

Binding Together the Elements of Episodes

Relational Memory and the Developmental Trajectory of the Hippocampus

Ingrid R. Olson and Nora S. Newcombe

Temple University

In my earliest memory, my grandfather is bald as a stone and he takes me to see the tigers. He puts on his hat, his big-buttoned raincoat, and I wear my lacquered shoes and velvet dress. It is autumn, and I am four years old (Obrecht, 2011).

There are many striking aspects to this opening passage from a popular novel, *The Tiger's Wife*, including its sense of strong love for the grandfather and its aura of nostalgia for the experiences of the past. However, for developmentalists, the passage also poses a challenge. How is it possible that the narrator claims to remember nothing before the age of 4 years, when decades of research suggest that even very young infants form memories? There are a variety of answers to this question, which has been called the puzzle of infantile (or childhood) amnesia.

The proposed solutions to the puzzle are discussed at length by Bauer (Chapter 22). However, for now, let us simply note that the various approaches differ along several dimensions. One dimension is whether or not neural substrates are considered. Many explanations are fundamentally social and cultural, focusing on developmental changes such as the acquisition of language and of narrative skill, the advent of the self concept, and the impact of adult conversations emphasizing shared memory (e.g., Fivush & Nelson, 2004). While these factors are undoubtedly important, other explanations suggest that there may also be age-related changes in the neural substrates supporting memory (Newcombe, Lloyd, & Balcomb, 2011; Newcombe, Lloyd, & Ratliff, 2007). A second dimension of variation concerns one of the classic debates in developmental psychology: whether change is continuous or discontinuous, quantitative or qualitative. Some investigators adopt a strong continuity view (Rovee-Collier & Cuevas, 2009). Other investigators emphasize discontinuity, specifically by arguing that there is a sharp transition around the age of 2 years (Newcombe et al., 2007).

There are many terms and definitions at play here, and untangling what we mean by *memory* is probably key to solving the puzzle of infantile amnesia. What Obrecht means by *memory* is

not what psychologists mean by *memory*, mostly because it turns out there are many different kinds of memory. What she means in using the word is what psychologists call *episodic* memory. Episodic memory can be defined as the ability to bind together the elements of episodes. It can also be regarded as a term similar but not identical to *relational* memory (a phrase much used in the cognitive neuroscience literature to describe associations or *binding* among items or elements presented together), and as a term similar but not identical to *autobiographical* memory (a phrase best used to describe the subset of episodic memories that have important self-related content, although it sometimes also includes semantic facts about the self). At their core, episodic and (most) autobiographical memories are relational memories because they are defined by their contextually rich associations. As such, we can use data from research on children's autobiographical memories to understand the development of relational memory.

It is important to understand that not *all* relational memories are episodic or autobiographical. To understand this issue, another term must be introduced: semantic memory. Semantic memory involves consciously accessible and publicly reportable information that may (or may not) be relational. Like episodic memory, it is also a type of explicit memory but it differs from episodic memory in important ways. The passage from *The Tiger's Wife* is striking in large part because of its precision about details, including not only what happened (seeing the tigers), but also who was involved (the grandfather), when the event occurred (autumn), and what everyone wore (the hat, the raincoat with its big buttons, the shoes, and the velvet dress). It is these details, and the fact that the details are related or bound together into an episode, which qualify this memory as what most people are willing to call an "earliest" memory and what psychologists would call an episodic or autobiographical memory. The protagonist must clearly have earlier explicit memories of a semantic kind: she presumably had already learned to talk and she likely knew what tigers were (i.e., that they are fierce, have stripes, etc). However, that kind of semantic memory seems different to most people from memories of particular instances of tiger viewing.

Once we draw a sharp distinction between episodic and semantic memory, we can be clearer about a possible answer to the problem of infantile amnesia. Before the age of 2 years, while there is much evidence for declarative or explicit memory of the semantic kind, there may be limited ability to bind together elements in such a way as to form an episodic or relational or autobiographical memory (see Section IV: Autobiographical Memory, this volume). Although the time of the earliest memory varies somewhat in the range of 2–4 years, depending on factors including gender, culture, and age of the person (e.g., Peterson, Warren, & Short, 2011), credible reports of early memories dating before 2 years are rare, sparse, and inconsistent (Crawley & Eacott, 1999; Eacott & Crawley, 1998, 1999). This conclusion is supported by data from many studies of earliest memories (Rubin, 2000).

Furthermore, between the age of 2 and 6 years, binding may occur in a fashion that is considerably less secure than it will be in adulthood. Adults report childhood events as remembered, rather than simply known, at a median age of 6 years (Bruce, Dolan, & Phillips-Grant, 2000). Supporting this observation, experimental data show that children younger than 6 years may be more susceptible to source memory errors (Drummey & Newcombe, 1995), have difficulty distinguishing real from imagined events (Sluzenski, Newcombe, & Ottinger, 2004), have difficulty in binding items to locations (Sluzenski, Newcombe, & Kovacs, 2006), and show susceptibility to false alarms when familiar items and familiar locations are re-paired in unfamiliar ways (Lloyd, Doydum, & Newcombe, 2009). Difficulties of this kind may account for the fact that some people, such as the narrator in Obrecht's novel, do not report childhood

memories from earlier than 4 years of life. In fact, the development of binding may continue even during the school years, as shown by naturalistic, experimental, and neuroscientific investigations (e.g., Berntsen & Rubin, 2006; Ghetti & Angelini, 2008; Shing & Lindenberger, in press).

This chapter focuses on the idea that binding, or relational memory, is characterized by an initial discontinuity around the end of the second year of life, followed by a period of at least four (or likely more) subsequent years during which this kind of memory gradually strengthens but is still not at mature levels. This claim combines aspects of the qualitative and quantitative views of development, envisioning an initial discontinuity followed by continuous change. It also takes neural substrates very seriously, emphasizing development in the hippocampus in terms of the initial discontinuity, and developments there and elsewhere in terms of subsequent quantitative change. We focus largely on the initial discontinuity, although we also touch lightly on subsequent, more gradual change.

The initial part of the chapter is aimed at reviewing the literature from cognitive neuroscience on the definition and neural basis of binding and relational memory. Our hope is that setting developmental research on binding and relational memory in the context of this research will provide the basis for developmentalists to fully evaluate why the approach deserves serious consideration. We then review hippocampal anatomy and development. In the last part of the chapter, we examine the behavioral evidence for and against the hypothesis of an initial discontinuity, highlighting the unsettled issues and discussing the research still needed to fully evaluate it. Specifically, we briefly examine paradigms evaluating memory in infants and toddlers, including conjugate reinforcement, delayed non-match to sample (DNMS), visual paired comparison (VPC), delayed imitation, and studies of eye movements. For each, we consider the neural bases of performance (if known) and the question of whether the memories indexed are episodic or semantic, relational or non-relational. We end with discussion of novel paradigms, derived from research with non-human animals, which offer the hope of more directly assessing binding and relational memory in children as young as 1 and 2 years.

