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Medial temporal lobe memory in childhood: Developmental transitions

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Abstract

The medial temporal lobes (MTL) support declarative memory and mature structurally and functionally during the postnatal years in humans. Although recent work has addressed the development of declarative memory in early childhood, less is known about continued development beyond this period of time. The purpose of this investigation was to explore MTL-dependent memory across middle childhood. Children (6 – 10 years old) and adults completed two computerized tasks, place learning (PL) and transitive inference (TI), that each examined relational memory, as well as the flexible use of relational learning. Findings suggest that the development of relational memory precedes the development of the ability to use relational knowledge flexibly in novel situations. Implications for the development of underlying brain areas and ideas for future neuroimaging investigations are discussed.

Keywords

Hippocampus; medial temporal lobe; declarative memory development; transitive inference; place learning

The hippocampus has long been associated with memory (Eichenbaum, 2000; Moscovitch, et al., 2005; Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991). Classical work in brain lesioned adults suggests that the hippocampus and associated medial temporal lobe (MTL) cortices are necessary for declarative memory, specifically (see for review Milner, 2005). Damage to the MTL can result in permanent and severe impairments in long-term memory formation in both humans and animals (Squire, et al., 2004; Zola-Morgan, Squire, & Amaral, 1986). However, the role of the hippocampus appears to extend beyond the formation of memory for individual items or events. Research with rodents and non-human primates suggests that the hippocampus may be particularly involved in learning cognitive maps and spatial relationships among objects and context (O'Keefe, 1976; O'Keefe & Nadel, 1978; O'Keefe & Speakman, 1987). For example, animals with hippocampal or MTL lesions show profound impairments in place learning (Broadbent, Squire, & Clark, 2006; Lavenex, Amaral, & Lavenex, 2006). Likewise, the hippocampus is actively engaged in human neuroimaging studies of spatial navigation in virtual environments (see for review Burgess, Maguire, & O'Keefe, 2002). A broader view of hippocampal function proposes that this

region is more generally involved in learning the associations or relations among objects and environments, including, but not limited to spatial relations (Davachi & Wagner, 2002; Duzel, et al., 2003; Eichenbaum, 2000; Mishkin, Vargha-Khadem, & Gadian, 1998; O'Reilly & Rudy, 2001; Prince, Daselaar, & Cabeza, 2005), but see also (Manns & Squire, 1999; Squire, et al., 2004; Stark, Bayley, & Squire, 2002). Such associative or relational memory supports recollection of past experiences, but also allows one to draw inferences from relational knowledge and to use this knowledge flexibly in novel situations.

MTL and relational memory

In humans, neuroimaging studies show greater hippocampal activity during the binding of previously unassociated items and during the retrieval of learned associations compared to encoding or retrieval of single items (Giovanello, Schnyer, & Verfaellie, 2004; Kohler, Danckert, Gati, & Menon, 2005; Sperling, et al., 2001). For example, Giovanello et al. (2004) reported greater anterior hippocampal activation during the retrieval of previously learned word associations relative to the retrieval of individual word items. Similarly, adult amnesics with MTL damage show impairments in recognition memory for relational information (e.g., the spatial relations among items in a scene) (Hannula, Ryan, Tranel, & Cohen, 2007; Hannula, Tranel, & Cohen, 2006) as well as basic object-location associations (Kessels, de Haan, Kappelle, & Postma, 2001). Thus, both neuroimaging studies of healthy adults and behavioral studies of amnesic adults are consistent with a role for the hippocampus in the encoding and retrieval of relational memory.

Initial evidence for MTL involvement in flexible inference based on learned associations came from studies of transitive inference in rats. Dusek and Eichenbaum (1997) showed that although rats with hippocampal disconnection could learn a series of overlapping odor discriminations at the same rate as controls, they were unable to use their knowledge flexibly to make inferences about novel odor pairings. Similarly, neuroimaging studies in human adults have demonstrated greater hippocampal activity during tasks that require participants to make an inference from past knowledge, compared to during the recognition of previously learned associations (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Preston, Shrager, Dudukovic, & Gabrieli, 2004). Preston et al. (2004), for example, showed that recognition of the learned associations between faces and houses produced MTL activation. However, anterior hippocampal activity was greatest when participants made inferences about stimuli that had been indirectly related, as opposed to directly learned. Although comprising a small body of literature to date, these findings suggest that the hippocampus proper may be particularly involved in the inferential use of prior associative learning. Together, these studies suggest that tasks that require both relational memory and flexible use of previously learned associations will be the most likely to engage hippocampal and MTL brain regions. Two tasks that meet this requirement and have been used in both human and animal populations are spatial relational place learning (PL) and transitive inference (TI).

Spatial relational place learning (PL)

PL refers to the ability to encode and remember a spatial location in relation to the distance and direction of surrounding cues and landmarks. In contrast to cue learning, in which a location is associated with a salient local cue, PL requires using the relations among an array of environmental cues (Dupret, et al., 2008; Lavenex, et al., 2006; Overman, Pate, Moore, & Peuster, 1996). Place learning, like cue learning, involves allocentric, or viewpoint independent, coding. Recent studies suggest that the human hippocampal formation is particularly involved during allocentric, but not egocentric (viewpoint-dependent),

representations of space (e.g. see Burgess, 2002; Holdstock, et al., 2000; Parslow, et al., 2004).

The traditional animal PL task is the Morris water maze (Morris, 1981), which requires rodents to locate and re-locate a hidden platform in a circular arena of cloudy water. Rats must use the distal cues in the room to generate an allocentric (viewpoint-independent) representation of the pool. This task has been adapted for use with humans in both real-world (e.g. Bohbot, et al., 1998; Overman, et al., 1996) and computerized paradigms (Astur & Constable, 2002; Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Jacobs, Laurance, & Thomas, 1997; Jacobs, Thomas, Laurance, & Nadel, 1998), allowing study of the neural basis of PL across species.

Animal studies employing single cell recordings (Muller, Kubie, & Ranck, 1987; O'Keefe, 1976; O'Keefe & Speakman, 1987; Ono, Nakamura, Nishijo, & Eifuku, 1993), rodent lesions (Jarrard, 1993; Morris, Garrud, Rawlins, & O'Keefe, 1982) and primate lesions (Lavenex, et al., 2006), as well as human studies of brain-injured and normal adults (Bohbot, Iaria, & Petrides, 2004; Holdstock, et al., 2000; Maguire, et al., 1998; Maguire, Frackowiak, & Frith, 1996, 1997) collectively suggest a critical role for the hippocampus in PL. Adult imaging studies of virtual PL (Astur, et al., 2002) and other forms of spatial relational learning (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Kumaran & Maguire, 2005; Maguire, et al., 1998) show robust activation of MTL areas, including the hippocampus.

The development of rudimentary spatial abilities necessary for mature PL in humans begins before 16 months of age. Young infants demonstrate knowledge of an object's location in continuous space (Newcombe, Huttenlocher, & Learmonth, 1999) and can use local cues to find a marked location (Acredolo, 1978; Bremner, 1978a, 1978b), particularly if they have crawling and walking experience (Clearfield, 2004). Toddlers can retrieve objects using information about distance (Huttenlocher, Newcombe, & Sandberg, 1994) and geometric relations (Hermer & Spelke, 1994, 1996) and can use landmarks to reduce uncertainty about geometric relations (Learmonth, Nadel, & Newcombe, 2002; Learmonth, Newcombe, & Huttenlocher, 2001). Cue learning has been shown in 16 month-olds, who are able to use landmarks to allocentrically encode and remember object locations using local cues (Clearfield, 2004). However, the ability to use relations among more distant cues in PL appears to lag behind cue learning (Bushnell, McKenzie, Lawrence, & Connell, 1995; DeLoache & Brown, 1983), appearing after 20 months of age (Newcombe, Huttenlocher, Drummey, & Wiley, 1998). Delays in place learning development relative to cue learning are also seen in rodents. Rats under 21 days of age are unable to use distal landmarks to find the hidden platform in the Morris water maze (Rudy, Stadler-Morris, & Albert, 1987), and performance is similar to that of hippocampally-lesioned adult animals. Indeed, improvement in PL in rats appears related to the timing of hippocampal maturation (Kretschmann, Kammradt, Krauthausen, Sauer, & Wingert, 1986).

