Retrieval Flexibility and Reinstatement in the Developing Hippocampus

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ABSTRACT: Episodic memory improves during childhood and this improvement has been associated with age differences in hippocampal function, but previous research has not manipulated the possible underlying mechanisms. We tested the hypothesis that age-related differences in hippocampal activation may reflect changes in retrieval flexibility. We expected these activation differences to be observed most prominently in the anterior hippocampus. Functional magnetic resonance imaging (fMRI) data were collected from children ages 8 and 10, and adults (N = 63) during an associative recognition task that required participants to recognize pairs of pictures which either appeared in the same location as during encoding (Same location), or in a flipped location, such that each picture switched their location with the other member of the pair (Flipped location). Recognition of same-location pairs placed lower demands on flexible retrieval compared to recognition of flipped-location pairs. Behaviorally, 8-year-olds exhibited the strongest correct recognition gains for same-location compared to flipped-location pairs, and females unexpectedly outperformed males across all ages. When we examined correct recognition, adults recruited the hippocampal head more strongly for flipped- versus same-location pairs compared to both groups of children; in contrast both adults and 10-year-olds recruited the hippocampal tail more strongly for flipped-versus same-location pairs compared to 8-year-olds. This pattern was stronger in the left hippocampus and for females. Moreover hippocampal discrimination between recognized and forgotten items in the same-location condition was stronger in 8-year-olds compared to adults, and was stronger in the flipped-location condition in adults compared to 8-year-olds; this pattern was stronger in the left hippocampus. Individual differences in this discrimination contrast for flipped-location trials in the head and body predicted performance on an index of creative thinking. Overall, these results lend new support to the idea that hippocampal development may reflect change in retrieval flexibility with implications for additional forms of flexible cognition. © 2015 Wiley Periodicals, Inc.

KEY WORDS: children; episodic memory; flexibility; hippocampal development

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INTRODUCTION

Episodic memory, the ability to form and retrieve memories that include details about the spatio-temporal context in which events occurred (Tulving, 2002), is arguably most useful if it can be used to retrieve past experiences in the absence of elements of the original encoding context and across a variety of retrieval cues. However, numerous studies have demonstrated that retrieval is more difficult under conditions that do not reinstate aspects of the encoding context (e.g., Tulving and Thomson, 1973; Smith and Vela, 2001), and this may be particularly true for children (Ackerman, 1982; Paz-Alonso et al., 2008; Levy-Gigi and Vakil, 2010).

The development of strategic processes has been traditionally emphasized to explain children's difficulties with retrieval across different contexts (e.g., Levy-Gigi and Vakil, 2010); this emphasis reasonably highlights the contribution of PFC-mediated mechanisms (e.g., Ofen et al., 2012). However, more recent behavioral findings have emphasized changes in medial-temporal regions to explain developmental differences in contextual change effects (Edgin et al., 2014). Moreover, evidence that the hippocampus supports flexible retrieval (Giovanello et al., 2009; Zeithamova and Preston, 2010) and that hippocampal function develops into late childhood (e.g., Paz-Alonso et al., 2008) raises the question of whether changes in hippocampal function may also play a substantive role.

Importantly, the investigation of whether age differences in hippocampal function contribute to developmental improvements in retrieval flexibility could inform current discussion on functional differences along the anterior/posterior hippocampal axis which has recently gained momentum (e.g., Poppenk et al., 2013; Strange et al., 2014). Previous research has provided initial evidence that structural development of the hippocampus follows different trajectories depending on axis location (i.e., anterior versus posterior regions) (Gogtay et al., 2006; DeMaster et al., 2014), and that these different trajectories may have functional implications for memory development (DeMaster and Ghetti, 2013). For example, there is initial evidence that developmental differences in hippocampal activation profiles may be strong in more anterior regions, such as the hippocampal head (Ghetti et al.,

2010; DeMaster and Ghetti, 2013). This is interesting considering that activation in the anterior hippocampus has been linked with flexible retrieval (Giovanello et al., 2004, 2009), which, again, is known to be behaviorally particularly difficult for children (Gee and Pipe, 1995; Paz-Alonso et al., 2008). Specifically, in a study by Giovanello et al. (2009), participants were shown pairs of words during an encoding phase and then, during a retrieval phase, asked to identify old pairs (i.e., word pairs shown together during encoding); old pairs were presented in either the same or flipped location during retrieval. These authors reported that a cluster in the left hippocampal head was active for studied pairs regardless of whether they were presented in their original position or in the flipped position, which was considered a signature of retrieval flexibility. Despite these findings, previous developmental research has not directly manipulated retrieval flexibility, making it impossible to ascertain whether this factor contributes to observed age differences in hippocampal activation profiles.

In the present study, we used an experimental manipulation adapted from Giovanello et al. (2009) to examine whether developmental differences in hippocampal function along the anterior/posterior axis may contribute to the development of flexible memory retrieval.