The Hippocampus and Relational Memory

Conceptualization

The importance of the hippocampus in memory was first noted over 50 years ago, in a landmark study showing that bilateral damage to the human hippocampus and related medial temporal lobe structures causes severe memory impairments (Scoville & Milner, 1957). In the decade following that study, researchers focused on further describing the phenomenon and on producing an animal model of amnesia. Later, researchers began to ask the question of how best to characterize the role of the hippocampus in memory processes. Current research is most interested in the computational role of the hippocampus and supporting medial temporal lobe (MTL) structures in memory.

One theory that has gained prominence in the last 15 years is the *relational processing theory*. At the heart of this theory is the idea that the MTL is important for encoding into memory what has been described as binding, contextual, configural, or relational information (Cohen & Eichenbaum, 1993; Hirsh, 1974; Kim & Fanselow, 1992; O'Keefe & Nadel, 1978; Sutherland & Rudy, 1989). The underlying theme of these proposals is that the MTL is

important for binding together different elements of a memory trace to form a rich representation of an experienced episode (Eichenbaum, 1999).

According to Cohen and Eichenbaum, relational representations are “created by and can be used for comparing and contrasting individual items in memory, and weaving new items into the existing organization of memories.” This form of representation maintains the distinct nature of each object, both as an item unto itself but also as part of a larger-scale scene or event that holds onto the relevant relationships between items (Cohen & Eichenbaum, 1993). This goes beyond the formation of simple associations by indicating that relational memory can be about many different relationships—temporal or causal, for instance. Moreover, the items in their relationship retain their independence rather than being fused together.

Cohen and Eichenbaum’s formulation of relational memory helps to answer the question of whether the hippocampus is critical for both within-item associations (e.g., the color gray to the shape of a cat) and between-item associations (e.g., cat and yarn; Davachi, 2006). Within-item associations have long been studied in the visual attention literature, in the form of feature conjunctions, such as the color and orientation of an object (Treisman & Gelade, 1980). Although this literature also uses the term “binding” to describe the linkage of simple visual features, this kind of linkage is a qualitatively different form of binding than the associations formed on spatially and temporally separated items discussed in the episodic memory literature. In the former case, what we see is the *fused linkage* of integral features, such as color to shape, to form a single object (e.g., a red triangle) during perceptual processing. In contrast, memory binding involves the linkage of discrete items or features, such as a face and name to a particular time and place in which you met someone. Visual feature binding has been closely linked to the functionality of the inferior parietal cortex (Treisman, 1998) rather than to the hippocampus. Much evidence points toward the conclusion that the hippocampus is involved in binding information that is *not* integrated by earlier, sensory brain areas (Mishkin, Vargha-Khadem, & Gadian, 1998; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006; Piekema, Rijpkema, Fernandez, & Kessels, 2010). Visual feature binding has been studied developmentally (e.g., Ross-Sheehy, Oakes & Luck, 2003; see Oakes and Luck, Chapter 8, this volume), but it is not the kind of binding that is central to the mystery of infantile amnesia.

Findings from neuropsychology

Cases of medial temporal lobe amnesia have been used as a model system for exploring the effects of MTL damage on memory. Such damage is usually caused by oxygen deprivation (e.g., anoxia/hypoxia), viral infection, or traumatic brain injury. Naturally occurring focal lesions in brain areas of interest are rare, variable in size and location, and usually occur in people of advanced age or with other co-morbid health disorders. The focal lesion literature is characterized by small sample sizes and repeated testing of the same patients, sometimes over decades, such as the famous patient H. M. Nevertheless, findings from such patients have proved to be invaluable in understanding the function of the hippocampus and related structures. The major strength of the lesion approach is that one can show that a brain–behavior relationship is causal, whereas this cannot be shown with neuroimaging (Fellows et al., 2005). The only other non-invasive cognitive neuroscience method that offers a similar degree of causal induction is brain stimulation, and that method cannot be used with deep brain structures like the hippocampus.

Findings from several laboratories, using different stimuli and different patient cohorts, have provided evidence in support of the relational memory theory. In early studies,

investigators reported that amnesics had profound difficulties in remembering learned word pairs as compared to single words (Cermak, 1976; Winocur & Weiskrantz, 1976). In these cases, brain scans were not available so it was not possible to verify the degree of extrahippocampal damage. Later studies in cases with confirmed hippocampal damage replicated these findings. For instance, in one study (Giovanello, Verfaellie, & Keane, 2003), patients with bilateral hippocampal damage and controls were required to remember many pairs of nouns, such as bicycle–salmon, cupcake–pillar, etc. At test, there were two possible conditions. In the *item recognition* condition, the task was to discriminate between items presented at study (e.g., bicycle) and items not presented at study (e.g., scooter). In the *associative recognition* condition, the task was to distinguish between intact pairs (e.g., cupcake–pillar) and rearranged pairs (e.g., cupcake–salmon). From an experimental design standpoint, it is very important that both intact and rearranged pairs consist of two studied items. To perform the associative memory task successfully, study participants must have intact memory for the associations formed at study; relying on familiarity for items that form part of the complex would lead to incorrect responses. The results showed that hippocampal damage was associated with associative memory deficits, but not item memory deficits (Giovanello et al., 2003). In another study, a highly intelligent patient with bilateral hippocampal damage due to viral encephalitis was tested on a range of tasks. The results showed that his memory for objects-in-locations was more than two standard deviations lower than that of matched controls. This deficit was apparent on both yes–no recognition tasks and on recall tasks (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005).

Hippocampal damage may lead to uneven deficits on relational memory tasks, depending on the type of relationship that must be formed. Several studies hint that the hippocampus is more necessary for between-category associations (face–voice) than within-category associations (face–face). Mayes and colleagues tested a patient, Y. R., with selective hippocampal lesions across a large range of memory tasks (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002). Y. R. performed normally on tests of item memory and within-category relational memory, but was impaired across a range of between-category relational memory tasks. Similar results have been reported for three young patients who had early insult to the hippocampal formation (Vargha-Khadem et al., 1997). They exhibited normal performance on recognizing pairs of words, non-words, unknown faces, and famous faces. In contrast, their recognition memory for object–location and face–voice associations was impaired.