Despite evidence of early PL abilities in toddlers, several investigators have claimed that mature human PL using relations among landmark cues is not seen until 5 to 10 years (Laurance, Learmonth, Nadel, & Jacobs, 2003; Lehnung, et al., 1998). For example, Overman and colleagues (1996) examined the development of PL using a "pool" filled with plastic packing chips, surrounded by a curtain with distinctive visual cues. They encouraged allocentric coding by having children re-locate hidden targets from different starting locations across trials. Children's ability to find a visible target was the same for all ages, but the distance traversed to re-locate the hidden target decreased systematically with age through age 7. Removal of extra-maze cues did not impair performance, however, some children reported use of a cue beyond the curtain and all children entered the maze at the same point across trials, leaving open the possibility that cue and response learning

strategies were used instead of place learning. Laurance, Learmonth, Nadel, & Jacobs (2003) characterized the development of PL between ages 5 and 10 using a virtual environment modeled after the Morris water maze. Older children were more likely to report the use of multiple distal cues as a PL strategy. However, the possibility that younger children used these cues, but had difficulty describing verbally their use, seems a plausible alternative explanation that calls for more systematic evaluation. In sum, despite evidence suggesting rudimentary PL before age three, mature PL abilities that involve use of relational strategies continue to emerge across middle childhood.

Transitive inference (TI)

A second associative or relational learning paradigm is the classic transitive inference task. TI involves inferring associations between indirectly related stimuli based on previous learning of a sequence of overlapping stimulus pairs ($A > B > C > D > E$). During training, participants view individual premise pairs (AB, BC, CD, DE) and learn by trial and error which stimulus in each pair is reinforced. For example, when presented with stimuli A and B, participants learn that stimulus A is correct; when presented with stimuli B and C, participants learn that stimulus B is correct. During the test, participants view learned premise pairs, along with novel inference pairs. For example, when presented with stimuli B and D, participants can use knowledge of $B > C$ and $C > D$ to infer that B is the correct answer. The BD pair is the critical test of TI. All other novel pairs include a stimulus from the edge of the sequence (i.e. AC, AD, AE, BE, CE) and can be solved by the simple rule, 'A is always correct and E is always incorrect'. In contrast, the correct response for the BD pair must be inferred from knowledge of the hierarchical structure learned during training.

As described above, disconnection of the hippocampus from either cortical or subcortical pathways in rats, and entorhinal cortex lesions in monkeys result in impaired BD inference performance (Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004; Dusek & Eichenbaum, 1997). In addition, human functional neuroimaging studies report that hippocampal activation is greatest during BD inference judgments, relative to memory for learned pairs (Greene, Gross, Elsinger, & Rao, 2006; Heckers, et al., 2004; Preston, et al., 2004; Rapp, 2004). Although evidence suggests hippocampal system involvement in TI, the actual cognitive processes involved remain controversial.

Disagreement exists regarding whether high-order inference processes are required to solve the TI problem (Moses, Villate, & Ryan, 2006), or whether participants simply respond on the basis of the relative associative strength of individual stimuli in the sequence (Frank, Rudy, Levy, & O'Reilly, 2005; Libben & Titone, 2008; Smith & Squire, 2005). Similarly, some investigators have suggested that participants can perform TI only if consciously aware of the hierarchical sequence (Libben & Titone, 2008; Moses, et al., 2006; Smith & Squire, 2005), whereas others have argued that awareness is not necessary for BD performance (Greene, 2007; Greene, et al., 2006; Greene, Spellman, Dusek, Eichenbaum, & Levy, 2001). In addition, several studies suggest that these factors may interact; the presence or absence of awareness may determine whether participants solve the task using high-order inference or via relative associative strength (Frank, et al., 2005; Libben & Titone, 2008; Smith & Squire, 2005). Still others have questioned the relative contribution of the hippocampus and frontal cortex in TI, highlighting the role of working memory in task performance (Acuna, Eliassen, Donoghue, & Sanes, 2002; Libben & Titone, 2008; Waltz, et al., 1999).

Despite these controversies, Greene et al. (2006) suggest that the TI task is a prototypical relational memory task because it involves learning a series of overlapping conditional discriminations that require participants to learn about the contextual relations among

stimuli. For example, participants must learn when stimulus C is paired with stimulus B, C is the incorrect response, but when stimulus C is paired with stimulus D, it is the correct response. In addition, learning of the initial premise pairs must be flexibly reorganized into a hierarchical sequence ($A > B > C > D > E$) in order to perform the critical BD inference pair.

Piaget (1928) was the first to identify the acquisition of TI as an important developmental milestone, suggesting that successful inference signals the transition from preoperational to operational thought around age 7. Since this time, research exploring the development of TI has found that the age of acquisition varies markedly across TI paradigms (for review, see Wright, 2001). Four- to 5- year old children can learn overlapping stimulus relations as is required in the transverse patterning paradigm (e.g. $A > B$; $B > C$; $C > A$; see Rudy, Keith, & Georgen, 1993). Some studies have shown that children of this age can also perform well on the critical pair (i.e. $B > D$) in the TI task, provided that they receive sufficient training on the premise pairs and can remember them at the time of test (Bryant & Trabasso, 1971). In contrast, other studies have shown that the strategies children use to solve the TI problem are not adult-like until the age of 12 (Perner & Mansbridge, 1983). Until now, studies of TI development have given little consideration to the neural basis of relational learning and the flexible use of relational knowledge.

Development of the MTL

Neuroanatomical studies of human brain development have shown that the hippocampus and surrounding cortices are formed relatively early in gestation (Seress & Abraham, 2008), allowing for rudimentary declarative memory functions such as recognition and recall to emerge during the first year of life (Nelson, 1995; Richmond & Nelson, 2007). Refinement of MTL structures is thought to continue until at least age five (Seress & Abraham, 2008) and perhaps beyond, consistent with research showing age-related changes in recognition and recall (Nelson, Thomas, & de Haan, 2008). Despite advances in pediatric neuroimaging, relatively few studies have directly addressed the functional development of the MTL in children. Some recent work suggests continued change in memory-related functions of the hippocampus and MTL across middle and late childhood (Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; Menon, Boyett-Anderson, & Reiss, 2005; Paz-Alonso, Ghetti, Donohue, Goodman, & Bunge, 2008), with either increased or decreased MTL activity with age. However, others suggest that MTL activity is equivalent for children and adults (ages 8–24) while activity in prefrontal cortex changes with age and behavioral memory performance (e.g. Ofen, et al., 2007).

In the current paper, we explore the development of MTL-dependent relational memory and the flexible use of relational knowledge during middle childhood (6–10 years of age). Specifically, we examine learning on two MTL dependent tasks, one spatial (PL) and one non-spatial (TI)¹, to determine whether common underlying patterns of behavior emerge across the tasks, suggesting the development of a general ability in relational memory. In addition, we compare relational and flexible memory within each task to examine the developmental time course of these two aspects of MTL-dependent learning and memory in spatial and non-spatial contexts.

¹The stimuli (patterned ovals) and methods (counter-balanced spatial presentation) employed in the transitive inference (TI) task are not inherently spatial. However, we cannot rule out the possibility that participants may use a spatial strategy to learn the pairs or sequence. It is possible that individuals may generate a cognitive “number line” by imagining the items in a linear spatial relation to one another. However, we consider the degree of spatial representation in this task is greatly reduced relative to the overt spatial navigation that participants experience in the PL task.

Methods

Participants

The participants for this cross-sectional study included 90 healthy children; 30 six year-olds ($M = 6.75$ years; 15 female), 30 eight year-olds ($M = 8.75$ years; 15 female), and 30 ten year-olds ($M = 10.70$ years 15 female). The children were recruited from an existing list of children whose parents had expressed interest in participating in child development research following their child's birth. All children completed both memory tasks. An adult comparison group was included for each task: 30 adults ($M = 41.92$ years; 17 female) for the spatial memory task and 34 adults ($M = 29.5$ years; 15 female) for the TI task. Adult participants were either parents of the recruited children or were recruited from the University community. This study was approved by the Human Subject's Committee of the Institutional Review Board at the University of Minnesota.

