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Growing Pains and Pleasures: How Emotional Learning Guides Development

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SUMMARY

The nervous system promotes adaptive responding to myriad environmental stimuli by ascribing emotion to specific stimulus domains. This affects the salience of different stimuli, facilitates learning, and likely involves the amygdala. Recent studies suggest a strong homology between adaptive responses that result from learning and those that emerge during development. As in motivated learning, developmental studies have found the salience of different classes of stimuli (eg peers) undergoes marked fluctuation across maturation and may involve differential amygdala engagement. We suggest that variability in amygdala response to different stimulus domains may play an active and functional role in shaping emerging cortical circuits across development by highlighting the importance of particular stimulus categories during sensitive periods of development.

Keywords

Sensitive periods; amygdala; cortex; social

INTRODUCTION

A primary function of the central nervous system is to optimally match behavior with environmental conditions. An important modulator of this process is emotion. Emotion can be construed as the synergistic response of multiple independent body systems in response to a stimulus¹. Emotion induction enables both an orchestrated response and flexible attribution of salience to environmental stimuli. Importantly differential emotional responses can be tailored to match the internal state of the organism with the stimulus or context in which it is encountered¹⁻³. Thus, an emotional response is an intrinsic signal ascribed to a stimulus that flexibly signals its importance. Another important function of emotion is that it facilitates learning by enhancing sensory experience, focusing attention, and promoting long-term consolidation of sensory experience⁴⁻⁶. Emotional responses also promote expression of optimal responses to emotion eliciting stimuli⁷ which can be rapidly executed during subsequent encounters.

Such emotional mediation effects are typically studied in a learning context where relatively rapid shifts in both emotion and behavior take place. Another process in which response tendencies are crafted by environmental conditions to optimize the match between individual and environment is development⁸ (Box 1). Indeed the similarities between learning and development are such that they are often considered analogous processes⁹ (Box 2). Many studies have demonstrated that in development, as in learning, emotional experiences induced by particular stimuli can act as a key modulator of stimulus impact and profoundly influence maturational outcome^{10–13}. Thus, just as in learning, emotional responses to stimuli in development play an important role in highlighting the significance of different stimuli and promote an ideal match between organism, behavior, and environment.

A key aspect of developmental adaptations is that the timing of stimulus encounters is of utmost importance. Development progresses through a series of sensitive periods or time windows during which particular classes of stimuli (or stimulus domains) are highly influential in affecting the course and trajectory of maturation^{14, 15}. This time-sensitive and domain specific property of development highlights the importance of maximizing the impact of relevant experiences during developmentally appropriate periods. While there are a number of factors that influence the potency of discrete classes of stimuli across development, here we suggest that differences in emotional response may be an important, and often overlooked, means of heightening the salience of environmental features at specific sensitive periods.

Based on a similar role in learning paradigms we suggest that an important neuronal hub in this process is the amygdala. The amygdala is thought to be a key region for the orchestration of emotional responding, and for the flexible attribution of salience to different stimuli in the environment. In addition the amygdala is a critical site for emotional facilitation of memory^{3, 16, 17}. A number of recent studies have revealed systematic differences in patterns of amygdala activity across development^{18–23} and differential consequences of amygdala damage incurred at discrete periods of development have also been observed^{24, 25}. These findings suggest that shifting amygdala-mediated affective processes are a key component of development. We argue that differential emotional reactivity and amygdala response in particular are likely to play an important role in highlighting developmentally relevant features of the environment. Such a fluctuation in amygdala sensitivity may serve to orient the organism to important features of the environment during sensitive maturational periods.

PERIODS OF SENSITIVITY AND INSENSITIVITY IN DEVELOPMENT: TIMING IS EVERYTHING

In broad terms, there are two components involved in the development of the nervous system. The first is an organizational framework which is primarily mediated by intrinsic factors such as gene expression, which spur the generation and elaboration of neurons and determine the general spatial organization of neural tissue^{26, 27}. In the second phase, the organizational framework is fine-tuned. This fine-tuning is based on use-dependent preservation or elimination of neural circuits, which ultimately results in an extensive

network of differentially weighted neural networks²⁸. This second, fine tuning, process is affected to a much greater extent by the environmental context than is establishment of the initial organizational framework^{27, 28}

The developmental tuning process is both protracted and serial. Recent findings indicate that the brain does not complete developmental maturation until early adulthood, and development proceeds in a piecemeal fashion with phylogenetically newer regions undergoing maturation subsequent to older regions^{29–32}. Thus, the fine tuning phase of development proceeds through a serial pattern of distinct sensitive periods and these are likely to extend from the first few years of life well into the third decade in humans^{15, 29, 33–35}.

The pattern of sensitive periods was first demonstrated in the visual system of nonhuman primates and cats by Nobel prize winning work of Hubel and Wiesel, where restriction of visual input for a brief period of development resulted in dramatic alterations in the maturation of the visual system at cellular, morphological, and functional levels²⁶. Many of these alterations persisted throughout life in spite of normative exposure to stimuli through late development and maturity. Similar phenomena have also been observed in humans in the development of the visual and auditory systems^{36, 37}. While the early work focused on visual experience broadly defined during specified developmental windows, more recent studies have revealed sub-domains of specificity within visual development where, for example, visual acuity and motion detection represent different periods of development when emerging circuits are sensitive to different aspects of visual experiences in the environment³⁶.

