Review

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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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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.