Participants were screened for birth and health history. Those born prematurely (<36 weeks gestation), born to mothers following high risk pregnancies, and born with medical histories that suggested marked neurological or psychiatric risk (e.g. non-febrile seizures, closed head injury, developmental delay, depression or anxiety, attention deficit hyperactivity disorder) were excluded from the study. Two additional children were excluded due to inattention and inability to complete tasks or computer malfunction. The majority of children were Caucasian and from middle or upper middle class homes.

Apparatus and Materials

A computerized place learning (PL) task was programmed using CG Arena software (W. Jake Jacobs, University of Arizona). Participants were seated in front of a 17" flat monitor and used a joystick (Logitech®, Attack™ 3) to navigate through the virtual environment. The virtual space was a multicolored view of a circular arena within a square room. The view was from the perspective of one standing on the floor of the room; the visual display did not include a representation of the subject. The square room measured $110 \times 110 \times 30$ units. The four walls of the room were blue, green, red, and yellow respectively (practice trials), or textured grey (experimental trials). The circular arena within the room consisted of either a purple (practice trials) or dark gray (experimental trials) textured wall (50 units radius $\times$ 3.5 units high). The subject's eye level was 2 units high. The ceiling was light gray and the floor was either dark gray (practice trials) or brown textured (experimental trials).

The transitive inference task was programmed using E-Prime software (Psychology Software Tools, Inc., 2002). The stimuli, which were five (A–E) colorful patterned ovals (Figure 1), were presented in pairs on a black background using a 16" monitor. Participants responded using a standard mouse.

Procedure

Place Learning (PL) Task—This task indexed participants' ability to re-locate a hidden target using multiple visual cues and their ability to use place memory flexibly by re-locating a hidden target when visual cues on all walls except the most distant from the target were no longer available. At the outset of training, participants practiced navigating through the virtual environment with the joystick in the practice room. Participants also returned to the practice room briefly between trials.

For experimental trials, each wall contained one to three salient icons as visual cues. Instructions were provided at the start of each trial (e.g. visible target, hidden target) and participants searched for a 10×10 unit target on the floor of the room. For hidden target trials, when the subject moved over top of the hidden target it became visible, a clicking

tone sounded and position was automatically frozen for up to 30 seconds. Maximum trial duration was 120 seconds. If a subject failed to locate the hidden target, the experimenter guided the subject to the target and repeated instructions to, “Take a good look around the room and remember where the hidden target is”, and a latency of 120 seconds was recorded.

Each participant completed ten trials (see Table 1). The first two were practice trials that required participants to navigate to a visible target with a local floor cue present. These visible target trials allowed participants to learn how to use the joystick, demonstrated whether participants understood the directions, and revealed whether or not participants recognized the computer display as a spatial environment. The remaining trials included an initial search trial to find a hidden target (trial 3), three hidden target memory trials from novel start locations with visual cues (trials 4–6), a hidden target memory trial with visual cues removed (trial 8) and a final visible target trial (trial 10). Trials 7 and 9 were memory trials, one with a repeated start location and one with no target, which were not included as part of this analysis.

The first experimental trial (3) was the “search” trial in which participants attempted to locate a hidden target. After finding the hidden target and before continuing to the memory trials, participants were instructed to notice and remember the hidden target location by ‘taking a good look around’ the virtual room. For memory trials, participants were instructed to re-locate the hidden target as quickly as possible. Each visually cued memory trial (trials 4–6) began with the subject facing the arena wall and required backing away from the wall to see the visual cues and begin a search. Start locations for cued memory trials were varied in a standardized manner to preclude the children's ability to rely on an egocentric strategy to re-locate the target. For the cue removal memory trial (8), participants began in the center of the room and cues were removed from all walls except for that most distant from the target, so that participants had to rely on an allocentric (spatial relational) representation of the environment to re-locate the target. In the final trial (10), the hidden target became visible. Performance on this last trial was used as a covariate to factor out general differences in latency and path length as a function of anticipated age-related differences in motor dexterity using the joystick.

Given studies of adults with hippocampal damage suggesting that deficits in PL are evident primarily when a delay of several minutes is imposed between learning and test (Burgess, et al., 2002; Holdstock, et al., 2000), half of the participants in each age group were randomly selected to experience a delay of two minutes between the search trial and the first memory trial, as well as between each subsequent memory trial. During the delay, participants named and counted colored stripes that appeared on square practice room walls to discourage verbal and mental rehearsal of target location. Total testing time for the PL task was 25 minutes.

Transitive Inference (TI) Task—The transitive inference (TI) task employed in the current study was based on that of Heckers et al. (2004) and included a training phase (3 runs) and a test phase. Participants held a standard mouse with two hands and were instructed to use the left thumb to press the left mouse button and their right thumb the press the right mouse button.

During the training phase, participants learned an ordered sequence of five oval stimuli (A>B>C>D>E) through sequential presentation of individual premise pairs (AB, BC, CD, and DE; Figure 2). One oval in each pair was reinforced as the correct response by the appearance of a smiling face (500ms) when the correct response was chosen. The relations among patterns was A>B>C>D>E, such that A was always correct when paired with B, B was correct when paired with C, etc. A given oval pair remained on the screen until a correct response was given. To avoid biases associated with particular visual features, the sequential

positions (A–E) of the individual oval stimuli were randomized across participants. Left/right position was also counterbalanced across trials. The inter-stimulus interval consisted of a black screen and was 200–800ms in duration.

Initially, participants were instructed to guess which oval in the premise pair was correct and then remember the correct oval in that pair. Following the procedure of Heckers et al. (2004) and to maximize learning of the correct responses, the first training run was “front loaded” such that participants saw 20 instances of pairs AB and BC, but only 10 of CD and DE. The second training run was “back loaded” such that participants saw 10 instances of AB and BC, but 20 of CD and DE. The third training run contained 6 instances of each pair and was used as an index of premise pair learning.

During the test phase, premise pairs (AB, BC, CD, DE) and five novel pairs (AC, AD, AE, BD, BE, CE) were each presented 6 times in one run of 60 trials. Participants were asked to identify the correct oval for familiar pairs and use what was learned from training to choose the oval likely to be correct for novel pairings. Premise pair trials required participants to remember the correct oval in a pair from training, whereas novel pair trials required the use of knowledge of the sequential hierarchy to infer the correct oval. The order of pair presentation was randomized across participants and the left/right position of ovals within a pair was counterbalanced across trials. No visual reinforcement was provided during the test phase. Task length for the TI task was approximately 20 minutes.

Data Analysis—For the PL task, latency and path length to the target were primary outcome variables. Relational learning was indexed by mean latency and path length to re-locate the hidden target with an array of visual cues available (trials 4–6). Flexible use of the relations among available cues and the hidden target location was indexed by latency and path length to the hidden target on the cue removal trial (trial 8). Primary outcome variables for TI were mean accuracy across premise pairs (AB, BC, CD, DE) and accuracy for the novel inference pair (BD). Premise pair accuracy was considered an index of relational learning, whereas BD accuracy was considered a measure of flexible use of relational memory. Age groups were compared using univariate and repeated measures ANOVAs, after excluding participants performing more than two standard deviations from the respective age group means. Post hoc pairwise comparisons were performed to compare differences between age groups. Bivariate correlations and linear regression analyses were performed to examine relations between path length and latency, and the degree to which memory for inner premise pairs BC and CD predicted performance on the critical BD pair, respectively.

Results

Place Learning (PL)

Navigating to a visible target—All age groups navigated to visible targets without difficulty. Latencies to visible targets (trials 1, 2, 10) were examined in repeated measures ANOVA with age group as a between subjects factor. A significant main effect of age group was observed, $F(3, 116) = 5.91, p < .001$. Post hoc tests showed that 6-year olds took longer to navigate to visible targets than 10-year olds ($p < .01$) and adults (trend, $p = .06$), whereas eight year olds took longer than 10-year olds ($p < .05$). A separate analysis of corresponding path length indicated a similar pattern $F(3, 116) = 4.14, p < .01$. Six year olds took significantly longer paths to visible targets than 10-year olds ($p < .05$) and adults ($p < .05$), with eight year olds falling in between. Given underlying age group differences in navigation to a visible target, latency and path length to the hidden target (trial 10) were used as covariates in memory trial analyses.