In addition to our main goal, we pursued a final, exploratory goal. Specifically, we asked whether hippocampal activity related to retrieval flexibility, particularly in the hippocampal head, was associated with the production of novel ideas in an independent task, the unusual uses task (Guilford, 1967). This task has been employed traditionally to assess divergent thinking (e.g., Damian and Robins, 2012), and performance deficits on this task have been demonstrated in amnesic patients with hippocampal lesions (Duff et al., 2013). This finding provides initial, but compelling, evidence that the hippocampus supports flexibility not only in the domain of memory, but also in other forms of thought including creativity and divergent thinking (Rubin et al., 2014). Here, we seek to contribute to this line of work by examining whether functional measures of flexible retrieval in the hippocampus are associated with the same assessment of creativity.

To achieve these goals, we conducted an fMRI study which assessed participants from 3 age groups, namely 8-year-olds, 10-year-olds, and young adults. These groups were selected because of evidence of age-related differences in episodic memory and retrieval-related hippocampal activity among them (Ghetti and Angelini, 2008; DeMaster et al., 2013). Previous behavioral studies have also demonstrated differences in retrieval flexibility among these age groups (Paz-Alonso et al., 2008; Townsend et al., 2010). For example, Townsend and colleagues (2010) examined performance on a task that required 6–10 year-old participants to locate a hidden target by navigating through a virtual environment and found stark improvements between 8- and 10-years of age when visual cues to the location of the target were removed; no improvement was observed between 6- and 8-years of age under this condition. In contrast, gradual improvements across all ages were observed when visual cues to the location, reducing the need for flexibility, were included.

We examined BOLD activation across our selected age groups during a retrieval task in which participants attempted to identify which pairs of objects (depicted pictorially on a screen) had or had not been encoded together (i.e., associative recognition). Following Giovanello et al. (2009), retrieval flexibility was manipulated by either retaining the original positions of the individual pair items (i.e., same-location condition), or by changing them. When positions were changed, the two items in the pair switched positions with each other (i.e., flipped-location condition). Activation profiles contrasting these two conditions were investigated in anatomically defined hippocampal regions along the anterior/posterior axis.

We predicted that the most pronounced age-related differences in activation would be observed in the hippocampal head. Adults were expected to recruit this region more strongly for recognition of flipped-location trials compared to children, particularly the 8-year-olds, because this sub-region has shown retrieval-related developmental differences (e.g., Paz-Alonso et al., 2008) and is also implicated in flexible retrieval in adults (e.g., Giovanello et al., 2004, 2009; but see Zeithamova and Preston, 2010). In addition, while adults were expected to recruit this region strongly for recognition of both same-location and flipped-location studied pairs consistent with findings by Giovanello et al. (2009), children, especially 8-year-olds, were expected to be more likely to show activation for recognition of same-location trials. This prediction reflects the hypothesis that children may be more likely to recruit the hippocampus if the elements of the original experience are presented at test in their exact form (i.e., exact reinstatement). This prediction is also in line with behavioral evidence that exact contextual reinstatement during retrieval is particularly beneficial for children (Paz-Alonso et al., 2008).

Despite these hypotheses, we note that the extant literature has not painted a coherent picture of age differences in hippocampal activation. For example, in a study examining episodic retrieval of item-location associations, children showed decreased memory-related hippocampal selectivity compared to adults across the entire hippocampus (DeMaster et al., 2013), but in another study examining retrieval of item-color associations, the hippocampal tail contributed to episodic retrieval in children but not adults (DeMaster and Ghetti, 2013; see also DeMaster et al., 2014 for evidence of structural analyses that are consistent with this finding). Finally, other studies have failed to find age-related differences in hippocampal function altogether (Güler and Thomas, 2013; Ofen et al., 2012). Discrepancies in the literature may be reduced by beginning to systematically manipulate factors that are thought to affect hippocampal function and episodic memory development. For example, previous studies employed tasks that ranged from single item recognition (Ofen et al., 2012) to retrieval of specific episodic detail (e.g., source retrieval, DeMaster & Ghetti, 2013); these different tasks arguably require different levels of retrieval flexibility, possibly influencing the extent of developmental differences in hippocampal contribution.

Finally, given the hypothesis that the hippocampus supports flexible cognition beyond memory (e.g., Rubin et al., 2014), we predicted that activation associated with flexible retrieval (i.e., retrieval of pairs presented in the flipped-location condition) would be specifically associated with performance on the unusual uses test, providing further evidence for a functional role of the hippocampus in flexible cognition beyond memory (Duff et al., 2013; Rubin et al., 2014).

MATERIALS AND METHODS

Participants

Participants included 63 individuals (32 females and 31 males) divided into three age groups: 18 8-year-olds (*M* age = 8.56, SD = 0.51; 11 females), 21 10-year-olds (*M* age = 10.48, SD = 0.60; 9 females), and 24 young adults (*M* age = 19.88, SD = 1.75; 12 females). An additional 8 children and 1 adult were excluded from analyses because of excessive movement (i.e., they produced more than 25% bad volumes within individual runs) and/or achieved chance performance on the behavioral task.