Findings from neuroimaging

The relational memory theory also receives support from neuroimaging findings. For instance, Davachi and Wagner (2002) asked study participants to remember triplets of visually presented nouns. There were two trial types. On rote trials, the task was to covertly rehearse the word triplet in the same order as was presented. On “order” trials, the task was to covertly reorder the words in order of subjective desirability. This task was considered relational because each word needed to be ordered relative to the desirability of the other words in the set. There was no probe task in the scanner. Outside of the scanner, memory for the in-scan materials was assessed. Behavioral performance of subsequent remembering was used to re-bin the fMRI data into “remembered” trials and “forgotten” trials, a technique that is called “subsequent memory analysis.” The results showed that relational processing was associated with greater activation of the bilateral hippocampus relative to item-based processing. Moreover, activation in the hippocampus during relational processing was correlated with subsequent memory

performance, thus directly linking hippocampal activations to performance levels (Davachi & Wagner, 2002).

A more conventional behavioral task was used by Qin and colleagues (Qin et al., 2009). Study participants were required to remember pairs of unrelated common objects, such as a duck and a roller-skate. The objects were presented one at a time so that the BOLD signal for each item could be deconvolved. Memory for items and item pairs was tested outside of the scanner, and data were re-binned for a subsequent memory analysis. The results showed that hippocampal activity at encoding was associated with later memory retrieval of item associations, while activity in a region just outside of the hippocampus, the parahippocampus, was associated with later memory retrieval of items. Many other studies have also reported greater hippocampal activations to relational memory as compared to item memory (reviewed by Davachi, 2006).

Neuroimaging studies of autobiographical memory retrieval have been less successful in identifying specific neural correlates, although the hippocampus is typically activated as part of a larger network (Svoboda, McKinnon, & Levine, 2006). Autobiographical memories may lead to widespread neural activations due to the individualized and emotional nature of these representations, the inferential processes used to reconstruct these memories, and the blend of semantic and episodic elements that define older autobiographical memories. Nevertheless, it is clear from decades of neuropsychology research that the formation and consolidation of autobiographical memories relies on the hippocampus.

Relational memory over short delay intervals

Initially the relational memory deficits of hippocampal amnesia were thought to be limited to long-term memory. This reflected the dominant view of the time, that the hippocampus had a role in memory that was tightly delineated by the amount of elapsed time between encoding and retrieval (Squire, Stark, & Clark, 2004). This view is somewhat peculiar in that the amount of elapsed time between encoding and retrieval was ad hoc—usually greater than 15 seconds—and had no basis in biological phenomenon associated with memory formation, such as protein synthesis.

Recent studies have shown that this view of the hippocampus is incorrect because this region is critical for relational memory even over very short delays. For instance, one of the authors of this chapter tested a group of patients with bilateral MTL lesions and age-matched controls in an experiment that required either feature memory or relational memory, over a short time interval (see Figure 13.1). The feature task required participants to remember either three common objects or three filled locations (e.g., three location place-markers). The relational memory task required participants to remember three objects *and* the locations in which they appeared. The results showed that patients with MTL damage had intact memory for only objects or only locations at delays of up to 8 seconds. The fact that item memory—memory for locations or for objects—did not differ between amnesic and control groups allowed us to assess whether amnesic patients had a *disproportionate* deficit in relational memory. Indeed, when required to remember an object in a location over an 8-second delay period, patients' memory was dramatically impaired (Olson, Page, Sledge, Chatterjee, & Verfaellie, 2006). Other groups have replicated and extended this finding using different stimuli and different patients with MTL damage (Hannula, Tranel, & Cohen, 2006; Konkel, Warren, Duff, Tranel, & Cohen, 2008).

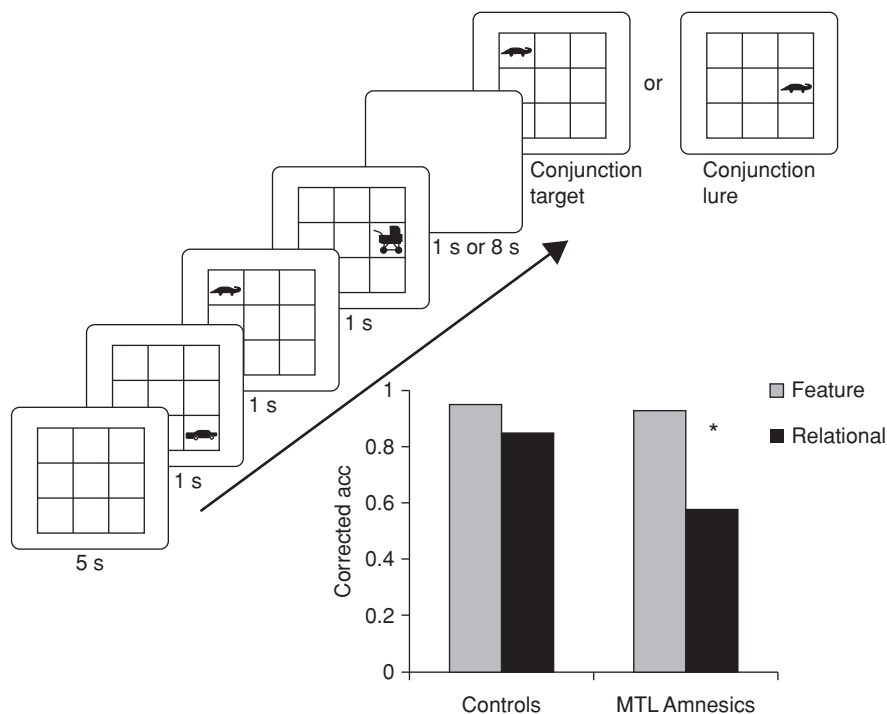


Figure 13.1 A depiction of the task and data from Olson and colleagues (2006). Study participants were required to remember sequentially presented common objects, locations, or both over an 8-second delay. The results showed that age-matched normal controls and amnesic patients with MTL damage had normal levels of memory performance when single features (objects or locations) had to be remembered. However, when required to remember the relationship between an object and the location in which it had appeared, the amnesic group showed a disproportionate deficit.

The neuroimaging literature is consistent with these neuropsychological findings. For instance, Piekema and colleagues (2006) conducted an event-related fMRI study in which participants were required to remember three sequentially presented items. Stimuli consisted of numbers that were presented in different colors and in different screen locations. An instructional cue presented at the start of each trial indicated which feature or feature associations had to be remembered, such as colors plus locations. After a 9–20-second delay, a probe item was presented and an old/new decision was elicited. The results showed that the right hippocampus was activated during the delay period of the trial and that activity was modulated by the type of information that needed to be maintained. Specifically, it was sensitive to feature combinations that included spatial information but not to single items or non-spatial-feature combinations (color–number combinations; Piekema et al., 2006).

