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Current Opinion in Behavioral Sciences

Effects of early-life stress on fear memory in the developing rat

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Infantile forgetting is a well-established, and ubiquitous, phenomenon that occurs in nearly all species, including humans. Despite this, recent advances have shown that apparently forgotten memories of early experiences can impact later behavior as well as the neurobiology underlying later learning. In addition, there is growing evidence that early-life adversity leads to faster maturation of the memory system, resulting in early experiences being explicitly recalled for longer periods of time. Understanding the neural mechanisms underpinning the effects of early stress on memory development may bring us closer to identifying novel treatment approaches for reversing the effects of early-life stress on memory and reducing subsequent risk for psychological disorders.

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Current Opinion in Behavioral Sciences 2015, **7**:xx–yy

This review comes from a themed issue on **Development and behavior**

Edited by **Frances A Champagne** and **Anthony R Isles**

doi:10.1016/j.cobeha.2015.10.003

2352-1546/Published by Elsevier Ltd.

Epidemiological evidence shows that early-life adversity is associated with increased prevalence and severity of mental health problems [1]; also see [2••]. For example, childhood abuse is associated with increased incidence of depression and anxiety disorders [3], while experimental allocation to continued childhood institutionalization in the Bucharest Early Intervention Project increased the incidence of a range of psychopathologies compared to children who were allocated to being put into foster care [4]. Given this evidence, it is unsurprising that both historical and contemporary theories of psychopathology emphasize the importance of early life experiences in the etiology of mental illness. For example, Mineka and Zinbarg [5] propose that early experiences act as a vulnerability (or resilience) factor that contribute to the likelihood of an anxiety disorder developing in response to future stressors.

A major problem for theories of psychopathology that emphasize the role of early learning is the transient nature of early memories. Across nearly all species, retention is dramatically shorter in developing individuals, a phenomenon known as childhood or infantile amnesia [6–9,10•]. The ubiquitous nature of infantile amnesia suggests that early life experiences should rapidly fade from memory, which is difficult to reconcile with the idea that such experiences have an especially marked influence on later behavior. There are several possible solutions to this apparent paradox, two of which are described below. The first is that apparently forgotten memories can still affect later behavior, and the second (which is the focus of this brief review) is that early-life adversity speeds up the maturation of adult-like memory.

The indirect effects of 'forgotten' early experiences

Early experience may leave a 'trace' that affects later behavior even though that experience is not explicitly, or consciously, recalled. That is, although the early experience may not be expressed in overt behavior, it still affects subsequent physiological responses or how future information is encoded [8]. As one example, the NMDA receptor is generally thought to be essential for new learning, but not for learning something the second time [11•]. In support of the idea that young animals retain a 'trace' of early experiences, infant rats trained on a fear conditioning task and then retrained on that same task following forgetting exhibit NMDA-independent re-learning [12]. In other words, the early learning experience altered the neurobiology of later learning even though the original memory was not behaviorally expressed also see [13].

Additional evidence that apparently forgotten infant memories can affect later behavior is provided by a recent study where infant rats were exposed to unpredictable and inescapable shocks in a particular context [14••]. As adults these animals expressed no fear of that context (i.e., the memory of the early traumatic experience had apparently been forgotten). Nonetheless, they exhibited stronger fear learning (to a different context) as well as increased expression of glucocorticoid receptors in the amygdala and atypical circadian patterns of basal corticosterone levels

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(with two, rather than one, peak) compared to previously untrained animals. Taken together, these studies provide clear evidence that infant experiences can have consequences later in life, even if a memory of that experience is not behaviorally expressed.

