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Review

Infantile amnesia: A neurogenic hypothesis

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In the late 19th Century, Sigmund Freud described the phenomenon in which people are unable to recall events from early childhood as infantile amnesia. Although universally observed, infantile amnesia is a paradox; adults have surprisingly few memories of early childhood despite the seemingly exuberant learning capacity of young children. How can these findings be reconciled? The mechanisms underlying this form of amnesia are the subject of much debate. Psychological/cognitive theories assert that the ability to maintain detailed, declarative-like memories in the long term correlates with the development of language, theory of mind, and/or sense of "self." However, the finding that experimental animals also show infantile amnesia suggests that this phenomenon cannot be explained fully in purely human terms. Biological explanations of infantile amnesia suggest that protracted postnatal development of key brain regions important for memory interferes with stable long-term memory storage, yet they do not clearly specify which particular aspects of brain maturation are causally related to infantile amnesia. Here, we propose a hypothesis of infantile amnesia that focuses on one specific aspect of postnatal brain development—the continued addition of new neurons to the hippocampus. Infants (humans, nonhuman primates, and rodents) exhibit high levels of hippocampal neurogenesis and an inability to form lasting memories. Interestingly, the decline of postnatal neurogenesis levels corresponds to the emergence of the ability to form stable long-term memory. We propose that high neurogenesis levels negatively regulate the ability to form enduring memories, most likely by replacing synaptic connections in preexisting hippocampal memory circuits.

We are the proud parents of a little girl who just turned 2 yr of age. To celebrate this milestone, we threw a party with all the trimmings (Elmo birthday cards, presents, sparkly birthday hats, and a chocolate cake topped with two pink candles). When we dimmed the lights and lit the candles, the birthday girl burst into tears. This event seems permanently etched in our memories, and we can vividly recall many details of the not-so-happy birthday. Our daughter remembered parts of this event, too, at least for a day or two (the next day, she exclaimed "no candles" while shaking her head vigorously). Have we scarred our daughter for life? Perhaps. But if she is like the rest of us, she will not explicitly remember the "birthday candle incident" when she is an adult. This phenomenon, in which adults are unable to remember specific events from our first few years of life, was named infantile amnesia by Sigmund Freud over 100 yr ago (Freud 1900, 1914). What is particularly intriguing about this phenomenon is that adults have very few memories of early childhood despite the seemingly exuberant learning capacity of young children. How can these seemingly disparate observations be reconciled? Here, we outline a novel neurobiological hypothesis of infantile (or childhood) amnesia that proposes that the loss of memory in infants and children is due to high levels of postnatal neurogenesis in the hippocampus.

Infantile amnesia—the phenomenon

Adults have difficulty recalling memories of early childhood, even though very young children are capable of forming memories

Freud developed his theory of infantile amnesia based on the observation that his adult patients rarely recalled memories of their first years of life (before 6–8 yr of age) (Freud 1900, 1914). This anecdotal evidence has been validated by over a century of empirical research, conducted across cultures using different techniques (Miles 1893; Henri and Henri 1895; Howe and Courage 1993; Nelson 1993; Peterson 2002; Wang 2003; Bauer 2006, 2007). Of course, much of the experimental evidence for infantile amnesia comes from retrospective studies (in which adults are asked to recall their first memories) which are laden with pitfalls and interpretive difficulties. Despite this, a strikingly similar pattern of results has emerged across these many studies: adults generally cannot remember events that occurred in the first 2–3 yr of life. In addition to this frank amnesia for early infancy, there is a second phase of infantile amnesia in which adults recall very few memories from ages 3–7 yr (Rubin 1982; Wetzler and Sweeney 1986; Rubin 2000; Peterson 2002). Therefore, infantile amnesia is not an all-or-none phenomenon, and there is no abrupt developmental transition from "no memory" to "memory." Instead, infantile amnesia describes the absence of memory for events occurring within the first 2–3 yr of life and "spotty" memory for events occurring from 3–7 yr of age (Pillemer and White 1989; Bruce et al. 2005; Fig. 1).

Can infantile amnesia be attributed to normal forgetting?

In adults, forgetting can be described as a linear function of the time since an event. Because there is a long delay between events acquired during infancy and potential recall in adulthood, it might be expected that these early life events are simply forgotten. To examine this, Rubin and colleagues sampled adults' memories across the life span (Rubin 1982, 2000; Peterson 2002). Subjects were given cue words (e.g., bicycle) and asked to provide a specific memory related to the cue word and estimate their age at the time of the event. The resulting distribution of memories clearly showed the two components of infantile amnesia (0–3 yr of age and 3–7 yr of age). Importantly, subjects reported far fewer memories for events that occurred between birth and 6–7 yr of age than would be predicted by simply extrapolating the adult forgetting curve (Wetzler and Sweeney 1986). Therefore, forgetting a

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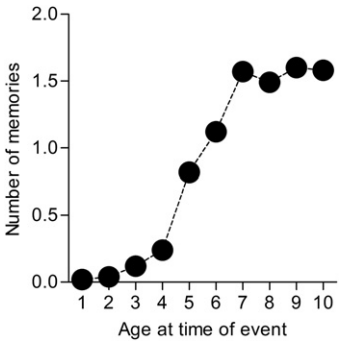

Figure 1. Infantile amnesia in humans. Distribution of autobiographical memories from the first decade of life showing two phases of infantile amnesia. Values (mean number of memories per yr) are approximate and based on Rubin and Schulkind (1997). Participants (20, 35, and 70 yr of age) reported very few memories before the age of three. The number of memories reported to have occurred from the ages of 3–7 yr increased linearly and leveled off from 7–10 yr of age.

memory with the passage of time alone cannot explain infantile amnesia.

Can infants form declarative memories?

What types of memories are lost in infantile amnesia? In adult memory research, different theoretical distinctions have been proposed to delineate different types of memory; the two most common categories are declarative versus nondeclarative memory (Squire 1994) or explicit versus implicit memory (Graf and Schacter 1985). Implicit memory refers to the unconscious learning that is expressed by changes in task performance as the result of experience. Testing this type of memory does not require participants to verbally declare things. In contrast, declarative/explicit memory refers to the conscious recollection of facts and events. While many experiences during infancy implicitly impact later life (e.g., Hackman et al. 2010), infantile amnesia typically refers to the absence of declarative memories from this period.

