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Emotional learning, stress, and development: An ever-changing landscape shaped by early-life experience

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Abstract

The capacity to learn to associate cues with negative outcomes is a highly adaptive process that appears to be conserved across species. However, when the cue is no longer a valid predictor of danger, but the emotional response persists, this can result in maladaptive behaviors, and in humans contribute to debilitating emotional disorders. Over the past several decades, work in neuroscience, psychiatry, psychology, and biology have uncovered key processes underlying, and structures governing, emotional responding and learning, as well as identified disruptions in the structural and functional integrity of these brain regions in models of pathology. In this review, we highlight some of this elegant body of work as well as incorporate emerging findings from the field of developmental neurobiology to emphasize how development contributes to changes in the ability to learn and express emotional responses, and how early experiences, such as stress, shape the development and functioning of these circuits.

Introduction

The study of emotional memory has garnered significant interest in recent years for its inherent role in various psychiatric disorders (1). Dysregulation of emotional memory systems is a principle component in many affective disorders, including depression, specific phobias, generalized anxiety disorder, agoraphobia, and post-traumatic stress disorder (PTSD). Specifically, alterations in memory processing for aversive or traumatic experiences lie at the heart of many clinical psychiatric disorders. By studying the neural circuitry of emotional memory, and aversive learning specifically, insight can be gained into not only how these systems function normally, but also how they may go awry in the case of pathology. By taking into account developmental, environmental, and genetic factors, the

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hope is that such insights will inform basic science, enhance translation to the clinic, and ultimately lead to better treatments and preventative measures for vulnerable populations.

In archetypical circumstances, fear learning is a highly adaptive, evolutionarily conserved process that allows one to respond appropriately to cues associated with danger in order to enhance future survival. In the case of psychiatric disorders, however, fear may persist long after an environmental threat has passed. This unrelenting, and often debilitating, form of fear is a core component of many anxiety and stress-related disorders, including post-traumatic stress disorder (PTSD), and often involves exaggerated and inappropriate fear responses, as well as a lack of reappraisal once a stimulus no longer holds predictive validity. It is estimated that 18.1% of Americans, or 40 million people, are living with a diagnosable anxiety disorder. In the U.S. the lifetime risk for depression is 3–5% for males and 8–10% for females, the lifetime risk for PTSD is 5% for males and 10% for females, and nearly 29% of people will develop some form of anxiety disorder (2, 3). Affective disorders cost the American people in excess of \$42 billion a year, which is approximately one third of the total \$148 billion spent on mental health (4–6). Furthermore, according to the World Health Organization, the burden of disease for neuropsychiatric disorders on the country exceeds that of any other medical condition, even doubling that of cardiovascular disease (4), and anxiety disorders pose the greatest threat to mental health worldwide (7).

It should also be noted that the risk for affective pathology increases in late childhood and peaks during adolescence and early adulthood, indicating that either the development or the expression of affective pathology is linked to key developmental events (8). While these disorders are treatable in many individuals, they carry with them high rates of comorbidity and recurrence (8). By understanding the neural basis of stress-associated disorders and focusing on early time points, before pathology has emerged, we open up the possibility of developing better, more effective interventions, that have the possibility of preventing the development of these devastating disorders. Adolescence, in particular, is a period associated with increased prevalence of psychopathology involving perturbation of emotion (9), and it is estimated that over seventy-five percent of adults with fear-related disorders met diagnostic criteria as children and adolescents (10, 11). Pediatric and adolescent-onset anxiety disorders are associated with increased symptom severity compared to disorders that emerge later in adulthood. Despite the fact that diagnosis of anxiety disorders peaks in pediatric and adolescent populations (2, 6, 12), fewer than one in five children or teens are expected to receive adequate treatment (5, 13, 14). In addition to developmental aspects, genetic variants, combined with environmental exposures to physiological and psychological stressors, can profoundly impact neural substrates implicated in fear and anxiety, rendering specific populations more or less susceptible to developing psychiatric disorders at different stages of their lives.

Specifically, early life stress (ELS) significantly increases the risk for the later development of affective pathology. A single stressor experienced during childhood increases the lifetime risk of anxiety or depressive pathology by approximately 30% (15). Sixty-four percent of individuals will experience at least one significant stressor during childhood (15). Having three or more adverse experiences early in life more than doubles the lifetime risk of developing affective pathology (15). In addition, there is a significant sex disparity in the

incidence of affective disorders, with females being nearly twice as likely as males to develop pathology (8, 16–27).