Although early work focused on the development of primary sensory systems, sensitive periods have been demonstrated in other emerging neural circuits as well including those involved in auditory and visual-spatial mapping³⁸; avian song learning³⁹; filial imprinting^{40, 41}; sexual imprinting^{42, 43}; language acquisition⁴⁴; cortisol homeostasis^{10, 11}; and face perception⁴⁵ processes. In all of these examples, the organization of the brain is particularly sensitive to domain-specific stimuli for a limited period of time in development. Exposure to the same stimuli either before or after the sensitive window is either ineffective in inducing organizational change, or more often, the ability to induce such changes is markedly blunted^{26, 36, 44}.

Furthermore, because the maturational sequence is protracted and staged³¹, different neural circuits undergo functional and structural development during different temporal windows for which only specific environmental conditions are relevant. Thus unique stimulus domains are developmentally relevant at specific periods^{14, 15}. Because of this, the impact of various environmental stimuli will depend on which circuits are concurrently undergoing maturation.

While the most robust evidence for sensitive periods in development has been found in the early postnatal period, mounting evidence suggests that sensitive periods for different domains also occur later in development^{46–48}. For example animal based studies have shown that exposure to chemosensory signals for a limited period of time around puberty are

uniquely capable of organizing neural circuits and behavioral responses related to reproduction⁴⁶. In both humans and animal models recent studies indicate that both brain and behavioral responses to many drugs of abuse appear to peak during the peri-pubertal period⁴⁸. Furthermore, in humans epidemiological studies have pointed to the adolescent period as a time when many emotional disorders initially emerge which has led some to suggest that this is a sensitive period for affective organization^{47, 48}. Finally, neuroimaging and histological investigations over the last several years have indicated that maturational changes continue to take place well beyond puberty^{31, 32}. Because periods of heightened sensitivity are likely to emerge whenever circuits are undergoing developmental fine-tuning, these findings suggest that sensitive periods are likely to extend into early adult life as well.

An important corollary to the thesis that development is marked by periods of heightened sensitivity is that development is also likely to be punctuated by periods during which the brain is relatively insensitive to particular sensory domains or periods of domain specific *insensitivity*, where environmental stimuli may be less efficacious in inducing learned adaptations, or produce distinct outcomes in children and adults. Several examples of such an effect have also been found. For instance, infant rats are incapable of developing an aversion to an odor that is associated with either an illness⁴⁹ or a shock⁴¹. This developmentally specific deficit in inhibitory learning may be an adaptive response because infants do not have many options when it comes to caregiver, nest location, or food; developing an aversion to any of these would be maladaptive, and tend to reduce survival rates^{41, 49}. Indeed Sullivan and colleagues have demonstrated that infant rats develop a *preference* for odors that are paired with shocks during the early infantile period⁴¹. Recently, developmentally specific deficits have also been demonstrated in fear extinction learning in both human and rodent models^{50, 51}. These studies have shown that relative to both juveniles and adults, adolescents are selectively impaired in the ability to extinguish an acquired fear in a pavlovian conditioning paradigm⁵⁰. Furthermore adolescents demonstrate a unique suppression of some types of fear learning that was acquired early in life⁵¹. While it is unclear what adaptive function such a fear inflexibility might convey, these findings do underscore the point that development is marked by periods of both heightened and diminished sensitivity to selective stimuli. As such an important feature of such pervasive emotional fluctuations development may be to accentuate the features that are relevant during the specific and time sensitive windows of sensitivity, and thereby match the maturational state of the organism with the environmental conditions in which development is taking place.

THE FUNCTIONAL ROLE OF EMOTION IN DEVELOPMENT

On a daily basis we are bombarded by stimuli. While some of the stimuli we encounter are significant, the vast majority are not. An important aspect of optimizing behavioral responses in a particular environment is to highlight the significant stimuli, and rapidly generate an appropriate response. Emotions serve an important role in this process. Emotion selectively enhances the sensory processing of stimuli thereby amplifying the signal imprint of select stimuli⁵. Emotions also coordinate and direct responses among a number of systems (like attention, endocrine, and locomotor responses) which tend otherwise to be orthogonal^{52, 53}. Finally emotions promote the long term memory of specific

stimuli^{5, 54, 556}, and often result in consistent learned behavior patterns^{5, 54–567}. Thus, through numerous means emotional experiences augment the imprint specific stimuli leave on the nervous system.

In a developmental context selective engagement of emotional experience may help guide the nervous system to seek out and incorporate specific stimulus domains that are most relevant for concurrent brain circuit maturation. In this way shifts in emotional sensitivity may be an intrinsic signal of development that highlights developmentally relevant features in the environment. One domain in which developmentally linked dynamic shifts in emotionality is particularly apparent is in response to social affiliative stimuli. Here, affective intensity varies in systematic ways for discrete social categories and events across development.

An example of such fluctuating emotional reactivity across development can be seen in results from a recent study that examined developmental changes in response of infant monkeys to maternal separation (see Fig 1). Across the first 6 months of life, there was a steady decline in emotional distress (vocalization frequency), in response to maternal separation⁵⁷. While this pattern could be viewed as the emergence of cortical systems involved in affect regulation⁵⁸ we believe that findings from other domains of affiliative behavior which indicate peaks and troughs of emotional responsiveness at different points in development support a more nuanced interpretation.

For example, in rodent studies of play, motivation to engage in bouts of free play with peers displays a marked inverted u across development with a peak occurring in the mid juvenile period between weaning and puberty^{59, 60}. At a slightly later point, during early puberty and adolescence, integration with peer groups rather than play becomes most motivationally salient⁶¹ and slightly later yet, interaction with romantic partners⁶² elicits stronger emotional reactions than at other points in development. Indeed emotional reactions to opposite sex peers is the most common sources of positive affect in adolescence and is also a leading cause of negative affective responses including depression⁶². Finally, sensory stimuli related to infants evoke strong emotional responses among mammalian mothers, including humans, immediately after they give birth⁶³. Although the postpartum period is not typically considered a developmental phase, the orchestrated shift in emotional responsiveness during this period is remarkably similar to other developmental shifts described above and so is included here.

