Review

Cell PRESS

The elusive engram: what can infantile amnesia tell us about memory?

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Revealing the engram is one of the greatest challenges in neuroscience. Many researchers focus on understanding the cellular and molecular mechanisms underlying the formation and maintenance of the engram, but an underutilized approach has been to investigate analogous processes associated with forgetting. Infant rodents present an ideal model for this purpose because they display a rapid form of non-pathological forgetting known as infantile amnesia (IA). Despite the widespread importance of this interesting phenomenon, the study of the neural bases of IA has remained largely neglected. Here, we consider what IA can tell us about memory. We argue that to understand the mechanisms underlying the engram we must also gain an appreciation of the mechanisms that drive forgetting.

Finding the engram

Memory structures our representations of ourselves as individuals, and allows us to learn from experience and to develop across our own lifetime and across generations. Indeed, as noted by Tsien, 'the importance of long-term memory is comparable with the significance of DNA' [1]. Unlike the insights gained in understanding the molecular bases of life (i.e., DNA), however, the search for how memories are encoded into a lasting physical representation in the brain (i.e., the engram) has proceeded at a much slower pace. Although significant progress has been made in elucidating the neural bases and molecular cascades underlying memory [2–4], many questions remain, including determination of the mechanism via which memories can persist across years (and even a lifetime) in the face of continual molecular turnover. In this review we look to the largely neglected phenomenon of infantile amnesia (IA) and consider what forgetting can tell us about memory. We argue that to understand the mechanisms underlying long-term memory (LTM), we must also gain an appreciation of the mechanisms that drive forgetting.

Infantile amnesia, the forgotten phenomenon

The term infantile amnesia was first coined by Freud [5] to describe the observation that we have very few, if any, memories from the first years of life (but see [6] for one notable exception). Another more widely used definition of this term is that it is the faster rate of forgetting observed in the young compared to adults [7]. Although IA was initially described in humans, it was subsequently shown to characterize early memories in all altricial species, making it an excellent model for translational research on forgetting (Box 1). In the first demonstration of IA in rats, Campbell and Campbell showed that animals trained from postnatal day (P) 18 through to P100 were equally apt at forming an association between the black side of a black–white shuttle box and footshock, and exhibited comparable passive avoidance of the black side when tested immediately after training [8]. However, after a training–test interval of 1 week, the P18 rats forgot the association. Adult rats, by contrast, exhibited excellent retention even when tested as long as 42 days after training. Hence, IA is characterized by impaired retention of medium-term and remote memories (i.e., those lasting for approximately 1 week or more) when initial levels of learning are equated, and is strongest in the infancy stage of development (<P21 in the rat).

Although IA has been well characterized in rodent models [9], the neurobiological basis of this phenomenon has remained relatively elusive, making it one of the few examples in which greater gains have been made from research using human subjects despite the existence of a tractable animal model [10–14]. Perhaps in recognition of that fact, a resurgence of animal research attempting to explain the neurobiology of IA has taken advantage of improved techniques available to probe the structural and molecular bases of memory [15,16]. In this review we highlight some of the candidate mechanisms that may be important in this forgetting phenomenon and discuss some novel manipulations through which their role in memory development can be tested. It is hoped that this review will stimulate more research into the neurobiological bases of IA and thereby provide alternative avenues through which to investigate the engram.

Learning the same but forgetting differently

Most research on memory development prior to publication of the study by Campbell and Campbell failed to adequately control for potential developmental differences in the degree of learning [17]. Therefore, it was impossible to determine if the faster rate of forgetting was due to memory differences or to differences in initial learning. In examining the processes underlying IA, it is essential that initial levels of learning are equated across the age groups.

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Keywords: infantile amnesia; memory; engram; forgetting; molecular mechanisms.

0166-2236/$ – see front matter
 http://dx.doi.org/10.1016/j.tins.2013.10.007

Box 1. Clinical implications of infantile amnesia

The study of forgetting in infant rats is likely to have significant clinical benefits because numerous anxiety disorders are characterized by the persistence of fear responses [84]. If infant-like forgetting could be promoted in adults, then this could be advantageous for the treatment or prevention of these disorders. For example, recent research has shown that the termination of a critical period of plasticity in infant rats, characterized by erasure-like extinction learning (i.e., no fear relapse), was correlated with the emergence of perineuronal nets (PNNs) around amygdala neurons [45] (see [85] for a conceptually related finding). Amazingly, that period of infant-like extinction could be reopened in adulthood if amygdala PNNs were degraded. It may be the case that infantile amnesia also represents a critical period of plasticity that becomes more adult-like following the formation of PNNs. If so, then the same treatment that results in more infant-like extinction might also result in higher rates of forgetting in adulthood.

