Published in final edited form as:
Neurosci Biobehav Rev. 2009 March ; 33(3): 432–441. doi:10.1016/j.neubiorev.2008.11.004.

Plasticity of defensive behavior and fear in early development

Christoph P. Wiedenmayer
Dept. Psychiatry, Columbia University, New York, NY 10032Div. Developmental Neuroscience, New York State Psychiatric Institute, New York, NY 10032

Abstract

Animals have the ability to respond to threatening situations with sets of defensive behaviors. This review demonstrates that defensive behaviors change during early life in mammals. First, unlearned responses are reorganized during early ontogeny and expressed in an age-specific way. Second, the expression of defensive responses is influenced by early experience prior to the first encounter with a threat. Third, once animals have been exposed to a threatening stimulus they subsequently modify their behavior. The neural bases of defensive behavior and the processes that alter them during development are discussed. Maturation of components and connections of the fear circuit seem to contribute to changes in unlearned fear responses. Early experience and learning modify these developmental processes and shape the expression of defensive behavior. Continuous reorganization of the neural substrate and defensive behavior during ontogeny seems to allow the animal to adjust to the conditions it encounters at a given age in a given environment. It is proposed that the developmental changes in defensive behavior can be conceptualized as phenotypic plasticity.

Keywords

learning; predation; neural maturation; ontogeny; adaptation

1. Introduction

In the wild, animals live with the constant threat of being attacked, injured and killed by predators and conspecifics. Animals that are able to respond to potential or actual threat have increased chances of survival (Lind and Cresswell, 2005; Vermeij, 1982). Behavioral responses that decrease the probability of the animal being attacked, injured or killed have been classified in functional terms as defensive behavior. Defensive behavior is phylogenetically old and exhibited by organisms throughout the animal kingdom (Hofer, 2002; Kats and Dill, 1998; Kavaliers and Choleris, 2001; Lima and Dill, 1990; Ydenberg and Dill, 1986). The perception of potential or actual danger activates specialized pathways in the brain that mediate defensive behavior. On a more conceptual level, it has been suggested that the activity of these neural circuits is associated with the central emotional states of fear and anxiety (Blanchard et al., 2003; Hendrie et al., 1996; Öhman and Mineka, 2001). Accordingly, responses to aversive and threatening stimuli also have been labeled fear- and anxiety-related behaviors (Boissy, 1995; Bolles and Fanselow, 1980).

Correspondence to: Christoph Wiedenmayer, Ph.D., Department of Psychiatry, Columbia University, 1051 Riverside Drive, Unit 40, New York, New York 10032, Phone: (212) 543-5973, Fax: (212) 543-6922, Email: E-mail: cpw14@columbia.edu.

Research on defensive behavior has generally focused on adult animals and several excellent reviews have described adult responses to threat (Apfelbach et al., 2005; Eilam, 2005; Kavaliers and Choleris, 2001). This strong interest in adult behavior is based on the commonly held view that the adult phenotype represents a species' behavioral repertoire. However, the behavioral response patterns an animal displays are not fixed but undergo changes during its lifetime. Some changes are subtle, for instance when a behavior pattern is exhibited more frequently. Other changes are more profound, when a new behavior appears in the animal's repertoire or another behavior is no longer displayed.

This review demonstrates that defensive behaviors change continuously throughout development. Development, or ontogeny, consists of all phenotypic change during the lifetime of an individual (Tinbergen, 1963; West-Eberhard, 2003). The focus of this review is on the early development of defensive behavior in young mammals. To understand proximate (mechanisms) and ultimate (functions) aspects of behavior (Mayr, 1961; Tinbergen, 1963), defensive behavior has to be examined under ecologically relevant conditions. Naturally occurring defensive behaviors are thus emphasized in this review. First, three different types of developmental changes in defensive behavior are identified. Second, the neural processes that underlie the developmental changes in defensive behavior are discussed. Third, it is argued that developmental changes have a function; they help animals to adaptively respond to the dynamics of environmental threats and dangers. Finally, it is proposed that developmental changes in defensive behavior can be conceptualized as a form of phenotypic plasticity.

This review aims to bring together findings from disparate disciplines including ethology, psychology, neurobiology and behavioral ecology to provide a coherent view on the ontogeny and plasticity of defensive behavior and fear.

2. Developmental changes in defensive behavior

In the wild, the young of several rodent, lagomorph and carnivore species spend the first weeks of life in enclosed nest areas or burrows (Nowak, 1999). When they emerge from their natal burrows they are exposed to predators and conspecifics that pose significant threats. Young animals, however, have the ability to respond to dangerous situations. Belding's ground squirrels, for example, are threatened by predators including coyotes, badgers and birds of prey (Mateo, 1996). On their first day above ground, they immediately respond to alarm and non-alarm calls emitted by adult colony members. They enter the burrow or freeze above ground. They also freeze to squeals that are emitted by young ground squirrels when attacked by infanticidal adult squirrels. This pattern of defensive responses changes during the following days. The young ground squirrels become more selective and begin to respond more distinctively to alarm calls that signal predators compared to non-alarm calls. Three weeks after emergence from the burrow and shortly before dispersal, their defensive behavior has further changed but is still different from adults. They freeze less, stay alert longer and run to the burrow more often (Mateo, 1996). Similar developmental changes in response patterns of defensive behavior are exhibited by the young of other burrow dwelling mammals including wild rabbits (Vitale, 1989) and mongooses (Clutton-Brock et al., 1999; Hollen and Manser, 2006).

These studies demonstrate that mammals growing up in the wild possess repertoires of defensive behaviors. Defensive behaviors are exhibited in response to predatory or conspecific threat and decrease the chances of being injured or killed. They include freezing, flight, avoidance, hiding and defensive aggression (Albert and Walsh, 1984; Barros and Tomaz, 2002; Blanchard and Blanchard, 1988). Most importantly, these studies show that defensive behaviors undergo changes during development. The changes in behavior can be grouped in the following way: 1) The young of some species are able to exhibit an appropriate response the first time they encounter a threat. The pattern of the response depends, however, on the age of the animal, indicating that unlearned responses are reorganized during development. 2) Environmental conditions influence the animal's response to threatening situations. Individual experience in early ontogeny shapes the expression of defensive behavior later in life. 3) When the animal is exposed to the same threatening stimulus repeatedly during its lifetime, it can learn about properties of the situation and modify its behavior in subsequent encounters. In the following, these three types of changes are illustrated and discussed in more detail.

2.1 Changes in unlearned behaviors during development

In the face of an attack, the ability to respond immediately and effectively is crucial for individual survival. In some mammal species, infant animals exhibit fully functional defensive behaviors the first time they are confronted with a threat, typically a predator or a conspecific. As described above, when young animals emerge from their burrows they immediately exhibit defensive behaviors. Immediate defensive responses can also be detected shortly after birth in young ungulates. When newborn red deer were exposed to an approaching human or dog barks they exhibited a freezing response within the first hour after birth (Espmark and Langvatn, 1985).

Conceptually, first encounter responses can be considered to be unlearned if they do not depend on previous interactions with the stimulus itself and are thus not acquired through associative learning, habituation, sensitization or other forms of learning. In free-ranging animals, it is inherently difficult to determine if a behavior is unlearned because encounter histories are in most cases not known. Individual experience of an animal can be better controlled under laboratory condition. Naive animals of different ages can be exposed to the same stimulus and developmental changes in response patterns across ontogeny that are independent of previous contact with the stimulus can be compared. Working in the laboratory does not necessarily mean that animals are tested in ‘unnatural’, i.e. ecologically not relevant, situations. Researchers have become increasingly aware of the relevance of predator threat in the investigation of unlearned defensive behavior in laboratory rodents (Apfelbach et al., 2005; Blanchard and Blanchard, 2003; Kavaliers and Choleris, 2001). Several studies have demonstrated that unlearned defensive behaviors can vary among animals of different ages.

Unlearned defensive behavior to predator threats in the laboratory has been investigated mainly in the rat. When 20- or 50-day-old rats were placed in an arena with a live cat they suppressed exploratory behaviors such as rearing and became immobile (Bronstein and Hirsch, 1976). The older, weaned rats were more attentive and froze longer in more distant areas away from the cat, indicating that the intensity of the defensive response depends on the age of the rat. Cat odor cues alone are effective in inducing defensive responses in young rats. When soiled cat litter was presented to preweaning and weaned rats, they froze at both ages but weaned rats seem to be more responsive (Wiedenmayer et al., 2005). An age-dependent increase in responsivity also was found in young rats that were exposed to a wooden block impregnated with cat odor (Hubbard et al., 2004). Weaned rats showed increased avoidance, decreased activity and contact with the block compared to preweaning rats.