For animals, human encroachment and climate change have led to loss of habitat (and breeding grounds) and destruction of food sources. In humans, increasing civil unrest, famine, and poverty have resulted in an unprecedented 65 million individuals being displaced and nearly 650 million children worldwide who lack adequate shelter, water, or health services. Across species, these effects have diminished the ability of parents to care for and nurture offspring, increasing the incidence of early life stress, with consequences for emotional and behavioral development that extend beyond borders and across species. The goal of this review is to provide novel insight into the development of key circuitry supporting the development of emotional learning and emotional regulation and the mechanisms by which changes in species expected environments, such as diminished early life care, alter the development of these processes.

Many forms of emotional pathology are thought to have their root in aberrant development of brain regions responsible for emotional responding as well as emotion regulation. Specifically, several key regions associated with the control of emotional learning have been identified, including the amygdala, hippocampus, and sub-regions of the prefrontal cortex. Recent work has identified unique effects of developmental status, exposure to early life stress, as well as genetic background on the development and functioning of these brain structures. Specifically, work from our lab has found that exposure to early life stress is associated with a precocious process of maturation for at least a subset of these structures, effects that are mirrored in human studies of functional brain activation to emotional cues and functional connectivity. How these changes contribute to increased risk for pathological outcomes, as well as the molecular drivers of altered maturation of these regions represent a fertile area of investigation to potentially identify the neural substrates of pathology, and to identify both novel treatments as well as optimal timing of intervention. Critical work, leveraging models of emotional learning that can be tracked over developmental time frames have the potential to shed light on this important question.

Modeling fear in the laboratory: Pavlovian Conditioning

Considered by many to be the father of modern neuroscience, Santiago Ramon y Cajal stated over a century ago that “the brain is a world consisting of a number of unexplored continents and great stretches of unknown territory” (28). While many unanswered questions about the brain undoubtedly remain, great advances in recent years have uncovered a wealth of information about the neural circuitry involved in fear acquisition, expression, and extinction, offering glimpses into anxiety disorder etiology and treatment.

Fine-grained work in nonhuman animals combined with advances in functional neuroimaging (through PET and fMRI scans) have revealed neural processes involved in fear regulation. Observations across clinical patient cases, healthy human subjects, and non-human animals all substantiate a preservation of fear acquisition and extinction learning mechanisms and basic architecture across species. As a result, rodent models have the potential to provide unique insights into the development and functioning of these circuits,

neural mechanisms supporting core features (endophenotypes) that comprise more complex emotional disorders, and a testing ground to explore novel interventions and treatments of cores symptoms of these debilitating conditions (1, 29)

Through the use of associative learning techniques that are based on the principles of classical conditioning, long-lasting, aversive memories can be quickly formed in the rodent (30). This form of learning in animal models is frequently relied upon due to the simplicity of the paradigm, the rapid induction of fear, and the high level of experimental control (31). As such, behavioral paradigms relying on Pavlovian principles have become standard for studying fear in both humans and nonhuman animals (32). Typically, an inherently threatening and/or unpleasant stimulus, such as an electric shock or aversive noise, serves as an unconditioned stimulus (US), while a previously neutral stimulus, such as a light flicker or tone, serves as the conditioned stimulus (CS). Through single or multiple pairings of the CS with the US, an association is formed such that the CS becomes predictive of the US. Eventually, after the CS-US association has been learned, presentations of the CS alone are capable of driving a nearly identical fear response that which is induced by exposure to the US alone. This conditioned response (CR) is often characterized physiologically by changes in autonomic arousal and behavior, which can be observed in the rodent as freezing behavior and as galvanic skin response (GSR) in humans. Once the CS-US association has been formed, the CR can then be extinguished by giving multiple presentations of the CS alone, in the absence of the US. The initial CS-US pairing is not forgotten during the extinction process, but rather a new memory is formed, in which the CS is no longer predictive of threat (33). Extinction learning, not to be confused with the process of mere forgetting, is a learning process in which the learned output associated with CS must be inhibited (34, 35). By presenting the CS repeatedly, in the absence of any US, one can reevaluate the predictive validity of the CS as a signal of an impending US, thus learning that a stimulus that was once associated with threat is no longer a valid predictor of that threat. Uncovering information behind the mechanisms involved in fear acquisition, and extinction in particular, has wide clinical implications, as the most common and validated treatment for anxiety disorders involves exposure-based therapy, which relies heavily upon extinction principles for reevaluating existing contingencies (36). Strong cross-species preservation of the neural circuitry implicated in fear extinction learning is supported by human and nonhuman animal extinction studies, further bolstering the translational potential of rodent models for studying fear regulation and extinction (37).