While the examples cited above focus on changing emotional attributions within the social context, developmental fluctuations of emotional responsiveness are not limited to interpersonal or social processes. For example emotional responses to stimulus color⁶⁴; darkness⁶⁵; novelty⁶⁶; risky situations⁶⁷; psychoactive substances⁴⁸; and other stimuli and contexts that are not explicitly social⁶⁸ vary across development, with peak responsiveness occurring at different points in maturation. We believe these shifts in emotional reactivity are an important and regulated aspect of development that serve to orient, enhance, and orchestrate brain maturation by highlighting the significant stimuli in the environment that will guide fine tuning of the nervous system at key sensitive periods.

THE ROLE OF THE AMYGDALA

Emotions are clearly complex phenomena and as indicated above, emotional experience likely results from the orchestrated response of multiple neuronal regions rather than being embedded in any single structure^{1, 53}. That being said, however, it is clear that regions in the limbic system and related subcortical structures play a particularly prominent role in generating emotional responses because they are strongly interconnected with multiple sensory and effector systems^{1, 2, 69}. A particularly important limbic region in the present context is the amygdala. The amygdala is prominently featured in many models of emotion^{3, 16, 17, 54, 70, 71}. In addition the amygdala has been specifically implicated in many of the processes we highlight here including emotionally mediated shifts in attention, enhanced perceptual processing, and long term consolidation of emotional experiences^{5, 6, 17, 72}.

Recent conceptualizations of amygdala function suggest a primary role is assigning salience to stimuli^{5, 6, 17, 72}. Importantly, amygdala activity signifies salience for stimuli which are both appetitive and aversive, and for stimuli whose salience is both innate (snakes) or acquired (ie CS+)^{3, 16, 17, 70, 72, 73}. Another important feature of amygdala function in several recent models is the flexibility of salience attribution to the same stimulus. The magnitude of amygdala response can vary to the same stimulus at different points in time or in different contexts, and this variance tracks the concurrent value of the stimulus to the organism^{3, 17}. These features of the amygdala make it ideally suited to selectively track the importance of different stimulus domains across development as well. As we have argued above, dynamic shifts in the value of different stimulus domains take place across normative development. As development progresses, some stimuli (eg a kiss from mother) lose value while other stimuli (eg a kiss from a potential mate) gain in value. We propose that in development, just as in learning, the amygdala plays the specific role of enhancing the value of stimuli during sensitive periods of development and this then functions to highlight specific environmental features that are used in the fine tuning phase of neural circuit maturation.

There are several indications from recent developmental studies suggesting that the amygdala may play such a role. Although the amygdala begins to mature early in fetal life and is fully functional at birth, many studies have demonstrated dynamic changes in amygdala structure and function across development. For example, volumetric changes in the amygdala continue through puberty,^{71, 74} and dysregulation in the trajectory of this growth are linked with neurodevelopmental disorders such as autism⁷⁴ whose symptoms include deficits in social development. In addition, developmental changes in gene expression⁷⁵ and differential patterns of activity in amygdala induced by similar stimulus conditions have been observed in both human and animal models of development^{41, 71}. Moreover, functional changes in amygdala responsiveness have been linked to changes in circulating steroid levels that are associated with specific developmental milestones such as weaning⁴¹ and puberty⁷¹. Thus physiological indices of developmental transitions may mediate behavior shifts via effects on amygdala function.

Several neuroimaging studies have also noted differences in functional activation of the amygdala during normative development. Across a wide developmental span of 4–17 years of age, a recent study reported declining amygdala activation to images of unfamiliar adults which tracked the decline in measures of stranger anxiety²³. This finding suggests that the normative reduction in stranger anxiety that occurs across development may be mediated by declines in salience that the amygdala ascribes to unfamiliar adults. A number of studies have also reported developmental shifts in amygdala response to unfamiliar faces across later stages of development. When viewing emotional faces, and fearful faces in particular, activity in amygdala increases from childhood to adolescence, and then declines from adolescence to adulthood^{19, 21}. These findings suggest that the amygdala may highlight the salience of social expressions during a developmental period when monitoring emotional experiences of peers is highly relevant for development.^{22, 61}

Finally, more direct evidence for a functional role in development has been obtained from studies that show lesions to the amygdala produce fundamentally different patterns of behavior as a function of the developmental stage during which the lesion occurred. In non-human primates, young monkeys who received amygdala lesions as neonates displayed a pattern of extreme *fearfulness* when they interacted with peers⁷⁶. This contrasts with findings from animals who sustained the same lesion later in development. Monkeys who received amygdala lesions as juveniles or young adults displayed a pattern of social behavior that is marked by *reduced* levels of fear^{24, 77}. The interpretation of these discrepant findings is that the amygdala plays a developmentally specific role in guiding social learning. Animals that had very little social experience with an intact amygdala were unable to use the amygdala to guide behavior during early social interactions, and therefore failed to acquire rudimentary patterns of social behavior or social expectations and consequently were chronically socially dysfunctional, fearful and submissive^{76, 78}. In contrast, juvenile animals who had a functional amygdala during early peer interactions established basic rules and expectations of peer behavior, and therefore were not fearful in a social context. In fact the low levels of fear exhibited by the juvenile-lesioned animals along with other differences in social behavior suggest deficits in completely different domains of behavior (such as wariness and dominance) which are typically acquired during adolescence^{77, 79}. Moreover, although the magnitude of these effects diminished over the course of development in both groups of monkeys distinct patterns in most functions did persist into adulthood suggesting that amygdala modulated social behavior in development has persistent effects^{78, 80}

