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Research article

Ontogeny of memory: An update on 40 years of work on infantile amnesia

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HIGHLIGHTS

- Infantile amnesia is the phenomenon of accelerated forgetting in young animals.
- We review progress made over the last 40 years in understanding infantile amnesia.
- The neurobiological causes of infantile amnesia appear to be multifaceted.
- Late development of the hippocampus, amygdala and prefrontal cortex all contribute.
- Developmental changes in neurotransmitter systems also appear to be involved.

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ABSTRACT

Given the profound influence that early life experiences can have upon psychosocial functioning later in life, it is intriguing that most adults fail to recall autobiographical events from their early childhood years. Infantile amnesia is the term used to describe this phenomenon of accelerated forgetting during infancy, and it is not unique to humans. Over the years, information garnered from animal studies has provided clues as to the neurobiological basis of infantile amnesia. The purpose of this review is to provide a neurobiological update on what we now know about infantile amnesia since the publication of Campbell and Spear's seminal review on the topic more than 40 years ago. We present evidence that infantile amnesia is unlikely to be explained by a unitary theory, with the protracted development of multiple brain regions and neurotransmitter systems important for learning and memory likely to be involved. The recent discovery that exposure to early life stress can alleviate infantile amnesia offers a potential explanation as to how early adversity can so profoundly affect mental health in adulthood, and understanding the neurobiological basis for this early transition may lead to the development of effective therapeutic interventions.

1. Introduction

Early life experiences play a pivotal role in shaping personality and psychosocial functioning into adulthood. For example, early life adversity in humans is associated with increased risk of developing mental illnesses such as depression and anxiety [1–6], and maternal separation in non-human primates imposes long-term detrimental effects upon behaviour [7–9].

Given the importance of these first few years of life, it is intriguing that most adults fail to maintain autobiographical memories from this critical period. In general, when adults are asked to remember their earliest memories, they rarely recall events that occurred before the age of 3 and have spotty recollection of experiences that occurred between 3 and 7 years of age [10–16]. This apparent childhood memory deficit is not caused by an inability at this age to form episodic memories [17]. In a study where children aged between 5 and 10 were asked to recall their earliest memories, they frequently recalled events that occurred when they were younger than 1 year old—and some as young as 1 month [18,19]. In contrast, children aged between 12 and 13 failed to recall any

Abbreviations: CS, conditioned stimulus; GABA, gamma-aminobutyric acid; MAPK, mitogen-activated protein kinase; mPFC, medial prefrontal cortex; NMDA, *N*-methyl-D-aspartate; NMDAr, *N*-methyl-D-aspartate receptor; PFC, prefrontal cortex; pMAPK, phosphorylated mitogen-activated protein kinase; PL, prelimbic cortex; US, unconditioned stimulus.

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events that occurred prior to the age of 1, suggesting that a child's earliest episodic memory recollection is influenced by that child's current age [18,20]. Mere passage of time is insufficient to explain the transience of these memories formed in early childhood. For example, a 40 year old adult can readily remember events that occurred when they were 21, however, a 20 year old would be hard-pressed to recall an event that occurred when they were 1 year old. This indicates that our remembering ability increases with development and maturation. In other words, the rate of spontaneous forgetting is more rapid the younger our age. This phenomenon was first described in the literature over a century ago [21], but Freud was the first to refer to this accelerated forgetting as 'infantile amnesia' [22].

Compared to the extraordinary amount of progress made in understanding the mechanisms of learning and memory [23], we still have a poor understanding of spontaneous forgetting. Dementias such as Alzheimer's disease are characterised by pathological forgetting, and anxiety disorders such as post-traumatic stress disorder involve an inability to forget a traumatic experience. Therefore, uncovering the secrets underlying forgetting is crucial. Most of what we understand about the mechanisms of forgetting has been derived from studies of infantile amnesia, as this form of spontaneous forgetting is relatively easy to observe and manipulate in a laboratory setting. The purpose of this review is to provide an update of what we have learned over the 40+ years since the publication of Campbell and Spear's seminal review on the ontogeny of memory written largely based on infantile amnesia studies [24]. We aim to uncover how memory develops across the lifespan and what factors can influence this developmental trajectory, the mechanisms by which early memories are formed and rapidly forgotten, and address the paradox of how childhood experiences, though seldom remembered, are capable of dramatically influencing later development.