The early development of defensive behavior has been well studied in young rats in the context of infanticidal threat. In various mammal groups, including rodents, carnivores and primates, adult males kill unrelated offspring to increase their own reproductive success (van Schaik and Janson, 2000). In rats, adult males exhibit a strong tendency to attack and kill preweaning pups (Brown, 1986; Mennella and Moltz, 1988). Young rats have the ability to respond the first time they encounter an adult male rat. They stop ongoing behavior and freeze when exposed to an unfamiliar adult male rat (Moriceau et al., 2004; Takahashi, 1992b; Wiedenmayer and Barr, 1998), but not when exposed to a familiar male rat (Takahashi, 1994). Being immobile appears to decrease the chances to attract an adult male rat (Thor et al., 1981). When the pups get older, freezing decreases gradually and they do not freeze to a male rat after weaning (Takahashi, 1992a; Wiedenmayer and Barr, 1998; Wiedenmayer and Barr, 2001b). Moreover, the developmental time course of the freezing response differs between individuals. Whereas on postnatal day 14, variability is small and all rats freeze when in the presence of the male, about a third of the animals do not freeze on day 21 (Wiedenmayer and Barr, 1998). Therefore, learning-independent processes lead to changes in defensive behavior during the first weeks of life and result in differences between animals of the same age.

A more artificial stimulus, electric shock, has been widely used to investigate behavioral responses to aversive stimulation in laboratory rodents. Electric shocks are not part of the natural environments in which rodents have evolved and have thus not participated in shaping defensive mechanisms. Electric shocks nevertheless elicit defensive behaviors and it has been argued that animals perceive them as part of an attack because they are painful (Fanselow and Lester, 1988; Suarez and Gallup, 1981). In the shock-probe burying test, an electrified probe is inserted into the wall of a testing cage (de Boer and Koolhaas, 2003). When a rat explores the cage and touches the probe, it receives an electric shock. The rat’s response is to push cage bedding over the probe. Three- but not 2-week-old rats buried a shock probe the first time they encountered it and received a shock, indicating that this response is not dependent on previous experience with this situation but dependent on the developmental age of the rat (López-Rubalcava et al., 1996; Pinel et al., 1989). When rats were tested during weeks 4 – 11, they increasingly spent more time burying the probe until burying leveled off in young adulthood (López-Rubalcava et al., 1996).

Taken together, these findings clearly demonstrate that young mammals have the ability to exhibit defensive behavior the first time they encounter a threat. Intensity, type and patterning of the unlearned response depend on the age at which the animal expresses the response for the first time. Findings with naive animals show that processes independent of a direct interaction with the threatening stimulus appear to contribute to the differences in the defensive response between age groups. Unlearned age-dependent changes represent the first type of developmental change in defensive behavior.

2.2. Experience-dependent changes in defensive behavior

‘Unlearned behavior’ does not imply that the behavior is predetermined or independent of external influences (Samuels, 2004). There is evidence that a range of experiences early in ontogeny can influence how the animal responds to a threatening stimulus later in life.

Early experience such as rearing condition shapes the development of antipredator behavior in rodents before emergence from the burrow and before any predator encounter. The responses to playbacks of alarm calls were compared in captivity-reared and wild Beldings’ ground squirrels (Mateo and Holmes, 1999b). Captivity-reared juveniles were more responsive to alarm calls. They ran to a refuge more often, stayed alert longer but did not discriminate between different types of alarm calls signaling low or high threat. In contrast, free-living juveniles started discriminating between calls at an earlier age. These behavioral differences appear to have been the consequence of the rearing history of the ground squirrels before they emerged (Mateo and Holmes, 1999a; Mateo and Holmes, 1999b). The authors hypothesized that pups in captivity were exposed to higher levels of auditory stimulation in their burrows than pups growing up in the wild (Mateo and Holmes, 1999a).

Even though shock-probe burying seems to be an unlearned defensive response (see above), various early experiences can affect its expression. Young rats that grew up in cages without bedding were exposed to a shock probe in a cage containing bedding at different ages (Pinel et al., 1989). They pushed bedding and buried the shock probe for the first time on postnatal day 40. In contrast, young rats that grew up with bedding performed their first defensive burying as early as day 25. Burying in the deprived rats also was less coordinated and differed in duration from rats that had been exposed to bedding during the first weeks of life. Risk assessment behavior, however, was not altered, indicating that rats deprived of bedding were not impaired in perceiving the shock probe as aversive (Pinel et al., 1989).

The development of defensive responses to a shock probe can be influenced by social variables as well. When they grew up with littermates, adolescent rats displayed more defensive burying and less freezing after they had come in contact with a shock probe compared to rats that grew up isolated or with an adult female (Arakawa, 2007). Another important formative factor in mammals is maternal care. Mothers differ in the quality and quantity of care they provide to their offspring. Variation in maternal care influences defensive behavior in the offspring (Champagne and Curley, 2005; Diorio and Meaney, 2007). Rats that had received high maternal care as pups exhibited less burying of the shock probe and froze less than rats that had received low maternal care (Menard et al., 2004). The authors argue that high care rats were less fearful and perceived the shock probe to be less threatening. According to this interpretation, maternal care seems to affect the development of central emotional states that later in life control defensive behavior. The maternal environment plays a role in shaping offspring behavior in primates as well. Bonnet macaques grew up with mothers submitted to variable and uncertain food supply (Rosenblum et al., 2001). As adolescents, when exposed to a human intruder, they showed increased fear-related behaviors compared to the offspring of mothers from stable food environments.

These studies demonstrate that early experience can shape defensive behavior by influencing the development of perceptual, central or motor components of behavioral systems. Response patterns of young animals to threatening situations thus depend on previous individual experience. This represents another type of behavioral change during development.

2.3. Learned changes in defensive behavior

It is highly adaptive for an animal to recognize danger and respond effectively during a first encounter. As previously described, young animals of certain species are born with the capacity to exhibit unlearned defensive behaviors because evolutionary processes have fixed these traits in their behavioral repertoires (Blumstein, 2006). Other species, however, lack this capacity. They either do not recognize a stimulus as dangerous or respond to a stimulus in a non-specific way. For example, laboratory-reared rhesus monkeys do not exhibit defensive behavior when exposed to snakes and snake models compared with wild-caught monkeys (Joslin et al., 1964; Mineka et al., 1984). The same lack of defensive behavior is found in New World monkeys. Laboratory-reared adult and juvenile squirrel monkeys do not inhibit feeding and do not display emotional behavior when confronting a snake (Murray and King, 1973). Young California ground squirrels without previous experience respond to snakes but in a non-specific way. In the wild, California ground squirrels spray sand at venomous rattlesnakes but not at non-venomous gopher snakes. When reared in captivity, young California ground squirrels do not discriminate between dangerous and not dangerous snakes and throw sand at both species with the same frequency (Coss et al., 1993).

In these cases, animals have to acquire either a defensive response or modify an existing one. Learning occurs when the animal experiences a dangerous situation and subsequent to the exposure to specific stimuli modifies its behavior. Studies of predator learning in the wild demonstrate rapid modifications of defensive behavior. Ungulate prey species can learn within a generation to avoid and flee large carnivores that are reintroduced in their habitat (Berger, 2007).

Learning about threatening situations in early development has been studied mainly under controlled conditions with the paradigm of Pavlovian fear conditioning. Pavlovian fear conditioning is a form of associative learning when the animal is exposed to two stimuli at the same time. An unconditioned aversive stimulus, which induces a defensive response, is paired with a neutral stimulus. Learning is assumed when, after training, the former neutral stimulus, the conditioned stimulus, has become effective in inducing the defensive response itself. At the same time the animal learns about the context in which it is exposed to the unconditioned stimulus. When it is placed back in the same context, it exhibits the defensive response as well. In this type of research the unconditioned stimulus is typically an electric shock and the conditioned stimulus a tone or a light. This paradigm has been successfully adopted to investigate fear learning in young animals and has resulted in an extensive body of literature (Hunt and Richardson, 2007; Rudy, 1993; Spear and Rudy, 1991; Stanton, 2000). However, only one study has been published that involves the ecological context of predatory threat. Eighteen-, 26-and 38-day-old rats were exposed to a wooden block impregnated with cat odor in a testing chamber (Hubbard et al., 2004). After 24 hrs, the rats were re-exposed to the wooden block but this time without the odor. The test measured whether the rats had formed an association between the predator odor and the cues/context in which they had been tested. The 26- and 38-days-old rats exhibited increased avoidance behavior and reduced locomotion. In addition, the 38-days-old rats showed increased freezing. These findings indicate that rats as young as 26 days of age are able to learn about cues and contexts in which they have previously encountered predator cues, whereas younger animals do not have this capacity.