Sharpening relational processing theory

Although the relational memory hypothesis enjoys a great deal of popularity, it is plagued by a lack of specificity that gives rise to interpretive problems and questions. A first issue is how exactly to define the terms “relational” and “associative.” Association formation encompasses

an exceptionally broad set of features/items/concepts that are linked through their spatial and temporal proximity. The environment is rich with sights, sounds, smells, and feelings. Thus, when an item is encoded into memory, it could potentially be bound to any number of temporally co-occurring contextual features in the external context—the time, place, temperature, etc., that accompany the study session—as well as features of the internal context—the thoughts, feelings, and emotions that accompany the study session. However, research on human memory has shown again and again that we only retain a fraction of what we experience. The question then is, how can we predict which bits of this exceptionally rich array of information will be bound up into an episodic memory?

One plausible answer is that what matters in association formation is the subset of information that is attended. In animal research, attention is typically drawn to the variables of interest by using stimuli that are biologically salient, such as food or pain. In human studies, attention is manipulated by constraining the environment and directing attention via instructional cues. As we go about our lives, however, the environment is replete with information and there is no helpful experimenter to tell us what to attend to. Although one would predict that this would lead to a chaotic, fragmented memory system, without any thematic thread linking the episodes together, this does not occur. Some contextual features may carry more biological significance and thus may be weighted more strongly than others.

One candidate category of information is spatial information. The very definition of episodic memory—a *record of a person's experience that holds dated information and spatio-temporal relations* (Tulving, 1983)—attests to the importance of spatial information in episodic memory. There is a long history of research linking hippocampal function to the quintessential spatial memory task, navigation. Indeed, even partial hippocampal loss gives rise to navigational impairments in humans (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). One piece of evidence supporting the central relevance of spatial information to episodic memory is the finding that spatial context plays a unique role in the updating of episodic memory (Hupbach, Hardt, Gomez, & Nadel, 2008).

Second, the relational processing theory does not specify whether the hippocampus supports all forms of relational memory or only a subset of relational memory processes. It has been claimed that “hippocampal amnesia impairs all manner of relational memory” (Konkel et al., 2008). However, this statement is an exaggeration of the true state of things since it is known that some types of association formation can occur in the absence of an intact hippocampus. For instance, as a child, I learned that Lincoln is the capitol of Nebraska and that Nebraska is located in the northern Midwest. This knowledge is clearly relational, yet it probably does not rely on the hippocampus, given that it seems to be a semantic memory. Findings from patients with developmental amnesia who have atrophic hippocampi due to neurological events early in life speak to this point. The famous developmental amnesic “Jon” has above-average intelligence, normal speech, and can acquire new semantic memories (Vargha-Khadem et al., 1997). The acquisition rate of semantic knowledge is somewhat slower than that of normal individuals, requiring additional repetitions, but the fact remains that a normally functioning hippocampus does not appear to be essential for acquiring semantic knowledge, much of which is relational (e.g., Vargha-Khadem et al., 1997).

The complementary learning systems (CLS) model of memory (Norman & O'Reilly, 2003) proposes that the hippocampus is specialized for the rapid and automatic acquisition of information so that it can be recalled later on based on partial cues, a function termed *pattern completion*. It is further proposed that the hippocampus assigns distinct, pattern-separated representations to stimuli, a property that allows the hippocampus to rapidly extract the distinct

aspects of an event. In contrast, the neocortex learns slowly and incrementally via the use of overlapping representations which allows it to form general (as opposed to specific), gist-like representations. Evidence for the view is primarily derived from rodent research, as well as computational models. This model predicts that the hippocampus will be required for the encoding and retrieval of stimuli that occur only once, for instance, the appearance of an object in a location. It would not be required for relational processing tasks in which the associations are created by repetition. In most instances, this would include the learning of concepts and facts (e.g., semantic memory), conditioning, and procedural learning. Arguments and evidence of this kind reinforce the point made at the beginning of the chapter, namely that children may be learning in an explicit and even relational way in the first two years of life, *but forming semantic but not episodic memories*.

Third, the relational processing theory unintentionally gives rise to the idea that the brain has two completely distinct memory systems, one for processing item memories and one for processing relational memories. Although this view is tempting in its simplicity, it is more likely that hippocampal functioning is not binary; rather, its recruitment parallels the degree to which relational processes are emphasized by the stimuli and task. The relational memory view that we advocate holds that the hippocampus will be recruited to some degree by item memory tasks but to a much greater degree by tasks that demand relational memory processing for accurate performance. This helps explain why item memory deficits have been observed after MTL damage (Olson, Moore, Stark, & Chatterjee, 2006), but larger deficits are observed when relational memory processes are tapped (Olson, Page et al., 2006). Indeed, a double dissociation between item and relational memory has yet to be shown, hinting that these processes are closely aligned.

Last, the relationship between relational memory processing and other signatures of hippocampal processing such as novelty processing and delay-related performance decrements is not clear (Squire et al., 2004). One possibility is that the hippocampus has functions that transcend relational processing, while still being solely responsible for creating relational memories. Another possibility is that these functions interact in meaningful ways.

Hippocampal Anatomy and Development

Given the importance of the medial temporal lobe memory system to relational memory and binding, it would seem natural to wonder if the absence of episodic memories from the first two years of life might be linked to hippocampal change. One way to address the hypothesis would be to seek direct evidence concerning anatomical and structural change. We will begin by discussing the anatomy of the hippocampus and surrounding tissue, and then present what is known about development (also see Bachevalier, Chapter 6, this volume).

Anatomy

The hippocampus is an evolutionarily ancient cortical structure comprised of only three layers, rather than the six-layered structure of the neocortex. It consists of mirrored left and right structures. Moving along the transverse axis, the hippocampal formation can be broken down further into constituent parts that form a linked information pathway: the dentate gyrus, the cornu ammonis (CA1-CA4), and the subiculum (Amaral & Lavenex, 2007). There also appears to be differentiation along the long axis on the hippocampus, also known as the

anterior-posterior axis. Studies in monkeys (Colombo, Fernandez, Nakamura, & Gross, 1998) and rats (Moser & Moser, 1998) have shown that the long axis of the hippocampus can be subdivided into functionally distinct regions. Human brain imaging research, as well as studies of rodents, indicates that the posterior hippocampus has a preferential role in forming spatial memories (Bannerman et al., 2004; Colombo et al., 1998; I. Lee & Kesner, 2003; Maguire et al., 2000; Moser, Moser, & Andersen, 1993). In contrast, the anterior hippocampus appears to be more strongly involved in relational or associative memories (Schacter & Wagner, 1999a, 1999b).