Effects of delay on memory—To examine effects of delay, a series of univariate ANOVAs was performed with delay version (no delay versus 60 seconds delay) and age group as between subjects' factors. Dependent variables were latency and path length to hidden target for memory trials. Neither main effects of delay nor interactions with age were evident. Therefore, for the remaining analyses, delay versions were collapsed within age groups.

Navigating to a hidden target using multiple visual cues (relational memory)—

Once participants located the hidden target via initial search (trial 3), they were asked to re-locate the target from novel start locations across three successive memory trials (4–6), using multiple, consistently available visual cues on the outer walls of the arena. All participants successfully re-located the hidden target within 120 seconds in at least two of the three memory trials. Five participants (one in the 6-year-old and two each from the 10-year-old and adult groups) were excluded from analyses based on mean latencies and path lengths across trials 4–6 that were more than two standard deviations above age group means. Latency and path length means and standard deviations are presented in Table 2 and Table 3. Figure 3 shows a developmental improvement in the latency to find the hidden target. A univariate ANOVA with age as the between subjects factor, mean latency for memory trials 4–6 as the dependent variable, and latency to target in the corresponding visible target trial as a covariate showed a main effect of age group, $F(3, 110) = 11.38, p < .001$. Post hoc tests showed that 6-year olds took longer to navigate to the hidden target using multiple visual cues compared to 8-year olds ($p < .05$), 10-year olds ($p < .001$) and adults ($p < .001$). Eight-year olds had longer latencies than 10-year olds ($p < .001$) and adults ($p < .001$), who exhibited similar latencies. No other pairwise comparisons reached statistical significance.

A similar age effect was found for path length to hidden target for trials 4–6, $F(3, 110) = 13.93, p < .001$. Six-year olds showed longer path lengths than 8-year olds ($p < .01$), 10-year olds ($p < .001$) and adults ($p < .001$). Eight-year olds had longer paths than 10-year olds ($p < .001$) and adults ($p < .01$), who exhibited similar latencies. Bivariate correlations showed significant linear relations between latency and path length across 6 [$r(29) = .90, p < .001$], 8 [$r(30) = .93, p < .001$], 10 [$r(28) = .88, p < .001$] and adult [$r(28) = .92, p < .001$] groups.

Navigating to a hidden target with cues removed (flexible memory)—To

examine flexible use of spatial relational memory, latency and path length to the hidden target were examined for trial 8 when cues were removed (Table 2 and Table 3). Six additional participants (three 10-year olds and three adults), all of whom failed to locate the hidden target, were excluded given trial 8 latencies and path lengths more than two standard deviations above the respective age group mean. Eighty percent (80%) of 6- and 8- year olds, and 100% of 10- year olds and adults, successfully located the hidden target with cues removed.

To examine age related effects for latency to the hidden target, a univariate ANOVA was performed with age group as the between subjects factor, latency to target in the cue-removal trial (8) as the dependent variable, and latency in the visible target trial (10) as a covariate. A main effect of age group was evident, $F(3, 104) = 5.19, p < .005$. Post-hoc pairwise comparisons showed that although 6- and 8-year-old groups showed similar latencies to the hidden target with visual cues removed, both groups were significantly slower than the 10-year-old group ($p < .01, p < .005$), which performed similarly to adults. Age-related effects of path length mirrored those of latency, $F(3, 104) = 5.97, p < .005$. Bivariate correlations showed significant linear relations between latency and path length across 6 [$r(29) = .97, p < .001$], 8 [$r(30) = .97, p < .001$], 10 [$r(25) = .96, p < .001$] and adult

[$r(25) = .94, p < .001$] groups. Repeated measures ANOVAs with memory condition (visual cues, cues removed) as the repeated factor and group as the between subjects factor did not suggest an age group by condition interaction for either latency, $F(3, 104) = .75, p = .53$, or path length, $F(3, 104) = 1.8, p = .15$.

Transitive Inference (TI)

Memory for premise pairs (AB, BC, CD, DE)—Nine participants (one from the 6-year-old group; two from the 8-year-old group; and three each from the 10-year old and adult groups) were excluded from analyses based on premise pair accuracy more than two standard deviations from respective age means. Mean premise pair accuracy after initial training was 77% for 6-year olds, 91% for 8-year olds, 95% for 10-year olds and 95% for adults. Means and standard deviations are presented in Table 4. A univariate ANOVA with age as a between subjects factor and premise pair accuracy (training run 3) as the dependent variable indicated a significant main effect of age group, $F(3, 111) = 17.77, p < .001$. Post-hoc tests showed that the 6-year-old group was significantly less accurate than the 8-year-old, 10-year-old and adult groups (p 's $< .05$), which were not statistically distinguishable from one another. The main effect of age in training run 3 held when premise pair performance in training run 3 and the test run were considered together in a repeated measures ANOVA, $F(3, 111) = 15.04, p < .05$. No age group by condition interaction was present, $F(3, 111) = 1.30, p = .28$, although a significant drop in performance occurred from training run 3 to the test run across groups once visual reinforcement was removed ($p < .001$).

To examine premise pair effects, a repeated measures ANOVA with age group as a between subjects factor and accuracy on AB, BC, CD, and DE pairs during training run 3 as four levels of the dependent variable was performed. A main effect of premise pair was evident, $F(3, 109) = 18.09, p < .001$. Post-hoc pairwise comparisons showed that accuracy for edge pairs (AB, DE) was significantly higher than for other pairs (BC, CD; p 's $< .01$), which were no different from one another.

Evidence of Transitive Inference (BD pair)—Given performance more than two standard deviations below the respective age group BD accuracy means, two additional participants (both adults with 0% BD accuracy), were excluded from this series of analyses. In the test run, mean accuracy for the critical BD pair was 60% for 6-year olds, 58% for 8-year olds, 75% for 10-year olds and 80% for adults (Table 4). To examine the development of TI, a univariate ANOVA was conducted with age group as a between subjects factor and BD pair accuracy as the dependent variable. A main effect of age group was observed, $F(3, 109) = 3.66, p < .05$. The 6- and 8-year-old groups were not statistically different from each other in accuracy ($p = .86$), and both were less accurate than the adult group (p 's $< .05$; Figure 4). Ten year-olds' performance on the critical BD pair was indistinguishable from that of adults ($p = .53$). Variability in BD pair performance was high across all age groups. One sample t-tests for individual age groups showed that mean accuracy for BD pair was significantly greater than chance for 10-year-old ($t(26) = 5.23, p < .001$) and adult ($t(28) = 5.82, p < .001$) groups, but not for 6- and 8-year-old groups.

Bivariate linear regression analyses revealed developmental differences in the extent to which inner premise pair accuracy (BC, CD) in the test run predicted BD inference accuracy (Table 5). Inner premise pair accuracy accounted for 39% and 36% of the variance in BD performance in 6- and 8-year olds (p 's $< .001$), but less than 10% of the variance in BD performance in 10-year olds and adults. A repeated measures ANOVA with memory condition (BC, CD versus BD) as the repeated factor and group as the between subjects factor showed no age group by memory condition interaction, $F(3, 111) = .73, p = .54$.

Discussion

Recent conceptualizations of declarative memory have pointed to the role of MTL, specifically the hippocampus, in relational learning and the flexible use of relational memory (Eichenbaum, 2000; Eichenbaum, 2001, 2004; Eichenbaum & Cohen, 2001; Manns & Eichenbaum, 2006; Manns, Howard, & Eichenbaum, 2007). Here we tested 6-, 8-, 10-year olds and adults on place learning (PL) and transitive inference (TI) tasks to characterize the developmental time course of relational memory. Although the two tasks involve different forms of memory (i.e. spatial and object relations), common developmental patterns were evident.