The capacity to form and verbally recall declarative memories gradually emerges as an infant develops (from ~24–36 mo of age) (Eisenberg 1985; Peterson and McCabe 1987; Miller and Sperry 1988; Hudson 1991; McCabe and Peterson 1991; Hudson et al. 1992, 1995; Harley and Reese 1999; Peterson et al. 1999; Peterson 2002). For instance, 3-yr-old children accurately recount "important" life events (a trip to McDonald's) when prompted (Nelson and Gruendel 1981). Even in the absence of such prompting, children verbally recall specific event/autobiographical memories. For instance, Nelson eavesdropped on the "crib talk" (i.e., talking to oneself alone before sleep) of her 2.5-yr-old daughter, who clearly described a unique episode (buying a doll) that was not rehearsed with, or structured by, her parents (Nelson 1989; Harley and Reese 1999; Nelson and Fivush 2004). Together, these and other studies are remarkable in that they reveal that children form and verbally report event memories, yet these same memories are inaccessible when these children become adults. If these types of memories can be formed, what is their fate?

Older children remember longer

One predominant view is that, although children can learn and remember information for a short period of time, these memories are quickly forgotten or become otherwise inaccessible (Bauer 2007; Rovee-Collier and Cuevas 2009). That is, given equivalent levels of encoding, older infants remember for longer than younger infants. Support for age-related changes in childhood forgetting derives from several findings. For instance, Rovee-Collier and colleagues showed that memory retention increases linearly with the age of the child at the time of training (Rovee-Collier 1997; Rovee-Collier and Cuevas 2009; Fig. 2). The absolute difference in retention was striking—although 2-mo-old infants exhibited memory that lasted 24 h, 18-mo-old infants exhibited retention for as long as 13 wk. Because all infants were trained to the same criterion, the authors concluded that the age-related changes in memory retention were independent of possible differences in the original encoding of the information.

A similar pattern of results—that older children remember for longer than younger children—has been observed across several tasks, including deferred imitation (Barr et al. 1996; Herbert and Hayne 2000; Carver and Bauer 2001; Bauer 2007), visual paired comparison (Fantz 1956; Herbert and Hayne 2000; Morgan and Hayne 2006a,b, 2011), and autobiographical memory (Ornstein et al. 1997; van Abbema and Bauer 2005; Tustin and Hayne 2010) tests. Together, these findings converge to show that, although young children can acquire memories, they forget faster than older children. This faster forgetting is independent of the task used to measure memory and is argued to be independent of differences in memory encoding. Intriguingly, rodents exhibit a strikingly similar age-dependent amnesia.

Infantile amnesia is recapitulated in rodent species

Some of the earliest studies of infantile amnesia in rodents were conducted by Campbell and colleagues, starting in the 1960s (Campbell and Campbell 1962; Campbell et al. 1968, 1974; Coulter et al. 1976; Stehouwer and Campbell 1980). These researchers trained rats of different ages (18- to 100-d old) in an aversively motivated place discrimination task and tested memory retention 0, 7, 21, or 42 d later (Campbell and Campbell 1962). All groups of rats showed perfect (or near perfect) retention if tested immediately following training, indicating that rats of all ages

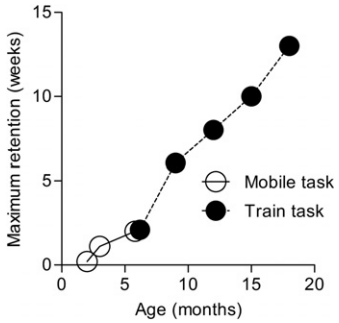

Figure 2. Memory retention increases gradually with age of children. Rovee-Collier and colleagues used a mobile conjugate reinforcement task (in which infants learn to kick their foot in order to rotate an overhead mobile) to assess learning and memory in young infants (2- to 7-mo-olds) and a variant of this task (in which infants learn to press a lever to move a toy train) in older infants (6- to 18-mo-olds). These researchers argue that these tasks also tap into declarative memory in infants (Rovee-Collier 1997). When infants of different ages (ranging from 2 to 18 mo) are trained to the same criterion in the mobile (open circles) or train (closed circles) task, the duration of memory retention increases linearly as a function of age. Immediate retention was equivalent across all ages. However, young infants show memory retention for only a few days, whereas older infants show longer memory retention on a comparable train task. Importantly, at 6 mo of age, retention on these two operant tasks is equivalent. Based on data from Rovee-Collier (1999) and with permission of SAGE Publications © 1999.

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formed equivalent place memories. However, the ability to retain this information depended upon the age of the rats at the time of training. Whereas the youngest rats (18 d old, infants) showed rapid forgetting, rats that were 54 d old or older at the time of training (adults) showed perfect memory 42 d later (Fig. 3).

This core finding—that memory persistence is proportional to age at the time of training—has been replicated across a broad range of tasks, including conditioned suppression (Campbell and Campbell 1962), passive avoidance (Feigley and Spear 1970; Schulenburg et al. 1971; Campbell et al. 1974), active avoidance (Kirby 1963; Klein and Spear 1969; Campbell et al. 1974), appetitive discrimination (Campbell et al. 1968), contextual fear conditioning (Rudy and Morledge 1994; Weber et al. 2006), novel object recognition (Anderson et al. 2004), and water maze (Brown and Kraemer 1997). Importantly, each of these tasks uses stimuli with different properties and has different performance demands, indicating that this pattern of results is generalized across many memory tasks. Therefore, infantile amnesia is a robust, and very likely, universal cross-species phenomenon.

Theories of infantile amnesia

Why are memories acquired in infancy beyond recall in adulthood? This question has provoked much debate and a diverse range of theories have been put forward to explain this phenomenon. As these theories approach infantile amnesia from different research traditions, they are pitched at different levels of analyses (but are not necessarily mutually exclusive).