Animals can learn about dangerous stimuli when they directly interact with them. Such individual learning is, however, costly because direct interactions with a predator or aggressive conspecific may be fatal. Injury or death can be circumvented when the animal learns from experienced companions instead (Griffin, 2004). Social learning is given when the animal uses social information to modify its behavior. In many mammal species, the young learn to recognize and avoid dangerous situations by observing family or group members. Juvenile black-tailed prairie dogs were exposed to a snake, hawk or ferret in an outdoor enclosure (Shier and Owings, 2007). Snake and hawk but not ferret exposure elicited defensive behaviors including reduced activity, vocalization and withdrawal into a shelter. The prairie dogs were then repeatedly exposed to the three predators for 5 weeks either in the presence or absence of an experienced adult female. Juvenile prairie dogs that were trained with an experienced adult increased defensive behavior to all three predators over time compared to juveniles without a demonstrator. These findings indicate that initial defensive responses can be modified when the juveniles observe the behavior of a demonstrator, which indicates social learning. Social learning seems to be necessary for snake avoidance in another rodent species, the kangaroo rat. Adult, wild-caught kangaroo rats suppressed their activity when exposed to a snake in a laboratory setting (Yoerg and Shier, 1997). In contrast, 25-day-old captive-born kangaroo rats did not respond when exposed to a snake in a test arena. However, when they were exposed to a snake in the presence of their wild-caught mother, they stayed closer to their mother than in the control condition without a snake. Close proximity was no longer shown when they were 50 days old. These findings indicate that young kangaroo rats have to learn anti-snake behavior and that learning is shaped by maternal influences during a certain developmental period (Yoerg and Shier, 1997). As in rodents, young rhesus monkeys learn to avoid snakes through social cues (Mineka et al., 1984). Adolescent rhesus monkeys observed the defensive behavior of their wild-reared parents when they were exposed to snakes and snake models. Within one observation trial, the adolescent monkeys displayed defensive behavior themselves and still displayed it when re-exposed three months later. Defensive responses were learned selectively to relevant threat stimuli only. When monkeys watched observers respond fearfully to flowers, they did not acquire defensive behaviors to flowers (Cook and Mineka, 1990).

These findings demonstrate that animals can modify their behavior early in ontogeny through individual and social learning. Direct interactions with threatening stimuli affect subsequent encounters with these stimuli. Learning results in stimulus-specific and long-lasting changes in defensive behavior. Learning is thus another type of behavioral change during development. It can be concluded that defensive behavior is not characterized by a dichotomy between young and adult phenotypes but rather by continuous change and reorganization during development in an age-specific and environment-specific way. It has to be noted that the dynamic change in behavior over time does not necessarily exclude trait stability. Even when behavioral expression patterns change during ontogeny, individual animals may consistently be more fearful or less fearful. For example, the response pattern elicited by threatening situations changed during this first year of life in rhesus monkey but individual differences in defensive behavior remained stable (Kalin and Shelton, 1998).

3. Neural processes underlying the developmental changes in defensive behavior

Three types of developmental changes in defensive behavior have been distinguished: changes in unlearned behavior, experience-dependent changes and learning *sensu stricto*. What is the neural substrate that underlies defensive behavior and what are the neural processes that mediate these three types of changes in defensive behaviors during early ontogeny?

In adult mammals, defensive behavior is mediated by specific neural pathways, the fear circuit, that consist of multiple interconnected forebrain and brainstem areas including the amygdala, the hippocampus and the periaqueductal gray (LeDoux, 2000; Rosen, 2004). The amygdala receives input from multiple sensory systems, assesses the emotional salience of stimuli and initiates defensive behaviors. Studies in various species have demonstrated the central role of the amygdala in responses to predator threat (Kalin et al., 2001; Meredith and Westberry, 2004; Takahashi et al., 2007; Vazdarjanova et al., 2001). The only study that investigated the role of the amygdala in defensive behavior in young animals was carried out by our group and used the paradigm of infanticidal threat in preweaning rats. Exposure to an adult male rat activated the medial amygdala and inactivation of this nucleus abolished the pups’ freezing response (Chen et al., 2006).

The hippocampus is another forebrain structure that processes predator cues and mediates defensive responses in adult animals (Beekman et al., 2005; Blanchard and Blanchard, 1972; Heale et al., 1994; Mesches et al., 1999; Pentkowski et al., 2006). Again, a role of the hippocampus in defensive behavior in young animals has been demonstrated in the context of infanticidal threat. Hippocampal lesion and in particular lesion of dentate granule cells reduced freezing in 14-day-old rats when they were exposed to an unfamiliar adult male rat (Takahashi, 1995).

The periaqueductal gray is organized in longitudinal columns along the midbrain that mediate different defensive response patterns in adult animals. The dorsolateral column produces escape behaviors including jumping and running, and the ventrolateral column freezing behavior (Bandler et al., 2000; Brandao et al., 2008). Lesion of the ventrolateral periaqueductal gray reduced freezing in adult rats exposed to a cat (De Oca et al., 1998; Farook et al., 2004). The periaqueductal gray appears to have a similar function in young animals. Stimulation of the dorsal periaqueductal gray triggered activity and escape behavior in young rats between postnatal days 7 and 21 (Goodwin and Barr, 1998), and lesion of the ventral periaqueductal gray reduced freezing in 14-day-old rats exposed to an adult male rat (Wiedenmayer et al., 2000).

On the circuit level, defensive behavior in young animals seems thus to be controlled by the same brain structures that mediate adult defensive behavior. But since defensive behavior changes during development, these structures and their connections must undergo changes as well. In the following the neural processes that may contribute to developmental changes are summarized. They are grouped according to the three types of behavioral changes outlined above.

3.1. Changes in the neural substrate underlying unlearned behavior

The defensive response a naive animal exhibits the first time it encounters a threatening stimulus depends on its age. The processes that change the expression of unlearned defensive behavior during development seem to involve maturation of the components of the fear circuit. It has been proposed that during early ontogeny perceptual, central and motor components form, mature and connect with each other (Hogan, 1988) and that the continuous transformation of the neural substrate results in behaviors characteristic for specific developmental stages (Prechtl, 1981).

The amygdala of the rat, for example, changes continuously during the perinatal period. It forms in the embryo and continues to grow postnatally. New neurons are generated and differentiate (Bayer, 1980; Berdel and Morys, 2000), increasing the size of the nuclei of the amygdala up to an age of 14 days (Berdel et al., 1997). The expression of receptors on the cell membrane and their subunits changes over time in a nucleus-specific way (Lopez de Armentia and Sah, 2003). Accordingly, synaptic transmission shows age-specific patterns (Lopez de Armentia and Sah, 2003; Thompson et al., 2008). Other areas of the fear circuit including the hippocampus undergo similar maturational changes (Dumas, 2005).

Unfortunately, it is not well understood how these neural changes relate to age-specific changes in unlearned defensive behavior. It has been proposed that components of the fear circuit become functional in early ontogeny and thus contribute to the onset of defensive behavior. Studies of the rat amygdala have provided strong evidence for this view. As described above, rat pups freeze in the presence of an adult male rat and this unlearned defensive behavior is first shown around postnatal day 12 (Takahashi, 1992b). At that age but not in younger animals, male exposure activates the amygdala (Moriceau et al., 2004). Onset of amygdala function seems to be induced by glucocorticoids. Corticosterone levels are low between postnatal day 1 and 12 the in the rat (Levine, 2001; Sapolsky and Meaney, 1986). The surge in corticosterone secretion at the end of this stress-hyporesponsive period could thus act as a switch to initiate amygdala function and turn on the expression of defensive behavior (Moriceau et al., 2006). Supporting this model, corticosterone administration in 8-day-old pups induced freezing in the presence of the male rat and removal of the adrenal glands of 12-day-old pups inhibited freezing (Moriceau et al., 2004).

Hormones play also a significant role in the developmental activation of another area of the fear circuit, the hippocampus. When rat pups were adrenalectomized, they did not freeze when exposed to an adult male rat on postnatal day 14 (Takahashi and Rubin, 1993). The ability to freeze was restored when corticosterone was infused directly into the dorsal hippocampus of adrenalectomized pups (Takahashi, 1995). Because adrenal glands were removed and corticosterone was infused through implants 5 days before exposure to the male rat, corticosterone seems to play an organizational role in the circuit that mediates unlearned fear (Takahashi, 1995).

Another process that appears to contribute to changes in unlearned fear involves the maturation of connections between brain areas. During early development, circuits are assembled and become functional through increased synaptic connectivity (Rinaman et al., 2000). In the rat, the connections between the amygdala and other areas of the fear circuit, including prefrontal cortex and bed nucleus of the stria terminalis, mature postnatally. These projections are rearranged, become less diffuse and increase in density (Bouwmeester et al., 2002a; Bouwmeester et al., 2002b; Cooke and Simerly, 2005). The increase in connections is accompanied by an increase in synapse formation in the target areas (Cunningham et al., 2002; Cunningham et al., 2008). A significant increase in synapse formation occurs between postnatal days 20 and 40 (Andersen and Teicher, 2004).