The hippocampus constitutes the heart of the medial temporal lobe memory system but there are other structures within this system whose functions are only now being uncovered. These are adjacent MTL structures: entorhinal and perirhinal cortices, and portions of the parahippocampal gyrus. In most cases of MTL amnesia, portions of these structures are damaged, although in some rare cases (usually anoxic injury) only the hippocampus is damaged.

Much of the current research on the MTL is focused on discerning the functional role of these regions in memory. Although developmental research has yet to take on the challenge of understanding how the development of various areas creates development at the behavioral level, this task is clearly important for the next wave of research progress. We will briefly summarize this large literature. The entorhinal cortex is thought to serve as an interface between the hippocampus and neocortex, and thus it has an important general role in navigation and episodic memory. Perirhinal cortex and posterior parahippocampus have more specialized functions. Perirhinal cortex receives sensory input from visual, olfactory, and somatosensory cortices. It appears to be involved in high-level object perception and memory (Murray & Bussey, 1999), although it has also been suggested to play an important role in a particular type of memory retrieval: familiarity as contrasted with recollection (Brown & Aggleton, 2001). Patients with lesions that include this region (because it is very unusual to have a lesion restricted to this area) have difficulties telling apart closely related exemplars such as faces (Lee et al., 2006; Lee et al., 2005). In contrast, the posterior parahippocampus, which receives input from the retrosplenial cortex and portions of the posterior parietal cortex (Wixted & Squire, 2011), appears to have a specific role in the mnemonic encoding of scene information. Patients with lesions to this area cannot recognize or encode into memory scenes, especially when the scenes are relatively featureless, such as bathrooms (Epstein, 2008). Neuroimaging studies show that the posterior parahippocampus is activated by a wide variety of scenic information including outdoor scenes, room scenes, and even scenes comprised of legos (Epstein, 2008).

Development

The human hippocampus undergoes dramatic maturational changes through the first two years of life (see Figure 13.2), with slower continuing change after that, appearing to end around age 12 (Utsunomiya, Takana, Okazaki, & Mitsudome, 1999).

Gogtay and colleagues (Gogtay et al., 2006) conducted a longitudinal study of hippocampal maturation in a cohort of 31 subjects beginning at age 4 and going up to age 25. Study participants received an MRI every 2 years for 6–10 years. Slices were collected along the long axis of the hippocampus. This study is unusual because it had a longitudinal design, a design that is costly and difficult to implement, especially in neuroimaging, and because the hippocampal sub-regions were examined. The results showed that overall volume of the hippocampus did not change with age (see also Ofen et al., 2007), in line with prior work showing that volumetric maturation is modest after age 2 (Utsunomiya et al., 1999). However,

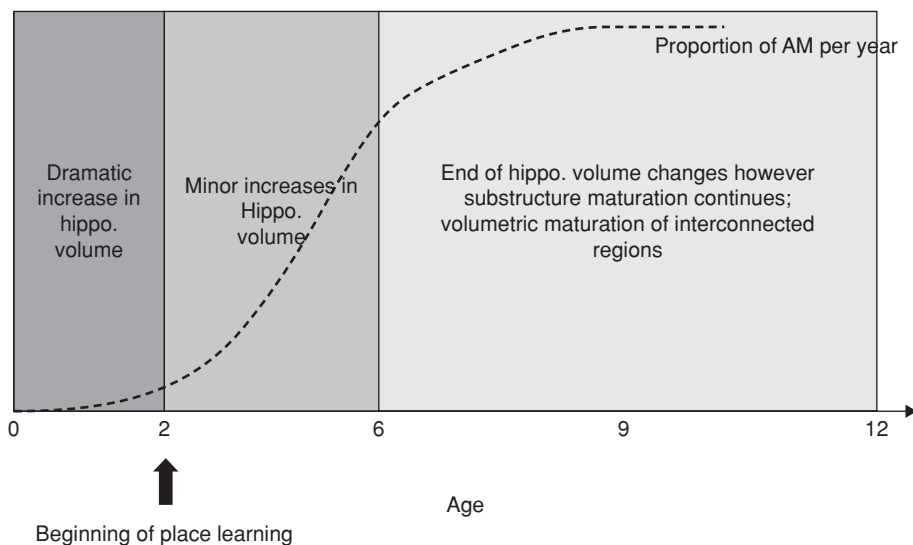


Figure 13.2 The relationship between hippocampal maturation and behavioral indices of episodic memory. The gray vertical bands represent changes in human hippocampal volume with age (Utsunomiya et al., 1999). The dashed line shows the proportion of autobiographical memories with age (re-plotted from Rubin, 2000). Between the ages of 0–2, there are few autobiographical memories, possibly because the hippocampus is undergoing dramatic structural changes. The fruits of these structural changes are seen after the age of 2, where a moderately mature hippocampus allows for the formation of relational memories. This is reflected in the abrupt increase in the number of autobiographical memories and the beginning of place learning (represented by the vertical arrow; Balcomb et al., 2011; Newcombe et al., 1998). The number of memories and structural changes in the hippocampus continue until about age 7, after which time the number of autobiographical memories is at mature levels.

there were local volume changes: anterior sub-regions of the hippocampus experienced volume loss while posterior sub-regions experienced volume gain. The authors speculate that, over the course of development, there is increased specialization of function in the posterior pole of the hippocampus for the processing of spatial memories, possibly leading to the distinct developmental trajectory of this region.

It is important to bear in mind that structures that are interconnected with the hippocampus will be undergoing maturation as well (Bachevalier & Vargha-Khadem, 2005), and at a different time scale than that of the hippocampus. For instance, the prefrontal cortex is tightly interconnected with the anterior hippocampus, and it has a protracted maturational profile (Poldrack, 2010). The maturation of this region likely affects neural activity and connectivity within the hippocampus and, subsequently, hippocampal processing. Thus, the dynamic interplay of maturational processes, both within and outside of the hippocampus, will affect hippocampal relational memory (Poldrack, 2010).

We currently do not have the data to accurately model the effects of endogenous and exogenous maturation on hippocampal processing. The clearest developmental data are from studies of volumetric changes, and these data indicate that the most important timeframe for hippocampal maturation is the first two years of life. One implication of this is that it may be impossible to form relational memories before the age of 2, simply because the hippocampus

is too immature. The fruits of early maturational processes will be seen after the age of 2, when a moderately mature hippocampus can allow for the formation of relational memories, albeit ones that are fragile for several years. Thus, developmental changes in relational memory performance should trail hippocampus maturation in a highly predictable manner.

Evaluating Relational Processing over the First 3 Years of Life

So far, we have argued that relational processing is a key hippocampal function, and that cited data suggest rapid change in hippocampal volume during the first 2 years of life, with some continuing change of a more subtle sort after that. Are these neural changes correlated with changes in behavioral capabilities?