Human cognitive/psychological theories

Human psychological theories emphasize that the ability to form enduring memories (the offset of infantile amnesia) in humans coincides with emergence of developmental milestones, such as the acquisition of a sense of "self" (Howe and Courage 1993), theory of mind (Perner and Ruffman 1995), or language (Nelson 1993; Harley and Reese 1999; Simcock and Hayne 2002). Certainly, verbal reminiscing may aid memory retention, and the concept of self would help humans encode and store enduring personal memories. However, given that infantile amnesia is observed in nonhuman species, it is unlikely that this phenomenon can be explained fully using purely human concepts.

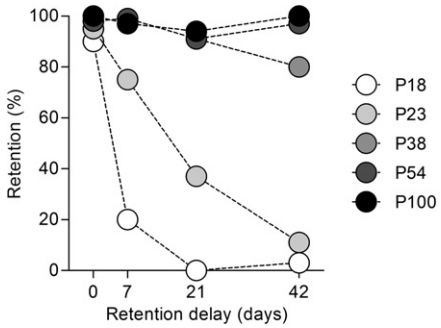

Figure 3. Infantile amnesia in rats. Rats trained at a young age (P18) show rapid forgetting, whereas as rats trained at later time points show much longer memory retention on an aversively motivated place discrimination task. Importantly, all rats (regardless of age at training) showed intact memory if tested immediately following training, indicating that rats of all ages formed equivalent place memories. Based on data (now in the public domain) from Campbell and Campbell (1962).

Impairment in memory encoding, storage, or recall

Information processing theories postulate that infantile amnesia results from impaired memory encoding, storage, and/or retrieval. Although it makes intuitive sense that if a normal memory is never acquired by an infant, then this memory cannot be recalled when the child reaches adulthood, experimental evidence from both human and rodent studies does not fully support this notion. For example, in the early infantile amnesia experiments in rats, both the rate of acquisition as well as initial memory expression (tested shortly after training) were equivalent in infant and adult rats (Kirby 1963; Feigley and Spear 1970; Campbell et al. 1974), suggesting that initial differences in learning and/or memory expression could not account for the accelerated forgetting observed in infant rats. Moreover, even when infant rats were overtrained in a passive avoidance task, they still showed more rapid forgetting than adult rats (Feigley and Spear 1970; Schulenburg et al. 1971).

Other explanations of infantile amnesia focus on memory retrieval and postulate that the memories formed in childhood are permanently stored and always exist, but that these memories simply cannot be accessed during adulthood (Hayne and Rovee-Collier 1995). For instance, Freud believed that our earliest memories were acquired and stored in pristine condition but actively repressed due to their emotionally and sexually charged content (Freud 1899). In this way, Freud was perhaps the first (and strongest) proponent of the "memory retrieval deficit" hypothesis of infantile amnesia. Although Freud's notion of repression has been largely discounted, the retrieval deficit hypothesis of infantile amnesia is consistent with findings that memories are maximally recalled when the retrieval conditions (both internal and external) closely match the conditions at encoding, similar to state-dependency (Tulving and Thompson 1973; Tulving 1983). Because adults can never recapitulate the conditions of infancy, this theory holds, we cannot recall memories acquired during this time.

Biological theories: the 'immature brain' vs. 'ongoing brain maturation'

Biological or neurological accounts of infantile amnesia stress two closely related ideas: either that infantile amnesia occurs because key structures for memory formation and storage are insufficiently mature at the time of memory formation to process these memories ("immature brain" theories) or, alternatively, that the very process of ongoing maturation interferes with stable memory consolidation ("ongoing brain maturation" theories). Support for these biological theories comes from findings that, although much of the human brain is fully formed at birth, the two key regions for declarative memory, the cortex and hippocampus, show protracted postnatal development (Eriksson et al. 1998; Knoth et al. 2010; Sierra et al. 2011). Some theories falling into the "immature brain" category posit infantile amnesia results from the cortex not yet being "online" in infants (Pillemer and White 1989; Nelson 1997, 2000). Indeed, although all six layers of the human cortex may be observed by the seventh gestational month, other important aspects of cortical maturity (e.g., adult levels of synaptic density, myelination, etc.) are not realized fully until puberty and beyond (Huttenlocher and Dabholkar 1997; Giedd et al. 1999; Bauer 2008). The rapid myelination that occurs in the first year in humans may account for the age-related changes in processing speed observed in several memory tasks (Richmond and Nelson 2007). That is, the finding that older infants encode some types of information faster than younger infants (e.g., Rose et al. 1982; Hayne 2004) might be due to faster information processing resulting from more efficient transmission of electrical impulses with increasing myelination. Whether changes in myelination (or other slowly maturing aspects of cortical integrity) are

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causally related to infantile amnesia, however, remains to be determined.

In addition to the cortex, the hippocampus, and especially the dentate gyrus (DG) region of the hippocampus, shows protracted postnatal development in many species, including humans (e.g., Eriksson et al. 1998; Knoth et al. 2010; Sierra et al. 2011). For instance, in humans, although the cytoarchitecture of the hippocampus is formed by 24–25 wk of gestation (Humphrey 1967; Seress et al. 2001) and the overall structure of the hippocampal formation largely resembles the adult by the end of the second trimester (Abraham et al. 2001), new neurons continue to be added to the DG layer of the hippocampus well after birth (Eriksson et al. 1998; Knoth et al. 2010; Sierra et al. 2011). Other "immature brain" theories suggest that this prolonged hippocampal development can account for infantile amnesia (Alvarado and Bachevalier 2000; Richmond and Nelson 2007). Indeed, the protracted development of the hippocampus, particularly the DG, after birth in monkeys is consistent with their emerging ability to form and retain episodic-like memories (Alvarado and Bachevalier 2000; Payne et al. 2010). For instance, although infant macaque monkeys (4 wk of age) show the ability to learn and form a memory (novelty preference) in the visual paired-comparison task (Gunderson and Sackett 1984; Gunderson and Swartz 1985; Bachevalier et al. 1993), memory stability gradually increases with age (from 1.5 to 18 mo) (Zeamer et al. 2010).