The functional consequences of circuit formation on behavior are poorly understood. Newly formed connections could alter the functional output of the fear circuit by promoting or inhibiting defensive behavior. For example, the maturation of an inhibitory connection could result in the cessation of a behavior. A brain area known to regulate other brain areas is the prefrontal cortex (Miller and Cohen, 2001). The medial prefrontal cortex projects to areas of the fear circuit including the amygdala and the periaqueductal gray and inhibits their activities (Paré et al., 2004; Quirk and Beer, 2006). Inhibitory effects of the medial prefrontal cortex on learned fear behavior have been demonstrated in adult rats (Milad and Quirk, 2002). The prefrontal cortex does not seem to be functional in 12-day-old rats but mediates extinction of a learned response only 5 days later, in 17-day-old pups (Nair et al., 2001). This inability at a younger age seems to result from a lack of functional connectivity of the prefrontal cortex with other brain areas of the neural network (Nair et al., 2001). Changes in the capacity of the prefrontal cortex to modulate behavior could thus explain the age-related changes in unlearned fear behavior. It could be argued that the maturation of the prefrontal cortex results in the inhibition of fear at an age when a stimulus is no longer threatening. For example, the fear response of young rats when exposed to an adult male rat stops after weaning (Wiedenmayer and Barr, 2001b). In conclusion, maturation of the components of the fear circuit and their connections seem to contribute to the changes in unlearned defensive behavior during development.

3.2. Experience-dependent changes of the fear circuit

The developmental processes that organize the fear circuit are influenced by external factors. A factor that has recently received considerable attention is maternal care in rodents. Environmental conditions influence the investment of the dam in her pups and the quality and quantity of maternal care they receive (Macri and Würbel, 2006). Through variation in maternal care, mothers transmit information about local conditions to the offspring and thus influence their responsivity later in life. A multitude of studies have shown that the behavior of the adult offspring reflects the care they received. For example, pups that experienced high maternal licking and grooming are less anxious as adults (Diorio and Meaney, 2007).

During the neonatal period, the maternal environment influences the maturation of components of the fear circuit including the amygdala and hippocampus (Diorio and Meaney, 2007; Kaffman and Meaney, 2007). Connections between fear circuit components increase during the first eight postnatal days in the rat (Rinaman et al., 2000). Connectivity is however decreased when pups are repeatedly separated from their mother during this brief developmental period (Card et al., 2005). Maternal separation can also affect synapse formation. Early development is characterized by an overproduction of synapses that are subsequently pruned to adult levels. Rat pups were repeatedly separated from their mothers between postnatal days 2 and 20 and their brains analyzed for the number of synapses (Andersen and Teicher, 2004). Control rats had an overproduction of synapses in the hippocampus on day 60 but this overproduction was prevented in rats that had been repeatedly separated. A similar effect was found in a rodent species with bi-parental rearing. Removal of the father altered the synaptic organization of the prefrontal cortex in degus pups (Ovtscharoff et al., 2006). In contrast to maternal separation, increased maternal care stimulates the development of the hippocampus. New neurons are produced throughout ontogeny in the dentate gyrus of the hippocampus in rats (Doetsch and Hen, 2005). High maternal care increased number of surviving cells on postnatal day 21 and this increase lasted into adulthood (Bredy et al., 2003).

It has become clear most recently that experience-induced neuronal alterations are the result of rearrangements of chromatin and DNA structure in the cell nucleus (Duman and Newton, 2007; Jaenisch and Bird, 2003). Insight into the molecular processes contributing to individual differences in defensive behavior has been gained by comparing the effects of naturally occurring variation in maternal care (Kaffman and Meaney, 2007; Meaney and Szyf, 2005). High maternal care during the early postnatal period reverses DNA methylation and makes DNA more accessible to transcription. This leads to gene expression, which is stable over extended periods of time, and contributes to alterations in the neural substrate.

In sum, early experience affects the molecular and cellular organization of the fear circuit. It is, however, poorly understood how fear circuit changes result in differential emotional responsivity across ontogeny. Studies are needed that compare developmental trajectories and defensive behavior of animals with different rearing histories.

3.3. Changes in the fear circuit during learning

In contrast to early experience, learning *sensu stricto* is given when the animal directly interacts with a threatening stimulus and subsequently modifies its behavior. Our understanding of the neural mechanisms of learning has considerably improved during the last two decades (Milner et al., 1998). In particular, Pavlovian fear conditioning has proved to be a highly potent paradigm to investigate the neural mechanisms of defensive behavior and learning (Fanselow and Poulos, 2005; LaBar and Cabeza, 2006; Maren and Quirk, 2004; Paré et al., 2004). Components of the fear pathway are involved in the acquisition, consolidation and retrieval of fear memories. Input from the unconditioned aversive stimulus is strong and activates neurons within the fear pathway that mediate the defensive response. In contrast, input from the conditioned stimulus is weak and does not elicit a response. When unconditioned and conditioned stimuli are paired, their signals converge on neurons in areas such as the amygdala and strengthen the synaptic connections between neurons involved. Subsequently, transmission of the conditioned stimulus is enhanced and it has become strong enough to induce defensive behavior on its own (Sigurdsson et al., 2007).

The molecular and cellular basis of fear association learning has been thoroughly characterized in adult animals but virtually nothing is known about fear learning in young animals. The only study that investigated the neural substrate of fear learning in infancy used odor conditioning in preweaning rats (Moriceau et al., 2006). Twelve-day-old pups learned to avoid peppermint odor after it had been paired with tail shocks. Inactivation of the amygdala disrupted this odor-shock association. In contrast, 8-day-old pups did not avoid the odor after shock pairings. Avoidance learning was however induced at the younger age when corticosterone was infused into the amygdala. It seems that a surge in corticosterone before day 12 acts as a switch to turn on fear conditioning (Moriceau et al., 2006). These findings indicate that the amygdala mediates fear conditioning in young rats, as it does in adults (Muller et al., 1997), but only after a certain age. As discussed above, neuroendocrine processes render this area functional in early postnatal development and allow it to support both conditioned and unconditioned defensive behavior.

In sum, these studies demonstrate that the fear circuit undergoes profound changes during ontogeny and that these changes are driven by maturational processes, experience and learning. In spite of the tremendous progress in revealing the molecular and cellular processes of neural development our knowledge of how they translate into defensive behavior is still limited.

4. Functional aspects of changes in defensive behavior

To fully understand behavioral changes during development, we need to consider their functions. Functional considerations address questions about the adaptive value of behavior

(Tinbergen, 1963). A behavior is adaptive when it increases the chances of survival and reproduction for the individual displaying it compared to alternative behaviors in a given environment (Reeve and Sherman, 1993; Ridley, 2004). Two theoretical frameworks have been used to explain the functional significance and adaptive value of the changes in defensive behavior during early ontogeny.

From one point of view, the defensive behavior of infant animals is not fully functional in early ontogeny. Defensive behavior has to be refined and modified during certain periods of development until it provides maximal protection and survival benefits. As shown above, the young of some mammal species are equipped with a general ability to respond to potentially harmful stimuli. When survival is critical, for example under threat of predation, natural selection may favor fast but unspecific response patterns (Bolles, 1970). However, this initial response is general and not fully adequate because evolutionary processes do not select for short-lasting particularities of local conditions. Rather, response patterns have to be adjusted to local predator threat during development (Griffin, 2004). Individual experience, provided by maternal care, and learning are processes that modify the animal’s behavior in a way that it becomes more effective and thus is more likely to decrease chances of injury or death. For example, as described above, juvenile Belding’s ground squirrels are not able to discriminate between alarm and non-alarm calls the first day when they emerge from the natal burrow (Mateo, 1996). They respond to both types of calls with defensive behavior. This indicates that at that age they have the general ability to recognize and respond to calls of conspecifics. However, their defensive behavior is not fully functional because responding is unspecific and thus costly in terms of time and energy expenditure. But young ground squirrels are able to rapidly modify their behavior and within five days they selectively respond with defensive behavior to alarm calls only (Mateo, 1996). Young ground squirrels thus adjust their defensive behavior to local characteristics of predation through learning processes such as association learning.

In other species, young animals do not have the ability to perform an appropriate response during the first encounter with a dangerous stimulus. They have to fully acquire defensive behavior. Monkeys of several species do not exhibit defensive behavior the first time they are exposed to a snake (Joslin et al., 1964; Mineka et al., 1984; Murray and King, 1973). But young monkeys are able to rapidly and specifically learn about dangers. During a single trial, juvenile rhesus monkeys learned to associate their parents’ reactions with snakes (Mineka et al., 1984) whereas they did not form readily an association between their parents’ defensive responses and flowers (Cook and Mineka, 1990). The dependency on acquired behavior becomes evident when animals leave their home range and thus the environment they know. Vervet monkeys suffer high mortality rates from predation when they migrate into an unfamiliar area (Isbell et al., 1993). In evolutionary terms, natural selection may favor the ability to rapidly acquire a defensive response instead of possessing a more general but less effective unlearned response if environmental conditions are locally variable.