Participants were right-hand dominant and native English speakers. Exclusion criteria included color blindness, vision impairment not correctable with contacts, history of head trauma, presence of neurological or psychiatric disorders, and prescription medications other than antibiotics and those prescribed to reduce seasonal allergies. Standard prescreening procedures were followed to exclude individuals who could not safely participate in MRI research. Participants were also excluded from analyses if they obtained a score 1 standard-deviation below the mean on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (i.e., 1 child and 2 adults).

Tasks and Procedures

The experiment was conducted at the UC Davis Center for Neuroscience. Upon arrival, informed consent was obtained and an MRI safety screening form was completed (by parent/guardian if child participant or by self if adult participant) and reviewed by the examiner. All participants then participated in a mock MRI session during which they practiced remaining still while hearing the scanning noises and looking at a computer screen. After, participants completed the vocabulary and matrix reasoning subtests from the WASI (to yield a full scale IQ score). They then proceeded to the memory task, and finally completed the unusual uses task.

Memory Task

To ensure that participants understood the instructions, practice encoding and retrieval phases (each consisting of 14 trials) preceded the scanning session. For encoding trials, participants were informed that that they would see a series of 2 pictures presented vertically on the screen (Fig. 1a) and their memory for the pairs would be tested later. We elected to align the pairs in vertically instead of horizontal as in Giovanello et al. (2009) because of a left picture selection bias was uncovered during piloting. For each trial, they were asked to use a response pad to make a button press indicating which of the two pictures represented the heavier object; based on piloting, this relative-weight judgment could be done accurately across ages within the trial time, and allowed participants to process the co-occurrence of the two pictures while still maintaining them as separate representations. Upon completion of the encoding trials, the practice retrieval phase began. Participants were informed that each retrieval trial would consist of 2 pictures from the encoding phase presented vertically on the screen, and that some of the picture pairs would be the same as previously studied during encoding (i.e., old pairs), and some would consist of previously-studied pictures rearranged to form new pairs (Fig. 1b). For each trial, participants were asked to indicate if the pictures were presented together in the same pairing as at encoding, or in a new pairing. Participants were informed that the location of some of the pictures would switch, bur their goal remained to determine whether or not the pictures had been studied in the same pairing regardless of their spatial arrangement. Participants responded by pressing either the "together" or the "not together" button on the response pad.

The actual memory task followed this practice session. It included 3 scanning sessions, each comprised of an encoding and a retrieval run (lasting 5 minutes and 8 minutes, respectively). The encoding task (Fig. 1a) included 84 trials. Each encoding trial remained on the screen for 1500 ms, followed by a black screen with a white fixation cross during a jittered interval (1500–7500 ms). Encoding instructions were identical to those provided during the practice phase. Functional data collected during encoding are not reported here.