In PL, children were consistently able to re-locate a hidden target from varying start locations when an array of visual cues was available, showing evidence of the ability to learn and remember relations between visual cues and an object location using allocentric coding. Consistent with previous findings (Learmonth et al., 2003), steady improvement in speed and path length to re-locate a hidden target with multiple available cues was evident between 6 and 10 years of age, with adult-like performance reached by age 10. Importantly, because local cues were available to guide target re-location in both studies, participants may have used a cue learning strategy, rather than a spatial relational PL strategy that requires use of relations among cues. Thus, to examine flexible use of relational memory, we removed visual cues most immediate to the hidden target, requiring participants to use memory for the relations among cues in the larger environment to infer the location of the hidden target. In the absence of local cues, 6- and 8- year olds had more difficulty, took longer paths and were slower in locating the hidden target, relative to 10- year olds and adults, suggesting less effective use of a spatial relational PL strategy in younger children. These findings are consistent with previous reports suggesting a delay in the use of spatial relational strategies, with a shift in PL strategy use between age 8 and 10 years of age (Lehnung, et al., 1998; Overman, et al., 1996).

Developmental patterns of relational learning and flexible use of relational memory in TI mirrored those seen in PL. Children as young as age 6 were capable of learning relations within individual object pairs. All children learned the initial premise pairs and performed well above chance during premise testing. These findings are consistent with previous reports showing that 6-year-old children can learn the relations between pictures of arbitrarily paired animals and scenes and remember stimulus combinations over short delays (Sluzenski, Newcombe, & Kovacs, 2006). Similarly, studies using transverse patterning (i.e. $A > B$, $B > C$, $C > A$) and conditional discrimination (context 1: $A > B$; context 2: $B > A$) tasks have shown that children older than 4 1/2 years are able to learn stimulus relations that overlap and are context dependent (Rudy, et al., 1993). Our results showed a gradual improvement in relational memory between 6 and 10 years with adult-like performance by age 10, which is similar to the extant literature describing development of recognition abilities across childhood (Nelson, et al., 2008). In contrast, performance on the critical BD pair, which requires participants to use memory of the hierarchical sequence ($A > B > C > D > E$) to infer to the correct answer, showed a developmental shift between 8 and 10 years of age. Although 10- year olds showed mature TI abilities, 6- and 8- year olds performed similarly to each other and at chance, suggesting an undeveloped ability to use relational memory flexibly to infer BD relations.

Consistent with reports by Bryant and Trabasso (1971), the current data show that in 6- and 8- year olds, memory for the inner premise pairs ($B > C$ and $C > D$) correlated positively with BD performance. In contrast, there was no such relation in 10- year olds and adults. This pattern points to qualitative differences in the cognitive processes that older and younger children use to perform the BD inference. Neuroimaging work in adults has shown that

behavioral performance and hippocampal activation during inner premise pair learning (B>C and C>D) predicts subsequent BD performance (Greene, et al., 2006). As such, the relation between premise learning and BD performance seen in 6- and 8- year olds may point to the role of the developing MTL in TI during this period. In 10- year olds and adults, this relation no longer holds, suggesting a shift in the cognitive processes that are used in task performance. Some work with adults has shown that explicit awareness of the stimulus hierarchy is necessary for performance on the BD inference trial (Libben & Titone, 2008; Martin & Alsop, 2004; Moses, et al., 2006; Smith & Squire, 2005). Although we did not directly measure participants' awareness in the current study, it is possible that older children and adults were more likely to become aware of the sequence during training than younger children. Thus, younger children may have relied more on memory for individual premise pairs than knowledge of a hierarchical sequence in performing the critical BD inference. Future research should address the extent to which age-related differences in explicit awareness may contribute to improvements in BD performance with development.

If relational learning is indeed subserved by the hippocampus, then we would expect parallels between the timing of structural maturation of these areas and relational memory development. Our data suggest that relational learning in PL and TI develops gradually between age 6 and 10, whereas the ability to flexibly use relational memory to make inferences in novel situations lags behind and is characterized by a marked developmental shift between ages 8 and 10. Given that human hippocampal maturation is thought to be largely complete soon after age 5 (Seress & Abraham, 2008), additional explanations for the delay in relational learning development, and particularly the shift in flexible use of relational memory between 8 and 10 years, are important to consider.

One alternative explanation for delayed relational memory development relates to the potential involvement of surrounding and interconnected MTL areas including the parahippocampal, perirhinal and entorhinal cortices in relational processing (see Kohler, et al., 2005; Manns & Eichenbaum, 2006) and the maturational patterns of these areas. For example, perirhinal cortex and areas TH/TF are also necessary for object-place associations in monkeys (Bachevalier & Nemanic, 2008). Similarly, in humans, perirhinal and anterior parahippocampal cortices are activated alongside the anterior hippocampus in an object relations task, and posterior parahippocampal cortex is activated with posterior hippocampus in a spatial relational processing task (Pihlajamäki, et al., 2004). Parahippocampal activation has also been shown for old compared to new spatial and object relations (Düzel, et al., 2003). Finally, medial entorhinal cortex may be involved in disambiguating overlapping relations in sequential experiences (Lipton & Eichenbaum, 2008).

Morphologically, the parahippocampal, entorhinal and perirhinal cortices and their connections show maturational changes across the first 2 years of life in primates (see review, Alvarado & Bachevalier, 2000). However, the exact timing of functional maturity remains unclear. Regardless, existing evidence supports the idea of a similar time frame for structural and functional development across medial temporal lobe areas. Currently, no evidence supports a human MTL maturation pattern that accounts for continued development of relational learning or a shift in flexible use of relational memory in middle childhood.

A second explanation for delayed relational memory development is that later developing circuitry outside the MTL is necessary for mature flexible use of relational memory, (Libben & Titone, 2008; Martin & Alsop, 2004; Moses, et al., 2006; Smith & Squire, 2005). Given that flexible relational memory involves inference-making and may recruit executive functions such as strategic search, the possible role of prefrontal cortex should be considered (see review, Simons & Spiers, 2003). Human neuroimaging findings support frontal

involvement in relational processing. For example, Weldenken and Bunge (2009) suggest that the hippocampus may be recruited in TI tasks when relations among stimuli must be retrieved from long term memory, however, it is the rostrolateral prefrontal cortex that is recruited during the process of relational integration. In this fMRI study, participants made inferences based on the integration of relations among two stimulus sources, however, the displays were shown throughout the trial and thus participants were not required to draw on long term memory. During this task, the rostrolateral prefrontal cortex (RLPFC) was preferentially activated during inference trials relative to trials that solved by directly considering a single stimulus source. These results are consistent with those of Heckers et al., (2004) also reported bilateral frontal activation, alongside hippocampal activation, during adults' TI performance. Although human imaging studies examining activation patterns with place learning are preliminary and sparse (Astur & Constable, 2002), several fMRI reports of spatial memory and navigation do suggest frontal involvement (see, Ghaem, et al., 1997; Maguire, et al., 1998).

Human frontal lobe maturation progresses in a back-to-front direction. Prefrontal regions including the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC), show delayed grey matter development that continues between ages 8 and 12 (Gogtay, et al., 2004). The idea of MTL-frontal networks supporting memory functions is not new. Neuroimaging findings across basic cognitive functions including memory retrieval have identified activation patterns in mid dorsolateral and ventrolateral PFC (Duncan & Owen, 2000). Similarly, functional imaging studies have shown DLPFC, VLPFC and anterior PFC involvement in updating/maintenance, selection/manipulation/monitoring of information, and selection of processes/subgoals, respectively, in memory processing (see, Fletcher & Henson, 2001). Most recently, Murray and Ranganath (2007) found DLPFC and VLPFC activation that was greater during relational compared to item-specific encoding for word pairs. DLPFC activity also predicted successful memory for word pair associations, whereas VLPFC activation predicted successful memory for both associations and items. Collectively, these findings further support the idea of frontal involvement in relational memory processes. Thus, although animal and human findings suggest that the MTL is intimately involved in and necessary for relational memory in PL and TI, MTL-frontal connectivity and mature functioning of related frontal lobe circuitry may be necessary for mature relational memory, particularly that which requires flexibility and inference.

The present study characterizes middle childhood development of place learning and transitive inference, in which the MTL is thought to play a putative role. However, our findings suggest the need for future developmental research that considers the role of both MTL and frontal circuitry in relational learning and flexible use of relational memory during childhood. Importantly, one limitation of the present study was the cross-sectional design. Cross-sectional designs are influenced by inter-individual variance and cohort effects. Therefore, future studies that use longitudinal designs to examine developmental patterns of relational memory across middle childhood are necessary.