Distinct from these "immature brain" accounts are "ongoing brain maturation" accounts emphasizing that age-dependent/ontogenetic changes in memory persistence play out against a rapidly evolving brainscape, and it is the process of maturation itself (rather than the maturational state per se) that interferes with the storage of memories formed during infancy. For example:

> "In the simplest sense, it seems quite possible that continued neurological development *following* the acquisition of a learned response could act to either disrupt the memory-storage mechanism(s) or to block retrieval of previously learned material." [Campbell and Spear 1972, p. 225; emphasis added.]

The key idea here is that, while memory formation is more or less normal in infants, continued brain maturation *after* initial acquisition may interfere with stabilization or consolidation of the memory trace. This hypothesis was initially examined in rodent studies where they either attempted to slow or accelerate brain maturation during the retention delay (reasoning that slowing maturation might counteract forgetting, whereas accelerating brain maturation might promote forgetting). The challenge for these early studies was that the tools available to manipulate brain maturation were blunt (e.g., hormonal or neurotoxic manipulations designed to slow or accelerate maturation likely had many off-target effects). Moreover, it was not clear whether specific or general aspects of maturation should be targeted. For the most part, these early attempts to manipulate brain maturation and examine infantile amnesia ended in failure (Campbell 1984).

Here, we propose that one specific aspect of ongoing brain maturation—the continued postnatal production of new neurons in the hippocampus—regulates the ability to form enduring hippocampus-dependent memories. As described above, in a variety of animals, including humans, new neurons continue to be added to the hippocampus, a brain region generally agreed to be important for memory. Interestingly, the levels of neurogenesis and memory stability are inversely related: The inability to form stable, persistent memories in early life coincides with a period of high neurogenesis, whereas the ability to form stable, persistent memories only emerges at later developmental periods as the rate of neurogenesis declines (Fig. 4). How might the addition of neurons disrupt an established memory? We suggest that the integration of these "new neurons" degrades existing memories by either increasing the excitability (and therefore instability) of hippocampal memory networks or replacing synaptic connections in preexisting hippocampal memory circuits. This neurogenic hypothesis of infantile amnesia builds on the original ideas of Campbell and Spears (1972) and integrates contemporary views of how ongoing neurogenesis impacts hippocampal circuit function and information storage (Chambers et al. 2004; Deisseroth et al. 2004; Meltzer et al. 2005; Wiskott et al. 2006; Treves et al. 2008). Below, we review some existing evidence for this neurogenic hypothesis of infantile amnesia before outlining two direct tests of the hypothesis.

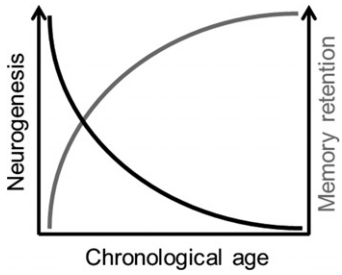

Figure 4. The neurogenic hypothesis of infantile amnesia. Levels of neurogenesis (black) and memory stability/retention (gray) are inversely related: The inability to form stable, persistent memories in early life coincides with a period of high neurogenesis, whereas the ability to form stable, persistent memories only emerges at later developmental periods as the rate of neurogenesis declines.

Circumstantial evidence for the neurogenic hypothesis of infantile amnesia

Memory stability and neurogenesis are inversely related: As hippocampal neurogenesis declines, the ability to form stable memories emerges

Whereas in most brain regions, neurogenesis is largely completed at birth, in the DG of the hippocampus, new neurons continue to be added throughout development into adulthood. Once controversial (Rakic 2002), the idea that neurogenesis may persist beyond birth is now accepted (Zhao et al. 2008). In the mammalian brain (including the human brain) (Eriksson et al. 1998; Knoth et al. 2010; Sierra et al. 2011), adult neurogenesis is limited to two regions: (1) the subventricular zone (SVZ) of the lateral ventricle (new neurons migrate from here along the rostral migratory stream to populate the olfactory bulb); and (2) the subgranular zone (SGZ) of the hippocampus (new neurons migrate the short distance from the SGZ to the inner granule cell layer [GCL] of the DG) (Zhao et al. 2008). Neurogenesis outside of these regions may occur following injury but is otherwise negligible under nonpathological conditions.

While postnatal hippocampal neurogenesis is regulated by a number of factors, it is most profoundly regulated by age (Seki and Arai 1995; Kuhn et al. 1996; Piatti et al. 2006): Across species, neuron production in the hippocampus typically peaks soon after birth and steadily declines thereafter. For example, in rats, the rate of hippocampal neurogenesis decreases by half between 1 and 2 mo of age, and by 18 mo of age, rates of neurogenesis are ~100-fold lower than initial levels (Seki and Arai 1995; Fig. 5A). Similarly, although most neurons in the nonhuman primate hippocampal formation are generated prenatally (Nowakowski and Rakic 1981; Eckenhoff and Rakic 1988; Arnold and Trojanowski

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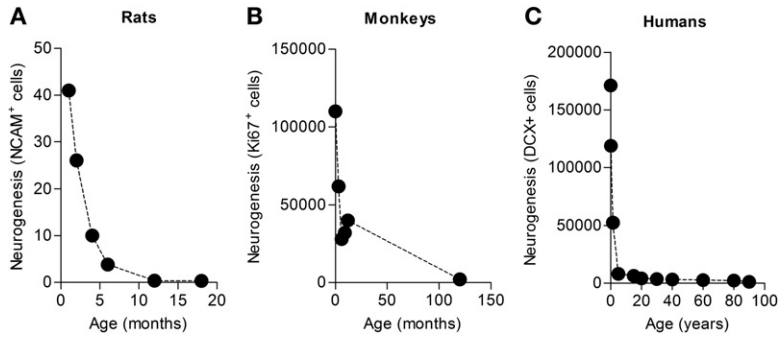

Figure 5. Rates of hippocampal neurogenesis decrease with age in both rats and humans. (*A*) In rats, the rate of hippocampal neurogenesis (as determined by the number of NCAM$^+$ cells) decreases by half between 1 and 2 mo of age, and by 18 mo of age, rates of neurogenesis are ~100-fold lower than initial levels (adapted from Seki and Arai 1995 with permission of Wolters Kluwer Health © 1995). A similar decay in hippocampal neurogenesis rate is observed in (*B*) monkeys (determined by the number of Ki67$^+$ cells) (adapted from Jabès et al. 2010 with permission of John Wiley and Sons © 2010) and (*C*) humans (determined by the number of doublecortin$^+$ cells) (Knoth et al. 2010).