After the first encoding run, participants began their first retrieval run (Fig. 1b). Individual pictures in the previously studied pairs (i.e., old pairs) and rearranged pairs were either presented in the same location as during encoding (i.e., Old-Same location and Rearranged-Same location, respectively) or in a flipped location (i.e., Old-Flipped location or Rearranged-Flipped location). These rearranged pairs were necessary to ensure that we could obtain a behavioral assessment, separately for same- and flipped-location conditions, of participants' memory for the association between pairs of pictures and not memory for the individual pictures alone. In addition to Rearranged-Same location and Rearranged-Flipped location pairs, new pairings of pictures not shown during encoding were created to form completely Novel trials; since old/new item discriminations should be less demanding in this condition, performance on these trials was used to establish that participants generally attended to the task and followed the instructions. Completely novel pairs were also included as a behavioral control to ensure that children could discriminate strongly between studied items and novel items. In total, 96 pairs were presented during each retrieval run (21 Old-Same location, 21 Old-Flipped location, 21 Rearranged-Same
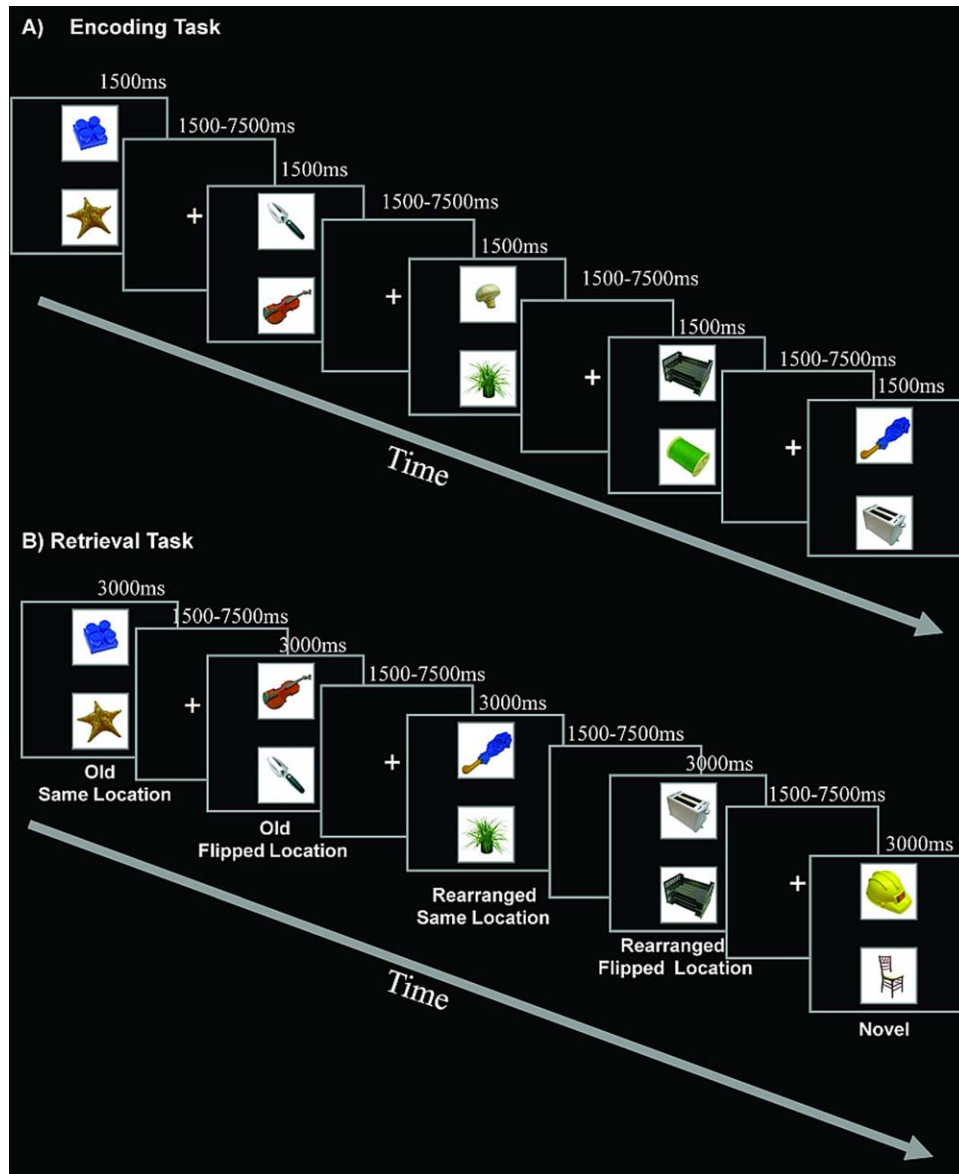
FIGURE 1.   Associative recognition task including encoding (A) and retrieval (B) phases. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

location, 21 Rearranged-Flipped location, and 12 Novel trials). Picture pairs remained on the screen for 3000 ms followed by a black screen with a white fixation cross during a jittered interval (1500–7500 ms). Retrieval instructions were identical to those provided during the practice phase.

A 5-minute break was provided during the actual memory task to reduce fatigue. This break typically took place after the second retrieval run, and never in between an encoding and retrieval run in order to maintain a comparable interval between encoding and retrieval across runs and participants. During the break, participants were removed from the scanner and encouraged to engage in light stretching outside the scanning room.

Unusual Uses Task (Guilford, 1967; Damian and Robins, 2012). After their scanning session, participants completed an adaptation of the unusual uses task. Participants were asked to list as many uncommon uses for a common household object (i.e., a brick) they could think of within a 2-minute period. Participants' responses were coded for number of novel uses; reliability was achieved across two independent coders (Alpha = 0.98). These scores were then used for correlational analyses to examine associations with hippocampal activation. Due to time constraints, we were unable to collect this measure for 7 participants (3 children and 4 adults).

*f*MRI **Data Acquisition and Analysis.** *f*MRI data were acquired on a Siemens 3T Skyra scanner. Brief rest periods were provided before each of the functional scans. All functional data were acquired with a gradient echo EPI sequence (TR = 1500 ms, TE = 25 ms, no inter-slice gap, flip

Mean and Standard Deviations for Behavioral Variables as a Function of Age and Sex

	8-year-olds		10-year-olds		Adults	
	Female	Male	Female	Male	Female	Male
Hits						
Old Same Location	0.61 (0.16)	0.55 (0.06)	0.69 (0.13)	0.62 (0.16)	0.65 (0.11)	0.72 (0.10)
Old Flipped Location	0.55 (0.16)	0.54 (0.09)	0.62 (0.16)	0.61 (0.13)	0.65 (0.12)	0.66 (0.11)
False Alarms						
Rearranged Same Location	0.49 (0.12)	0.44 (0.14)	0.49 (0.08)	0.45 (0.10)	0.41 (0.17)	0.44 (0.09)
Rearranged Flipped Location	0.40 (0.15)	0.48 (0.08)	0.43 (0.11)	0.44 (0.13)	0.38 (0.19)	0.44 (0.08)
New Pairs	0.23 (0.14)	0.23 (0.14)	0.17 (0.20)	0.32 (0.18)	0.13 (0.13)	0.30 (0.31)

angle $= 90°$, FOV $= 204$). Each volume consisted of 37, 3-mm axial slices. After functional scans, a high-resolution MPRAGE anatomical scan was acquired, but these data are not included in the present report.