Related to the view that the responses in early ontogeny are not fully formed is the concept of developmental immaturity. A threatened animal may not show the most appropriate behavior because sensory or motor components are not yet mature and do not allow the full range of behaviors typical for older animals. For example, the gradual development of motor control allows altricial mammals to perform fast locomotion such as running only after a certain age. During the first days of life, red deer calves become immobile when a predator approached but after approximately one week, they flee (Espmark and Langvatn, 1985). The onset of the flight response did not correlate with age but depended on body weight. Since body weight indicates physical development, the authors argue that newborn deer calves are limited in their defensive behavior. Only when their motor system has matured enough young red deer can switch to running. Brain areas that support defensive behavior may not be functional in early life.

Neonatal rats do not display fear responses when exposed to an adult male rat (Wiedenmayer and Barr, 1998) because the critical brain area, the amygdala, is immature at that age and does not process the threatening stimulus (Moriceau et al., 2004; Wiedenmayer and Barr, 2001a).

In conclusion, maturational processes, experience and learning modify an individual's defensive behavior during the course of its early life. The function of these processes is to better adapt the growing organism to specific environmental conditions. Development is, according to this view, preparation for maturity (Oppenheim, 1981).

A contrasting viewpoint posits that behavioral differences between age groups do not reflect ongoing adjustments that result in a more mature phenotype, but rather that these differences represent age-specific adaptations (Alberts and Cramer, 1988; Oppenheim, 1981). Young animals have to survive very unique environmental conditions that can be fundamentally different from those of adults. Specific selection pressures have thus resulted in behavioral traits that help the growing organism to deal with problems restricted to particular stages of development.

The risk of being injured or killed by a predator or conspecific is not constant across ontogeny but varies depending on age. When animals are more vulnerable during a certain developmental period, the theory of ontogenetic adaptation predicts that they possess enhanced defensive capabilities during this period. A temporal association between increased risk and increased defensive reactivity has been found in young rats in the context of infanticide committed by adult male rats. Infanticide is highest after birth and is no longer shown once the offspring is weaned (Paul and Kupferschmidt, 1975; Takushi et al., 1983). Following the temporal dynamics of infanticidal threat, young rats exhibit defensive freezing when exposed to an unfamiliar adult male rat before but not after weaning (Wiedenmayer et al., 2005). This decrease of freezing is stimulus specific. Freezing to a loud noise does not change (Chen et al., 2006). Predation risk can significantly increase when animals change their habitat in the course of ontogeny. When young mammals emerge from their natal burrows for the first time, they are confronted with an array of novel dangers such as aerial and terrestrial predators. Emerging juveniles differ from older animals in their response patterns to threatening stimuli. California ground squirrel pups spend more time in covered habitat and monitoring their environment compared to juvenile or adult squirrels (Hanson and Coss, 2001). Infant rabbits are more responsive to a raptor model and flee faster into their burrows than adult rabbits (Vitale, 1989). Mongoose pups do not discriminate between alarm calls signaling different threat levels but withdraw readily into their burrows (Hollen and Manser, 2006). After weaning, young rats leave their natal nest and burrow and expand their home range (Calhoun, 1963), which makes them more vulnerable to predation. Responsivity to cat odor cues is more pronounced in weaned than preweaning rats and increases with age (Hubbard et al., 2004; Wiedenmayer et al., 2005). Because vulnerability is high at these ages, the overreaction of infant animals could be adaptive and increase chances of survival. Finally, animals can also change their defensive behavior in accordance with their lifetime histories (Wolf et al., 2007). Older animals at the end of their reproductive period may take more risks than young animals that have not yet reproduced (Borowski, 2002). In sum, differential vulnerability can lead to age-specific response patterns that represent ontogenetic adaptations.

The survival value of specific defensive behaviors has rarely been assessed experimentally in young mammals. We thus know little of the ultimate reasons for developmental changes in defensive behavior. It could be argue that the two proposed functional explanations, preparation for maturity and ontogenetic adaptations, are not mutually exclusive. A young animal has to survive its current environment and at the same time has to anticipate future conditions. The functions of developmental changes in defensive behavior could thus be twofold: they are adaptations and anticipations (Alberts and Cramer, 1988).

5. Developmental plasticity of defensive behavior

Development has traditionally been viewed as the emergence of new, intrinsically determined behavior patterns that unfold in a gradual way during the course of a lifetime. According to this view, the organism is the product of inherited factors that predetermine its form and function. Genetic information is, however, only one element in the processes that contribute to phenotypic variation. Several theoretical frameworks have recently conceptualized the genotype – phenotype relationship, in particular how genes relate to behavior. Even though these frameworks vary widely in scope, they commonly agree that there are no direct one-to-one mappings between genes and behavioral phenotypes. Multiple factors are causally involved in the pathway from genetic elements to phenotypic traits (Bateson, 2001; Gottesman and Hanson, 2005; Gottlieb, 2007; Johnston and Edwards, 2002; Raser and O'Shea, 2005; Rutter, 2007). During development internal and external factors interact and produce behavioral phenotypes that again interact in a reiterate fashion with local conditions (Oyama et al., 2001). Development is thus a process during which genes, environment and accidents participate in constructing phenotypes. Gene-environment interactions continue throughout ontogeny resulting in dynamic changes in phenotypes. At any time point in an organism's life, a phenotype is the consequence of the previous form of the phenotype (Lewontin, 1983). According to this view, a single genotype can result in different phenotypes under different environmental conditions, or different genotypes can produce the same phenotype under comparable environmental conditions. The ability of an organism to respond to internal and external environmental influences and develop distinct morphological, physiological and behavioral traits is called phenotypic plasticity (Pigliucci, 2001; Stearns, 1989; West-Eberhard, 2003). It is central to our understanding of phenotypic variation that changes and modifications in behavioral mechanisms occur during development (West-Eberhard, 2003).

The developmental changes in defensive behavior discussed above can be conceptualized as forms of phenotypic plasticity. Young animals are equipped with unlearned defensive responses, a consequence of phylogenetic inheritance. Encounters with predators and conspecifics have been shaping the behavioral organization of animals through evolutionary times and have resulted in behavioral adaptations (Blumstein, 2006; Vermeij, 1982). Evolutionary processes have thus produced mechanisms that allow animals to exhibit appropriate behaviors the first time they are exposed to a threatening stimulus. But these response patterns are not fixed but expressed in an age-specific way. The processes that contribute to the changes of these circuits and thus to age-specific unlearned behaviors are poorly understood. Intrinsic cellular and molecular processes continue throughout early ontogeny to construct, transform and reorganize behavioral mechanisms. Changes in the patterns of gene expression (Jablonka and Lamb, 2002; Wu and Morris, 2001) seem to underlie these maturational processes and to contribute to variation in behavioral phenotypes. The formation of the neural mechanisms mediating defensive behavior is influenced by external factors. As discussed above, social and ecological variables affect the molecular processes that construct the components and connections of the fear circuit. Postnatal experience, for instance, modifies the underlying neural substrate and hence the expression of the defensive response later in life. Because individuals vary in their experience they develop different defensive phenotypes. Finally, learning *sensu stricto* further helps animals to adjust their defensive responses to local conditions. Young animals learn about threatening and non-threatening stimuli and modify their behavior accordingly. Because environments differ in threat levels, learning produces individual variation in defensive behavior. Taken together, the three different types of changes in defensive behavior all contribute to variation in behavior during development and thus to phenotypic plasticity.

Another aspect of developmental plasticity that needs to be considered here is the problem of abnormal development. It is beyond the scope of this review to discuss the relationship between plasticity of defensive behavior and developmental psychopathology. But the distinction of different types of developmental changes could inform the investigation of the processes that result in maladaptive behavior. It could help to identify the factors that influence the developmental trajectory of an individual animal and drive it towards a maladaptive outcome. Disruption of maturational processes, early aversive experience and learning about a traumatic event can all contribute to an impaired neurobehavioral development that results in pathological fear, anxiety and depression (Grossman et al., 2003; Leonardo and Hen, 2008; Pittenger and Duman, 2008; Tsankova et al., 2007).

In conclusion, the studies discussed in this review provide clear evidence that defensive behavior is not static but is continuously reorganized during development. Maturational processes and individual experience participate in shaping the neural substrate and hence the expression of defensive responses. The processes that modify the neural mechanisms underlying defensive behavior and thus contribute to their developmental changes result in phenotypic plasticity. The alterations in brain and behavior appear to be adaptive because they allow animals to meet the demands of a dynamic environment and changes in threat levels. Ultimately, the function of plasticity is to adjust defensive mechanisms to local ecological and social conditions during the different stages of ontogeny.

Acknowledgements

I would like to thank Christopher B. Braun, Catherine Monk and Myron A. Hofer for their helpful comments on the manuscript. This work was supported by NIH grants MH071751 and MH 73994.

References

Albert DJ, Walsh ML. Neural systems and the inhibitory modulation of agonistic behavior: A comparison of mammalian species. Neurosci Biobehav Rev 1984;8:5–24. [PubMed: 6374531]

Alberts, JR.; Cramer, CP. Ecology and experience: Sources of means and meaning of developmental change. In: Blass, EM., editor. Developmental Psychobiology and Behavioral Ecology. Plenum Press; New York: 1988. p. 1-39.

Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacol 2004;29:1988–1993.

Apfelbach R, Blanchard DC, Blanchard RJ, Hayes RA, McGregor IS. The effects of predator odors in mammalian prey species: A review of field and laboratory studies. Neurosci Biobehav Rev 2005;29:1123–1144. [PubMed: 16085312]

Arakawa H. Ontogenetic interaction between social relationships and defensive burying behavior in the rat. Physiol Behav 2007;90:751–759. [PubMed: 17291551]

Bandler R, Keay KA, Floyd N, Price J. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping Brain Res Bull 2000;53:95–104.

Barros M, Tomaz C. Non-human primate models for investigating fear and anxiety. Neurosci Biobehav Rev 2002;26:187–201. [PubMed: 11856558]

Bateson P. Where does our behaviour come from? J Biosci 2001;26:561–570. [PubMed: 11807286]

Bayer SA. Quantitative ^{3}H-thymidine radiographic analyses of neurogenesis in the rat amygdala. J Comp Neurol 1980;194:845–875. [PubMed: 7204644]

Beekman M, Flachskamm C, Linthorst ACE. Effects of exposure to a predator on behaviour and serotonergic neurotransmission in different brain regions of C57bl/6N mice. Eu J Neurosci 2005;21:2825–2836.

Berdel B, Morys J. Expression of calbindin-D28k and parvalbumin during development of rat’s basolateral amygdaloid complex. Int J Dev Neurosci 2000;18:501–513. [PubMed: 10884595]

Berdel B, Morys J, Maciejewska B. Neuronal changes in the basolateral complex during development of the amygdala of the rat. Int J Dev Neurosci 1997;15:755–765. [PubMed: 9402226]

Berger J. Carnivore repatriation and holarctic prey: Narrowing the deficit in ecological effectiveness. Conservation Biol 2007;21:1105–1116.

Blanchard DC, Blanchard RJ. Ethoexperimental approaches to the biology of emotion. Annu Rev Psychol 1988;39:43–68. [PubMed: 2894198]

Blanchard DC, Griebel G, Blanchard RJ. Conditioning and residual emotionality effects of predator stimuli: some reflections on stress and emotion. Prog Neuro-Psychopharmacol Biol Psychiat 2003;27:1177–1185.

Blanchard RJ, Blanchard DC. Effects of hippocampal lesions on the rat's reaction to a cat. J Comp Physiol Psychol 1972;78:77–82. [PubMed: 5027344]

Blanchard RJ, Blanchard DC. Bringing natural behaviors into the laboratory: a tribute to Paul MacLean. Physiol Behav 2003;79:515–524. [PubMed: 12954446]

Blumstein DT. The multipredator hypothesis and the evolutionary persistence of antipredator behavior. Ethology 2006;112:209–217.

Boissy A. Fear and fearfulness in animals. Q Rev Biol 1995;70:165–191. [PubMed: 7610234]

Bolles RC. Species-specific defense reactions and avoidance learning. Psychol Rev 1970;77:32–48.

Bolles RC, Fanselow MS. A perceptual-defensive-recuperative model of fear and pain. Behav Brain Sci 1980;3:291–323.

Borowski Z. Individual and seasonal differences in antipredatory behaviour of root voles - a field experiment. Can J Zool 2002;80:1520–1525.

Bouwmeester H, Smits K, van Ree JM. Neonatal development of projections to the basolateral amygdala from prefrontal and thalamic structures in rat. J Comp Neurol 2002a;450:241–255. [PubMed: 12209853]

Bouwmeester H, Wolterink G, van Ree JM. Neonatal development of projections from the basolateral amygdala to prefrontal, striatal, and thalamic structures in rat. J Comp Neurol 2002b;442:239–249. [PubMed: 11774339]

Brandao ML, Zanoveli JM, Ruiz-Martinez RC, Oliveira LC, Landeira-Fernandez J. Different patterns of freezing behavior organized in the periaqueductal gray of rats: Association with different types of anxiety. Behav Brain Res 2008;188:1–13. [PubMed: 18054397]

Bredy TW, Grant RJ, Champagne DL, Meaney MJ. Maternal care influences neuronal survival in the hippocampus of the rat. Eu J Neurosci 2003;18:2903–2909.

Bronstein PM, Hirsch SM. Ontogeny of defensive reactions in Norway rats. J Comp Physiol Psychol 1976;90:620–629. [PubMed: 950390]

Brown RE. Social and hormonal factors influencing infanticide and its suppression in adult male Long-Evans rats. J Comp Psychol 1986;100:155–161. [PubMed: 3720284]

Calhoun, JB. The Ecology and Sociology of the Norway Rat. U.S. Department of Health, Education, and Welfare; Bethesda, MD: 1963.

Card JP, Levitt P, Gluhovsky M, Rinaman L. Early experience modifies the postnatal assembly of autonomic emotional motor circuits in rats. J Neurosci 2005;25:9102–9111. [PubMed: 16207869]

Champagne FA, Curley JP. How social experiences influence the brain. Curr Op Neurobiol 2005;15:704–709. [PubMed: 16260130]

Chen SWC, Shemyakin A, Wiedenmayer CP. The role of the amygdala and olfaction in unconditioned fear in developing rats. J Neurosci 2006;26:233–240. [PubMed: 16399692]

Clutton-Brock TH, Gaynor D, McIlrath GM, Maccoll ADC, Kansky R, Chadwick P, Manser M, Skinner JD, Brotherton PNM. Predation, group size and mortality in a cooperative mongoose, *Suricata suricatta*. J Anim Ecol 1999;68:672–683.

Cook M, Mineka S. Selective associations in the observational conditioning of fear in rhesus monkeys. J Expm Psychol: Anim Behav Proc 1990;16:372–389.

Cooke BM, Simerly RB. Ontogeny of bidirectional connections between the medial nucleus of the amygdala and the principle bed nucleus of the stria terminalis in the rat. J Comp Neurol 2005;489:42–58. [PubMed: 15977169]

Coss RG, Gusé KL, Poran NS, Smith DG. Development of antisnake defenses in California ground squirrels (*Spermophilus beecheyi*): II. Microevolutionary effects of relaxed selection from rattlesnakes Behaviour 1993;124:137–164.

Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. J Comp Neurol 2002;453:116–130. [PubMed: 12373778]

Cunningham MG, Bhattacharyya S, Benes FM. Increasing interaction of amygdalar afferents with GABAergic interneurons between birth and adulthood. Cereb Cortex 2008;18:1529–1535. [PubMed: 17971342]

de Boer SF, Koolhaas JM. Defensive burying in rodents: ethology, neurobiology and psychopharmacology. Eu J Neurosci 2003;463:135–161.

De Oca BM, DeCola JP, Maren S, Fanselow MS. Distinct regions of the periaqueductal gray are involved in the acquisition and expression of defensive responses. J Neurosci 1998;18:3426–3432. [PubMed: 9547249]

Diorio J, Meaney MJ. Maternal programming of defensive responses through sustained effects on gene expression. J Psychiatry Neurosci 2007;32:275–284. [PubMed: 17653296]

Doetsch F, Hen R. Young and excitable: the function of new neurons in the adult mammalian brain. Curr Op Neurobiol 2005;15:121–128. [PubMed: 15721754]

Duman RS, Newton SS. Epigenetic marking and neuronal plasticity. Biol Psychiatry 2007;62:1–3. [PubMed: 17572174]

Dumas TC. Late postnatal maturation of excitatory synaptic transmission permits adult-like expression of hippocampal-dependent behaviors. Hippocampus 2005;15:562–578. [PubMed: 15884034]

Eilam D. Die hard: A blend of freezing and fleeing as a dynamic defense -implications for the control of defensive behavior. Neurosci Biobehav Rev 2005;29:1181–1191. [PubMed: 16085311]

Espmark Y, Langvatn R. Development and habituation of cardiac and behavioral responses in young red deer calves (*Cervus elaphus*) exposed to alarm stimuli. J Mammalogy 1985;66:702–711.

Fanselow, MS.; Lester, LS. A functional behavioristic approach to aversively motivated behavior: predatory imminence as a determinant of the topography of defensive behavior. In: Bolles, RC.; Beecher, MD., editors. Evolution and Learning. Lawrence Erlbaum; Hillsdale: 1988. p. 185-212.

Fanselow MS, Poulos AM. The neuroscience of mammalian associative learning. Annu Rev Psychol 2005;56:207–234. [PubMed: 15709934]

Farook JM, Wang Q, Moochhala SM, Zhu ZY, Lee L, Wong PTH. Distinct regions of periaqueductal gray (PAG) are involved in freezing behavior in hooded PVG rats on the cat-freezing test apparatus. Neurosci Lett 2004;354:139–142. [PubMed: 14698458]

Goodwin GA, Barr GA. Behavioral and heart rate effects of infusing kainic acid into the dorsal midbrain during early development in the rat. Dev Brain Res 1998;107:11–20. [PubMed: 9602029]

Gottesman II, Hanson DR. Human development: Biological and genetic processes. Annu Rev Psychol 2005;56:263–286. [PubMed: 15709936]

Gottlieb G. Probabilistic epigenesis. Dev Science 2007;10:1–11.