Potential molecular mechanisms underlying IA

In the past 20 years there has been considerable interest in elucidating the molecular bases of memory. By contrast, far less is known about the molecular correlates of memory loss. One reason for the relative lack of animal research on forgetting, especially for learned fear, is that adult animals typically recall fear memories for a very long time [18]. However, as indicated above, forgetting, even of fear associations, occurs fairly rapidly early in life. This presents a perfect, although surprisingly underutilized, model in which to study the neural bases of forgetting. Some of the neural bases proposed to be important for memory in the adult that may also be important for IA are reviewed below.

Protein kinase–phosphatase balance

One set of molecules importantly involved in memory are protein kinases and protein phosphatases [19–22]. Whereas the phosphorylation of protein kinases facilitates various forms of memory, the expression of protein phosphatases appears to act as an off switch, dephosphorylating and opposing kinase-facilitated processes. It has been suggested that memory formation is therefore either promoted or inhibited, depending on whether the balance is tipped in favor of kinase or phosphatase expression [23]. For example, the protein kinase Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is critically involved in both the induction and maintenance of long-term potentiation (LTP) [23], a widely accepted cellular model of LTM [24,25]. The activity of CAMKII is opposed by the phosphatase calcineurin (CaN), which has opposite effects on LTP and memory, leading to the characterization of CaN as a memory suppressor [26,27]. Increasing or decreasing the activity of CaN impairs or facilitates, respectively, the expression of LTP [19], and higher levels of methylation of the CaN gene are associated with LTM maintenance [26]. Although very little work has been done examining the expression or activity of these proteins early in life, there is some evidence from rodent models suggesting that CAMKII levels are low in early postnatal development and increase rapidly over the first 2 weeks of life [28,29]. This suggests that infant forgetting could be driven by an imbalance in the expression of CAMKII and its opposing phosphatase CaN (Table 1). This imbalance could result in greater suppression of memory by relatively higher levels of CaN activity at the time of retrieval. Indeed, one study showed that inhibition of CaN activity in the olfactory bulbs of infant rats (through infusion of the CaN inhibitor FK506) extended the retention of an odor preference memory, suggesting that CaN activity may be involved in infant forgetting [30]. Furthermore, increased activity of protein phosphatases has been observed in aged animals and implicated in a range of memory disorders [31]. For instance, individuals with Alzheimer's disease exhibit substantial changes in protein activity levels, with CaN expression drastically increased and CaMKII phosphorylation decreased [31–33]. Hence, increased CaN activity in the brain may be associated with memory failures that occur both later in life and early in development.

Developmental differences in the expression of PKMζ

Although an alteration in the balance between kinases and phosphatases is one potential mechanism mediating IA, numerous other molecules have been shown to be important for the LTM persistence in adults and could also be involved in infant forgetting. For instance, it has been suggested that sustained activation of PKMζ, an atypical isoform of protein kinase C (PKC), is important for the persistence of long-term memories in adults. Specifically, studies have shown that inhibition of PKMζ expression in the hippocampus or neocortex erased spatial memories that were formed several weeks earlier [34–36], although several recent studies have questioned the role of PKMζ in memory [37–39]. Could decreased levels of PKMζ early in life underlie IA? Interestingly, PKMζ is expressed at low levels at birth in the rat and remains relatively stable for the first month of life [40]. Determination of whether less PKMζ is recruited during memory formation in infancy and whether this is associated with greater forgetting will be an interesting avenue to explore in future studies.

Another possibility, however, is that PKMζ functions differently in the infant brain compared to the adult brain. It was recently demonstrated that basal synaptic transmission in the perirhinal cortex of rats in early development (P14) was maintained by constitutively active PKMζ [41]. The same set of studies showed that whereas PKMζ controlled LTP expression in perirhinal slices from adult animals, PKMζ was not required for basal activity in this brain region. Furthermore, the authors showed that PKMζ levels were higher in perirhinal cortex in P14 rats than in the adult, suggesting that PKMζ plays a role in maintaining infant synapses in a tonically active state. These results support the idea that PKMζ may not be involved in infant plasticity owing to its role in maintaining basal synaptic activity early in life. Further studies on the role of PKMζ in regions that support the formation and maintenance of fear memories (e.g., the amygdala) will be important in elucidating the role of this molecule in IA.