Our understanding of and ability to measure MTL structure, function and connectivity in the developing child has been limited. However, continuing advances in pediatric structural, functional and diffusion tensor imaging will allow us to better address developmental questions about the neural basis of relational memory. Future studies examining brain activation patterns in school-aged children using tasks such as TI and PL are now achievable and warranted.

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References

- Acredolo L. Development of spatial orientation in infancy. *Developmental Psychology*. 1978; 14(3): 224–234.
- Acuna B, Eliassen J, Donoghue JP, Sanes J. Frontal and parietal lobe activation during transitive inference in humans. *Cerebral Cortex*. 2002; 12:1312–1321. [PubMed: 12427681]
- Alvarado M, Bachevalier J. Revisiting the maturation of medial temporal lobe memory functions in primates. *Learning and Memory*. 2000; 7:244–256. [PubMed: 11040255]
- Astur RS, Constable RT. Hippocampus Activation during Virtual Tasks: Comparing the Morris Water Task with the 8-Arm Maze during fMRI; Paper presented at the Cognitive Neuroscience Society; San Francisco. 2002.
- Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behavioral Brain Research*. 2002; 132(1):77–84.
- Bachevalier J, Nemanic S. Memory for spatial location and object-place associations are differently processed by the hippocampal formation, parahippocampal areas TH/TF and perirhinal cortex. *Hippocampus*. 2008; 18(1):64–80. [PubMed: 17924520]
- Bohbot VD, Iaria G, Petrides M. Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. *Neuropsychology*. 2004; 18(3):418–425. [PubMed: 15291720]
- Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. *Neuropsychologia*. 1998; 36(11):1217–1238. [PubMed: 9842767]
- Bremner JG. Egocentric versus allocentric spatial coding in nine-month-old infants: Factors influencing the choice of code. *Developmental Psychology*. 1978a; 14(4):346–355.
- Bremner JG. Spatial errors made by infants: Inadequate spatial cues or evidence of egocentrism? *British Journal of Psychology*. 1978b; 69(1):77–84. [PubMed: 626806]
- Broadbent N, Squire L, Clark R. Reversible hippocampal lesions disrupt water maze performance during both recent and remote memory tests. *Learning and Memory*. 2006; 13:187–191. [PubMed: 16585794]
- Bryant P, Trabasso T. Transitive inference and memory in young children. *Nature*. 1971; 232:456–458. [PubMed: 4937205]
- Buckmaster C, Eichenbaum H, Amaral D, Suzuki W, Rapp P. Entorhinal cortex lesions disrupt the relational organization of memory in monkeys. *Journal of Neuroscience*. 2004; 24:9811–9825. [PubMed: 15525766]
- Burgess N. The hippocampus, space, and viewpoints in episodic memory. *Quarterly Journal of Experimental Psychology*. 2002; 55(4):1057–1080. [PubMed: 12420984]
- Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron*. 2002; 35(4):625–641. [PubMed: 12194864]
- Bushnell E, McKenzie B, Lawrence D, Connell S. The spatial coding strategies of one-year-old infants in a locomotor search task. *Child development*. 1995; 66:937–958. [PubMed: 7671659]
- Chiu CYP, Schmithorst VJ, Brown R, Holland S, Dunn S. Making memories: A cross-sectional investigation of episodic memory encoding in childhood using fMRI. *Developmental Neuropsychology*. 2006; 29:321–340. [PubMed: 16515409]
- Clearfield MW. The role of crawling and walking experience in infant spatial memory. *Journal of Experimental Child Psychology*. 2004; 89(3):214–241. [PubMed: 15501452]

- Davachi L, Wagner AD. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *J Neurophysiol.* 2002; 88(2):982–990. [PubMed: 12163547]
- DeLoache J, Brown A. Very young children's memory for the location of objects in a large scale-environment. *Child development.* 1983; 54:888–897. [PubMed: 6617310]
- Duncan J, Owen A. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences.* 2000; 23(10):475–483. [PubMed: 11006464]
- Dupret D, Revest JM, Koehl M, Ichas F, De Giorgi F, Costet P, et al. Spatial relational memory requires hippocampal adult neurogenesis. *PLoS ONE.* 2008; 3(4):e1959. [PubMed: 18509506]
- Dusek J, Eichenbaum H. The hippocampus and memory for orderly stimulus relations. *Proceedings of the National Academy of Science.* 1997; 94:7109–7114.
- Duzel E, Habib R, Rotte M, Guderian S, Tulving E, Heinze HJ. Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. *Journal of Neuroscience.* 2003; 23(28):9439–9444. [PubMed: 14561873]
- Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience.* 2000; 1(1):41–50.
- Eichenbaum H. The hippocampus and declarative memory: Cognitive mechanisms and neural codes. *Behavioral Brain Research.* 2001; 127(1–2):199–207.
- Eichenbaum H. Hippocampus: Cognitive processes and neural representations that underlie declarative memory. *Neuron.* 2004; 44:109–120. [PubMed: 15450164]
- Eichenbaum, H.; Cohen, N. From conditioning to conscious recollection: Memory systems of the brain. New York: Oxford University Press; 2001.
- Fletcher PC, Henson RN. Frontal lobes and human memory: Insights from neuroimaging. *Brain.* 2001; 124(5):849–881. [PubMed: 11335690]
- Frank M, Rudy J, Levy W, O'Reilly R. When logic fails: Implicit transitive inference in humans. *Memory & Cognition.* 2005; 33:742–750.
- Ghaem O, Mellet E, Crivello F, Tzourio N, Mazoyer B, Berthoz A, et al. Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *Neuroreport.* 1997; 8(3):739–744. [PubMed: 9106758]
- Giovanello K, Schnyer D, Verfaellie M. A critical role for the anterior hippocampus in relational memory: Evidence from an fMRI study comparing associative and item recognition. *Hippocampus.* 2004; 14:5–8. [PubMed: 15058477]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Science.* 2004; 101(21):8174–8179.
- Greene A. Human hippocampal-dependent tasks: Is awareness necessary or sufficient? *Hippocampus.* 2007; 17:429–433. [PubMed: 17455198]
- Greene A, Gross W, Elsinger C, Rao S. An fMRI analysis of the human hippocampus: Inference, context, and task awareness. *Journal of Cognitive Neuroscience.* 2006; 18:1156–1173. [PubMed: 16839289]
- Greene A, Spellman B, Dusek J, Eichenbaum H, Levy W. Relational learning with and without awareness: Transitive inference using nonverbal stimuli in humans. *Memory and Cognition.* 2001; 29:893–902.
- Hannula D, Ryan J, Tranel D, Cohen N. Rapid onset relational memory effects are evident in eye movement behavior, but not in hippocampal amnesia. *Journal of Cognitive Neuroscience.* 2007; 19:1690–1705. [PubMed: 17854282]
- Hannula D, Tranel D, Cohen N. The long and the short of it: Relational memory impairments in amnesia, even at short lags. *Journal of Neuroscience.* 2006; 26:8352–8359. [PubMed: 16899730]
- Heckers S, Zalesak M, Weiss A, Ditman T, Titone D. Hippocampal activation during transitive inference in humans. *Hippocampus.* 2004; 14:153–162. [PubMed: 15098721]
- Hermer L, Spelke E. A geometric process of spatial reorientation in young children. *Nature.* 1994; 370:57–59. [PubMed: 8015605]
- Hermer L, Spelke E. Modularity and development: the case of spatial reorientation. *Cognition.* 1996; 61(3):195–232. [PubMed: 8990972]