Griffin AS. Social learning about predators: A review and prospectus. Learn Behav 2004;32:131–140. [PubMed: 15161148]

Grossman AW, Churchill JD, McKinney BC, Kodish IM, Otte SL, Greenough WT. Experience effects on brain development: possible contributions to psychopathology. J Child Psychol Psychiatry 2003;44:33–63. [PubMed: 12553412]

Hanson MT, Coss RG. Age differences in arousal and vigilance in California ground squirrels (*Spermophilus beecheyi*). Dev Psychobiol 2001;39:199–206. [PubMed: 11745313]

Heale VR, Vanderwolf CH, Kavaliers M. Components of weasel and fox odors elicit fast wave bursts in the dentate gyrus of rats. Behav Brain Res 1994;63:159–165. [PubMed: 7999299]

Hendrie CA, Weiss SM, Eilam D. Exploration and predation models of anxiety: evidence from laboratory and wild species. Pharmacol Biochem Behav 1996;54:13–20. [PubMed: 8728534]

Hofer, MA. Evolutionary concepts of anxiety. In: Stein, DJ.; Hollander, E., editors. Textbook of Anxiety Disorders. American Psychiatric Publishing; Washington, DC: 2002. p. 57-69.

Hogan, JA. Cause and function in the development of behavior systems. In: Blass, EM., editor. Developmental Psychobiology and Behavioral Ecology. Plenum Press; New York: 1988. p. 63-106.

Hollen LI, Manser MB. Ontogeny of alarm call responses in meerkats, *Suricata suricatta*: the roles of age, sex and nearby conspecifics. Anim Behav 2006;72:1345–1353.

Hubbard DT, Blanchard DC, Yang M, Markham CM, Gervacio A, Chun-I L, Blanchard RJ. Development of defensive behavior and conditioning to cat odor in the rat. Physiol Behav 2004;80:525–530. [PubMed: 14741237]

Hunt PS, Richardson R. Pharmacological dissociation of trace and long-delay fear conditioning in young rats. Neurobiol Learn Memory 2007;87:86–92.

Isbell LA, Cheney DL, Seyfarth RM. Are immigrant vervet monkeys, Cercopithecus aethiops, at greater risk of mortality than residents? Anim Behav 1993;45:729–734.

Jablonka E, Lamb MJ. The changing concept of epigenetics. Ann NY Acad Sci 2002;981:82–96. [PubMed: 12547675]

Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature Genet 2003;33:245–254. [PubMed: 12610534]

Johnston TD, Edwards L. Genes, interactions, and the development of behavior. Psychol Rev 2002;109:26–34. [PubMed: 11863039]

Joslin J, Fletcher H, Emlen J. A comparison of the responses to snakes of lab- and wild-reared rhesus monkeys. Anim Behav 1964;12:348–352.

Kaffman A, Meaney MJ. Neurodevelopmental sequelae of postnatal maternal care in rodents: clinical and research implications of molecular insights. J Child Psychol Psychiatry 2007;48:224–244. [PubMed: 17355397]

Kalin NH, Shelton SE. Ontogeny and stability of separation and threat-induced defensive behaviors in rhesus monkeys during the first year of life. Am J Primatol 1998;44:125–135. [PubMed: 9503124]

Kalin NH, Shelton SE, Davidson RJ, Kelley AE. The primate amygdala mediates acute fear but not the behavioral and physiological components of anxious temperament. J Neurosci 2001;21:2067–2074. [PubMed: 11245690]

Kats LB, Dill LM. The scent of death: Chemosensory assessment of predation risk by prey animals. Ecoscience 1998;5:361–394.

Kavaliers M, Choleris E. Antipredator responses and defensive behavior: ecological and ethological approaches for the neurosciences. Neurosci Biobehav Rev 2001;25:577–586. [PubMed: 11801283]

LaBar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nature Rev Neurosci 2006;7:54–64. [PubMed: 16371950]

LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000;23:155–184. [PubMed: 10845062]

Leonardo ED, Hen R. Anxiety as a developmental disorder. Neuropsychopharmacol 2008;33:134–140.

Levine S. Primary social relationships influence the development of the hypothalamic-pituitary-adrenal axis in the rat. Physiol Behav 2001;73:255–260. [PubMed: 11438350]

Lewontin, RC. Gene, organism and environment. In: Bendall, DS., editor. Evolution: From Molecules to Men. Cambridge University Press; Cambridge: 1983. p. 273-285.

Lima SL, Dill LM. Behavioral decisions made under the risk of predation: a review and prospectus. Can J Zool 1990;68:619–640.

Lind J, Cresswell W. Determining the fitness consequences of antipredation behavior. Behav Ecol 2005;16:945–956.

Lopez de Armentia M, Sah P. Development and subunit composition of synaptic NMDA receptors in the amygdala: NR2B synapses in the adult central amygdala. J Neurosci 2003;23:6876–6883. [PubMed: 12890782]

López-Rubalcava C, Fernández-Guasti A, Urbá-Holmgren R. Age-dependent differences in the rat's conditioned defensive burying behavior: Effect of 5-HT$_{1A}$ compounds. Dev Psychobiol 1996;29:157–169. [PubMed: 8919093]

Macri S, Würbel H. Developmental plasticity of HPA and fear responses in rats: A critical review of the maternal mediation hypothesis. Horm Behav 2006;50:667–680. [PubMed: 16890940]

Maren S, Quirk GJ. Neuronal signalling of fear memory. Nature Rev Neurosci 2004;5:844–852. [PubMed: 15496862]

Mateo JM. The development of alarm-call response behaviour in free-living juvenile Belding's ground squirrels. Anim Behav 1996;52:489–505.

Mateo JM, Holmes WG. How rearing history affects alarm-call responses of Belding's ground squirrels (*Spermophilus beldingi*, Sciuridae). Ethology 1999a;105:207–222.

Mateo JM, Holmes WG. Plasticity of alarm-call response development in Belding's ground squirrels (*Spermophilus beldingi*, Sciuridae). Ethology 1999b;105:193–206.

Mayr E. Cause and effect in biology. Science 1961;134:1501–1506. [PubMed: 14471768]

Meaney MJ, Szyf M. Maternal care as a model for experience-dependent chromatin plasticity? TINS 2005;28:456–463. [PubMed: 16054244]

Menard JL, Champagne DL, Meaney MJ. Variations of maternal care differentially influence 'fear' reactivity and regional patterns of cFos immunoreactivity in response to the shock-probe burying test. Neuroscience 2004;129:297–308. [PubMed: 15501588]

Mennella JA, Moltz H. Infanticide in rats: male strategy and female counter- strategy. Physiol Behav 1988;42:19–28. [PubMed: 3387474]

Meredith M, Westberry JM. Distinctive responses in the medial amygdala to same-species and different-species pheromones. J Neurosci 2004;24:5719–5725. [PubMed: 15215294]

Mesches MH, Fleshner M, Heman KL, Rose GM, Diamond DM. Exposing rats to a predator blocks primed burst potentiation in the hippocampus in vitro. J Neurosci 1999;19(1–5):RC18. [PubMed: 10407060]

Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 2002;420:70–74. [PubMed: 12422216]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202. [PubMed: 11283309]

Milner B, Squire LR, Kandel ER. Cognitive neuroscience and the study of memory. Neuron 1998;20:445–468. [PubMed: 9539121]

Mineka S, Davidson M, Cook M, Keir R. Observational conditioning of snake fear in rhesus monkeys. J Abnorm Psychol 1984;93:355–372. [PubMed: 6542574]

Moriceau S, Roth TL, Okotoghaide T, Sullivan RM. Corticosterone controls the developmental emergence of fear and amygdala function to predator odors in infant rat pups. Int J Dev Neurosci 2004;22:415–422. [PubMed: 15380840]

Moriceau S, Wilson DA, Levine S, Sullivan RM. Dual circuitry for odor-shock conditioning during infancy: Corticosterone switches between fear and attraction via amygdala. J Neurosci 2006;26:6737–6748. [PubMed: 16793881]

Muller J, Corodimas KP, Fridel Z, LeDoux JE. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. Behav Neurosci 1997;111:683–691. [PubMed: 9267646]

Murray SG, King JE. Snake avoidance in feral and laboratory reared squirrel monkeys. Behaviour 1973;47:281–289.

Nair HP, Berndt JD, Barrett D, Gonzalez-Lima F. Maturation of extinction behavior in infant rats: large-scale regional interactions with medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex. J Neurosci 2001;21:4400–4407. [PubMed: 11404426]

Nowak, RM. Walker's Mammals of the World. The Johns Hopkins University Press; Baltimore: 1999.