Another protein that may be of interest for the persistence of LTM is BDNF. Inhibition of hippocampal BDNF expression 10 h after fear conditioning blocked memory retention at 7 days but not at 2 days, suggesting that there is a late wave of protein synthesis important for memory persistence but not memory formation [42]. Whether this late consolidation wave also occurs in the infant rat following fear conditioning remains to be determined.

Table 1. Putative mnemonic mechanisms and their hypothesized and known patterns of activity or expression in early postnatal development (relative to adults)

	Proposed stage of memory[a]	Putative and known expression/activity during infancy[b]	Hypothesized action for memory retention	Refs
CAMKII	Short and intermediate	↓	Facilitating	[23,28,29]
Calcineurin	Short and intermediate	↑	Impairing	[19,31–33,86]
PKMζ	Short and intermediate	↓	Facilitating	[34–36,40,41]
PNN patterning	Remote	↓	Facilitating	[1,45]
Neurogenesis	Remote	↑	Impairing	[15,17]
DNA methylation	Short, intermediate, and remote	Role for methylation may be limited to developmental programming in infancy	Dependent upon target (methylation of memory suppressor genes, e.g., calcineurin, should facilitate memory)	[26,57–59,87]
Prelimbic activity	Intermediate and remote	↓	Facilitating	[16,88]
Physiology of amygdala inhibitory interneurons	Unknown; believed to enhance information transfer between brain regions that might assist with remote memory storage	Immature	Facilitating	[50,73,74]

[a]The term 'short' indicates memories that are stored for hours to days, 'intermediate' refers to memories that are stored for weeks to months, and 'remote' denotes memories that are stored for many months to a lifetime.

[b]Known ontogenetic activity is indicated by arrows in green; putative ontogenetic activity (as determined from the literature and interactions with other molecules/markers with known ontogenetic patterns) is indicated by the red arrow.

Perineuronal net patterning and remote memory storage

One of the problems with molecular theories of memory is explaining how memories persist in the face of metabolic turnover; that is, these approaches have difficulty accounting for how memories are maintained across long periods of time despite complete exchange of the proteins that are believed to represent memory [43,44]. Many 'memory molecules' (e.g., CAMKII) have circumvented that problem by utilizing a process that allows copying of information across successive generations of molecules through an autophosphorylating switch or autocatalytic activity [23]. However, although such functions might allow memory to be maintained in the short and intermediate term (i.e., days to months), the viability of memory maintenance by such switches over extremely long periods of time (a lifetime) has been challenged [1]. Rather, it has been suggested that for memory maintenance in the remote long term, a stable physical representation of the memory is required that is not subject to recopying.

One potential set of candidates that could serve as stable memory storage sites are perineuronal nets (PNNs). PNNs are condensed chondroitin sulfate proteoglycan (CSPG) containing extracellular matrix proteins surrounding the dendrites, axons, and cell bodies of neurons and are particularly stable because they are remote from the intracellular machinery that degrades proteins. It was recently suggested that the pattern of holes in the extracellular matrix could act as a physical scaffold to preserve the location and strength of synapses across a lifetime, despite the transfer of molecules inside the neuron [1]. Interestingly, the fact that PNNs are not widely expressed in the amygdala at the time when IA is prevalent [45] suggests that PNNs might also be important for the phenomenon of rapid infant forgetting. That is, infant memories may be so labile because of the lack of extracellular matrix proteins available to create physically stable patterned memory nets around neurons. If this were true, then it may be possible to reactivate IA in adults by degrading PNNs in the amygdala (such studies would be of great interest clinically; Box 1).

Low levels of PNNs could also contribute to IA through the regulation of firing patterns of the neurons they surround. Specifically, PNNs preferentially surround parvalbumin (PV)-positive inhibitory interneurons in the brain and contribute to the fast-spiking patterns of these neurons [46], a property believed to drive oscillatory activity in the brain [47–49]. Interestingly, particular frequencies of oscillations (e.g., gamma and theta) are involved in the retrieval of fear memories [47,50]. Hence, it is possible that infant rats have difficulty in recalling experiences because the electrophysiological properties of their neurons do not support retrieval of remote memories.