Data for individual participants were analyzed with the general linear model in SPM8 (Wellcome Department of Cognitive Neurology, London) and convolved with a canonical hemodynamic response function (HRF). Functional images were corrected for differences in slice acquisition timing, and were realigned to the first volume by means of rigid body motion correction with sinc interpolation. Structural images were co-registered to the functional images and then spatially normalized to the T1 template in SPM. These normalization parameters were then applied to the functional images. Functional images were spatially smoothed with a 6-mm full-width half-maximum isotropic Gaussian kernel. To correct for effects of participant motion, volumes with motion in excess of 1 mm or signal change in excess of 2% were detected and replaced with interpolated values using ArtRepair (Mazaika et al., 2009). Our model also included six motion parameters, describing scan-to-scan translation and rotation, as covariates of non-interest.

Task effects were modeled via epoch regressors, aligned to the onset of each retrieval trial and with durations equal to response times. This GLM was used to compute the least-squares parameter estimate of the height of the best-fitting synthetic response function for each trial type at each voxel.

Region-of-interest (ROI) analyses were performed using MarsBar (Brett et al., 2002). To investigate age-related differences in regional hippocampal contribution to retrieval, we conducted analyses on anatomical ROIs corresponding to the head, body, and tail of the hippocampus. As in our previous research (DeMaster and Ghetti, 2013; DeMaster et al., 2013), the ROI for the hippocampal head extended from the first slice where MarsBar identifies this structure to the point at which the hippocampus appears to narrow and loses its round shape digitations (left: $Y = -20$ and right: $Y = -18$; this coordinate is different in the left and right hemispheres because of a slight head tilt in the SPM template). The ROI for the hippocampal tail started at the first slice that showed the fornix separate from the hippocampus (left: $Y = -36$ and right: $Y = -34$).

The hippocampal body included all voxels between the end of the head and the beginning of the tail.

RESULTS

Behavioral Results

Preliminary analyses revealed that female participants overall outperformed male participants. Thus, we included sex as a factor in all of our analyses. To examine age-related differences in behavior, we first compared rates of recognition as a function of trial type. Thus, we conducted a 3 (Age group: 8-year-old, 10-year-old, adult) X 2 (Sex: Female vs. Male) X 5 (Trial type: Old-Same location, Old-Flipped location, Rearranged-Same location, Rearranged-Flipped location, Novel) mixed ANOVA.

Results revealed a main effect of trial type, $F_{4, 228} = 117.29$, $p < 0.001$, $\eta_p^2 = 0.67$, such that overall hit rates for studied pairs were higher than false-alarm rates for rearranged pairs, $p < 0.001$, which were in turn higher than false-alarm rates for completely novel pairs, $p < 0.001$; these significant differences were reliable within each age group. A significant age by trial type interaction was also found, $F_{4, 28} = 2.46$, $p = 0.01$, $\eta_p^2 = 0.08$, such that the difference between hits and false alarms was reduced in 8-year-olds compared to 10-year-olds, $p < 0.01$, which in turn was reduced compared to adults, $p < 0.05$ (Table 1 shows old response rates by accuracy). Furthermore, same-location hits were significantly higher than flipped-location hits in 8-year-olds, $p < 0.05$, but not in the other age groups who correctly identified old pairs at similar rates regardless of whether they were presented in the same or flipped locations, $p_s \geq 0.11$. In addition, there was a significant sex X trial interaction, $F_{4, 228} = 3.33$, $p = 0.01$, $\eta_p^2 = 0.06$, such that across ages, females but not males exhibited increased hit rates for same-location compared to flipped location trials, $p < 0.05$, and males committed more false alarms to novel pairs compared to females, $p < 0.05$. Finally, though implied by this omnibus ANOVA, we confirmed that a reliable ability to discriminate between studied and rearranged pairs was
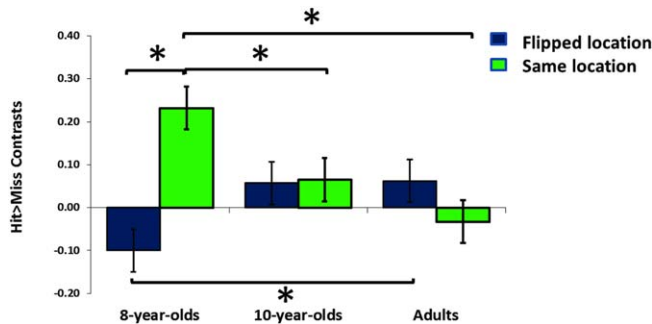
FIGURE 2. **Left hippocampal activation across the entire sample, collapsing across head, body, and tail regions, for Hit > Miss trials as a function of age and trial type. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary. com.]**

observed in each age group as indicated by corrected recognition scores (hits *minus* false alarms for studied pairs and rearranged pairs) being different from zero (8-year-olds: Same, $M = 0.12$, SD = 0.10; Flipped, $M = 0.11$, SD = 0.06; $t_s(17) \geq 4.82$, $p_s < 0.0001$; 10-year-olds: Same, $M = 0.19$, SD = 0.13; Flipped, $M = 0.18$, SD = 0.13; $t_s(20) \geq 6.21$, $p_s < 0.0001$; Adults: Same, $M = 0.26$, SD = 0.15; Flipped, $M = 0.25$, SD = 0.15; $t_s(23) \geq 7.78$, $p_s < 0.0001$).