Modeling early life stress in the laboratory

Stressors consist of anything that challenges the survival of the organism (38, 39). Modest levels of stress are inevitable, and may in fact be the catalyst for experience-dependent changes in physiology and behavior, supporting structural and functional changes associated with memory consolidation, behavioral regulation, and developmental process (39–43). However, chronic or excessively high levels of stress (toxic stress) have been shown to have deleterious effects, impacting neural structure and functional plasticity of the brain as well as contributing to negative health outcomes (44–50). As important as the absolute level of stress, is the timing of stress exposure, with exposure to stress early in life having particularly potent and lasting effect. Early in life, parental and social interactions can often

serve as a buffer against the negative consequences of stress on physiology and learning (51–57). However, if rearing conditions are suboptimal, parental stress can be rapidly transmitted to the offspring and serve as the primary source of stress, driving changes in development and neurobehavioral outcomes (58–68).

In rodents, multiple paradigms exist to induce early life stress (ELS) through manipulation in maternal care, including maternal handling (58), maternal separation (59, 69), maternal deprivation (68, 70), natural variation in the quality of maternal care (71), and maternal bedding manipulation paradigms (61, 62, 64, 67, 72). The recent use of maternal bedding manipulation paradigms offers advantages over other approaches as (1) it mirrors loss of resources to care for the young, (2) induces stress in the dam resulting in reliable changes in the dynamic interactions between mother and pup (e.g. fragmentation of maternal care in the form of more forays away from the nest), and (3) increases variability in the time and duration of care bouts (62, 73). Furthermore, use of this paradigm allows for a sustained induction of ELS throughout a defined period during the first weeks of life, limits experimenter impact associated with handling and observation, and limits the introduction of additional variables that can impact neurodevelopment, including sustained effects on thermoregulation and malnutrition. This model has been well characterized, leads to reliable induction of stress in pup, and effects that have been replicated by more than a half a dozen labs (64, 66, 67, 72, 74–77). In addition, this form of manipulation appears to have potent effects on the development of circuits underlying both the fear response as well as regulation of the stress axis (78, 79).

Underlying neural circuitry of fear processing and stress related disorders

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 (80) and in 1937, Kluver and Bucy demonstrated that monkeys with temporal lobe resections displayed many preternatural behaviors, including complete loss of fear (81). Despite advances made during the turn of the century, it was not until the late 1950's, when it was discovered that a group of nuclei buried within the temporal lobe was responsible for these changes in fear behaviors (82–84). 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 (85). While normal, healthy subjects express a fear response, as evidenced by increased skin conductance response (SCR) to a CS paired with an aversive noise, temporal lobectomy patients are unable to express a similar autonomic fear response, despite the fact that their verbal description of the CS-US connection is intact (85).

Validating these structural-functional relationships of brain and behavior observed in patient populations, unilateral amygdala damage in fear-conditioned rats results in attenuated fear expression, as evidenced by decreased levels of freezing behavior (86). After probing further into fear neural circuitry through lesion, inactivation, electrophysiological, molecular, and pharmacological studies, the amygdala has been confirmed to be a key structure involved in fear acquisition (31, 87–90). During standard auditory fear conditioning, both the aversive

stimulus such as a foot-shock (US) and auditory signal such as a tone (CS) converge, temporally and spatially, in the lateral nucleus of the amygdala (LA) (91–93). Generally, the US alone (but not CS) drives activity of the LA to produce an output from the central amygdala (CE) to generate a fear response. Likely due to the temporal and spatial convergence of the US and CS signals in the LA, following repeated pairings, the CS alone (independent of the US) becomes capable of driving activity within the LA and an output from the CE.

While the basal (BA) and lateral (LA) nuclei (collectively known as the BLA) are considered to make up the primary sensory interface involved in fear learning and acquisition, the central nucleus (CE) is the amygdala's interface to fear response systems (30). Once sensory information is integrated by the BLA, this information is relayed to the CE both directly and indirectly (93, 94). After the intra-amygdaloid message has been conveyed from BLA to CE, the CE can drive various responses via its divergent projections to downstream efferent structures. CE projections target various hypothalamic and brainstem nuclei responsible for engaging autonomic responses such as increased heart rate, blood pressure, respiration, freezing behavior, acoustic startle, and glucocorticoid release (93, 95)

Importantly, contextual cues and surrounding environmental factors have 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 (BA) of the amygdala are implicated in contextual information processing during fear acquisition (33, 96) and lesions to dorsal hippocampus disrupt both acquisition and expression of contextual fear (97–99). While the CE remains the prime site in the amygdala that is responsible for driving autonomic responses and fear behaviors, hippocampal-BA integration of contextual information can alter downstream CE activity and affect subsequent behaviors. By picking up on environmentally relevant cues, the hippocampus can provide a direct signal to drive a fear response as well as 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 (30).