Finally there have been similar findings of developmental specificity of deficits observed in humans who received amygdala lesions either early in life or as adults²⁵. Relative to the adult-lesioned patients, those who sustained amygdala damage either neonatally or during early childhood demonstrated specific deficits in interpreting nuanced social language like ironic or figurative statements and were significantly impaired in interpreting emotional signals of other individuals. The authors suggest that this impairment highlights a specific role of the amygdala in acquiring social knowledge in early development. A process which is facilitated by amygdala guided salience of social cues¹⁶.

LONG TERM EFFECTS OF EMOTION IN DEVELOPMENT

An important function of emotionally guided developmental change that we are postulating here is that the changes persist beyond the emotional experience. Limbic regions, like the amygdala and hippocampus, play a key role in orchestrating emotional responses and facilitating learning during the initial exposures to stimuli. However, over time, both the emotional response and limbic activity evoked by a particular stimulus wanes, even as a behavior patterns persist. In other words, as emotionally mediated memories become consolidated, they promote flexible behavior patterns that are largely independent of the original emotional context, or the emotionally mediated neuronal structures originally engaged by this context.

Emotional learning studies have found that long term emotionally modulated memories are consolidated in distributed neocortical networks, which may be engaged in the absence of the initial emotional experience^{6, 81}. For example, learning-based plasticity generated by fear conditioning has been detected in the amygdala, but also in local connectivity and functional activation patterns within the neocortex⁸². Recent animal models of amygdala mediated pavlovian conditioning have revealed functional modifications in responsiveness of neocortical circuits that are generated when a neutral conditioned stimulus is paired with electrical stimulation of the amygdala^{6, 81}. These cortical changes persist for a long period of time and are subsequently independent of amygdala activity. A similar pattern of persistent changes in brain and behavior that persist independently of the original emotional context or neural underpinnings has been demonstrated in other paradigms as well^{83,84}. Thus in traditional learning paradigms emotional modulation of stimuli generates a pattern of learning in which long term memories are instantiated in cortical rather than limbic function and the behavior persists independent of original emotional modulatory effects.

We recently observed a developmental effect that resembles this phenomenon in development²⁰ (see Fig 2). In this task adolescent and adult participants underwent neuroimaging as they viewed faces paired (CS+) or unpaired (CS-) with an aversive sound. Adolescents were unable to accurately label the two CS stimuli, but engaged the amygdala significantly more to CS+ than CS- images. In contrast, adults were able to rapidly categorize the two stimulus classes but displayed relatively little differential amygdala activity. Importantly adults but not adolescents engaged a region of lateral prefrontal cortex when making safety assessment (CS-→Cs+). In the present context we believe these findings highlight two themes of this review. First, because associating emotions with faces is a developmentally pertinent task for adolescents, such an experience is likely to be more salient, and engage the amygdala to a greater extent in adolescents than adults. Second, because of previous developmental experiences, adults have undergone a cortical transfer of this process. Such a corticalization has enabled adults to explicitly categorize facial stimuli much more easily than adolescents. Thus amygdala-guided experiences in development generated an amygdala independent capability in mature adults

This feature of emotional memory, which permits emotion to act as a temporary guide for long term adaptive patterns of responding, is ideally suited for developmental adaptations that persist across the lifespan. Indeed, many studies have shown that extreme emotional

experiences during specific and brief periods of development can generate persistent alterations in perceptual processing¹²; endocrine homeostasis⁸⁵; social behavior^{13, 86} and a number of other nervous system functions^{35, 87, 88} that persist well beyond the original emotional experience. If specific stimulus domains (i.e., peers) evoke emotional attributions while distinct neural networks are being formed, long-term adaptations to specific environmental conditions may be facilitated. Internally mediated shifts in emotional attributions may therefore be an important mechanism for highlighting developmentally relevant components of the environment and guiding maturation of specific neural networks (see Fig 3).

Our model is depicted schematically in Figure Three in which different stimulus domains are depicted across the top and developmental phases are represented as vertical rows. Differential amygdala activation in response to select stimulus domains occurs across development which fine tunes emerging circuits and results in long term stable patterns of brain function.

COMPLIMENTARY PERSPECTIVES

Finally while we do present unique perspectives, we note that several complimentary viewpoints particularly in regards to a functional role of emotion in development have recently appeared in the literature. Galvan⁹ observed the similar mechanisms involved in learning and developmentally mediated plasticity and Lourenco and Casey⁸⁹ discussed the role of non-linear patterns of emotion and learning in development; Pfeifer and Allen⁹⁰, and Crone and Dahl³³, have also suggested ways in which emotion may facilitate flexibility and adaptation across development; and Bjork and colleagues discussed how contextual variability may relate to developmental differences in emotion⁹¹. Finally, Scherf et al proposed that steroid hormones released at puberty may lead to a re-organization of behavior via their effects on the amygdala and consequent shifts in emotional behavior⁷¹. Although each of these perspectives vary somewhat in details and primary focus, they all present a perspective in which emotion and learning are central to the developmental experience.

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HIGHLIGHTS

Learning and development enable adaptive changes in brain via similar neurobiological mechanisms

Emotion plays important role in facilitating both learning and development

Amygdala-mediated motional sensitivity and stimulus salience change across development in domain specific ways.