Although our manipulation of retrieval location (i.e., whether pictures were presented in the same or flipped location during retrieval compared to encoding) did not affect hit rates for older children and adults, it did affect their response times. A 3 (age group) X 2 (sex) 5 (trial type) mixed ANOVA on response times revealed a significant main effect of trial type, $F_{4,\ 228} = 4.11$, $p < 0.01$, $\eta_p^2 = 0.07$, such that across ages same-location hits were associated with significantly faster response times, $M = 1508.8$ ms $\pm$ 33.3, compared to flipped-location hits, $M = 1549.0$ ms $\pm$ 36.9, $p < 0.05$, and same-location false alarms were endorsed more quickly, $M = 1497.3$ ms $\pm$ 36.4, compared to flipped-location false alarms, $M = 1551.7$ ms $\pm$ 40.2, $p_s < 0.05$. The main effect of age was not significant, $F_{2,59} = 1.73$, $p = 0.19$, $\eta_p^2 = 0.06$. Also, sex differences in response times were not found either as main effects or in interaction with other variables, $p_s \geq 0.54$.

*f*MRI Results

Age Differences in Flexible Retrieval and Reinstatement. To examine age-related and region-related differences in hippocampal contribution to flexible retrieval versus rigid reinstatement, we analyzed the data in two ways. First, we focused on differences between flipped and same location pairs in contrasts between correctly recognized pairs (i.e., Old-Same location and Old-Flipped location hits) and forgotten pairs (i.e., Old-Same location and Old-Flipped location misses) to examine if the hippocampus discriminated between these classes of items indicating memory retention.

Second, we focused on activation differences between correctly recognized studied pairs that were presented in the

flipped location at retrieval (i.e., Old-Flipped location hits) versus the same location at retrieval (i.e., Old-Same location hits); we included only trials that were correctly recognized to limit the examination of age differences to trials that had been successfully retrieved, thereby reducing potential age-related confounds. This analysis enabled us to strictly examine effects of our flexibility manipulation among accurate recognitions and to make the most direct comparison to Giovanello et al.'s results (2009). Indeed, one of the results that served as a basis for our hypotheses emerged from their comparison of activation between studied pairs whose members were presented in the same position at retrieval and pairs whose members were presented in a reversed positon at retrieval.

Finally, we examined activation in the left and right hippocampus separately because we did not have specific hypotheses concerning laterality effects and developmental differences in flexible retrieval, but were nevertheless interested in providing a thorough examination of the results.

Discrimination between recognized and forgotten trials. For the first analysis, we entered the contrast values for hits>misses in a 3 (Age: 8-year-old, 10-year-old, adult) X 2 (Sex: Female vs. Male) X 3 (Hippocampal region: Head, Body, Tail) X 2 (Trial type: Flipped vs. Same) mixed ANOVA for the left and right hippocampus separately. In the left hippocampus, we found a main effect of region, $F_{2,114} = 6.99$, $p = 0.001$, $\eta_p^2 = 0.11$, such that overall the body and tail ($M = 0.06 \pm 0.03$ and $M = 0.09 \pm 0.03$) showed stronger discrimination between recognized and forgotten items than did the head across both same- and flipped-location pairs ($M = -0.02 \pm 0.04$), $p_s < 0.05$. No main or interactive effects of sex were found, $p_s > 0.30$. Of most interest for the current goals, was a significant Age X Trial type interaction, $F_{2,114} = 4.24$, $p = 0.019$, $\eta_p^2 = 0.13$, which was preserved when behavioral performance was included as a covariate, $F_{2,112} = 3.46$, $p = 0.04$, $\eta_p^2 = 0.11$. As shown in Figure 2, in 8-year-olds, collapsing across the head, body, and tail regions, the left hippocampus discriminated between correctly recognized and forgotten for same-location pairs more strongly than for flipped-location pairs; this discrimination for same-location pairs was stronger than adults' discrimination for the same type of trials, $p_s < 0.05$. In contrast, both adults and 10-year-olds showed stronger activation for flipped-location pairs than 8-year-olds ($p < 0.05$ and $p = 0.07$, respectively). No main or interactive effects of sex were found, $p_s > 0.39$. This interaction was not found in the right hippocampus in which only a main effect of region was found, $F_{2,114} = 4.92$, $p = 0.01$, $\eta_p^2 = 0.08$. Similar to the left hippocampus, the body and the tail ($M = 0.06 \pm 0.03$ and $M = 0.09 \pm 0.03$) showed stronger discrimination between recognized and forgotten items than did the head ($M = 0.02 \pm 0.04$), $p_s < 0.05$.