Whereas patients with selective amygdala damage lack the prototypical autonomic response associated with fear-conditioning, patients with selective damage to the hippocampus are unable to verbally describe any CS-US association, despite being able to drive appropriate autonomic responses to the CS (100). This double dissociation of fear conditioning and declarative knowledge involving the hippocampus and amygdala in humans parallels findings from animal models (100).

Increased spike-firing in amygdala neurons (91), and long-term potentiation (LTP), or enduring synaptic plasticity, has been shown to occur at synapses in the hippocampus and amygdala during fear conditioning and expression (90, 101, 102). 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 (88, 103–105) further confirming the role of these two structures in fear acquisition and expression. Disruption of downstream signaling cascades, including protein kinase A (PKA) (106) 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 (107, 108).

Stress and Development of Fear Learning

The development of structures underlying fear learning undergo a protracted development. Indeed, work by the Frankland, Hunt, Stanton, Sullivan, and Richardson labs, as well as others, have carefully mapped the course of development of various aspects of fear learning. As one example, Sullivan and colleagues identify some of the earliest emerging forms of fear learning through their work assessing the development of odor-shock pairing during the postnatal period. In this work, they have found that up until P10, rat pups learn to approach an odor even after it has been paired with a painful stimulus, such as 0.5 mA shock. This appetitive association is thought to be the results of low basal levels of corticosterone, leading to limited engagement of the amygdala, and elevations in noradrenergic signaling (109). This appetitive association persists until around P10–P12, when there is a transition to the prototypical fear associated learning. At this time, odor shock pairing drives elevated corticosterone levels, enhanced activity of the BLA, and learned avoidance of the odor in the future (110, 111). Importantly, the development of fear-associated learning is sensitive to the early environment, and particularly to exposure to early life stress. Sullivan and colleagues went on to show that rats reared in an environment in which they manipulated maternal bedding, or rats exposed to corticosterone during the early postnatal period (prior to P7), were able to engage the amygdala in response to odor-shock pairings a full three days earlier, at P7, and generated a fear response/avoidance when presented with the odor in the future (112). Thus, the ability to map a CS-US pairing as well as the form of the learned response is highly dependent upon the age at which animals are tested, the developmental status of the structures supporting the learning, and the ontogeny of these behaviors can be significantly impacted by the early environment.

Extinction of conditioned fear

Once the CS-US associations has been acquired and consolidated via amygdala and hippocampal plasticity, repeated presentations of the CS alone, in the absence of any US, can lead to modifications of the initial fear memory. This inhibitory form of new learning requires a reappraisal of the once-threatening CS, shifting the CS's role from a cue of danger to a cue of safety and underlies the basis for cognitive behavior therapy (CBT). Through multiple presentations, or sessions, the previously fearful behavioral response becomes extinguished, resulting in a diminished CR. While the amygdala itself plays a significant role in extinction learning (113), lesions to cortical areas have also been shown to interfere with extinction learning (114) demonstrating that the extinction process requires top-down control and interactions between both cortical and subcortical regions (1).

Cortical regions implicated in the extinction of conditioned fear include areas of the prefrontal cortex, a region that is important for integrating information as well as regulating behavioral outputs whenever the emotional salience of a given stimulus changes (93). The ventromedial prefrontal cortex (vmPFC), in particular, has been shown to be important for making the switch from fear expression to fear inhibition during fear extinction learning and

retention of extinction memory (115–117). Further subdividing this cortical area, distinct subregions within the vmPFC have been implicated in either the expression or extinction of conditioned fear (118–120). Specifically, the dorsally located prelimbic cortex (PL) is associated with production and sustained expression of conditioned fear responses (121) whereas the more ventrally located infralimbic cortex (IL) is associated with consolidation, retention and recall of fear extinction memory (122–124). Importantly, the ventromedial prefrontal-hippocampal network can modulate extinction learning by picking up on contextual cues present in the surrounding environment (125–128) and lead to appropriate alterations in behavior. With continued presentations of a given CS in the absence of a US during extinction, the vmPFC exerts inhibitory effects on amygdala circuitry, particularly through its excitatory glutamatergic projections to intra-amygdalar inhibitory GABAergic interneurons (116). These inhibitory interneurons, or intercalated cells (ITC cells), can be activated by PL or LA neurons during fear conditioning to relieve inhibition on inhibitory CE neurons, thus resulting in expression of fear and associated autonomic responses. During extinction learning, however, a subset of ITC cells can be activated by inputs from IL and inhibitory neurons within PL, which are modulated by the hippocampus, and lead to downstream active inhibition of CE output neurons, thus inhibiting 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 in distinct environments. Human subjects with thicker vmPFCs have been shown to have significantly enhanced fear extinction compared to control subjects (129) whereas PTSD populations, with persistently generalized and inappropriate fear responses, tend to show exaggerated amygdala reactivity with reduced mPFC and hippocampal activation (130–132). 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. Studies with nonhuman animals, healthy human subjects, and clinical populations highlight a conserved role for this vmPFC-hippocampal-amygdalar circuit in the mature adult brain for mediating appropriate responses to potentially threatening cues. 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.