Öhman A, Mineka S. Fears, phobias, and preparedness: towards an evolved module of fear and fear learning. Biol Rev 2001;108:483–522.

Oppenheim, RW. Ontogenetic adaptations and retrogressive processes in the development of the nervous system and behavior: a neuroembryological perspective. In: Connolly, KJ.; Prechtl, HFR., editors. Maturation and Development: Biological and Psychological Perspectives. Spastics International Medical Publications; London: 1981. p. 73-109.

Ovtscharoff W, Helmeke C, Braun K. Lack of paternal care affects synaptic development in the anterior cingulate cortex. Brain Res 2006;1116:58–63. [PubMed: 16945352]

Oyama, S.; Griffiths, PE.; Gray, RD., editors. Cycles of Contingency. The MIT Press; Cambridge: 2001.

Paré D, Quirk GJ, LeDoux JE. New vistas on amygdala networks in conditioned fear. J Neurophysiol 2004;92:1–9. [PubMed: 15212433]

Paul L, Kupferschmidt J. Killing of conspecific and mouse young by male rats. J Comp Physiol Psychol 1975;88:755–763.

Pentkowski NS, Blanchard DC, Lever C, Litvin Y, Blanchard RJ. Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. Eu J Neurosci 2006;23:2185–2196.

Pigliucci, M. Phenotypic Plasticity. The Johns Hopkins University Press; Baltimore: 2001.

Pinel JPJ, Symons LA, Christensen BK, Tees RC. Development of defensive burying in *Rattus norvegicus*: Experience and defensive responses. J Comp Psychol 1989;103:359–365. [PubMed: 2598622]

Pittenger C, Duman RS. Stress, depression, and neuroplasticity: A convergence of mechanisms. Neuropsychopharmacol 2008;33:88–109.

Prechtl, HFR. The study of neural development as a perspective of clinical problems. In: Connolly, KJ.; Prechtl, HFR., editors. Maturation and Development. Spastics International Medical Publications; London: 1981. p. 198

Quirk GJ, Beer JS. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Op Neurobiol 2006;16:723–727. [PubMed: 17084617]

Raser JM, O'Shea EK. Noise in gene expression: Origins, consequences, and control. Science 2005;309:2010–2013. [PubMed: 16179466]

Reeve HK, Sherman PW. Adaptation and the goals of evolutionary research. Q Rev Biol 1993;68:1–32.

Ridley, M. Evolution. Blackwell Publishing; Oxford: 2004.

Rinaman L, Levitt P, Card JP. Progressive postnatal assembly of limbic-autonomic circuits revealed by central transneuronal transport of pseudorabies virus. J Neurosci 2000;20:2731–2741. [PubMed: 10729354]

Rosen JB. The neurobiology of conditioned and unconditioned fear: A neurobehavioral system analysis of the amygdala. Behav Cogn Neurosci Rev 2004;3:23–41. [PubMed: 15191640]

Rosenblum LA, Forger C, Noland S, Trost RC, Coplan JD. Response of adolescent bonnet macaques to an acute fear stimulus as a function of early rearing conditions. Dev Psychobiol 2001;39:40–45. [PubMed: 11507708]

Rudy JW. Contextual conditioning and auditory cue conditioning dissociate during development. Behav Neurosci 1993;107:887–891. [PubMed: 8280399]

Rutter M. Gene-environment interdependence. Dev Science 2007;10:12–18.

Samuels R. Innateness in cognitive science. TICS 2004;8:136–141.

Sapolsky RM, Meaney MJ. Maturation of the adrenocortical stress response: neuroendocrine control mechanisms and stress hyporesponsive period. Brain Res Rev 1986;11:65–76.

Shier DM, Owings DH. Effects of social learning on predator training and postrelease survival in juvenile black-tailed prairie dogs, Cynomys ludovicianus. Anim Behav 2007;73:567–577.

Sigurdsson T, Doyere V, Cain CK, LeDoux JE. Long-term potentiation in the amygdala: A cellular mechanism of fear learning and memory. Neuropharmacol 2007;52:215–227.

Spear, NE.; Rudy, JW. Tests of the ontogeny of learning and memory: Issues, methods, and results. In: Shair, HN.; Barr, GA.; Hofer, MA., editors. Developmental Psychobiology: New Methods and Changing Concepts. Oxford University Press; New York: 1991. p. 84-113.

Stanton ME. Multiple memory systems, development and conditioning. Behav Brain Res 2000;110:25–37. [PubMed: 10802301]

Stearns SC. The evolutionary significance of phenotypic plasticity. BioScience 1989;39:436–445.

Suarez SD, Gallup GG. An ethological analysis of open-field behavior in rats and mice. Learn Motiv 1981;12:342–363.

Takahashi LK. Developmental expression of defensive responses during exposure to conspecific adults in preweanling rats (*Rattus norvegicus*). J Comp Psychol 1992a;106:69–77. [PubMed: 1313347]

Takahashi LK. Ontogeny of behavioral inhibition induced by unfamiliar adult male conspecifics in preweanling rats. Physiol Behav 1992b;52:493–498. [PubMed: 1409910]

Takahashi LK. Stimulus control of behavioral inhibition in the preweanling rat. Physiol Behav 1994;55:717–721. [PubMed: 8190800]

Takahashi LK. Glucocorticoids, the hippocampus, and behavioral inhibition in the preweanling rat. J Neurosci 1995;15:6023–6034. [PubMed: 7666186]

Takahashi LK, Hubbard DT, Lee I, Dar Y, Sipes SM. Predator odor-induced conditioned fear involves the basolateral and medial amygdala. Behav Neurosci 2007;121:100–110. [PubMed: 17324054]

Takahashi LK, Rubin WW. Corticosteroid induction of threat-induced behavioral inhibition in preweanling rats. Behav Neurosci 1993;107:860–866. [PubMed: 8280395]

Takushi RY, Flannelly KJ, Blanchard DC, Blanchard RJ. Maternal aggression in two strains of laboratory rats. Agg Behav 1983;9:120.

Thompson JV, Sullivan RM, Wilson DA. Developmental emergence of fear learning corresponds with changes in amygdala synaptic plasticity. Brain Res 2008;1200:58–65. [PubMed: 18295751]

Thor DH, Wainwright KL, Holloway WR. Attraction to mobile and immobile conspecifics. Anim Learn Behav 1981;9:363–367.

Tinbergen N. On aims and methods of ethology. Z Tierpsychol 1963;20:410–433.

Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. Nature Rev Neurosci 2007;8:355–367. [PubMed: 17453016]

van Schaik, CP.; Janson, CH., editors. Infanticide by males and its implications. Cambridge University Press; Cambridge: 2000.

Vazdarjanova A, Cahill L, McGaugh JL. Disrupting basolateral amygdala function impairs unconditioned freezing and avoidance in rats. Eu J Neurosci 2001;14:709–718.

Vermeij GJ. Unsuccessful predation and evolution. Am Naturalist 1982;120:701–720.

Vitale AF. Changes in the anti-predator responses of wild rabbits, *Oryctolagus cuniculus* (L.), with age and experience. Behaviour 1989;110:47–61.

West-Eberhard, MJ. Developmental Plasticity and Evolution. Oxford University Press; Oxford: 2003.

Wiedenmayer CP, Barr GA. Ontogeny of defensive behavior and analgesia in rat pups exposed to an adult male rat. Physiol Behav 1998;63:261–269. [PubMed: 9423968]

Wiedenmayer CP, Barr GA. Developmental changes in c-fos expression to an age-specific social stressor in infant rats. Behav Brain Res 2001a;126:147–157. [PubMed: 11704260]

Wiedenmayer CP, Barr GA. Developmental changes in responsivity to threat are stimulus-specific in rats. Dev Psychobiol 2001b;39:1–7. [PubMed: 11507704]

Wiedenmayer CP, Goodwin GA, Barr GA. The effect of periaqueductal gray lesions on responses to age-specific threats in infant rats. Dev Brain Res 2000;120:191–198. [PubMed: 10775771]

Wiedenmayer CP, Magarinos AM, McEwen BS, Barr GA. Age-specific threats induce CRF expression in the paraventricular nucleus of the hypothalamus and hippocampus of young rats. Horm Behav 2005;47:139–150. [PubMed: 15664017]

Wolf M, van Doorn GS, Leimar O, Weissing FJ. Life-history trade-offs favour the evolution of animal personalities. Nature 2007;447:581–585. [PubMed: 17538618]

Wu, C-t; Morris, JR. Genes, genetics, and epigenetics: A correspondence. Science 2001;293:1103–1105. [PubMed: 11498582]

Ydenberg RC, Dill LM. The economics of fleeing from predators. Adv Study Behav 1986;16:229–249.

Yoerg SI, Shier DM. Maternal presence and rearing condition affect responses to a live predator in kangaroo rats (*Dipodomys heermanni arenae*). J Comp Psychol 1997;111:362–369. [PubMed: 9419881]