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Developmental and neurobehavioral transitions in survival circuits

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Although animals of all ages experience threats, the neurobehavioral response to threat shows fundamental changes across development in altricial species, including humans and rodents. Although the mature animal has an arsenal of defensive strategies to engage, including attack, escape, hide or freeze, the motorically immature infant exhibits age-appropriate responses to threats that involve approach to the caregiver for protection. The neurobiology supporting this difference relies on both the immature state of the infant brain and neural networks specifically adapted to its unique environmental niche. Using examples from innate threats, we review the development of threat survival circuit neurobiology to illustrate developmental transitions and the important role of the caregiver in controlling the infant's neurobehavioral response to threat.

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Introduction

Survival circuits are important for all species, regardless of age and environment, to coordinate organismal state changes to meet primordial needs of safety and access to resources [1–3]. However, individual strategies and behavior can vary widely across species and across the lifespan. For example, in altricial species such as humans and rodents, the neurobehavioral response to threat is critical for survival at all ages, yet this system shows fundamental changes over development. Although the adult has an arsenal of defensive strategies to engage, including attacking, escape, hiding or freezing, the motorically immature infant exhibits age-appropriate responses to threats that involve approach to the caregiver for protection. The neurobiology supporting the unique infant survival circuitry for threat defense responses relies on both the immature state of the infant brain and adaptation to its unique environmental niche within the caregiver–infant dyad. For example, an adult might attack prey, but the infant would approach the caregiver to seek safety and protection. Furthermore, a growing number of studies on human children and infant rodents have shown that the quality of caregiving can modulate how infants respond to perceived threats and stressful stimuli. Using examples from innate and learned threats in rodents, we review the development of threat neurobiology and use pups' responses to predator odor and odor-shock learning to illustrate developmental transitions.

Development of infant innate threat system: infant alone

In young children, and other altricial species, there appears to be some innate response to threat, indicated by startles, crying and changes in position in response to strong noxious sensory stimuli (i.e. painful medical procedures, loud noises, rough handling, falling down, snakes). Although these responses also exist in adults, the complex offensive and defensive responses to threat seen in adults is not present and generally delayed until some independence from the caregiver is achieved, such as temporary excursions out of the home, nest or burrow. The immature infant is helpless to defend itself from a predator, having neither the motor skills, strength nor agility required [4,5]. Instead, the infant approaches the caregiver for protection [6]. For instance, studies have shown that very young children are more reluctant to leave caregivers to seek refuge from a perceived threat than older children [6], and that caregiver presence can buffer startle responses to an innate threat in young infants [7]. A similar pattern in the development of threat response behaviors has been documented in myriad species, including rabbits, birds and nonhuman primates (for review, see [8]).

Little is known about the development of brain networks that support threat responses in humans. We do know that pain responses in newborns fail to engage the amygdala [9], a brain area that robustly responds to threat in older humans and other animals [10,11] and which continues to develop postnatally in humans [12]. The amygdala is thought to be engaged in threat responding in children by about 7 months of age: infants at this age, but not younger, show a bias in processing fearful faces compared to novel facial expressions [13•], although early life adversity appears to accelerate the development of this behavior [14]. Imaging studies suggest considerable amygdala maturation and a decline in overall excitability by around 10 years of age in children [15].

A more detailed understanding of the dynamics of assessing the age-specific threat system and the neurobiology of threat responding has emerged through the study of developing rodents. More adult-like threat responses, such as immobility and freezing, emerge around postnatal day (PN) 10; this is the same age when pups begin to make brief excursions outside the nest and when the amygdala becomes functionally integrated into the threat response system [16–19]. However, specific circumstances that are ecologically significant have been shown to engage defense responses to a threatening odor in pups younger than PN10. Although these young pups fail to respond with adult-like responses to predator odors, pups placed outside the nest will stop emitting ultrasonic vocalizations to induce retrieval by their mother if novel male odor is present [20•,21]; as male rats will eat unfamiliar infants, this odor signals a salient threat to young pups [21–24].

This novel male odor also engages a circuit that overlaps with the adult threat system [25]. Specifically, male odor activates the olfactory bulb (OB), anterior piriform (olfactory) cortex (aPCX) and CA1 of the hippocampus at PN7. The OB and aPCX are activated in response to predator odor in adults, suggesting that these areas support the response to predator odor throughout development [26,27]. Additional areas are recruited at PN14, when adult-like responses are present: the pPCX, BLA complex, MeA and OFC. By weaning age (~PN23) the adult threat circuit is present and the full range of predator odors producing robust adult threat responses is present [28,29]. The specific contributions of these diverse areas in the infant response to predator odor are not known, although these results suggest increasing diversity of active regions as animals mature and develop adult-like defense responses.

Infant innate threat system requires stress hormones for expression

The immature infant amygdala [30], while sufficiently developed to support a response threat, requires the presence of the stress hormone corticosterone (CORT) to be activated in response to threat [18,31–34]. This was first shown by Takahashi and colleagues: using novel male odor as the threatening stimulus, they demonstrated that injecting CORT in pups younger than PN10 evoked a precocious defense response to predator odor, while eliminating CORT in older pups prevented the freezing response to predator odor [19,35]. This CORT-dependent responding contrasts sharply with the adult threat system [10]. Specifically, adult rat defense responses to threat involve complex, experienced-based behavioral choices between options ranging from hiding to fighting. This behavior system relies on an elaborate network of brain regions, which includes the amygdala. Although stress hormones can modulate this system, they are not required for the expression of defensive responses [36].

The hypothalamic–pituitary–adrenal (HPA) axis is the main pathway for activating the stress response, although very young pups have a ‘stress hypo-responsive period’ (SHRP) with very low levels of endogenous CORT; this SHRP is thought to underlie the failure of the HPA axis to be engaged in response to threat at this age [37]. The SHRP ends as a threat-induced CORT response reaches a critical threshold at PN10: at this age, the amygdala becomes active during innate threat exposure to support behavioral expression of freezing and, as will be discussed below, during learning about threat [38,39].

There appears to be a similar stress hypo-responsive period in human children, though the specific time-course is unknown (Figure 1). Infants exhibit a period of dampened cortisol reactivity that develops over the first year of life (6–12 months) [40] and basal cortisol levels remain low through the preschool period [41]. Learning about fearsome stimuli is also blunted at this age: swimming trauma experienced before age 7 years old (needing to be rescued) was not associated with fear of swimming when measured at age 18 [42]. On the other hand, late-onset (after 18 years old) dental fear was associated with aversive conditioning experiences at the dentist’s office [43] while early-onset dental fear was not. These studies are consistent with the hypothesis that in early development, low endogenous stress hormone levels prevent the amygdala-dependent fear system from becoming engaged in learning about threat.

Thus, there is a critical role for stress hormones in the immature threat responding system in early life [44], although early life trauma can cause the precocious emergence of this system [39]. Specifically, this dependence upon CORT to engage threat response networks means that life experiences that increase stress hormone levels (i.e. early life maltreatment and trauma) will produce a precocious responding to threat with more adult-like behaviors (emergence at PN10 in pups changes to PN7), rather than approaching the mother for protection [39]. In children, increased stress in early life accelerates amygdala engagement in threat responding [45]. Maternal threat responses can also induce precocious emergence of amygdala-dependent threat responses, as will be reviewed below.

Development of infant innate threat system: attenuation by caregiver presence

The natural ecological niche for infants of many altricial species is close proximity to the caregiver [46]. As such, assessment of threat responses within this context reveals age-specific responses to threats. In young children, we

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