- Holdstock J, Mayes A, Cezayirli E, Isaac C, Aggleton J, Roberts N. A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. *Neuropsychologia*. 2000; 38:410–425. [PubMed: 10683392]
- Huttenlocher J, Newcombe N, Sandberg E. The coding of spatial location in young children. *Cognitive Psychology*. 1994; 27:115–148. [PubMed: 7956105]
- Iaria G, Petrides M, Dagher A, Pike B, Bohbot VD. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *Journal of Neuroscience*. 2003; 23(13):5945–5952. [PubMed: 12843299]
- Jacobs WJ, Laurance HE, Thomas KG. Place learning in virtual space I: Acquisition, overshadowing, and transfer. *Learning and Motivation*. 1997; 28:521–541.
- Jacobs WJ, Thomas KG, Laurance HE, Nadel L. Place learning in virtual space II: Topographical relations as one dimension of stimulus control. *Learning and Motivation*. 1998; 29:288–308.
- Jarrard LE. On the role of the hippocampus in learning and memory in the rat. *Behavioral and Neural Biology*. 1993; 60(1):9–26. [PubMed: 8216164]
- Kessels RP, de Haan EH, Kappelle LJ, Postma A. Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. *Brain Res Brain Res Rev*. 2001; 35(3):295–303. [PubMed: 11423159]
- Kohler S, Danckert S, Gati J, Menon R. Novelty response to relational and non-relational information in the hippocampus and parahippocampal region: A comparison based on event-related fMRI. *Hippocampus*. 2005; 15:763–774. [PubMed: 15999342]
- Kretschmann H, Kammradt G, Krauthausen I, Sauer B, Wingert F. Brain growth in man. *Bibliotheca anatomica*. 1986; 28:1–26. [PubMed: 3707509]
- Kumaran D, Maguire EA. The human hippocampus: Cognitive maps or relational memory? *Journal of Neuroscience*. 2005; 25(31):7254–7259. [PubMed: 16079407]
- Laurance H, Learmonth A, Nadel L, Jacobs WJ. Maturation of Spatial Navigation Strategies: Convergent Findings from Computerized Spatial Environments and Self-Report. *Journal of Cognition and Development*. 2003; 4(2):211–238.
- Lavenex P, Amaral D, Lavenex P. Hippocampal lesion prevents spatial relational learning in adult macaque monkeys. *Journal of Neuroscience*. 2006; 26:4546–4558. [PubMed: 16641234]
- Learmonth A, Nadel L, Newcombe N. Children's use of landmarks: Implications for modularity theory. *Psychological Science*. 2002; 13(4):337–341. [PubMed: 12137136]
- Learmonth A, Newcombe N, Huttenlocher J. Toddlers' use of metric information and landmarks to reorient. *Journal of Experimental Child Psychology*. 2001; 80:225–244. [PubMed: 11583524]
- Lehning M, Leplow B, Friege L, Herzog A, Ferstl R, Mehdorn M. Development of spatial memory and spatial orientation in preschoolers and primary school children. *British Journal of Psychology*. 1998; 89:463–480. [PubMed: 9734301]
- Libben M, Titone D. The role of awareness and working memory in human transitive inference. *Behavioural Processes*. 2008; 77:43–54. [PubMed: 17703897]
- Lipton PA, Eichenbaum H. Complementary roles of hippocampus and medial entorhinal cortex in episodic memory. *Neural Plasticity*. 2008; 2008:2–8.
- Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J. Knowing where and getting there: a human navigation network. *Science*. 1998; 280(5365):921–924. [PubMed: 9572740]
- Maguire EA, Frackowiak RS, Frith CD. Learning to find your way: a role for the human hippocampal formation. *Proceedings of the Royal Society B-Biological Sciences*. 1996; 263(1377):1745–1750.
- Maguire EA, Frackowiak RS, Frith CD. Recalling routes around London: activation of the right hippocampus in taxi drivers. *Journal of Neuroscience*. 1997; 17(18):7103–7110. [PubMed: 9278544]
- Manns J, Eichenbaum H. Evolution of declarative memory. *Hippocampus*. 2006; 16(9):795–808. [PubMed: 16881079]
- Manns J, Howard MW, Eichenbaum H. Gradual changes in hippocampal activity support remembering the order of events. *Neuron*. 2007; 56(3):530–540. [PubMed: 17988635]

- Manns J, Squire L. Impaired recognition memory on the Doors and People Test after damage limited to the hippocampal region. *Hippocampus*. 1999; 9(5):495–499. [PubMed: 10560919]
- Martin N, Alsop B. Transitive inference and awareness in humans. *Behavioural Processes*. 2004; 67:157–165. [PubMed: 15240053]
- Menon V, Boyett-Anderson JM, Reiss AL. Maturation of medial temporal lobe response and connectivity during memory encoding. *Cognitive Brain Research*. 2005; 25(1):379–385. [PubMed: 16122916]
- Milner B. The medial temporal-lobe amnesic syndrome. *Psychiatr Clin North Am*. 2005; 28(3):599–611. 609. [PubMed: 16122569]
- Mishkin M, Vargha-Khadem F, Gadian DG. Amnesia and the organization of the hippocampal system. *Hippocampus*. 1998; 8(3):212–216. [PubMed: 9662136]
- Morris R. Spatial localization does not require the presence of local cues. *Learning and Motivation*. 1981; 12:239–260.
- Morris R, Garrud P, Rawlins JN, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. *Nature*. 1982; 297(5868):681–683. [PubMed: 7088155]
- Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, et al. Functional neuroanatomy of remote episodic, semantic, and spatial memory: A unified account based on multiple trace theory. *Journal of Anatomy*. 2005; 207:35–66. [PubMed: 16011544]
- Moses S, Villate C, Ryan J. An investigation of learning strategy supporting transitive inference performance in humans compared to other species. *Neuropsychologia*. 2006; 44:1370–1387. [PubMed: 16503340]
- Muller RU, Kubie JL, Ranck JB Jr. Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *Journal of Neuroscience*. 1987; 7(7):1935–1950. [PubMed: 3612225]
- Murray L, Ranganath C. The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *Journal of Neuroscience*. 2007; 27(20):5515–5522. [PubMed: 17507573]
- Nelson CA. The ontogeny of human memory: A cognitive neuroscience perspective. *Developmental Psychology*. 1995; 31:723–728.
- Nelson, CA.; Thomas, K.; de Haan, M. Neural bases of cognitive development. In: Damon, W.; Lerner, R., editors. *Child and Adolescent Development: An advanced course*. Hoboken, NJ: Wiley & Sons; 2008.
- Newcombe N, Huttenlocher J, Drummey A, Wiley J. The development of spatial location coding: Place learning and dead reckoning in the second and third years. *Cognitive Development*. 1998; 13(2):185–200.
- Newcombe N, Huttenlocher J, Learmonth A. Infants' coding of location in continuous space. *Infant Behavior and Development*. 1999; 22(4):483–510.
- O'Keefe J. Place units in the hippocampus of the freely moving rat. *Experimental Neurology*. 1976; 51:78–109. [PubMed: 1261644]
- O'Keefe, J.; Nadel, L. *The hippocampus as a cognitive map*. Oxford: Clarendon Press; 1978.
- O'Keefe J, Speakman A. Single unit activity in the rat hippocampus during a spatial memory task. *Experimental Brain Research*. 1987; (68):1–27.
- O'Reilly RC, Rudy JW. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. *Psychol Rev*. 2001; 108(2):311–345. [PubMed: 11381832]
- Ofen N, Kao Y, Sokol-Hessner P, Kim H, Whitfield-Gabrieli S, Gabrieli J. Development of the declarative memory system in the human brain. *Nature Neuroscience*. 2007; 10:1198–1205.
- Ono T, Nakamura K, Nishijo H, Eifuku S. Monkey hippocampal neurons related to spatial and nonspatial functions. *Journal of Neurophysiology*. 1993; 70(4):1516–1529. [PubMed: 8283212]
- Overman W, Pate BJ, Moore K, Peuster A. Ontogeny of place learning in children as measured in the radial arm maze, morris search task, and open field task. *Behavioral Neuroscience*. 1996; 110(6):1205–1228. [PubMed: 8986326]
- Parslow D, Fleminger S, Rose D, Brooks B, Gray J, Giampietro V, et al. Allocentric spatial memory activation of the hippocampal formation measured with fMRI. *Neuropsychology*. 2004; 18:450–461. [PubMed: 15291723]