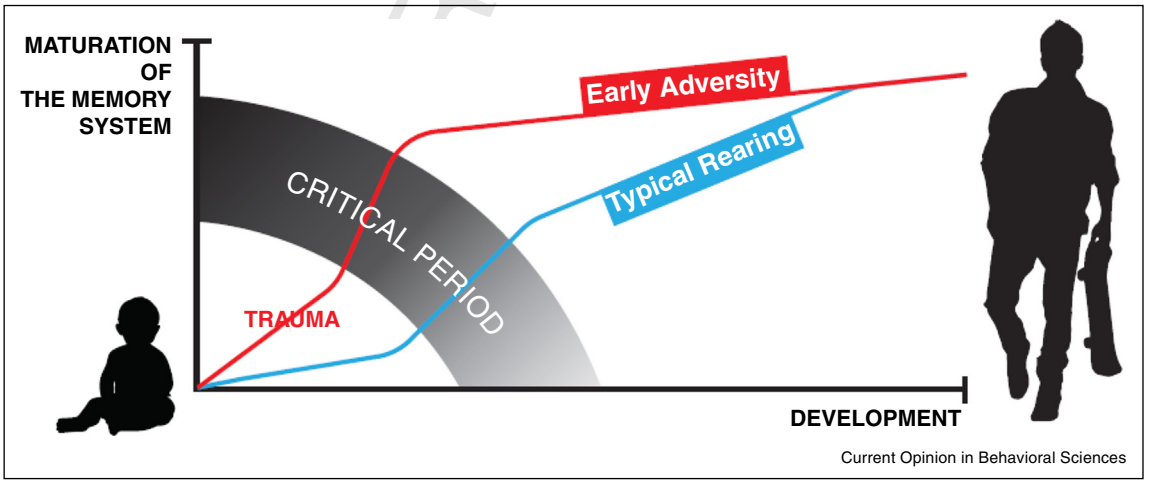
The effect of early adverse experiences on memory maturation

Another possible solution to the apparent paradox noted above is that early-life stress/trauma alters the normal developmental trajectory of memory (see Figure 1). In other words, the experience of early trauma may allow subsequent memories to evade developmental forgetting processes and to persist into adulthood (i.e., be explicitly recalled and expressed). Indeed, we recently reported that exposure to maternal separation rearing (a potent stressor for both the parent and offspring) results in adult-like retention in infant rats. Specifically, while standard-reared infants forgot aversive associations after 10 days, infants exposed to maternal separation exhibited long-lasting fear associations that were expressed up to 30 days post-conditioning ([16]; see Figure 2). Put another way, stressful rearing experiences rendered infant memories resilient against forgetting.

Chronic maternal separation is not the only early experience that affects the developmental trajectory of memory. Other studies reported that exposure to glucocorticoids or to an acute stressor has a similar effect on memory maturation. For example, memory retention at a long delay (i.e., 7–14 days post conditioning) is significantly better in infants exposed to an acute separation experience on P9 (24 hour maternal deprivation) [17] and in non-separated infants reared by a mother given the stress hormone corticosterone in her drinking water [16]. In addition, an earlier paper reported that repeated daily experience with any of a number of stressors (i.e., shock, hypothermia, or restraint) led to infant rats exhibiting longer-lasting memory for both aversive *and* appetitive tasks [18••]. Together, these studies demonstrate that exposure to high levels of stress in infancy accelerates memory development.

While the effect of stress on memory development has been investigated more extensively in rodent models, there is evidence that similar effects occur in humans. For example, one recent study found that adults exposed to familial stress (i.e., separation or divorce) prior to their 7th birthday reported earlier memories than adults who experienced this familial stress after their 7th birthday; that is, childhood amnesia appears to have ended at a younger age for those who experienced this type of stress earlier in life [19•]. Further, the age of earliest memory recollection was negatively correlated with the degree of stress reported (i.e., greater separation stress was associated with earlier memories). A similar finding was observed in a subsequent study where children 7–11 years of age, rather than adults, were asked about their earliest memories [20]. Children from 'non-nuclear' families (most which had experienced separation/divorce) reported earlier memories than did children from nuclear families. Although both of these studies used retrospective reports, their results are consistent with the notion that high levels of stress early in life accelerates maturation of memory, leading to early experiences being explicitly retained for longer periods of time.

Figure 1



Memory retention increases over the lifespan across species, with the most marked improvements occurring early in life. This period of rapid memory development corresponds with critical periods of structural and functional changes in the brain, such as the development of perineuronal nets, changes in the balance of kinases/phosphatases, and decreases in neurogenesis (for a review of molecular/cellular signals involved in critical periods see Takesian and Hensch [15]). In the context of early-life stress, memory appears to develop more rapidly, which may be a behavioral manifestation of an underlying shift in the turning on/off of these critical period signals.