Correct recognition. For the second analysis, we used the most specific contrast, namely activation for flipped>same for correctly recognized items. Thus, we entered this contrast value in a 3 (Age: 8-year-old, 10-year-old, adult) X 2 (Sex: Female vs. Male) X 3 (Hippocampal region: Head, Body, Tail) mixed ANOVA for the left and right hippocampus separately. In the left hippocampus, results revealed a significant age X sex X
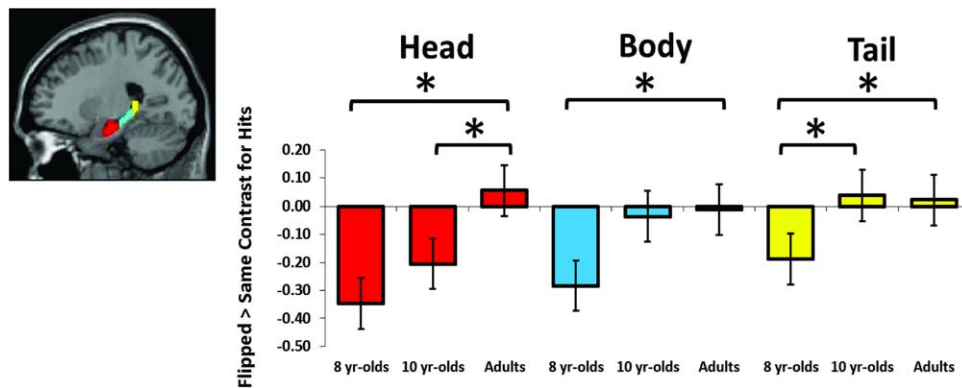
FIGURE 3. Left hippocampal activation for Flipped-Location > Same-Location hits as a function of age and sub-region. Only female participants are shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

region interaction, $F_{4,114} = 2.63$, $p < 0.05$, $\eta_p^2 = 0.08$. Among females, patterns of activation differed as a function of age and hippocampal sub-region. As evident from Figure 3, both groups of children recruited the head significantly more for same versus flipped location hits compared to adults, $p_s < 0.05$, as indicated by the negative sign of the contrast value. In contrast, only younger children recruited the hippocampal tail for same versus flipped location hits compared to older children and adults, $p_s < 0.05$. The pattern of activation in the body was in between the other two, such that younger children recruited this sub-region more strongly for same versus flipped location hits compared to adults, $p < 0.05$, but older children did not differ from either group. Overall, the adults were the only age group for whom hippocampal activation did not vary as a function of the retrieval manipulation. This pattern of results was not evident in males whose activation levels did not differ as a function of age or sub-region, $p_s > 0.24$. This 3-way interaction retained statistical significance when behavioral performance (either hit rates or hit minus false alarm rates) was included as a covariate, $F_{4,112} = 2.59$, $p < 0.05$, $\eta_p^2 = 0.08$.

In the right hippocampus, there were no significant main or interactive effects; the age X sex X region interaction found in the left hippocampus was not statistically significant, $F_{4,114} = 1.79$, $p = 0.14$, $\eta_p^2 = 0.06$. However, the pattern of results in the right hippocampus was not dissimilar to that in the left; indeed, the significant age X sex X region interaction was confirmed when hippocampal side was added as a factor in an Omnibus ANOVA, $F_{4,114} = 2.87$, $p < 0.05$, $\eta_p^2 = 0.09$.

Associations between Hippocampal Activation and Creative Thinking. The results reported above indicated that the left hippocampus responded to the flexibility manipulation introduced in the study. Next, we explored the associations between these left hippocampal activations and creative thinking to assess potential implications of hippocampal flexibility for other psychological constructs. Number of valid uses on the unusual uses task was significantly correlated with memory discrimination scores (i.e., hits-false alarms) for flipped-location trials, $r = 0.31$, $p < 0.05$, but not for same-location trials, $r = 0.20$, $p = 0.14$. Age

was significantly associated with both memory discrimination scores, $rs = 0.40$, $p_s < 0.01$, and age and sex were associated with the patterns of activations reported earlier. Thus, partial correlation analyses were conducted to examine the association between number of valid uses on the unusual uses task and activation for hit>miss contrasts with age, sex, and memory performance partialled out. These partial correlational analyses allow us to explore whether individual differences in the extent to which the hippocampus is engaged for flexible retrieval trials, beyond developmental differences, is related to creative thinking. In the present study, we did not have a large enough sample size to examine these correlations separately for each age group. Nevertheless, participants from different age groups are identified with different symbols in Figure 4, to make it descriptively apparent whether or not the aggregate correlation across the entire sample results from similar associations within each age group.

We found that the number of valid uses was significantly correlated with the hit>miss contrast for Flipped-location trials in the left hippocampal head, $r = 0.30$, $p < 0.05$ (Fig. 4A), and body, $r = 0.29$, $p < 0.05$ (Fig. 4B), but not tail, $r = 0.09$, $p = 0.42$. These correlations were not significant for the hit>miss contrast for Same-location trials in any of the hippocampal sub-regions, $r_s < -0.09$, $p_s \geq 0.36$. Steiger's test confirmed that the correlations in the left hippocampal head and body for the hit>miss contrast for Flipped-location trials were significantly greater than their counterparts for Same-location trials, $p_s < 0.05$. Thus, only contrasts in the left hippocampal head and body were associated with creative thinking.