Emotional variability may help guide learning during developmentally sensitive periods

FUTURE DIRECTIONS

- An important remaining question is what triggers shifts in salience attribution across development. Intrinsic signals associated with developmental milestones like puberty and weaning have been linked to functional changes in the amygdala, yet other intrinsic signals are also likely and yet to be identified.
- Future work is needed to determine the extent to which systematic fluctuations in emotional responsiveness play a functional role in maturation of brain and behavior or simply reflect a non functional by-product of other maturational processes
- Structures besides the amygdala are likely involved in emotional modulation of learning. Expanding the developmental focus beyond the amygdala will also be important. For example recent studies suggest a similar developmental profile within the striatum may relate to risk taking and substance use in adolescence.
- Could emotional induction modify neuronal and behavioral patterns acquired during the critical periods, even after they have passed?
- Does emotionally modulated learning during sensitive periods inform onset trajectory or treatment of psychopathology?

BOX 1- DEVELOPMENT: A DANCE BETWEEN NATURE AND NURTURE

Although the central nervous system is one of the earliest organ systems to emerge during gestation, maturation is a protracted process. Indeed, in humans, neural development is now thought to extend well beyond puberty, into early adulthood³⁰. Over the first several years of life, brain development is marked by neurogenesis and establishment of new synaptic contacts. This expansion is then followed by a gradual refinement process which consists of synaptic pruning and myelination^{27, 30}. This refinement process follows a developmental sequence, from phylogenetically conserved regions involved in sensory and motor processes to regions involved in more complex functions like multisensory integration and socio-perceptual functions^{27, 30, 32}.

The extent to which developmental refinement is driven by intrinsic maturational processes or constructed primarily as a consequence of experiential inputs has been a source of considerable debate⁹². Over the last several decades, a pendulum has swung from nativist intrinsic explanations, to constructivist empirical explanations, which emphasize environmental contingencies. More recently, models have begun to characterize development as a culmination of the inseparable interaction between biological and environmental factors^{8, 11}. These models suggest that while there is a loosely defined sequence, timeline, and process associated with maturation of the nervous system, the output of this maturation is largely influenced by the environmental context in which development occurs. Some models also suggest a differential susceptibility to environmental influence⁸.

There are many examples that illustrate how developmental outcomes are shaped by interactions between biology and environment. A classic example is language. While language acquisition is a milestone of normative development, the specific language acquired is completely dependent on the context in which maturation occurs^{44, 93}. Similar examples of this principle are found across many domains and include “programming” the dynamics of the hypothalamo-pituitary-adrenal axis, where early stress can alter the homeostatic balance of cortisol detection and release^{11, 85}; tuning of sensory and perceptual sensitivity, where discrimination of subtle elements becomes more or less sensitive with early life exposure^{12, 41, 45}; acquisition of parental behavior patterns, which are influenced by patterns of one’s own parental behavior⁶³; and even adoption of preferred characteristics for subsequent mate preferences⁴³. Therefore for most neural circuits the final maturational outcome of depends completely on an interaction between genes and experience.

BOX 2: NEUROBIOLOGICAL MECHANISMS OF LEARNING AND DEVELOPMENT: STRENGTHENING CONNECTIONS

Over the last several decades great strides have been made in delineating the molecular mechanisms that mediate learning⁹⁴. Much of this research is guided by models of simple associative conditioning which demonstrate that synaptic strength between two weakly connected cells increases when they fire simultaneously⁹⁴. A key molecular component of this strengthening is activation of the glutamate NMDA receptor. This receptor acts as a “coincidence detector” that strengthens connectivity of co-active cells by opening calcium ion channels, which ultimately induces protein-based cellular changes responsible for long term stabilization of circuits^{82, 95}. Inhibitory GABAergic connections may also play an important modulatory role in this strengthening process. Because GABA exerts tonic inhibitory control on some NMDA circuits, modulation of GABA input is thought to be an important precursor for NMDA-mediated learning under some circumstances^{67, 82, 96}

Likewise, in development, circuit strength is refined through patterns of synaptic activity that are affected by environmental context²⁷. The early stages of this refinement are characterized by a highly dynamic phase of formation and retraction of synaptic contacts on newly formed dendritic spines⁹⁵. In a manner very similar to synaptic strengthening implicated in traditional hebbian learning, activity within these nascent synaptic contacts are stabilized and maintained via activation of NMDA receptors, influx of intracellular calcium ions, induction of transcription factors, and neurotrophin release⁹⁵. Moreover, recent evidence indicates that inhibitory GABA inputs may also help to tune receptive fields and gate neuronal sensitivity to environmental input across development⁹⁶. Thus, in both maturation and traditional learning, synaptic and circuit stabilization is a process of amplifying and strengthening connections that are weakly co-active. Mechanistically this depends on glutamate NMDA receptors, a cascade of events triggered by intracellular calcium influx, and GABA mediated inhibition of competing influences.

During critical developmental phases, rapid synaptic refinement occurs in specific circuits. Thus, environmental contexts which induce synapse-specific neuronal activity may have a particularly strong influence on specific circuit function. At a systems level, sensory processing has been used to model the effects of environment on brain organization across development. This work demonstrates the experience of visual, auditory, or somatosensory stimuli during specific developmental windows are critical for the organization of cortical circuitry, parcelation of cortical space and functional responsivity^{36, 37, 97}. These models of sensory development may serve as more general models of experiential influence during sensitive periods.