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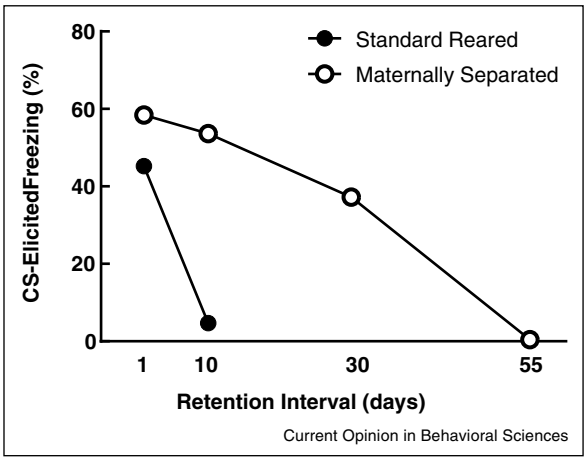
Figure 2



Typically-reared infant rats (labeled 'standard reared' in the figure) can learn to fear (as measured by freezing) a stimulus paired with shock but this memory quickly fades. In contrast, infant rats that had experienced early-life stress (in this case, repeated bouts of maternal separation; labeled 'maternally separated' in the figure) exhibit much longer-lasting memories of that learning experience.
Source: These data are re-drawn from Experiments 1 and 2 in Callaghan and Richardson [16].

Possible mechanisms mediating the effects of adverse early life experiences on the maturation of memory

There are several possible neural mechanisms through which exposure to early-life stress might alter the maturation of memory (see Figure 1). For simplicity, we describe these mechanisms separately but it is likely that they interact to some degree and that their relative importance differs depending on the exact nature of the early-life trauma.

The amygdala, the prefrontal cortex, and their connectivity play an important role in memory, especially of aversive events, and early stress may alter the timing of plasticity regulators in these structures. For example, the appearance of perineuronal nets (PNNs) around parvalbumin-expressing inhibitory cells occurs in the amygdala around the age of offset for infantile amnesia [21••]. Such nets have been suggested to function as structural scaffolds necessary for the maintenance of long term memories [22]. If early-life stress increases the rate of development of PNNSs then this would lead to enhanced structural support for the maintenance of longer-lasting memories [6,23].

Plasticity regulation could also be affected by early-life stress through changes in the balance between memory promoting and inhibiting molecules. Long-term memory in adults is thought to involve a balance between memory promoting protein kinases (e.g., calcium calmodulin-dependent protein kinase II; CAMKII) and memory inhibiting protein phosphatases (e.g., Calcinuerin) see [24,25]. These proteins appear to be developmentally regulated and it has been suggested that the relatively lower levels of CAMKII in the developing brain [26] might tip the balance in favor of memory inhibition [6]. Interestingly, maternal separation accelerates the maturation of CAMKII in the developing brain [27], which could lead to an earlier emergence of long-term memory.

Taking a broader view, it is possible that early-life stress alters maturation of memory through system-level effects. There is evidence, in adult rodents and humans, that fear expression involves both the amygdala and the prefrontal cortex (PFC) [28]. However, the PFC does not appear to be involved in fear memory in infant rodents. Temporary inactivation of the PFC (in particular the prelimbic subdivision) does not reduce expression of learned fear [29]. In addition, exposure to an innate fear stimulus (i.e., cat odor) does not increase neural activity in the PFC of infant rats [30]. If early-life stress causes the PFC to become involved in fear memory at a younger age, then this could contribute to longer lasting memory in these animals. Interestingly, Tottenham and her colleagues have found that children exposed to early-life stress exhibit altered connectivity patterns between the PFC and amygdala, with the previously-stressed children exhibiting a more mature pattern of connectivity (see Callaghan and Tottenham, this issue).

Finally, another candidate mechanism for how early-life trauma affects memory maturation involves neurogenesis. In a series of intriguing papers it was suggested that the high levels of neurogenesis during early development may contribute to infantile amnesia [7,31,32]. Indeed, reducing neurogenesis in infant mice using genetic or pharmacological procedures was found to increase the persistence of fear memory [33••]. Further, increasing neurogenesis in the hippocampus using either a naturalistic intervention (voluntary wheel running) or a pro-neurogenic drug, memantine (MEM), led to forgetting of a context fear memory in adult mice. The idea here is that although new neurons may be involved in encoding new memories [34–36] incorporating these new neurons into the neural circuitry might also negatively impact on retrieval of existing memories. Importantly, early-life stress has been found to reduce neurogenesis in infant (PND15) rats [37], see [38] for review. In other words, early-life stress-induced reductions in the normally high levels of infant neurogenesis may lead to longer lasting infant memories by lessening disruptions to the neural circuits in which those memories are encoded.