While this level of simplification is undoubtedly necessary for fine-tuning precise experimental manipulations, there is a risk of losing sight of broader scale integration between various brain systems and their many subdivisions (95). To further complicate the understanding of the already complex neural circuitry implicated in fear and aversive learning, the brain is dynamically changing across development in both rodents and humans, and changes in structural and functional maturation have a significant impact on resulting neural processes and behaviors. As the incidence of affective disorders, including anxiety disorders, peaks during childhood and adolescence in human populations (2), research into how the neural circuitry mediating aversive learning and emotion regulation is altered during neuro-developmental sensitive periods remains of great importance.

Sensitive Periods: Fear Learning and ELS

Fear Learning

Advances within the field of emotional memory over the past several decades yielded a wealth of information in regards to how fear memories are acquired, expressed, consolidated, and extinguished. In light of these behavioral, neural, and molecular advances, the systems mediating fear learning and aversive memory are often portrayed in diagrammatic representation as oversimplified, closed circuits, consisting of isolated brain regions, with primary focus on the thalamus for sensory input, amygdala for fear learning and expression, and prefrontal cortex for modulation of existing fear memories. Often this simplification fails to take into account the dynamic changes in regional development, and regional involvement in fear learning, over the course of early development. The inflated frequency of anxiety disorders in pediatric and adolescent populations highlights the importance of recognizing neural mechanisms of fear regulation from a developmental perspective.

Adolescence is a highly conserved developmental stage, both neurobehaviorally and physiologically, during which the adolescent must meet evolutionary pressures associated with sexual maturation (137), and as such, animal models offer face and construct validity for studying this particular subset of the developing population. While researchers have expanded upon findings from adult mice and rats to elegantly explore the ontogeny of conditioned fear expression and extinction and infantile memories (the focus of such work has primarily been on infant and juvenile models (134, 136, 138–143). Rodent models have only very recently started incorporating older, more intermediate, adolescent ages (144–149). Because adolescence is a time when the emergence of fear related disorders is peaking in human populations (2), the studying of its effects on animal models of fear conditioning models warrant further exploration. Of particular importance for this vulnerable age group are the deleterious effects such disorders can have on social and academic contexts (150), as well as the enhanced potential for persisting psychiatric disorder in adulthood (151). Because adolescence is also a time associated with prototypical increases in risky behavior and thrill seeking (152–154), seeking more effective treatments for anxiety and affective disorders in this population may also indirectly lead to reductions in substance abuse and other maladaptive behaviors often employed as forms of anxiolytic self-medication.

Highly conserved neural circuitry between rodents and humans has allowed for in-depth characterization of behavioral and molecular processes associated with emotional learning and memory and it has recently been shown, by our group and others, that there are sensitive periods for fear learning during adolescence (145, 149, 155–157). While critical periods of development have traditionally been referred to as windows of extreme interdependence between experience and behavior, after which a decrease in neural plasticity typically renders the behavioral outcome irreversible, sensitive periods as described in this review refer to windows of heightened plasticity during which neural development is especially sensitive to particular types of experiences (either more or less so)(158).

By examining fear-conditioning in mice, as they transitioned into and out of adolescence, we uncovered a novel aspect of fear learning in which contextual fear expression was