Box 3: ADAPTATION MECHANISMS UNIQUE TO DEVELOPMENT

While many of the same mechanisms are invoked to adapt the nervous system in development and learning, there are also important differences. One is the scale on which these changes occur. Traditional learning typically involves relatively modest modifications to synaptic strength, while developmental adaptations are typically large in scale^{26, 28}. The amount of experience needed to drive learning and developmental changes is also quite different. Marked developmental changes usually result from limited stimulus exposure, but learning generally requires more exposure²⁶. Organization of cortical space is one example of such differences. In development, limited exposure to sensory experiences can induce dramatic changes such as ocular dominance columns or tonotopic organization of the auditory cortex^{36, 37}. While changes to cortical architecture have also been noted following adult learning^{26, 98}, the changes are much more modest than those that occur during development.

While learning and development share many mechanisms of change, there are also some that are specific to development. Synaptic Pruning (SP) is one such mechanism in which synaptic contacts are eliminated in a systematic fashion^{27, 32}. SP occurs at various developmental periods in different brain regions, and is more drawn out in evolutionarily newer regions like granular prefrontal cortex and multi-modal association areas^{27, 32}. Indeed, in humans, SP appears to continue throughout the third decade of life, and may be one of the primary contributors to decline in gray matter that occurs between late childhood and early adulthood^{27, 31, 32}.

In addition to NMDA- and GABA-mediated stabilization of synapses seen in both learning and development, epigenetics is another mechanism by which adaptive neuronal changes may be facilitated. Epigenetics refers to modifications to the DNA, or the surrounding chromatin scaffolding (on which the DNA sits), that alters DNA transcription¹¹. While some modifications like acetylation tend to be dynamic across the lifespan⁹⁹, others, like methylation, occur primarily during early periods of maturation, and tend to result in lifelong (and sometimes trans-generational) inhibition of genetic expression^{11, 100}. Recently it has been shown that psychological experiences during a specified developmental window can also alter patterns of DNA methylation and these patterns generally persist throughout the life of the animal¹¹. In short, some but not all of the mechanisms of neural plasticity are shared between 'traditional' and 'developmental' learning; and the magnitude and duration of plastic changes may not be comparable in both forms of adaptation.

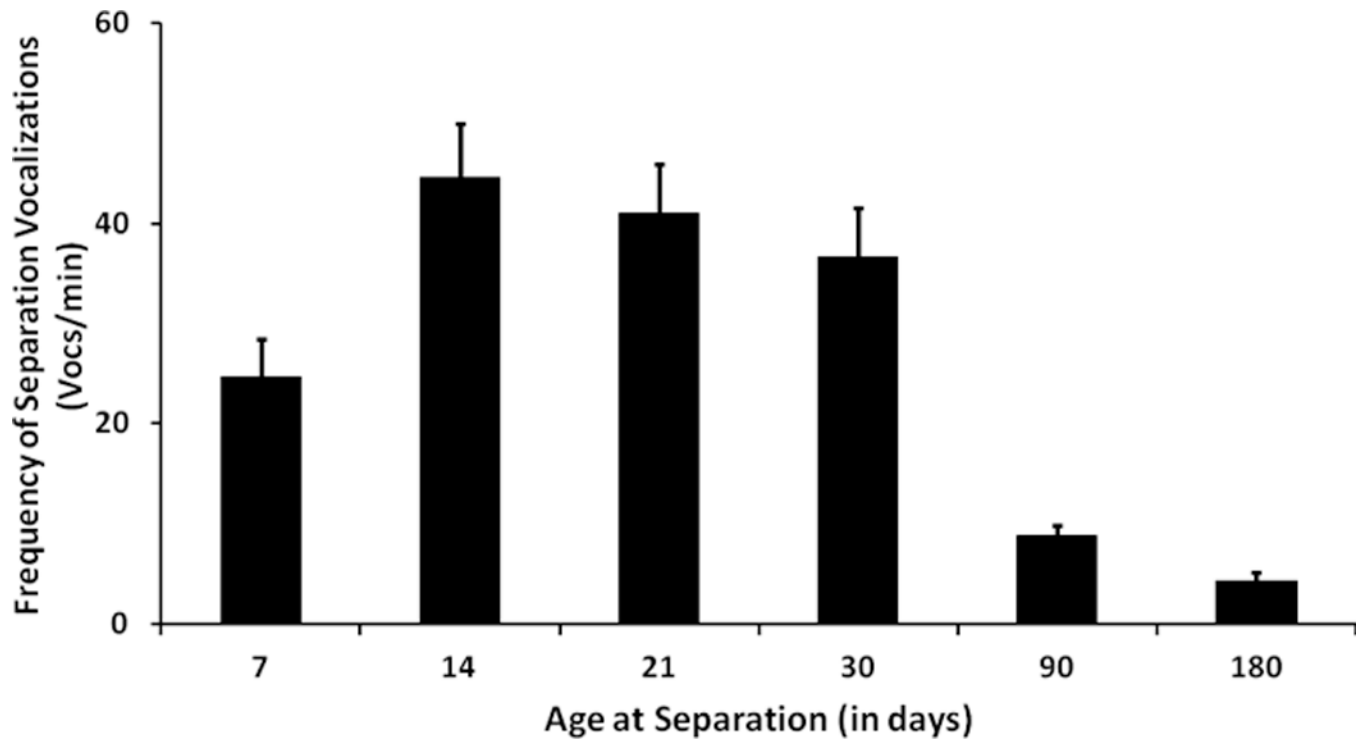


Fig One.