Treatment strategies

The discussion above illustrates just some of the mechanisms that could mediate the effects of early-life stress on memory development. As noted, these may act in concert or may be differentially engaged depending on the exact

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nature/timing of the stressor. One way to test these potential mechanisms would be to find treatments that reverse the effects of the stress on memory development. If these treatments affect one, or more, of the candidate mechanisms described above, then that would provide support for their involvement in the faster maturation of memory development following early-life stress. Further, such a finding would provide evidence of a treatment for humans exposed to early-life adversity.

There are a number of possible approaches here, but one potential avenue for treatment involves the relationship between the brain and the gut. There has been a surge of scientific interest in this issue, particularly with regards to the links between gastrointestinal and psychiatric dysfunction [39,40••,41]. High levels of comorbidity have been observed between functional gastrointestinal disorders (e.g., Irritable Bowel Syndrome; IBS) and various forms of psychopathology [42]. A critical determinant of gastrointestinal health is the delicate balance maintained between the millions of microorganisms that reside in the gastrointestinal tract. It is becoming clear that these organisms, collectively known as the microbiome, also have a role in brain function and behavior, particularly early in life [43]. A functioning microbiome is critical for normal development of the HPA axis, emotional behavior, and expression of various neurotransmitters, as illustrated by studies of germ-free mice raised in sterile conditions and essentially lacking a microbiome [44,45].

One unobtrusive method of altering the microbiome is via probiotic treatments. Probiotics are microorganisms defined by their ability to bring about health benefits to the host upon colonization of the gastrointestinal tract [46]. Probiotic treatments have previously been shown to address gastrointestinal consequences of stress across a variety of disorders, with some evidence that they may also reduce associated anxious and depressive symptoms [47]. Further, preliminary evidence from our laboratory shows that probiotics can reverse the behavioral effects of maternal separation on memory development (CSM Cowan et al., unpublished).

The next question is how exposure to probiotics reverses the effects of stress on memory development. It will be interesting to determine what effects, if any, exposure to probiotics has on the various candidate mechanisms described above, but there is already some interesting evidence concerning one of these mechanisms. Specifically, germ-free mice, who as described above essentially lack a microbiome, have higher rates of survival of new neurons in adulthood and a trend toward greater cell proliferation in the hippocampus [48]. Further, probiotics have been shown to reverse changes in neurogenesis induced by adult stress exposure [49], but their effects in the case of early-life stress have yet to be tested. This will be an interesting line of investigation given the potential value of such a safe, simple, and non-invasive treatment for early-life trauma.

Summary

Although there has been considerable attention directed toward understanding the neural and behavioral consequences of early-life stress in the adult, there have been much less attention directed at understanding what happens earlier in life. However, this is starting to change, in part due to increasing awareness of the fact that early-emerging anxiety disorders are both more difficult to treat and more costly [2••,50]. There are now several demonstrations, in both rats and humans, that early-life stress speeds up the maturation of memory (i.e., the offset of the infantile/childhood amnesia period happens earlier) and leads to early-acquired memories persisting for longer, which could at least partially account for the relationship between early-life trauma and later anxiety [51]. In addition, there is converging evidence across species that a variety of early life adversities (all involving the child-parent relationship) accelerate the development of emotional regulatory systems [52,53]. Not surprisingly, given the relative dearth of work in this area, we do not yet know the mechanisms underlying these changes in memory development, nor ways in which these effects can be reversed. However, in a recent study exposure to probiotics was found to reduce a number of symptoms in an animal model of autism spectrum disorder [54], and if anxiety disorders are also seen as being neurodevelopmental in origin then probiotics might be an effective treatment for such disorders. Finding safe, effective, low-cost treatment approaches that may 'rescue' individuals exposed to early-life trauma from neurodevelopmental disorders would be a substantial advancement with far-reaching benefits.

Conflict of interest

Nothing declared.

Acknowledgements

RR's research is supported by grants from the Australian Research Council (DP150104835) and the National Health and Medical Research Council (APP1031688); CC is supported by a Petre Foundation Scholarship and an UNSW Research Excellence Award; BC is supported by a CJ Martin Fellowship from the National Health and Medical Research Council (APP1091571); JK is supported by an Australian Postgraduate Award. We would like to thank Ryan Carceller for his assistance with the design of Figure 1.

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