suppressed in adolescent mice. This lack of contextual fear expression did not result from global impairments in fear memory acquisition or consolidation, as amygdala-dependent cued fear was intact at all developmental ages examined and correlated with electrophysiological recordings in their amygdalae. Interestingly, despite a suppression of contextual fear expression and corresponding blunted synaptic activity in the basal amygdala and decreased PI3K and MAPK signaling in the hippocampus during adolescence, mice were able to retrieve and express the contextual fear memory as they transitioned out of adolescence and into adulthood. This transition occurred in concordance with a delayed increase in basal amygdala activity, highlighting the importance of this developmental transition on behavioral, neural, and molecular outcomes. To our knowledge, the observed delayed expression of contextual fear represents a novel form of plasticity within the neural circuitry mediating fear learning in mice. The characterization of these developmentally regulated learning processes was performed using a mouse model without context pre-exposure facilitation effect (CPFE) procedures in effort to best parallel real-life traumatic experiences in which cues and contexts are experienced simultaneously. This contextual fear suppression has been replicated in adolescent mice when using background contextual fear conditioning (67) yet not when adolescent mice receive context pre-exposure facilitation effect (CPFE) in foreground contextual conditioning (135). Additionally, these studies employed a mouse model, as opposed to the more common rat model, which has been popularized in fear-conditioning studies for its robust and easily assayed behavioral responses. Studies with adolescent rats demonstrate intact contextual fear responses throughout development (138, 139, 159, 160) and may in part be due to the fact that mice exhibit earlier maturation of certain brain regions (161) and earlier onset of puberty (162, 163). Employing a developmental model in mice, as opposed to rats, however, allows for the future use of more established mouse genetics tools to explore age-dependent differences in emotional learning, genetic contributions to learning, consolidation, and fear expression, as well as study the interaction between these genetic differences and the early environment (for Gene X Development interactions, see (164)).

During this same sensitive developmental period of contextual fear suppression, cued fear expression appears to be intact and highly resistant to extinction - in both rodents and humans (145, 156, 165, 166), which is in contrast to extinction learning and retention in juvenile and adult animals. In addition, in adult rats significant sex differences have been observed in the manifestation of fear responding, with females showing a preferential bias toward engaging in escape behavior (rapid movement) in lieu of freezing (167), however, whether these differences are present earlier in development have not been fully established. The period of diminished capacity for extinction learning coincides with a time when the prefrontal cortex is undergoing maturational changes in the dynamic interaction between vmPFC and amygdala (168) and correlates with blunted infralimbic activity in rodents on fear extinction tasks (149, 156). Converging evidence from human and rodent studies suggests that insufficient top-down regulation of subcortical structures (169–172), such as the amygdala, may coincide with impairments in prototypical extinction learning. Because this top-down regulation is necessary for mediating successful extinction learning during re-exposure therapy often used in CBT, it is important to discern how developing populations with immaturities in the circuitry required for top-down control will respond to classic

extinction paradigms and studying the effects of adolescent development on fear learning and memory may offer great insight into better ways to treat vulnerable populations.

This increased prevalence for anxiety and affective disorders during adolescence coincides with a period of massive cortical rearrangement that is normally accompanied by drastic cognitive and behavioral changes (153) and longitudinal studies of brain maturation illustrate a nonlinear process that is not complete until the transition from late adolescence to early adulthood (173–175). Age-dependent, linear increases in white matter and nonlinear increases in gray matter progress in a regionally specific manner and are indicative of increased axonal myelination and synaptic pruning characteristic of cortical maturation (173, 174, 176, 177). Areas associated with sensory and motor processing mature first, while areas associated with top-down control, response inhibition, and executive function are the last to show functional maturation (173, 178). Prefrontal cortical regions, such as those implicated in fear extinction learning, undergo protracted development relative to subcortical structures including the amygdala. As reviewed above, through opposing IL and PL inputs, the mPFC is a functionally heterogeneous area, exerting bi-directional control over the amygdala during various aspects of fear conditioning (179, 180). During tasks involving self-regulation and re-appraisal, children show a greater and more diffuse activation of prefrontal loci compared to adults, suggestive of regional immaturity (169, 170, 181). It is of clinical interest to examine whether diffuse patterns of PFC activity, observed in children adolescence during tasks requiring control of subcortical structures, will also influence the precise interactions between inhibitory and excitatory hippocampal-prefrontal-amygdalar circuits during fear regulation. Moreover, healthy adolescent humans display higher basal activity in frontal-amygdala circuits regardless of the type of task being performed, again possibly due to immaturity of the circuit, which may alter the balance in excitation and inhibition of the finely tuned glutamatergic/GABAergic bi-directional projections to the amygdala (9, 116).

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, (182), development of the structure has been shown to continue through adolescence in both rodents and primates (183–185). Longitudinal scans of children and adolescents, between the ages of four and twenty-five years, reveal that postnatal hippocampal development is not homogenous and that distinct maturational profiles exist for specific subregions (186). 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. While the cause of these heterogeneous volume changes remains unknown, 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 (186). 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 (187), amygdala (94, 188), and hypothalamic-pituitary-adrenal axis (189), all 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, which shows that contextual fear