Neurogenesis resulting in a storage or retrieval failure

Another hypothesis that has recently been proposed is that IA might be related to high levels of neurogenesis in the infant brain [15]. Specifically, it was suggested that high levels of neurogenesis early in life lead to degradation of memory representations as new neurons are incorporated into existing memory networks (see [51,52] for a different perspective on the role of neurogenesis in forgetting). In their classic paper *Ontogeny of memory*, Campbell and Spear made a similar proposal for the importance of neurogenesis in forgetting but via a different process [17]. They suggested that 'it is quite possible that memories acquired early in development are stored with the same fidelity as adult memories, but that access to them is impeded by further central nervous system development' [17]. In other words, although both of these proposals implicate high levels of neurogenesis in forgetting, in the former case the forgetting is thought to be due to a storage failure (or disruption), whereas in the latter case it is due to a retrieval failure. There is substantial evidence that many cases of forgetting during infancy are due to a retrieval failure [53,54] (see [55] for a demonstration of IA as

Box 2. Is infantile amnesia a special form of forgetting?

Although elucidation of the mechanisms underlying IA will be important in its own right, it is likely to have implications for our understanding of other forms of forgetting and of memory. That is, many of the mechanisms of forgetting may be shared across IA, spontaneous forgetting in adulthood, and accelerated forgetting as in Alzheimer's disease. However, the fact that IA is a non-pathological form of natural forgetting perhaps makes it a particularly useful model in which to examine the processes contributing to persistent memory expression and memory breakdown. Indeed, if the mechanisms underlying IA were shown to be similar to those mediating other forms of forgetting (e.g., forgetting seen in aging), then it would provide a readily accessible, and more economical, model for testing the effectiveness of drugs and nootropic agents for memory loss before they are tested on more expensive aged animals.

retrieval failure using stringent tests recently developed by Hardt *et al.* [56]). However, the mechanisms of IA may differ with the length of the retention interval (i.e., IA may be due to a retrieval failure in the first few weeks but a result of a storage deficit after longer delays). In any case, neither of these approaches seems well suited to handle the forgetting that occurs in old age because of the very low levels of neurogenesis observed then (although forgetting in old age may be due to different, or additional, mechanisms; Box 2).

Epigenetics in memory storage

Another molecular mechanism that could support LTM involves epigenetic modifications, such as modification of DNA by cytosine methylation, known to regulate the transcriptional activity of genes. DNA methylation is a popular candidate for LTM because it fulfils two of the basic requirements for LTM: it is long-lasting and self-perpetuating [57–59]. Indeed, persistent methylation of the CaN gene occurred in the cortex of rats exposed to associative fear conditioning in adulthood, and disruption of this methylation pattern led to memory deficits [26]. The results of this study suggest that methylation of memory suppressor genes is recruited in certain brain regions to maintain remote memories across long periods of time, at least in adults. Interestingly, methylation of DNA can and does occur in the infant (postnatal) brain and is responsive to early experiences such as adversity [60–69]. Whether the role of DNA methylation in the postnatal brain is limited to determination of cell fate and developmental programming, or whether methylation is also recruited to support changes in gene expression underlying LTM, is currently unknown. However, a lack of learning-induced methylation of genes involved in LTM persistence (e.g., CaN) in the developing brain could be a contributing factor to IA occurrence. If so, then perhaps a switch in the primary role of methylation from developmental programming to learning-induced plasticity might signify the offset of the IA period; this remains to be investigated.

Prefrontal and amygdala interactions in LTM retrieval

One physical change in the brain that might be critical for the enhanced forgetting observed in infancy is the transition from prelimbic (PL)-independent to PL-dependent memory seen across the infancy to juvenile stages of development. Adult rats appear to require a functionally active PL to express learned fear at test [70]. However, a recent study using immunohistochemical and temporary inactivation procedures showed that the PL region of the prefrontal cortex (PFC) was not involved in expression of learned fear in infant (P17) rats but was involved in expression of learned fear in juvenile (P23) rats [16] (see [71,72] for conceptually similar studies in humans). A much simpler circuit (amygdala only; Figure 1) appears to mediate expression of fear memories in the infant rat, and retrieval of remote fear memories acquired in infancy may be more difficult after the adult circuit has matured.