In the spatial domain, the answer seems to be affirmative. A quintessential function of the hippocampus is supporting place learning, and the ability to engage in this kind of learning undergoes abrupt change at about 21 months of age (Balcomb, Newcombe, & Ferrara, in press; Newcombe, Huttenlocher, Drummey, & Wiley, 1998; for review in a comparative perspective, confirming a similar change in rodents, see Learmonth & Newcombe, 2010). Furthermore, important changes at approximately 2 years of age are seen in the ability to maintain memory for spatial location over a delay and maintaining memory for more than one spatial location at a time (Sluzenski et al., 2004).

However, a direct comparison of event memory and location memory in the second year of life has suggested that location memory may be more vulnerable to forgetting over a delay than event memory (Lukowski, Garcia, & Gauer, 2011), suggesting that results on the developmental course of spatial memory might not generalize to other kinds of relational memory. Thus, we clearly need to *directly* assess changes at the behavioral level in binding together the attributes of episodes, rather than relying on the data from spatial memory tasks.

There are many paradigms that have been used to evaluate early memory, before the age of 2 years, including delayed non-match to sample (DNMS), conjugate reinforcement, delayed imitation, visual paired comparison, and studies of eye movements. However, the neural bases of performance are not known for all of them, and it is not always clear whether the memories indexed are episodic or semantic, relational or non-relational. To gain insight into these issues, we briefly review each of these five paradigms. For further discussion of some of these paradigms, see Bauer (2007).

Delayed Non-Match to Sample (DNMS)

The DNMS task has been used extensively in research with non-human animals, and there is evidence that success depends on medial temporal lobe structures (e.g., Malkova, Bachevalier, Webster, & Mishkin, 2000). The task is simple enough to use with very young children: a novel object is presented, removed, and then presented again, together with a different novel object. The correct response is to select the object that differs from the one previously presented. Success is not seen until 21 months of age (Overman, Bachevalier, Turner, & Peuster, 1992), supporting the idea of a transition in hippocampal maturity at the end of the second year of life and the findings from place learning (Balcomb et al., in press).

There are two problems, however, with accepting this evidence as support for a developmental transition. First, babies succeed earlier when the reward for a correct choice is *directly*

attached to the selected object using Velcro on the base, rather than located in a well revealed by moving the selected object, due to the physical connectedness of the object and the reward (Diamond, Churchland, Cruess, & Kirkham, 1999; Diamond, Lee, & Hayden, 2003). While it is possible that the modified DNMS task does not require (as much) relational processing as the classic task, exactly because the object and the reward are physically connected, this hypothesis has not been directly evaluated. Second, recent research with monkeys who had undergone hippocampectomies, either neonatally or as adults, did *not* show impairments on DNMS (Heuer & Bachevalier, 2011). Damage to cortical areas adjacent to the hippocampus, reviewed earlier, may well have been responsible for the impairments seen in previous studies.

Conjugate Reinforcement

There has been extensive research on infant memory using a paradigm in which infants learn to kick in the presence of a distinctive cue, such as a mobile, with later assessment of their retention of the linkage between their kicking and the stimulus in a situation without reinforcement (i.e., the kicking no longer causes the mobile to move). It has been argued that infants' behavior in this paradigm indexes explicit memory, based on cataloguing parallels between studies of adults' explicit memory and how infants behave with the mobiles (Rovee-Collier, 1997). On the other hand, it is possible that reinforcement tasks tap implicit rather than explicit memory (e.g., Bauer, DeBoer, & Luowski, 2007). Recent studies show, however, that infants can establish relations between what they learn in the reinforcement paradigm and their memory as assessed using delayed imitation techniques, which are known to tap explicit memory (Barr, Rovee-Collier, & Learmonth, 2011; Cuevas, Rovee-Collier, & Learmonth, 2006). This fact suggests, but does not prove, that conjugate reinforcement may indeed assess explicit memory, but more research is needed.

The data do not, however, address the question of whether the memories are episodic or semantic. The fact that the overall developmental trend on the conjugate reinforcement tasks is toward a need for *less* specificity in the cues needed to trigger memory of the operant foot kick (Morgan & Hayne, 2011), coupled with the fact that repetition is an inherent aspect of the conjugate reinforcement paradigm (a common feature of the attainment of conceptual knowledge), suggests that these memories are semantic, which research has shown are not hippocampally based. In fact, from this point of view, the findings of Barr et al. (2011) and Cuevas et al. (2006) may simply reflect the fact that both conjugate reinforcement and delayed imitation assess semantic memory in the first year of life. We turn now to delayed imitation.

Delayed Imitation

There is widespread agreement that delayed imitation relies on explicit memory, and also that success in delayed imitation is observed as young as six months of age (Barr, Dowden, & Hayne, 1996; Barr, Rovee-Collier, & Campanella, 2005). However, even though there is early success, there is also considerable developmental change in how much can be remembered for how long (Bauer et al., 2007). Such changes continue through the preschool years for memory of the temporal order of long sequences of arbitrarily ordered events, with ERP data suggesting that recollection of contextual details may be increasingly involved in success in this paradigm (Riggins, Miller, Bauer, Georgieff, & Nelson, 2009).

In terms of the hypothesis of a developmental discontinuity in the second year, the crucial question is whether the delayed imitation tasks used with infants and toddlers index semantic or episodic memory. Bauer and Lukowski (2010) shed considerable light on this question. They evaluated forced recognition choices between various specific versions of the props used in the imitation tasks (e.g., a black wood stick versus a yellow plastic stick, both of which could be used to make a dancing toy). They found that memory for the specific item used was related to long-term memory for the events in 20-month-olds but not in 16-month-olds. They argued that there may be a developmental transition in the second year of life, in which memory for specific details becomes bound to memory for the gist of the event. This evidence points to an interesting hypothesis, namely that delayed imitation can index either semantic or episodic memory, but that it becomes increasingly episodic as children approach their second birthday (Bauer & Lukowski, 2010).

Visual Paired Comparison

The visual-paired comparison task (VPC) used to study infant memory is based on visual preference techniques originally developed to examine infant perception (Fantz, 1958). Infants are exposed to a single visual stimulus for a fixed period of time and then shown a new stimulus plus the old stimulus. If infants look longer at the new stimulus, it is inferred that they have a memory of the old stimulus. Rose and colleagues have argued that VPC is a measure of explicit memory, dependent on medial temporal lobe structures, including the hippocampus (Rose, Feldman, & Jankowski, 2007). In contrast, Snyder argued that performance on VPC may reflect an interaction between visual attention and memory, and may actually reflect implicit memory (Snyder, 2007).