1996), postnatal neurogenesis is observed in the DG of macaque monkeys (Gould et al. 1999; Kornack and Rakic 1999) and marmosets (Gould et al. 1998). Recently, Jabès and colleagues (2010) systematically examined postnatal hippocampal neurogenesis across the life-span of macaques. Using both exogenous (BrdU) and endogenous (Ki67) markers of cell proliferation and stereological counting techniques, they found high levels of cell proliferation in the monkey DG at birth through 3 mo of life, followed by an intermediate level which persisted throughout the first year of life and beyond (Fig. 5B). Finally, although an equivalent systematic study of neurogenesis across the lifespan of humans has not been conducted, a similar decay in the rate of hippocampal neurogenesis is observed (Knoth et al. 2010). By staining post-mortem human brain tissue for doublecortin, a protein that is predominantly expressed in immature neurons, Knoth and colleagues (2010) estimated there is an ~100-fold reduction in neurogenesis between 0 and 100 yr of age (Fig. 5C), a lifetime reduction in neurogenesis rates that is remarkably similar to that observed in rats as well as nonhuman primates.

These age-dependent changes in neurogenesis exhibit remarkably similar properties across species. For example, in the adult rat, the number of new neurons generated per day in the DG is roughly 2250, or 0.2% of the total number of neurons in the granule cell layer (Cameron and McKay 2001). In 5- to 10-yr-old (adult) monkeys, roughly 1300 neurons per day are added to the DG, or 0.02% of the total number of neurons in the granule cell layer. Given the differences in lifespan between monkeys and rats (the lifespan of a monkey is ~20–30 yr compared to 2–3 yr for rats), the overall contribution of postnatal neurogenesis in these two species is remarkably similar. Indeed, Jabès and colleagues estimate that ~40% of neurons are added to the monkey DG after birth. Together, these data suggest that postnatal neurogenesis could have a substantial impact on hippocampal circuit function in rodents and primates, including humans.

Precocious guinea pigs do not show infantile amnesia

That the decline in hippocampal neurogenesis levels in rats and primates coincides with an emerging ability to form enduring memories raises the fascinating possibility that these two phenomena are causally related. Although this has not been directly tested, there is some evidence from comparative studies of memory in different rodent species that strengthens this connection. Whereas altricial rodents (such as rats) have relatively brief gestation periods (~21 d), precocial rodents (such as guinea pigs) have much longer gestation periods (~65 d) (Altman and Das 1967). Unlike rats, guinea pigs are able to walk and see at birth, suggesting that guinea pigs are born with a more developed brain. Consistent with this, whereas there is an ~600% increase in brain weight from birth to full maturity in rats, the corresponding increase is only ~60% in guinea pigs (Dobbing and Sands 1979). In landmark experiments, Campbell and colleagues asked whether the guinea pigs' relative neurological maturity at birth might be associated with a precocious ability to form persistent memories (Campbell et al. 1974). These researchers trained rats and guinea pigs of different ages in an aversively motivated place discrimination task and tested memory retention across a 2-wk period. Both young (15–20 d old at the time of training) and older (25–35 d old at the time of training) rats showed robust acquisition of this task and intact memory retention one day after training. However, younger rats showed forgetting across the 2-wk retention period compared to the stable retention observed in adult rats. In stark contrast, guinea pigs did not show an age-dependent difference in memory persistence. Remarkably, 5-d-old guinea pigs remembered just as well as adult (100-d-old) guinea pigs up to 75 d after training (Fig. 6). A similar pattern of results was observed when memory retention was examined using passive avoidance (Campbell et al. 1974).

This difference in the ability of young rats and guinea pigs to form persistent memories directly mirrors differences in DG development between the two rodent species: Whereas ~80% of granule cells are added to the DG in the first 2 wk after birth in the rat, only ~20% of granule cells are added during the first postnatal month in the guinea pig (Schlessinger et al. 1975; Guidi et al. 2005). Therefore, the relative maturity of the DG (and lower levels of neurogenesis) may permit the formation of stable memories in newborn guinea pigs. Of course, many other aspects of brain development both inside and outside of the hippocampus may also be more advanced at birth in guinea pigs (e.g., white matter, dendritic arborization, etc.), and it is possible these may also contribute to memory stability in newborn guinea pigs. Nonetheless, the lack of forgetting in newborn guinea pigs is consistent with the idea that lower levels of hippocampal neurogenesis facilitate memory persistence.

Neurogenesis and degradation of existing memories: computational studies

Although postnatal (including adult) hippocampal neurogenesis recapitulates many aspects of embryonic neurogenesis, postnatal neurogenesis is unique in that new neurons must integrate into an established hippocampal circuit. This integration may have profound effects on overall hippocampal circuit function. Experimental studies have predominantly focused on the anterograde effects of neurogenesis on memory—that is, examining the impact of manipulating neurogenesis levels on subsequent memory formation in adult animals (Shors et al. 2001; Creer et al. 2010; Deng et al. 2010; Sahay et al. 2011a). However, computational approaches have additionally emphasized the impact of adult neurogenesis on already-stored information (or retrograde effects) and proposed that the addition of new neurons may degrade

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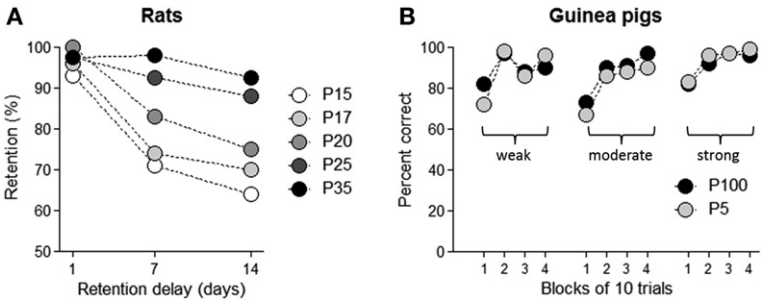

Figure 6. Cross-species evidence for the neurogenic hypothesis of infantile amnesia. (*A*) Altricial rodents (rats) with relatively brief gestation periods (and higher levels of postnatal neurogenesis) show evidence of infantile amnesia (younger rats forget sooner than older rats). (*B*) By contrast, precocial rodents (guinea pigs) have much longer gestation periods (and relatively lower levels of postnatal neurogenesis) and show no evidence of infantile amnesia. In fact, 5-d-old guinea pigs remembered just as well as adult (100-d-old) guinea pigs 75 d after either weak, moderate, or strong training in a place discrimination task. Adapted from Campbell et al. (1974).

existing memories (for review, see Aimone and Gage 2011). The idea that neurogenesis promotes memory degradation or forgetting echoes an earlier suggestion by Tsien and colleagues (Feng et al. 2001) and, when levels of hippocampal neurogenesis are considered across the lifespan, may explain the rapid forgetting of infantile amnesia.