Related to the lack of PL involvement in infant memory expression are findings from two elegant studies on amygdala function in the developing rat [73,74]. In both studies, physiological development of amygdala neurons was fairly dynamic across the early postnatal period, with a number of measures not reaching adult levels until approximately 4 weeks of age. Perhaps most important in terms of IA was the finding that PV-containing inhibitory interneurons in the amygdala emerged and matured during weeks 2–4 of life, approximately the same time that IA normally dissipates (and when PNNs begin to develop). As mentioned earlier, these interneurons play a particularly important role in coordinating activity between various neural regions that underlie memory [50], supporting the idea that IA may reflect a lack of coordinated activity between the amygdala and neocortical storage/retrieval sites. In other words, IA may occur because the memory trace is not

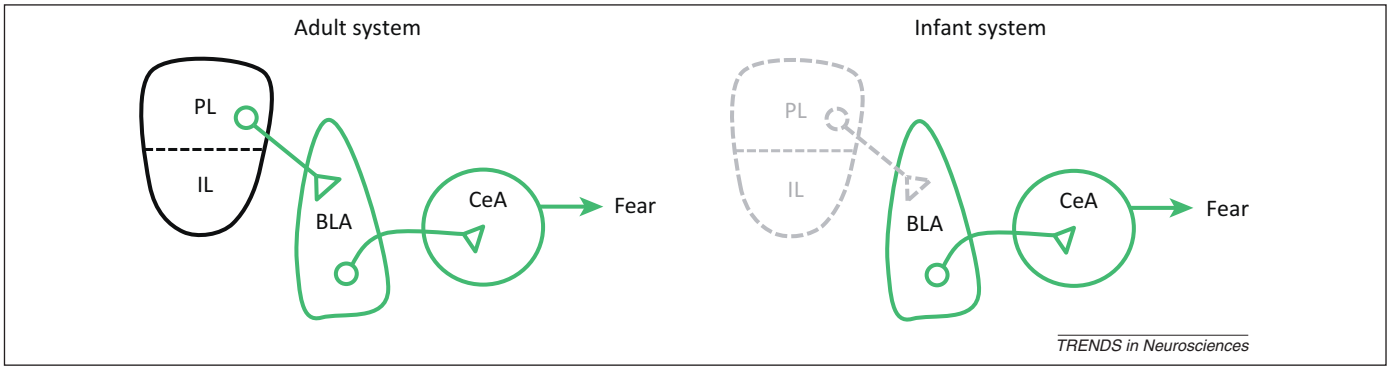

Figure 1. Proposed neural circuits mediating fear in adult and infant rats. In the adult system, prelimbic (PL) cortex activates the basolateral amygdala (BLA), which then excites neurons in the central amygdala (CeA), driving the expression of fear. In the infant system, the PL does not participate in fear expression, so fear appears to be driven by a simple circuit consisting of the amygdala alone.

adequately transferred into a stable remote storage/retrieval network.

In summary, although many promising candidates are currently being investigated for their role in memory maintenance in adults, whether developmental disruptions of these mechanisms are also involved in IA is an important question for future studies. In particular, differentiating the mechanisms involved in the maintenance of memories across very short to moderate to very remote periods of time should assist in identifying the myriad molecules, structures, and physiological factors involved in this very complex process. We may then begin to unravel whether the same mechanisms are involved in IA, spontaneous memory loss in adulthood, and memory loss in pathological aging (e.g., Alzheimer's disease; Box 2).

IA in the future: where are we heading?

One novel approach to studying IA will be to look at the impact of different environmental manipulations on the onset and offset of this rapid rate of forgetting. There are several benefits of this approach, including its clear clinical relevance. As just one example, we have shown that adverse rearing conditions lead to early emergence of adult-like memory. In those studies we found that rats exposed to repeated bouts of maternal separation (MS) across infancy exhibited adult-like fear memories earlier in development than rats exposed to typical rearing conditions [75]. Specifically, following fear conditioning at P17 standard-reared (SR) rats exhibited good retention when tested 1 day later, but poor retention when tested 10 days later (i.e., they showed IA). The MS rats, by contrast, exhibited near perfect retention across a 10-day interval following training in infancy, and even expressed conditioned fear up to 30 days later. Enhanced fear retention was also seen in infant rats that were suckled by mothers exposed to corticosterone in drinking water across the first 2 postnatal weeks [75]. Together these results demonstrate that exposure to stress or stress hormones dramatically reduces the age at which the IA period closes and suggest that exposure to early-life stress may accelerate emergence of the adult-like memory system. Understanding the molecular and cellular mechanisms that are altered or accelerated by early stress will yield interesting insights into the processes typically involved in the transition between IA and adult-like memory expression. Indeed, early-life stress is known to accelerate the maturation of a number of developmental processes important for the expression of adult-like memory in both rats and humans (e.g., myelination, CAMKII expression; amygdala–prefrontal connectivity [28,76–82]). Furthermore, retention of early memories in humans also appears to be regulated by the child–caregiver relationship [83]. Hence, MS might be a useful (and translatable) tool to cross-validate research findings regarding the molecular mechanisms involved in IA (e.g., proteins and structures critical for IA should be absent or expressed differently in the brains of MS infants).

