resistant to reversal of long-term potentiation, or PNN degradation might give rise to changes in local GABA-mediated inhibition. The latter mechanism is plausible given that PNNs form primarily around parvalbumin-positive GABAergic interneurons and that GABAergic neurotransmission mediates several forms of BLA synaptic plasticity (Gogolla *et al*, 2009).

Although inhibitory signaling in the amygdala matures in a juvenile developmental stage, GABAergic maturation in other brain regions continues well beyond this period. In particular, inhibitory neurotransmission in the prefrontal cortex increases throughout adolescence and does not reach peak levels until young adulthood (Kilb, 2012; Le Magueresse and Monyer, 2013). GABA signaling is not only involved in inhibitory synaptic transmission, but also regulates synapse elimination and axonal pruning (Wu *et al*, 2012). Thus, increases in prefrontal GABA may play an important organizing role in the restructuring of prefrontal-subcortical connectivity that occurs during adolescence. Brain-derived neurotrophic factor (BDNF) has been implicated in the promotion of GABAergic transmission in the cortex (Hong *et al*, 2008; Sakata *et al*, 2009). Cortical BDNF levels reach peak levels during early adolescence (Katoh-Semba *et al*, 1997), which may represent a mechanism regulating the timing of GABA maturation. Perineuronal nets also form later in the prefrontal cortex than in the

amygdala, reaching peak levels in early adulthood (Mauney *et al*, 2013). As in the amygdala, PNN formation may terminate plastic changes in prefrontal circuitry once the mature adult state is attained. Collectively, these neuroplastic changes in the cortex during adolescence coincide with a transitional phase spanning the juvenile stage in which fear learning and extinction are independent of the cortex and the mature adult stage in which these processes are dynamically regulated by vmPFC-subcortical circuitry (Baker *et al*, 2013) (Sotres-Bayon and Quirk, 2010). Elucidating the precise manner in which these changes in prefrontal plasticity during adolescence influence fear expression remains an important area for future investigation.

Although our present understanding of the mechanisms governing developmental changes in fear learning is rudimentary, there is clear evidence for common regulators of neural plasticity in both visual and affective brain circuits. The regulatory mechanisms discussed here are by no means exhaustive. For example, sex hormones also exert organizing effects on adolescent neurodevelopment (Spear, 2000) and modulate fear expression (Zeidan *et al*, 2011). Moreover, it is likely that a combination of cross-modal and domain-specific regulatory mechanisms shape brain development. Finally, although we focused here on the common regulators of neuroplasticity in both the visual system and the aversive learning neurocircuitry, similar mechanisms may also regulate developmental changes in reward learning and the associated corticostriatal circuitry (Haber and Knutson, 2009). Understanding the developmental regulation of neuroplasticity in reward-related circuits is especially important in light of the heightened vulnerability to addiction during adolescence (Chambers *et al*, 2003).

RENEWING PLASTICITY AS A MECHANISM TO CHANGE FEAR

One of the best examples of parallel mechanisms for renewing plasticity in both visual and fear-related plasticity comes from studies involving modulation of the serotonin system. Chronic administration of a selective serotonin reuptake inhibitor, fluoxetine, has been shown to reinstate ocular dominance plasticity in adulthood and promotes the recovery of visual functions in adult amblyopic animals (Vetencourt *et al*, 2008). Interestingly, fluoxetine administration to adult animals also produces enhanced extinction that resembles fear erasure (Karpova *et al*, 2011), similar to the learning observed in pre-adolescent mice prior to the initiation of the molecular 'brakes' that stabilize fear memories (Gogolla *et al*, 2009). In the fluoxetine-treated mice, levels of the growth factor BDNF were increased in the amygdala, and synaptic plasticity within the amygdala was enhanced, similar to what has been observed in the visual cortex. In addition, fluoxetine treatment led to a reduction in the number of PNNs in neurons expressing parvalbumin in the BLA, suggesting a shift to a more immature state, leading to changes in the local inhibitory neurons in this region.

A recent behavioral intervention termed reconsolidation update, which relies upon presenting extinction training within a temporal window opened by an isolated CS presentation, also leads to persistent attenuation of the fear memory (Monfils *et al*, 2009; Schiller *et al*, 2009). This intervention suggests that the original fear memory trace may be significantly altered to incorporate the CS–no US learning before re-storage. The result is thought to be a modified memory trace representing the new significance of the CS, which does not promote the return of fear. The molecular mechanisms underlying this form of memory erasure has involved synaptic removal of calcium-AMPA receptor in the lateral amygdala (Clem and Huganir, 2010). In addition, it has recently been shown that this updating procedure epigenetically regulates the expression of a number of plasticity genes in the hippocampus, some which may downregulate molecular 'brakes' on plasticity (Gräff *et al*, 2014). Interestingly, administration of an HDAC2 inhibitor during reconsolidation led to erasure of not only recent but also remote fear memories. These latter studies indicate that pharmacological agents that alter epigenetic regulation of fear memory may constitute another strategy to renew plasticity to permanently attenuate fear memories.

CLINICAL IMPLICATIONS

Fear conditioning has been proposed as a model for the real-world learning processes through which cues and contexts associated with traumatic events come to evoke fear. Consistent with this model, patients with anxiety disorders have been found to exhibit altered fear learning and extinction (Lissek *et al*, 2005; Milad *et al*, 2008; Milad *et al*, 2009). Anxiety disorders typically have their onset in adolescence (Kessler *et al*, 2005), highlighting the importance of understanding the mechanisms underlying both the typical and dysregulated development of the fear neurocircuitry. The basic mechanistic understanding of critical periods within the visual system have informed developmentally timed treatments for disorders such as amblyopia. Similarly, treatments for fear-related disorders such as post-traumatic stress disorder might be tailored as a function of age to employ specific interventions at a developmental stage when they may be most effective. As an example, the attenuation of fear extinction associated with adolescent development may hinder responses to traditional psychotherapy, such as cognitive behavioral therapy (CBT). Because CBT desensitizes an individual to anxiogenic stimuli through repeated exposures (ie extinction learning), future studies aimed at examining whether this treatment is effective during adolescence, when extinction learning is attenuated, may provide insight into how to optimize treatment strategies for anxious individuals. Finally, gaining better understanding of the molecular 'brakes' on fear-related plasticity will inform future targeted pharmacological interventions that could be used in combination with the behavioral intervention to reopen

windows of plasticity to attenuate fear and anxiety-symptoms, which are core features of numerous psychiatric disorders.

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