These computational models typically use a simple, three-layer architecture (an input [entorhinal cortex], middle [DG], and output [CA3] layer), with neurogenesis modeled by either replacing mature neurons or adding new neurons to the middle DG layer (Chambers et al. 2004; Deisseroth et al. 2004; Meltzer et al. 2005; Wiskott et al. 2006). As mature dentate neurons constitute a critical component of the memory trace in these models, replacing these essential neurons (perhaps unsurprisingly) leads to memory degradation. However, results from experimental studies suggest that neurons that are committed to a memory trace may actually have a survival advantage (Leuner et al. 2004), suggesting that these mature memory-committed neurons are not likely to be replaced. Moreover, in some computational models, memory loss is still predicted when new neurons are simply added to the circuit, rather than replacing existing neurons (Deisseroth et al. 2004; Meltzer et al. 2005). This finding suggests that the integration of new neurons into an existing network may produce network-wide changes, leading to the degradation of already stored information. Consistent with this degradation hypothesis, decreasing adult hippocampal neurogenesis promotes, rather than disrupts, the long-lasting maintenance of hippocampal long-term potentiation in vivo (Kitamura et al. 2009).

There may be at least two ways in which adding new neurons might degrade existing memories. First, the integration of new neurons necessarily alters the wiring of existing hippocampal networks. As memory fidelity likely depends on the precise spatiotemporal activation of hippocampal neurons, any changes in network architecture would likely result in information loss. In this regard, it is particularly interesting that the formation of de novo afferent and efferent synaptic connections is a competitive process, with newborn neurons' synaptic connections frequently coexisting with, or even replacing, the synaptic connections of established neurons (Toni et al. 2007, 2008; Yasuda et al. 2011). Moreover, new neurons may have a competitive advantage over existing neurons in terms of afferent and efferent synaptic connections (Kim et al. 2011). Therefore, the invasion of new neurons into a preexisting circuit may disrupt the integrity of previously formed synapses, leading ultimately to the loss of stored information.

Second, immature granule neurons are more excitable than mature granule neurons (Schmidt-Hieber et al. 2004; Ge et al. 2007). Therefore, the addition of new excitable neurons into hippocampal circuits would result in an increase in overall excitatory drive both within the DG (via recurrent DG networks) and in downstream CA3 networks (through direct mossy fiber connections). In order to avoid the maladaptive consequences of overexcitation (e.g., seizures), this increase in excitation would likely invoke homeostatic mechanisms that regulate neuronal and/or circuit excitability (Karmarkar and Buonomano 2006). Such homeostatic changes may include decreasing the intrinsic excitability of DG/CA3 neurons (Desai et al. 1999; Golowasch et al. 1999; Brickley et al. 2001) or neuron-wide synaptic rescaling (e.g., loss/endocytosis of synaptic GluA2 receptors) (Frohlich et al. 2008; Turrigiano 2008), which may eventually lead to the silencing of some synapses, thus compromising information storage (Meltzer et al. 2005).

Are sufficient numbers of new neurons being added to the existing hippocampal circuit to impact the fidelity of stored memories? In young adult rodents, several thousand new neurons are generated daily (Cameron and McKay 2001). While not all of these new neurons survive, they still represent a sizable proportion of all dentate granule cells. For example, in the 3-mo-old rat, new neurons (defined as <8 wk of age) are estimated to make up >25% of the entire granule cell population. This percentage drops with age, but even so, at 12 mo, new neurons likely account for 5% of all dentate granule cells (Snyder and Cameron 2011). Each dentate granule cell contacts roughly 10–15 CA3 pyramidal neurons via large mossy fiber terminals (Acsady et al. 1998). These specialized contacts ensure powerful and reliable firing of downstream CA3 pyramidal neurons (Henze et al. 2002) and, therefore, even sparse activation of dentate granule cells can influence the activity of a large proportion of hippocampal CA3 neurons (Treves et al. 2008). In a similar vein, as new neurons integrate into hippocampal circuitry, they likely make contacts with a large number of CA3 target cells (in fact, adult-generated granule cells may even make more contacts on target CA3 neurons than granule cells generated earlier on during embryonic or postnatal development [Yasuda et al. 2011]). The establishment of these new synaptic connections necessarily alters the architecture of existing DG-CA3 networks, very likely leading to degradation (or loss) of information stored in those connections. It is, then, reasonable to predict that the amount of memory loss would depend on levels of hippocampal neurogenesis. When levels are high (during infancy), a larger proportion of DG-CA3 synapses would be impacted, leading to greater memory loss. In contrast, when neurogenesis levels are greatly reduced (during adulthood), fewer DG-CA3 synapses would be impacted by the integration of new neurons, resulting in greater memory stability.