expression during pre-adolescent ages is intact, temporarily suppressed during adolescence, and then reemerges again during adulthood, 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 region of the brain may alter the structural and functional connectivity with another region of the brain. Convergent data from adolescent and adult rodent contextual fear studies highlight the importance of the developing hippocampus in mediating both cued and contextual fear responses during this sensitive period. Recent work from our group utilizing retrograde tracers reveals that there is enhanced structural connectivity between the ventral hippocampus and PL during adolescence compared to juvenile and adult mice and that this surge is from hippocampal neurons projecting to PL (157). Two-photon imaging of the developing mPFC reveals that this period of enhanced structural connectivity also coincides with a surge in formation of excitatory post-synaptic dendritic spines in the mPFC that occurs during adolescence. Dense populations of PL-projecting cell bodies within the BLA were also significantly increased from juvenile period to adolescence and subsequently decreased by adulthood, which highlights the non-linear maturation within the mPFC-hippocampal-amygdala circuit. This temporary surge in connectivity between BLA and PL (projecting from BLA to PL) during adolescence may maintain a positive feedback loop contributing to the extinction-resistant cued fear expression at this age (145, 156). Given the importance hippocampal-PL inputs for suppressing fear expression (128, 190, 191), we sought to maximally target the contextual component of a prior conditioned fear by combining cued and contextual extinction into one session. While the surge in vCA1-PL connectivity may be insufficient to override PL-BLA activation during cued extinction, this vCA1-PL activation may be utilized for persistently suppressing contextual fear and exploiting this enhanced capacity for contextual extinction in a combinatorial context-cue extinction session offered significant benefit to cued extinction alone during this adolescent sensitive period (157), while also offering a benefit to adult mice, albeit not as robust a difference given that cued fear extinction alone is effective in this older age group. Moreover, utilizing the contextual component of an adolescent fear memory—during a time when it was not behaviorally expressed – prevented the fear from re-emerging when they mice entered adulthood, highlighting the potential for prophylactic behavioral treatments specifically during this adolescent sensitive period.

Stress and the stability of fear memories

Interestingly, like the development of fear learning, the stability as well as ability to suppress the learned emotional response is dependent upon developmental status. For example, cued fear conditioning in the form of tone shock pairings are reliably used in the adult animals to induce relatively stable and long-lived fear associated memories. However, at P17, these memories appear to be more fleeting. Specifically, rodents undergoing tone shock pairings prior to P17 typically retain this memory for only about 10 days (133–135), a phenomenon that has been termed infantile amnesia. Unlike adult memories, which require top down modulation to suppress the learned fear response, these memories appear to degrade. However, over the course of development these memories become far more stable, an effect that may be related to the development of frontal regions, including the PL, which is critical

for sustaining the fear response or changes in molecular and synaptic processes engaged in the consolidation of these memories. Still others have argued that instability in the system during this stage may contribute to the fleeting nature of memories early in life (135). The developmental course of this infantile amnesia period may also be sensitive to early life stress or early life priming with stress hormones. For example, Callaghan & Richardson found that maternal separation stress or CORT exposure during the early postnatal period (P2–P14), resulted in far more stable memories in rats fear conditioned at P17, with memories lasting for up to 30 days post conditioning (136). In a related series of studies, Callaghan and Richardson tested the effects of this same form of stress on fear renewal and fear reinstatement. Typically, rats conditioned at P17, lose the fear memory and are resistant to relapse or show no signs of prior conditioning during reinstatement. Interestingly, rats exposed to maternal separation did show signs of fear renewal and fear reinstatement following protracted delays, suggesting an adult-like system in the P17 rats (136). The authors argue that early life stress and/or Cort exposure leads to precocious maturation of the GABA-ergic system to support this early transition. Regardless, it again appears that the stability, form, and regional engagement of neural structures is highly dependent upon developmental status, and that the ontogeny of these behavioral is susceptible to early environment.

Early life stress

As outlined above, dynamic changes in the neural architecture, connectivity, and functional development of hippocampus, amygdala and frontal cortex serve to support learning and expression of emotional behaviors. These regions are known to be highly sensitive to changes in circulating levels of the stress hormone corticosterone (CORT). Engagement of CORT receptors (MR and GR) are thought to be critical for supporting developmental change, augmenting plasticity, and driving structural and functional plasticity to support learning about signals of danger in the environment. However, when elevations in CORT or stress exposure becomes chronic, activation of this system can have toxic effects on neuronal function and cellular morphology, drive changes in MR and GR expression, diminish plasticity, and lead to decreased hippocampal volume, thinning of prefrontal cortical regions, and hypertrophy of the amygdala (49, 192–197). Altered structure and function of these regions have been heavily implicated in the development of stress-associated pathology. For example, in humans, reduced hippocampal volume is associated with major depressive disorder (198–200) as well as stress-related conditions, including post-traumatic stress disorder (PTSD) (201). Diminished hippocampal volume in these populations are thought to be the result of atrophy or loss of neurons and suppressed neurogenesis (possibly as a result of stress exposure). Consistent with such a hypothesis, the stimulation of the HPA system through chronic treatment with stress hormones can induce anxiety and depressive-like symptoms and mimic stress-induced dendritic atrophy (202–204), pyramidal cell modifications (205, 206) and suppression of hippocampal neurogenesis (46, 50, 207–210). Much of this work investigating stress effects on neural structure and function has been largely focused on the adult animal, with developmental work focusing on either the immediate consequence of stress on developmental process or outcomes in adolescence and adulthood, with few data points in between. An emerging body of work has begun to