Concluding remarks: reawakening interest in forgetting

In 1972 Campbell and Spear noted that one of their goals was to reawaken interest in IA, stimulating more research on this important phenomenon [17]. Although this was the case for studies in humans, the level of interest in this robust and pervasive effect in non-human animals dramatically decreased in the years following publication of their paper. As a result of a number of technological advances, the last two decades have seen significant improvements in our understanding of memory storage in the adult, revealing multiple candidates (molecular and structural) that could function together to produce memories that stand the test of time. Specifically, it appears that LTM may result from a cascade of changes, starting with calcium activation of kinases with the capacity for persistent or autocatalytic activity (such as CAMKII and PKMζ) and culminating in structural changes, as well as alterations in gene expression, that can store the memory for access at remote time points (Table 1). Whether IA represents a breakdown in all or a select few of these processes remains to be determined, but research directed at examining this issue is sure to lead

Box 3. Outstanding questions

- **Determining the mechanisms involved in short-, medium-, and remote long-term memory**
  Although research has begun to elucidate how memories are converted from a short-term (or working memory) store into a long-term store, the question of what mechanisms are involved in maintaining the LTM trace across remote (or lifetime) intervals remains open. Future studies determining the mechanisms involved in memory maintenance across very long intervals, as well as those involved in memory maintenance across moderate delays, will generate a richer understanding of the processes involved in memory and forgetting, and how we might manipulate those to precisely control how long memories are retained.
- **Effects of stress on putative memory storage mechanisms**
  The modulatory effects of stress on infant memory suggest that it will be important to determine whether various putative memory storage mechanisms develop differently in stressed and non-stressed infants. For example, the finding that maternally separated infants exhibit adult-like retention earlier in development might suggest that structures proposed to be important for remote memory that are absent in infancy [e.g., basolateral amygdala (BLA) PNNs] develop earlier in the maternally separated rat.
- **Comparison of infantile amnesia to other forms of memory**
  The usefulness of infantile amnesia as a model of spontaneous and pathological forgetting later in development is limited by the lack of research explicitly comparing IA to these other types of forgetting. To take full advantage of the IA model, we need to know which of the mechanisms involved in good retention in adults exhibit developmental dissociations and to understand the precise developmental trajectories of these mechanisms.
- **Interaction between putative memory mechanisms and memory reinstatement and reactivation**
  In many cases, IA represents a retrieval failure because a memory can be successfully reactivated or reinstated after it has been forgotten. It will be important to determine how such reactivation or reinstatement procedures interact with the putative memory mechanisms discussed in this review. For example, would a reactivation procedure produce memories of differing duration if it were performed at a stage when remote memory maintenance mechanisms were either present or not?
- **The role of protein synthesis in infant memories**
  Although it has been consistently shown that *de novo* protein synthesis is critical for generation of LTM in adults, whether new proteins are required to establish memories in infancy is unknown. Basic experiments need to be performed to systematically examine whether mechanisms known to be important for LTM in adults are required for the formation of memories from the infancy period of development.

to a richer understanding of the development of the engram. We hope that the time is now ripe for a renewed call for interest in the IA phenomenon and that the substantial strides made in the past two decades on the mechanisms underlying memory can be used as a resource to gain a better understanding of the neural processes mediating this ubiquitous form of forgetting. Furthermore, we hope that future studies on the process of IA will help to elucidate the mechanisms involved in memory across the lifespan (Box 3).

Acknowledgments

Preparation of this manuscript was supported by grants from the Australian Research Council (DP120104925) and the National Health and Medical Research Council (APP1031688) to R.R.

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