Figure One is a depiction of the frequency of cries emitted by rhesus monkey infants across the first 6 months of life during a period of separation from the mother. The systematic decline in this index of distress is similar to what has been observed in humans and we believe is a reflection of a shift in motivational state across development. Reprinted from⁵⁸

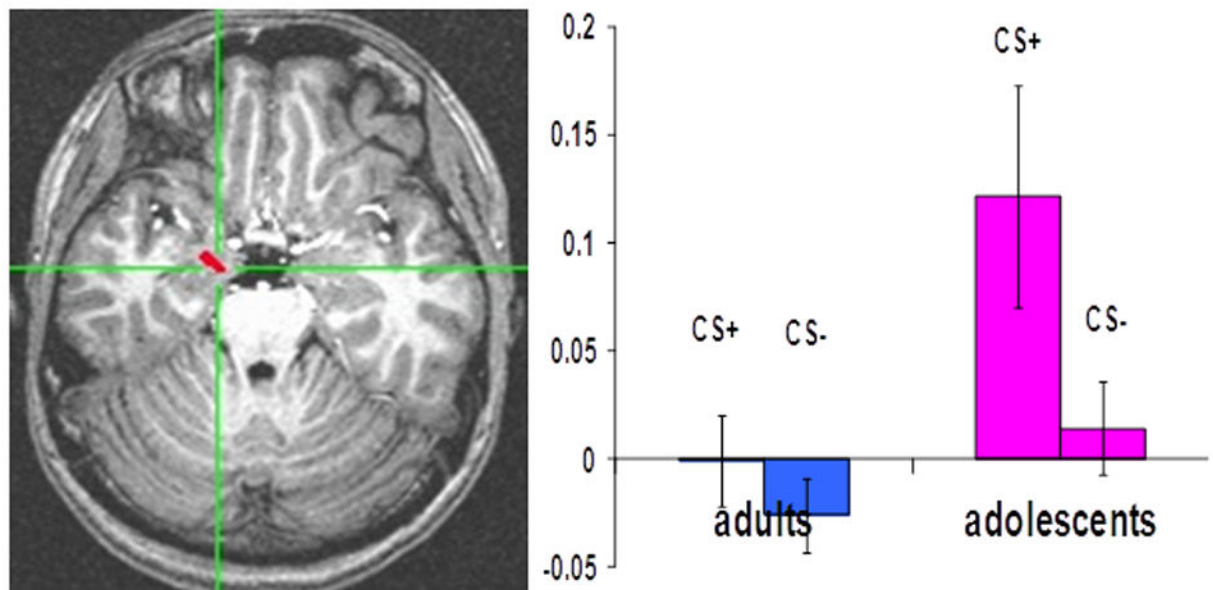
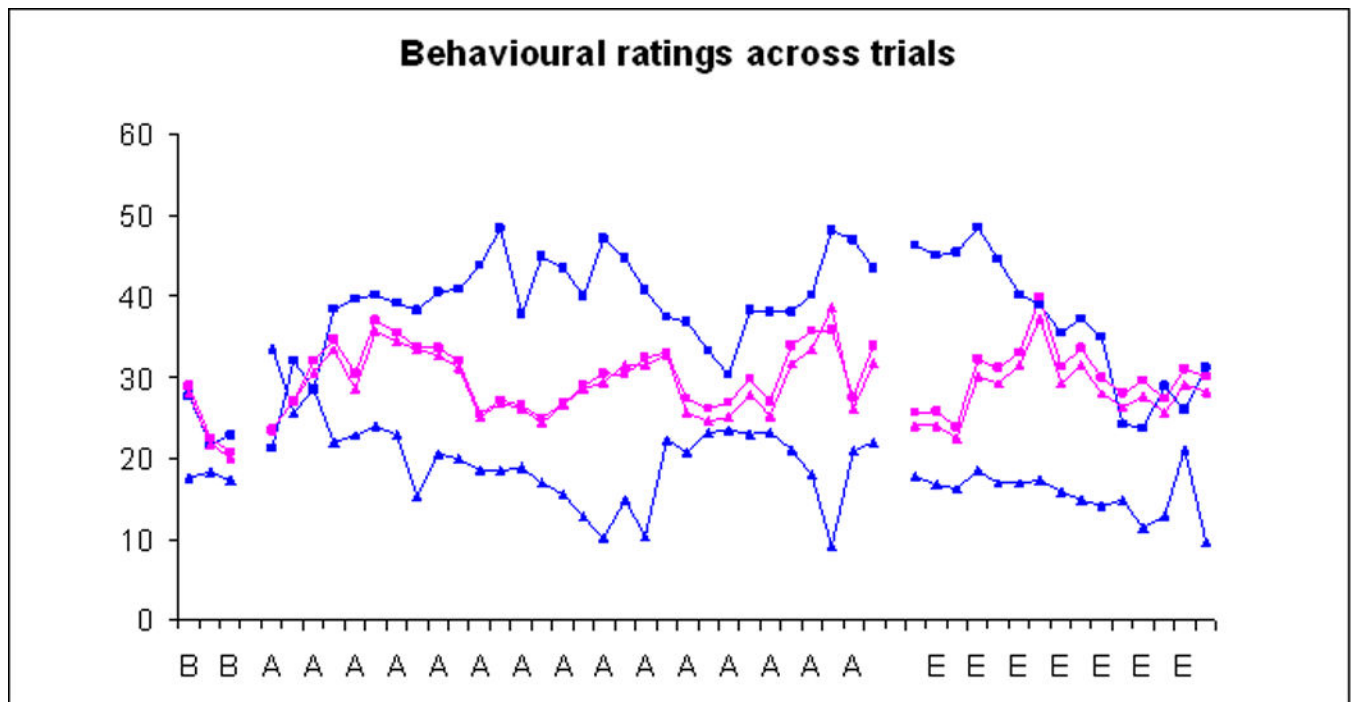