- Paz-Alonso P, Gheiti S, Donohue S, Goodman G, Bunge S. Neurodevelopmental correlates of true and false recognition. *Cerebral Cortex*. 2008; 18(9):2208–2216. [PubMed: 18203693]
- Perner J, Mansbridge D. Developmental differences in encoding length series. *Child development*. 1983; 54:710–719. [PubMed: 6851718]
- Piaget, J. *Judgement and reasoning in the child*. London: Routledge & Kegan Paul; 1928.
- Pihlajamäki M, Tanila H, Kononen M, Hanninen T, Hamalainen A, Soininen H, et al. Visual presentation of novel objects and new spatial arrangements of objects differentially activates the medial temporal lobe subareas in humans. *European Journal of Neuroscience*. 2004; 19(7):1939–1949. [PubMed: 15078568]
- Preston A, Shrager Y, Dudukovic N, Gabrieli J. Hippocampal contribution to the novel use of relational information in declarative memory. *Hippocampus*. 2004; 14:148–152. [PubMed: 15098720]
- Prince SE, Daselaar SM, Cabeza R. Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. *J Neurosci*. 2005; 25(5):1203–1210. [PubMed: 15689557]
- Rapp P. Who's the fairest of them all? Role of the human hippocampus in the relational organization of memory. *Hippocampus*. 2004; 14:141–142. [PubMed: 15098718]
- Richmond J, Nelson CA. Accounting for change in declarative memory: A cognitive neuroscience perspective. *Developmental Review*. 2007; 27:349–373. [PubMed: 18769510]
- Rudy J, Keith J, Georgen K. The effect of age on children's learning of problems that require a configural association solution. *Developmental Psychobiology*. 1993; 26:171–184. [PubMed: 8314437]
- Rudy J, Stadler-Morris S, Albert P. Ontogeny of spatial navigation behaviors in the rat: Dissociation of proximal- and distal-cue-based behaviors. *Behavioral Neuroscience*. 1987; 101:62–73. [PubMed: 3828056]
- Seress, L.; Abraham, H. Pre- and postnatal morphological development of the human hippocampal formation. In: Nelson, CA.; Luciana, M., editors. *Handbook of Developmental Cognitive Neuroscience*. 2nd ed. Cambridge, MA: MIT Press; 2008. p. 187–211.
- Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience*. 2003; 4:637–648.
- Sluzenski J, Newcombe N, Kovacs S. Binding, relational memory, and recall of naturalistic events: A developmental perspective. *Journal of Experimental Psychology: Learning, Memory, and Cognition*. 2006; 32:89–100.
- Smith C, Squire L. Declarative memory, awareness, and transitive inference. *Journal of Neuroscience*. 2005; 25:10138–10146. [PubMed: 16267221]
- Sperling R, Bates J, Cocchiarella A, Schacter D, Rosen B, Albert M. Encoding novel face-name associations: A functional MRI study. *Human Brain Mapping*. 2001; 14:129–139. [PubMed: 11559958]
- Squire L, Stark C, Clark R. The medial temporal lobe. *Annual Review of Neuroscience*. 2004; 27:279–306.
- Squire L, Zola-Morgan S. The medial temporal lobe memory system. *Science*. 1991; 253:1380–1386. [PubMed: 1896849]
- Stark CE, Bayley PJ, Squire L. Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning and Memory*. 2002; 9(5):238–242. [PubMed: 12359833]
- Waltz J, Knowlton B, Holyoak K, Boone K, Mishkin F, de Menezes Santos M, et al. A system for relational reasoning in human prefrontal cortex. *Psychological Science*. 1999; 10:119–125.
- Wendelken C, Bunge S. Transitive inference: Distinct contributions of rostrolateral prefrontal cortex and the hippocampus. *Journal of Cognitive Neuroscience*, early access online. 2009:1–11.
- Wright B. Reconceptualizing the transitive inference ability: A framework for existing and future research. *Developmental Review*. 2001; 21:375–422.
- Zola-Morgan S, Squire L, Amaral D. Human amnesia and the medial temporal lobe region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience*. 1986; 6:2950–2967. [PubMed: 3760943]

Figure 1.
Schematic illustrating the five oval stimuli for the TI task

Figure 2.
Premise pairs for the TI task

Figure 3.

Mean latency to locate the hidden target (seconds ± 1 SE) for 6, 8, 10- year olds and adults in the place learning (PL) task. Between 6 and 10 years, there is a gradual, linear decline in latency to relocate a hidden target using visual cues (relational memory). In contrast, latency to a hidden target with a subset of cues removed (flexible memory use) shows a significant shift between 8 and 10 years, with 6- and 8-year olds performing similarly and 10- year olds performing like adults.

Figure 4. Mean accuracy ($\pm 1SE$) for premise and BD inference pairs in the transitive inference (TI) task. Between 6 and 10 years, there is gradual improvement in premise pair accuracy (relational memory). In contrast, BD inference pair accuracy (flexible memory use) shows a significant shift between 8 and 10 years, with 6 and 8-year olds performing similarly and 10-year olds performing like adults.

Table 1

Trial number and types in the place learning (PL) task

Run	Trial	Trial Type
Practice		
	1	Navigate to visible target
	2	Navigate to visible target
Test		
	3	Initial search for hidden target
	4	Re-locate hidden target: place memory with multiple cues
	5	Re-locate hidden target: place memory with multiple cues
	6	Re-locate hidden target: place memory with multiple cues
	7	Re-locate hidden target: repeated start location
	8	Re-locate hidden target: place memory with cue removal
	9	Re-locate hidden target: no target appeared
	10	Navigate to now visible target: used as covariate

Table 2

Mean latencies (seconds) to locate the hidden target for relational and flexible trials in the place learning (PL) task

Age	6 Mean (SD)	8 Mean (SD)	10 Mean (SD)	Adult Mean (SD)
<i>Relational</i>	<i>n</i> = 29	<i>n</i> = 30	<i>n</i> = 28	<i>n</i> = 28
Trial 4	46.11 (40.64)	37.69 (36.22)	18.67 (13.20)	19.84 (12.33)
Trial 5	52.48 (40.43)	31.92 (31.09)	17.93 (7.93)	21.25 (12.28)
Trial 6	30.06 (31.14)	25.93 (26.23)	14.69 (8.04)	15.61 (8.92)
Trials 4–6	43.06 (22.97)	31.84 (22.71)	17.10 (6.80)	18.90 (6.92)
<i>Flexible</i>	<i>n</i> = 29	<i>n</i> = 30	<i>n</i> = 25	<i>n</i> = 25
Trial 8	50.85 (38.23)	52.84 (42.10)	24.83 (22.92)	28.31 (19.58)

Table 3

Mean path lengths (units) to locate the hidden target for relational and flexible trials in the place learning (PL) task

Age	6	8	10	Adult
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<i>Relational</i>	<i>n</i> = 29	<i>n</i> = 30	<i>n</i> = 28	<i>n</i> = 28
Trial 4	232.0 (206.7)	175.1 (167.6)	90.0 (47.62)	98.8 (66.1)
Trial 5	262.5 (201.3)	172.6 (144.0)	107.1 (41.1)	121.5 (58.7)
Trial 6	144.5 (138.4)	113.3 (105.9)	73.41 (44.6)	80.0 (54.4)
Trials 4–6	213.0 (116.2)	153.7 (99.7)	90.2 (27.5)	100.1 (39.0)
<i>Flexible</i>	<i>n</i> = 29	<i>n</i> = 30	<i>n</i> = 25	<i>n</i> = 25
Trial 8	261.3 (230.2)	294.3 (258.7)	118.8 (106.7)	126.4 (93.2)

Table 4

Mean accuracy for relational and flexible memory conditions in the transitive inference (TI) task

	Age	6	8	10	Adult
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<i>Relational</i>		<i>n</i> = 29	<i>n</i> = 28	<i>n</i> = 27	<i>n</i> = 31
Premise Pairs (Run 3)		.77 (.17)	.91 (.09)	.95 (.06)	.95 (.08)
Premise Pairs (Test run)		.72 (.17)	.80 (.16)	.90 (.11)	.88 (.15)
<i>Flexible</i>		<i>n</i> = 29	<i>n</i> = 28	<i>n</i> = 27	<i>n</i> = 29
BD Inference Pair		.60 (.30)	.58 (.38)	.75 (.25)	.80 (.28)

Table 5

Bivariate correlations for the relations between BC/CD premise pair accuracy (relational memory) and BD inference pair accuracy (flexible memory use) for the transitive inference (TI) task

Age	6	8	10	Adult
r	.63*	.60*	.17	.30
r ²	.39	.36	.03	.09

* Pearson correlation significant, $p < .05$