Neurogenesis and degradation of existing memories: experimental findings

We hypothesize that memory instability in infants (infantile amnesia) is due to high levels of hippocampal neurogenesis. This hypothesis predicts that increasing levels of neurogenesis alone in adult animals would be sufficient to destabilize existing memories. Some indirect evidence for this prediction comes from the

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examination of mice that are deficient for the synaptic protein α-calcium/calmodulin kinase II (α-CaMKII$^{+/-}$ mice) (Frankland et al. 2001, 2004; Yamasaki et al. 2008). In adult α-CaMKII$^{+/-}$ mice, there is a striking increase in the number of newborn neurons in the DG [adult mutant mice show 53% more BrdU-labeled (newborn) cells in the DG, as well as higher levels of immature neuronal markers (PSA-NCAM or calretinin) compared with wild-type littermate mice]. Moreover, adult α-CaMKII$^{+/-}$ mice also show an electrophysiological DG profile typically observed in infant wild-type rodents (e.g., increased intrinsic excitability and membrane resistance, reduced spike amplitude and spike number during sustained depolarization [Yamasaki et al. 2008]). Interestingly, in these adult mice with high levels of hippocampal neurogenesis, memory stability is supremely compromised. Adult α-CaMKII$^{+/-}$ mice are able to form new spatial and contextual memories, but memory retention is severely impaired (Frankland et al. 2001, 2004).

While these data are consistent with the idea that high levels of hippocampal neurogenesis promote forgetting, nonetheless, the α-CaMKII mutation produces other alterations (e.g., impaired cortical plasticity [Frankland et al. 2001] and infradian activity patterns [Yamasaki et al. 2008]) that could also impair memory consolidation. Additional studies examined the impact of *transiently* increasing neurogenesis on the stability of an already formed memory in adult mice. For example, it is well-known that environmental enrichment robustly increases neurogenesis in adult rodents. However, this enhancement is attenuated in mice with a forebrain deletion of presenilin-1 (PS-1-deficient mice) (Feng et al. 2001). Consistent with the idea that there is a trade-off between levels of neurogenesis and memory stability, when PS-1-deficient mice and their wild-type littermates were environmentally enriched following training in a contextual fear task, PS-1-deficient mice (with lower levels of neurogenesis over the 1-mo retention delay) showed stronger memory than wild-type mice. Kitamura and colleagues reported a closely related finding (Kitamura et al. 2009). Voluntary exercise—which also robustly increases hippocampal neurogenesis in adult rodents—regulated the dependence of a contextual fear memory on the hippocampus. While expression of contextual fear memories initially depends on the hippocampus, a few weeks following training, context fear memory can be expressed independently of the hippocampus (Kim and Fanselow 1992; but see Nadel and Moscovitch 1997; Sutherland and Lehmann 2011). This shift from a hippocampus-dependent to hippocampus-independent memory appears to be accelerated when neurogenesis is increased (Kitamura et al. 2009), consistent with the idea that increased neurogenesis facilitates the clearance of the memory from the hippocampus. Therefore, together these studies provide some circumstantial support for the idea that integration of new granule cells into hippocampal circuitry may promote the degradation and/or clearance of existing information from the hippocampus (Feng et al. 2001; Deisseroth et al. 2004; Inokuchi 2011).

Experimentally testing the neurogenic hypothesis of infantile amnesia

The studies reviewed above provide indirect evidence for our neurogenic hypothesis of infantile amnesia. To more formally evaluate this hypothesis, we believe two types of experiments are critical (outlined below). The core manipulation in these experiments involves specifically increasing or decreasing levels of hippocampal neurogenesis in young and adult mice. Fortunately, increasingly sophisticated mouse-genetic approaches are beginning to make these targeted manipulations possible, while minimizing potential off-target effects (Dupret et al. 2008; Yu et al. 2008; Deng et al. 2009; Sahay et al. 2011b).

Does increasing neurogenesis in adult animals after memory formation increase forgetting?

Making the hippocampus 'infantile' in an otherwise adult mouse

Our hypothesis is that infants cannot form long-lasting memories because of high levels of neurogenesis, which promotes the degradation/clearance of memories soon after they are acquired. This hypothesis predicts that transiently increasing hippocampal neurogenesis after memory formation in adult mice will promote forgetting of newly acquired information (Fig. 7A). Key for this experiment is that the hippocampus only be transformed from an adult state—in which stable, persistent memories are formed—to an infantile state—in which memories fade rapidly after formation. There are several methods that may be used to increase neurogenesis in adult mice, and these methods vary with respect to specificity. Some—such as environmental enrichment, voluntary exercise, and antidepressant treatment (Kempermann et al. 1997; van Praag et al. 1999; Malberg et al. 2000; Santarelli et al. 2003)—are relatively nonspecific. In addition to increasing neurogenesis, these manipulations likely have a number of off-target effects. Others—such as electrical stimulation of hippocampal afferents (e.g., perforant path stimulation) (Bruel-Jungerman et al. 2006; Stone et al. 2011a) and, in particular, genetic or pharmacological inhibition of apoptotic cell death (Pieper et al. 2010; Sahay et al. 2011b)—likely increase neurogenesis while producing fewer off-target effects. Interestingly, all of these manipulations typically increase adult hippocampal neurogenesis by roughly two- to threefold. In these experiments, it is important to evaluate the impact of increasing neurogenesis *after* memory formation on the subsequent stability of that memory (ensuring that initial encoding is not affected by the manipulation). We predict that (1) forgetting will be proportional to the duration and/or magnitude of increased neurogenesis, and (2) only hippocampus-dependent (and not hippocampus-independent) memories will be affected. Moreover, with time, some initially hippocampus-dependent memories may become hippocampus-independent (Frankland and Bontempi 2005; but see Nadel and Moscovitch 1997; Sutherland and Lehmann 2011). Therefore, we additionally predict that at remote time-points, initially hippocampus-dependent

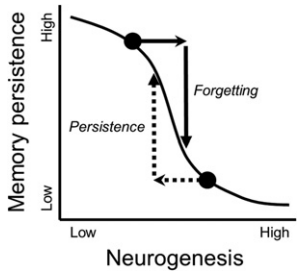

Figure 7. A test of the neurogenic hypothesis of infantile amnesia. Memory persistence is inversely correlated with levels of neurogenesis. Our hypothesis is that infants cannot form long-lasting memories because of high levels of neurogenesis, which promotes forgetting of recently acquired memories. We predict that making the hippocampus of an otherwise adult mouse "infantile" (increasing neurogenesis, solid black arrow) should promote forgetting of already acquired memories. On the other hand, making the hippocampus more "adult" in infant mice (decreasing neurogenesis, dotted black arrow) should promote memory persistence.

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memories likely become invulnerable to fluctuations in the rate of neurogenesis.

Does decreasing neurogenesis in infant animals after memory formation decrease forgetting?