2. Forgetting is pervasive

Infantile amnesia is a well-documented phenomenon in humans. Early investigations into the characteristics of childhood episodic memory sought to examine the contents and age of people's earliest memories by interviewing adults [14,21,25]. However many of these initial investigations were flawed as they failed to provide independent verification of the content of these memories, a control necessary because childhood memories are susceptible to confabulation by suggestions during interviewing [26]. Subsequent studies that were more methodologically sound have essentially agreed that adults rarely remember events from their childhood that occurred prior to the age of 3, and memories for events that occur between the ages of 3 and 7 are sparse [10–13]. In recent years, a number of theories have emerged that attempt to explain infantile amnesia in the context of human cognitive and social developmental milestones. For example, it has been suggested that as children develop language abilities they gradually learn to formulate their own autobiographical memories by talking about past events with their caregivers [17,27–29]. Others have argued that the emergence of the cognitive sense of self is critical, as it provides a 'personal frame of reference' for the organisation of memories [30,31]. Similarly, it has been proposed that the development of 'theory of mind' precedes the ability to remember an event as having been experienced, as opposed to simply known about [32].

While these various theories have helped us to understand the cognitive context in which infantile amnesia occurs in humans, it is important to note that infantile amnesia is not a uniquely human phenomenon. In an elegant series of experiments performed in 1962, B.A. Campbell and E.H. Campbell provided the first demonstration that infantile amnesia can be observed in rats [33]. Rats from 5 different age groups [postnatal day (P) 18, 23, 38, 54 and 100] were trained in an active avoidance task, where they were conditioned to associate one side of a two-compartment shuttle box with mild foot shocks. The memory of the conditioning sessions was measured by the latency to 'escape' when rats were placed back in the shock-paired compartment. All age groups exhibited quick escape latency when tested immediately, demonstrating comparable learning across the different age groups. However, it was found that the rate of forgetting was closely related to age. After a 7 day interval, rats trained at P18 and P23 exhibited slower avoidance of the shocked compartment and failed to exhibit any avoidance following a 21 day delay. In contrast, rats trained at P54 and P100 displayed no evidence of forgetting even following a 42 day retention interval.

This general finding that younger animals forget more rapidly than older ones has since been replicated numerous times with different learning procedures and in different species [34–38]. In fact, infantile amnesia has been observed in every altricial species examined; that is, animals that undergo extensive post-gestational development [24]. The discovery that infantile amnesia is relatively easy to study in animals opened the door for empirical investigations into its underlying neurobiology, and indeed most of what we now know of this phenomenon has been garnered from animal studies.

2.1. Developmental stages in humans and rodents

Rodents are by far the most frequently used species for the study of memory development. To enable a valid comparison to humans it is important to understand how particular developmental stages in the rodent correspond to those in the human on both a behavioural and neurobiological level. Traditionally, developmental stages in the rodent were based upon the timing of key structural events such as the brain growth spurt [39,40], but in the context of learning and memory we believe it is more appropriate to align developmental stages with the emergence of specific cognitive functions. Rodents up to P23 have been referred to as 'infants' in previous studies, presumably referring to a range of immaturity other than adolescence [41–45]. However, findings accumulating from the last few decades suggest that the cut-off for the end of infancy should be much earlier than this. For example, when rat pups are young and reliant upon maternal care for survival, they learn maternal odour preference to support attachment and feeding [46]. Prior to the age of P12, rat pups will paradoxically form an odour preference if an odour is paired with an aversive stimulus, a behaviour that is thought to promote maternal attachment in the face of adversity [47–49]. At around P10 when rat pups begin to explore the extra-nest environment for the first time [50], odour aversion learning begins to emerge, which coincides with engagement of the amygdala [51,52]. This transition marks what we believe should be considered nearing the end of infancy (equivalent to 0–12 months in humans). Similarly, due to the protracted development of the hippocampus, spatial abilities (large-scale maze navigation) do not fully emerge in human children until around 7 years of age [53]. In rats, consistent performance in equivalent spatial or configurational learning and memory tasks emerges at the end of the third postnatal week (P21) [54–56]. In light of this we consider P12–P21 to more accurately represent the juvenile period, to reflect young childhood in humans. We will refer to P21–P28 as the pre-adolescent period because P28 marks the emergence of many behavioural changes that characterise adolescence in humans such as increased time spent in social interactions and play behaviour [57,58] and this also coincides with timing of the growth spurt which peaks at 4–5 weeks of age [59]. It is important to note that P21–P28 has often been referred to as 'weanling' age in previous empirical studies, despite the rodents in those studies not being weaned and kept with the