Fig Two. Figure Two (a top panel) is a depiction of self reported fear of a CS+ (squares) and CS- (triangles) during an aversive conditioning paradigm in a group of psychiatrically healthy adolescents and young adults. Stimuli and ratings were collected during fMRI across acquisition (A) and non-reinforced extinction (E) trials. Concurrent activity in the amygdala is depicted in Fig 2b (bottom) in this same group of subjects. While adults rapidly develop a differential pattern of categorizing these two stimuli into fear and no fear groups, no such difference is apparent in the adolescents. In contrast adolescents but not adults displayed a

differential pattern of amygdala activation when viewing these same stimuli during fear acquisition training. Adults displayed a pattern of differential activation in the dorsolateral prefrontal cortex that tracked safety ratings. These data demonstrate the transient nature of amygdala activity across development and suggest that once domain specific categorical skills are acquired amygdala dependent functions are transferred to neocortex. Reprinted from²⁰

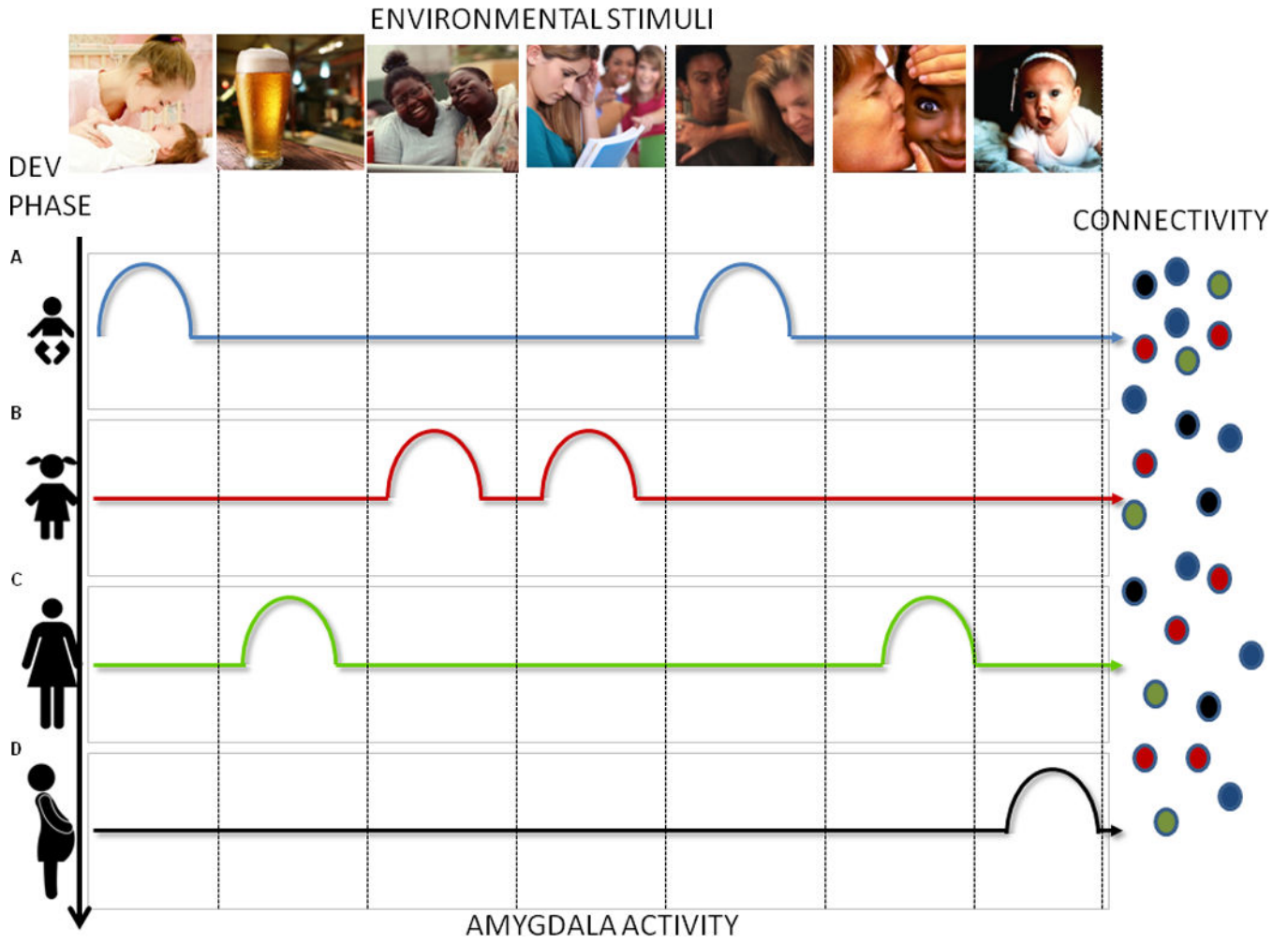


Fig Three. Figure three is a schematic representation of the proposed role for the amygdala in development. Different domains in the environment (ie caretakers, peers, babies) are depicted as images across the top while developmental phases are depicted in vertical rows on the left. Selective amygdala responses within each developmental phase to each stimulus domain are indicated by rows of colored bumps. Amygdala activation in response to each stimulus domain highlights the presence of this stimulus class in the environment and generates long term patterns of cortical connectivity depicted as small circular arrays on the right. Amygdala modulated circuit maturation that occurs during these specified developmental windows ultimately function independently of amygdala activity.