One way to think about VPC is in the context of research showing that adult recognition memory judgments are jointly determined by feelings of familiarity and by specific recollection (e.g., Yonelinas, 2002). Thus, performance on the VPC task, like performance on standard recognition tests, might be based on a blend of processes, supported at times by explicit recollection, or at other times by familiarity. At least two lines of evidence support the idea that VPC relies at least in part on familiarity, which is posited to *not* rely the hippocampus. One kind of data comes from work with human infants. Rose, Feldman, Jankowski, and Van Rossem (2011) analyzed data from a large sample of premature and typically developing infants, studied longitudinally at 1, 2, and 3 years using immediate and delayed VPC, imitation, and a measure of short-term memory. Structural equation modeling confirmed the existence of three factors: short-term memory, familiarity, and recollection. Recollection was assessed by the imitation task but not by the VPC tasks. Prematurity, with its associated risk of hypoxia and possible hippocampal damage, affected recollection, but not the other two memory components (Rose, Feldman, Jankowski, & Van Rossem, 2011). The second kind of data comes from research with monkeys given neonatal hippocampal lesions (Zeamer, Heuer, & Bachevalier, 2010). Zeamer and colleagues showed relatively normal initial performance on VPC, which they argued depended on spared medial temporal cortical areas, but also showed that the monkeys “grew into” a deficit on VPC relative to sham-operated controls, perhaps because the control monkeys began to use hippocampally based processes on the task.

In sum, there is good evidence that VPC measures explicit memory, but it may index familiarity rather than the recollective processes necessary for relational memory, at least early in development, and it may only be hippocampally dependent later in development (and then

only partially). In addition, VPC is tricky to use, because memory goes through phases of being manifest as a novelty preference or (later) as a familiarity preference, with null findings sometimes resulting not from the absence of memory but occurring due to the transition from preferring novel to preferring familiar (Richmond, Colombo, & Hayne, 2007). Worse, the delays at which these transitions occur vary with age (Morgan & Hayne, 2011).

Using Eye-Movement Measures as a Surrogate for Hippocampal Activations

One way to measure relational memory is through measuring patterns of eye movements. The number of eye movements (e.g., fixations and number of regions sampled) tends to decrease incrementally as a scene is repeated (Althoff & Cohen, 1999), reflecting behavioral habituation. However, if a region within the scene is altered, that is, there is a relational change, then normal adults show an increase in eye fixations to the altered region, suggesting that memory for the original item–location relationships has modulated viewing patterns (Hayhoe, Bensinger, & Ballard, 1998; Henderson & Hollingworth, 2003; Ryan, Althoff, Whitlow, & Cohen, 2000; Smith, Hopkins, & Squire, 2006). The alteration in eye movements can proceed with or without awareness (Hannula & Ranganath, 2008; Hannula, Ryan, Tranel, & Cohen, 2007; Holm, Eriksson, & Andersson, 2008), indicating that eye movements can serve as an indirect and non-verbal measure of memory.

While participants may be unaware of what their eyes are doing, the increased eye-sampling of relational changes is nevertheless linked to hippocampal processing. Ryan and colleagues (2000) recorded the eye movements of amnesic patients with bilateral hippocampal damage and matched controls while looking at pictures with changes in scenes. The results showed that the amnesic patients failed to show the eye-sampling bias to relational changes in previously studied scenes (Ryan et al., 2000). Moreover, an fMRI study found that hippocampal activations were correlated with the eye-sampling bias to relational changes in a scene (Hannula & Ranganath, 2008). Thus, the eye-sampling bias to relational changes can be considered a surrogate measure of hippocampal functioning.

Monitoring of eye movements to relational changes could thus be a useful tool for developmental studies where neuroimaging is difficult or impossible but one would like to have some insight into hippocampal function. The fact that no overt response is required makes it an ideal technique for studying preverbal children and infants (Richmond & Nelson, 2009). In Richmond and Nelson's study, nine-month-olds were shown face–scene combinations, and then memory for face–scene combinations was measured using eye tracking. Much like adults tested in a similar paradigm (Hannula et al., 2007), infants looked preferentially at familiar face–scene combinations compared to rearranged combinations. This leads to the surprising conclusion that relational memory (and the hippocampus that supports it) might be sufficiently mature in infancy to support relational memory. If true, it does not address the question of why children fail to demonstrate adult-like relational memory until the age of 6 years, when memory is measured through explicit response (Lloyd et al., 2009).

In fact, in an identical paradigm using the same stimuli, children of 4 years showed the preferential looking effect only in cases where they could also point to the correct face (given the background presented). When data were averaged over all trials, including trials on which children made errors, there was no effect (Koski, Olson, & Newcombe, 2012-accepted pending revisions). In addition, the same children showed chance performance in yes–no recognition, due to their extremely high false-alarm rate (see also Lloyd et al., 2009). One explanation for

these disparate findings is that relational memory is weak and fragile in infancy, potentially supported by neural regions other than the hippocampus (see the section titled “Summary and Conclusions” for more discussion of this issue).

Assessing Episodic Memory with Tasks Borrowed from Scrub Jays

The original concept of episodic memory, as defined by Endel Tulving, consisted of what–where–when components (Tulving, 1983). Such memories are relational and involve binding, but attention is focused on the temporal and spatial context. Recent research on the question of whether animals can demonstrate episodic-like memory has led to the invention of clever non-verbal paradigms. Perhaps the best-known one is a series of studies in which Clayton and colleagues have demonstrated that scrub jays show episodic-like memory (Clayton, Bussey, & Dickinson, 2003; Clayton, Bussey, Emery, & Dickinson, 2003; Clayton & Dickinson, 1998; de Kort, Dickinson, & Clayton, 2005). The jays were allowed to cache wax worms, which rot quickly, and peanuts, which remain unspoiled, in trays situated in unique contexts. The birds were allowed to search for the hidden food after either a short delay (in which case the worms would be fresh, and preferred over peanuts) or a long delay (in which case the worms would be spoiled). Jays searched for the wax worms after a short but not a long delay, suggesting that they remembered what (worms or peanuts), where (in different locations), and when (a short time ago or a long time ago), and that these memories were bound together (Clayton & Dickinson, 1998).

Other work using a different paradigm suggests that pigeons can also encode what, where, and when information (Singer & Zentall, 2007; Skov-Rackette, Miller, & Shettleworth, 2006). Rats also appear to demonstrate event memories that have what–where components bound together (Crystal, 2009; Eacott, Easton, & Zinkivskay, 2005; Kart-Teke, De Souza Silva, Houston, & Dere, 2006; Nemati & Whishaw, 2007), although there has been debate about temporal information (Babb & Crystal, 2006; Naqshbandi, Feeney, McKenzie, & Roberts, 2007).