Making the hippocampus 'adult' in an otherwise juvenile mouse

While a variety of evidence shows that infant rodents are able to form hippocampus-dependent memories, these memories do not persist and typically decay within days. If this instability is due to high rates of postnatal granule cell production, then we predict that suppressing neurogenesis will allow a young animal to form a stable, enduring (adult-like) memory (Fig. 7B). Transforming a juvenile hippocampus into an adult hippocampus is clearly a much tougher test of the hypothesis than increasing neurogenesis in adult rodents, as reducing neurogenesis at this early developmental stage might produce a range of off-target effects that may mask or compete with any pro-memory stability effects. Nonetheless, genetic, pharmacological, and irradiation-based approaches are available for suppressing neurogenesis, and there is a defined temporal window in which these manipulations could be applied. In the mouse and rat brain, neurogenesis is largely limited to the subgranular zone of the hippocampus and subventricular zone by ~2 wk following birth (and neurogenesis in these two regions alone persists into adulthood). Moreover, rodents <3 wk of age are typically unable to form stable hippocampus-dependent memories. Therefore, the neurogenic hypothesis of infantile amnesia could be tested by reducing neurogenesis after training in mice <3 wk of age to determine if memories are more persistent. Would such a manipulation completely rescue infantile amnesia? Factors other than hippocampal neurogenesis likely contribute to infantile amnesia. For example, the hippocampus interacts with a number of other structures (notably the cortex) during memory formation and maintenance. Therefore, protracted maturation of hippocampal-cortical connectivity or cortical structures for "permanent" storage (Alvarado and Bachevalier 2000; Richmond and Nelson 2007) may prevent complete rescue of infantile amnesia.

Some final thoughts

Is adult neurogenesis good or bad for memory? A matter of timing

The finding that neurogenesis persists into adulthood has generated a great deal of enthusiasm, centering on the idea that promoting this process would benefit memory (Aimone et al. 2011; Sahay et al. 2011a). Therefore, the suggestion that increasing neurogenesis in adult animals might actually destabilize existing hippocampus-dependent memories is, perhaps, counter-intuitive. Are these two ideas—that adult neurogenesis contributes to both memory degradation (Feng et al. 2001; Deisseroth et al. 2004) as well as storage (e.g., Shors 2008)—compatible? We believe they are and reflect the biphasic, maturation-dependent contribution of adult-generated neurons to hippocampal memory (Fig. 8). That is, the mnemonic effects of adding new neurons to the DG depend on timing.

The two phases of neurogenesis depend on the age of the adult-generated neurons. Shortly after they are born, newly generated granule cells migrate into the granule cell layer of the DG, and by ~2 wk they begin to make functional afferent and efferent connections (Zhao et al. 2006; Toni et al. 2007, 2008). It is the process of establishing new synaptic connections that alters the architecture of existing DG-CA3 networks, perhaps leading to degradation (or loss) of information already stored in those connections. However, as these new neurons continue to mature, they enter the second phase in which they acquire the potential to store memory (or become part of the memory trace). For example, immediate early gene mapping studies suggest that adult-generated neurons maximally contribute to hippocampal memory once they are four or more weeks in age (Kee et al. 2007; Stone et al. 2011b). Indeed, sufficiently mature adult-generated neurons have two key properties that may facilitate their ability to store memories. First, new neurons have "new" (silent?) synapses that may be specifically dedicated to storing new memories, and, second, new neurons are transiently more excitable and more plastic than their mature counterparts and, therefore, perhaps more readily incorporated into a memory trace.

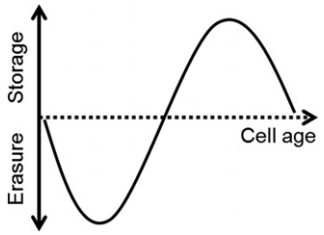

Figure 8. Adult neurogenesis and memory, a two-stage process. Adult neurogenesis contributes to both memory degradation/clearance (Feng et al. 2001; Deisseroth et al. 2004) as well as storage (e.g., Shors 2008), depending on the age of the cell. In the process of establishing new synaptic connections, new neurons alter the architecture of existing DG-CA3 networks, leading to degradation (or loss) of information stored in those connections. However, as these new neurons continue to mature, they enter the second phase where they acquire the potential to store memory and enhance memory storage.

Out with the old...

But why might memory degradation/clearance be adaptive? The pioneering memory researcher Théodule Ribot wrote that "forgetfulness, except in certain cases, is not a disease of memory, but a condition of its health and life" (Ribot 1882). Indeed, forgetting provides a mechanism for ridding the brain of unimportant information. Efficient forgetting, therefore, "unclutters" the hippocampus, allowing important new information to be more efficiently encoded (Martin et al. 2000; Altmann and Gray 2002; Schooler and Hertwig 2005). Such "adaptive" forgetting might facilitate the formation of new memories by simply increasing capacity (clearing space) and reducing interference between old, irrelevant memories and to-be-encoded information (Kraemer and Golding 1997; Wixted 2004). Indeed, the ability to block irrelevant information reduces the demands on the brain when trying to recall important information (Kuhl et al. 2007). Lifespan changes in levels of neurogenesis alter the balance between encoding and forgetting. During infancy, when neurogenesis levels are high, forgetting is favored, and so memories cannot endure. In late adulthood, when neurogenesis levels are low, insufficient clearance might lead to memory interference (i.e., too much unimportant information is retained). Sometime in between, there is a more optimal balance between encoding and forgetting.

Earlier models have proposed that the benefits of hippocampal neurogenesis-promoting activities (such as learning, exercise, or enrichment) are delayed (Kempermann 2008; Kim et al. 2011). That is, cells generated as a consequence of these types of activities (or the "neurogenic reserve") (Kempermann 2008) require sufficient time to differentiate into neurons, mature, and integrate into hippocampal circuitry before they promote memory function (Ge et al. 2007; Kee et al. 2007; Stone et al. 2011b). In contrast, we

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suggest that there are additional, more immediate benefits of increased neurogenesis. The integration of these new cells into hippocampal circuits may facilitate cognitive function by clearing older memories, reducing interference and increasing capacity.

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