uncover novel effects of early life stress on behavioral and emotional development and to track the evolution of these behaviors over early developmental time points.

Stress incurred early in development has particularly potent effects on developmental process, with changes being observed at the somatic, neural, and behavioral levels. Consistent with observations in the adult animal, in the developing hippocampus and cortex, ELS or stress hormone exposure lead to: diminished cell proliferation and increased cell death (194, 211, 212), enhanced turnover and progressive loss of dendritic arbors and spines (213–215), decreased synaptic density (216), and reduced volume in adolescence and adulthood (192, 193). Based upon these results it has been argued that stress may serve to truncate the process of neural growth through effects on these processes.

Recent work by our lab and others has found novel effects of early life stress on the maturation of a subset of these circuits. Specifically, we have found that early life stress in the form of altered maternal care, leads to an earlier arrival and peak in interneuron development in the hippocampus, as well as precocious expression of markers of myelination and synaptic maturity (67). In tracking the behavioral development of animals exposed to early life stress we find a precocious maturation of emotional learning, as mice exposed to ELS demonstrated an earlier emergence of contextual fear inhibition, as described above (67). Similar effects of early life stress and chronic early exposure to CORT have been found in other systems. For example, in rodents, priming of the developing brain with stress hormones leads to an earlier emergence of defensive behaviors (217, 218). ELS in the form of manipulations of maternal care or stress hormone exposure leads to a precocious switch from appetitive to aversive learning in a cued fear conditioning paradigm involving olfactory signals (110, 219), effects that have been correlated with earlier functional maturation of the amygdala. Still other groups have found that early stress exposure leads to more adult-like forms of fear extinction in juvenile animals (220), and that these effects seem to be dependent upon intact functioning of frontal inhibitory networks. Effects of ELS on emotional learning have also been found in humans, with individuals exposed to institutionalized rearing showing an earlier expression of adult-like functional connectivity between frontal and limbic brain regions compared with age matched controls (168) and more adult-like circuit activation when exposed to emotional stimuli.

Conclusion

Based upon this emerging body of work, it is becoming clear that emotional learning across childhood and adolescence is a dynamic process, grounded in nonlinear maturation of the neural circuitry associated with subsequent behavioral outcomes. Moreover, stress can profoundly impact the timing of circuit development, both impairing growth as well as stimulating maturation, which may have consequences for the development and continued functioning of circuits regulating emotional reactivity, as outlined in Summary Figure 1 which highlights findings from rodent models. Shifts in developmental timing have the potential to alter neural organization, the timing of sensitive periods, and functional coupling of brain regions, with implications for altered physiological and behavioral response to the environment throughout life. Understanding normative developmental change and the impact of the environment on the timing of these events is relevant to a broad scientific

audience but also has the potential to have an immediate impact on the development of translational programming aimed at prevention and timing of interventions for children and animals experiencing adversity (221), as well as for identifying factors mediating risk and resilience. Further research targeted toward a deeper understanding of both normative and aberrant developmental patterns has the potential to uncover novel findings about the maturation of neural circuitry implicated in emotional learning and behavior that may subsequently help improve intervention and treatment outcomes for specific vulnerable populations.

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Highlights

- Development of fear learning is dynamic process that changes dramatically across early life.
- The neural centers underlying fear learning undergo complex nonlinear changes in connectivity across postnatal developmental.
- The development of these centers regulating fear learning is highly sensitive to early environment.

Figure 1.

Developmental and stress associated effects on fear-conditioning in rodent models. Based upon an emerging body of work, we plot the time course of emergence and persistence of fear learning, expression, and extinction across the early life span. Plotted time course is based upon combined data from both mice and rats. Developmental emergence of behavioral profiles appears to mirror the sequential development of subcortical to cortical structures. To date, work in models employing early life stress (ELS) or stress hormone exposure has found these manipulations to accelerate the developmental onset multiple aspects of emotional learning, including neuroanatomical and behavioral outcomes.