Can these non-verbal paradigms be adapted for use with young children? Russell, Cheke, Clayton, and Meltzoff (2011) looked at what–where–when binding tasks in 3-, 4-, and 5-year-olds, in a future-oriented task based on the scrub jay research. Children were familiarized with what hot and cold storage boxes did to chocolate or cookies over short and long delay times, that is, that the chocolate melts in the hot box if the delay is long. They were then asked either to predict what box they would choose if they had to leave for a short or a long time, or to decide what food they wanted to put in the hot box if they had to leave for a short or a long time. The 3-year-old children did very poorly, although performance improved with age, but even 5-year-olds did not do very well, perhaps because inhibiting the desire to get chocolate, melted or not, was challenging to preschoolers.

Hayne and Imuta (2011) took a different approach, studying what–where–when memory in 3- and 4-year-old children using a hide-and-seek paradigm “designed with the scrub jay procedure in mind” (p. 318). Children selected three toys to hide in three different rooms in their own homes. After 5 minutes of book reading, the children were first asked verbally about the order in which they went to each room, what toy they hid in each room, and exactly where in each room that toy was hidden. They were then asked to take the experimenter on a tour to retrieve the toys, giving non-verbal evidence of memory. Four-year-olds were better than 3-year-olds at verbal recall, in addition to showing better behavioral recall for the order of rooms. The other behavioral measures were at ceiling (Hayne & Imuta, 2011).

This experiment is intriguing, but it invites follow up. First, conducting research in children's homes may be problematic; extremely familiar spatial contexts seem to support different patterns of performance than novel contexts, both in studies of spatial memory in infants (Feldman & Acredolo, 1979) and episodic memory in 5-year-olds (Hupbach, Gomez, & Nadel, 2011). Second, once children enter a particular room, the hiding location is unique to that room (e.g., Big Bird is under the purple couch). Thus, there is no need to bind together particular cues and particular contexts in a contingent relational fashion. Third, it would be desirable to be able to test children as young as 18 months in order to assess whether there is a discontinuity in binding toward the end of the second year.

In recent work, one of the authors has explored episodic-like memory in toddlers, using a what–where-context task (Balcomb, Newcombe, & Ferrara, March 2011). The paradigm used two rooms, two toys, two experimenters, and two identical sets of four containers (cylinder, box, basket, and bag). Both rooms held the same four containers, but arranged differently in each room. A different toy was hidden in a different container in each room. Children, therefore, experienced two contexts that shared the four containers, but differed in other features, and the toy's location. To succeed in this task, children had to remember two unique contexts rather than forming a general semantic representation. In one version of the task, we gave children an explicit memory cue (e.g., they were asked to find the *bubbles*), but in another version, they were simply asked to find the *toys*. The ability to make arbitrary object–object associations seemed to emerge at about 20 months, but only when children are provided with explicit recall cues. With more indirect cues, there was continuous incremental development to 5 years. The results suggest that children's associative episodic memory undergoes dramatic changes in early toddlerhood, continuing through the preschool years as their ability to make these associations becomes less reliant on immediate cues.

Later Developmental Change

Although we have focused this chapter on the hypothesis of an initial discontinuity in relational memory based on hippocampal maturation and linked to the offset of the period of dense amnesia termed *infantile amnesia*, we note that development in relational memory is far from complete at the age of 2 years. In fact, changes continue during the period from 2 to 6 years, in which autobiographical memories are sparser than would be predicted from simple forgetting curves, a period best called *childhood amnesia* and differentiated from infantile amnesia. Much research from our lab has examined this gradual improvement in relational memory (Drummey & Newcombe, 2002; Lloyd et al., 2009; Sluzenski et al., 2006), and other labs have found the same kinds of change (Bauer et al., 2012—in press). Recent research has even indicated that hippocampally based changes in relational memory extend further, into the school years and as late as the age of 10–11 years (Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Picard, Cousin, Guillery-Girard, Eustache, & Piolino, 2012; Townsend, Richmond, Vogel-Farley, & Thomas, 2010); for reviews, see (Ghetti & Bunge, 2012—in press; Raj & Bell, 2010).

Summary and Conclusions

In this chapter, we provided evidence for the idea that relational memory is characterized by an initial discontinuity around the end of the second year of life, followed by a period of at least

4 years during which this kind of memory gradually strengthens but is still not at mature levels. We linked this process to the development of the hippocampus which follows a developmental trajectory of rapid maturation from ages 0 to 2 years, followed by slower growth for a few years, and internal substructure growth into the teens (see Figure 13.2).

We also discussed tasks used to assess episodic memory in children such as DNMS, VPC, delayed imitation, and studies of eye movement sampling, and found that there are few instances in which performance on these tasks can be conclusively defined as episodic memory. We believe that one reason for this, which we term the *Swiss Army knife* reason, is that humans are wily problem-solvers who bring an array of cognitive tools to any given task. If one cognitive tool is immature and does not work, the task will be solved—perhaps sub-optimally—using a different cognitive tool. Thus, seemingly episodic memory tasks may be solved using non-episodic, non-hippocampal-based memory systems. There is a precedent for the Swiss army knife view: adults differ in the dominant strategy they use for spatial navigation, a quintessential hippocampal-based memory task. Some individuals use a route-based strategy that involves remembering a series of turns, whereas other individuals use a strategy based on encoding global position and visual landmarks (Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). The former system relies primarily on the habit learning system found in the basal ganglia, while the later strategy relies on the hippocampus.

This raises the question of whether memory in the first 2 years of life is primarily semantic and/or procedural. Newcombe and colleagues (Newcombe et al., 2007) previously argued that it may be more important for infants and toddlers to build semantic knowledge about a new world than remember episodic aspects of events and that an absence of episodic memory may even help retention of semantic knowledge. Given the immaturity of the hippocampus, it is plausible that children would use a non-hippocampal-based strategy for performing relational memory tasks until the age of 2 years, after which time they begin to transition to the more efficient and flexible hippocampal-based strategy. Unfortunately, we do not have data about the maturation of the human habit learning system in the basal ganglia. However, behavioral indices can be used to estimate the relative utilization of the habit learning system versus the hippocampus: (1) the habit learning system requires repeated exposures for acquisition, while the hippocampus has a rapid acquisition algorithm; and (2) the habit learning system creates relatively inflexible memory representations while the hippocampus creates flexible representations that can be retrieved from partial cues (Norman & O'Reilly, 2003).

Last, it is known that, in adults, hippocampal size can be modulated by certain types of experience, such as intensive navigation training (Maguire et al., 2000). It seems plausible that early life experiences, such as the age of language acquisition, would modulate the size and/or maturity of the hippocampus, and hence relational memory. Future research may wish to examine individual differences in the acquisition of cognitive milestones and their relationship to the development of relational memory.

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