Finally, correlations were not statistically significant when the most specific contrasts, flipped>same for correctly recognized items within each sub-region, were examined in relation to the unusual uses task, $r_s = 0.22$, $p_s \geq 0.11$.

Cortical engagement during associative recognition

Although the present manuscript focuses on hippocampal contribution to flexible retrieval, it is clear that our task
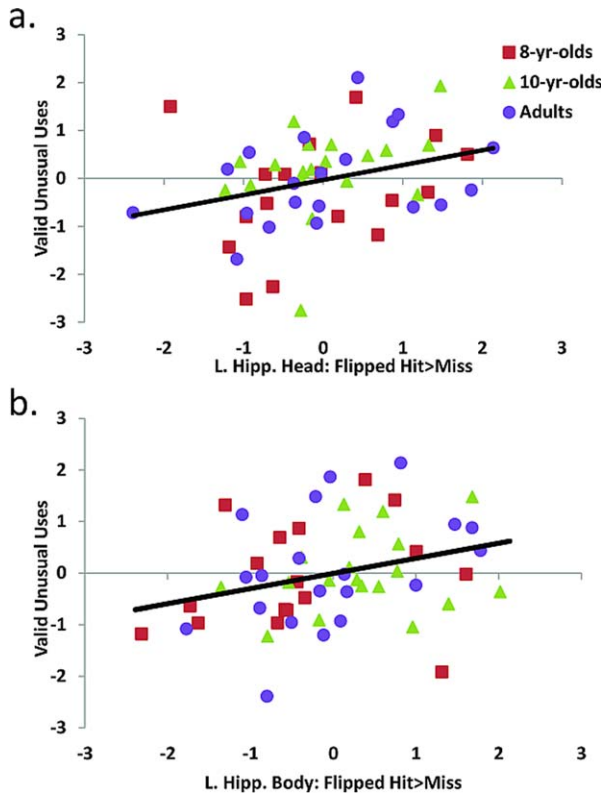
FIGURE 4. Correlation between creative thinking and activation for Hit > Miss Flipped-Location trials in the left hippocampal head (A) and body (B) across the entire sample. Standardized residuals are plotted corrected for age, sex, and behavioral performance (i.e., Hit-FA for rearranged pairs). Squares indicate 8-year-olds, triangles indicate 10-year-olds, and circles indicate adults. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

engages multiple cortical regions. We include figures showing the results of whole-brain voxel-wise analyses as an overview of these additional findings in the supplementary materials (Supporting Information Figs 1 and 2).

DISCUSSION

The main goal of the present study was to investigate hippocampal contribution to the development of flexible retrieval. A mismatch between encoding and retrieval contexts hinders memory retrieval (Tulving and Thomson, 1973; Smith and Vela, 2001), and this may be particularly true for children (e.g., Ackerman, 1982; Levy-Gigi and Vakil, 2010; Townsend et al., 2010). In this study, younger children indeed exhibited the greatest cost when greater retrieval flexibility was necessary: only 8-year-olds showed lower correct recognition for flipped versus same location pairs, though across all ages, the former were endorsed more slowly than the latter. Thus, behavioral findings converged with previous research.

We did not expect sex-related differences in behavior and we do not interpret them as reflecting specific differences in retrieval flexibility processes. The fact that males committed more false alarms to entirely novel pairs may suggest sex-differences in memory ability or perceived difficulty. While this possibility cannot be fully ruled out, we consider it an unlikely explanation for this difference. Males did not appear to exhibit longer response times on more difficult or incorrect trials, as is typically found when participants face task difficulty (e.g., Ackerman & Koriat, 2011; Lyons & Ghetti, 2011), thus suggesting overall lower engagement in the task. Nevertheless, given this difference, we accounted for sex in all analyses of hippocampal activation.

The central hypothesis motivating this study was that the development of flexible retrieval would reflect age differences in hippocampal recruitment, and that these differences may vary by hippocampal sub-region given evidence of developmental differences in functional and structural development along the longitudinal axis of this structure (Gogtay et al., 2006; DeMaster and Ghetti, 2013; DeMaster et al., 2014). To test this hypothesis, we conducted the first developmental neuroimaging study that directly manipulated retrieval flexibility demands. The wealth of behavioral results, including the current one, showing children's strong dependence on contextual reinstatement for episodic retrieval (e.g., Ackerman, 1982; Gee and Pipe, 1995; Paz-Alonso et al., 2008; Levy-Gigi and Vakil, 2010) motivated the hypothesis that younger children would be less likely to recruit the hippocampus for flexible retrieval. Recent behavioral research with typically developing children and children with Down syndrome whose hippocampal function is altered (Edgin et al., 2014) lent further support to the notion that reduced flexibility in children may be in part accounted for by hippocampal development.

When we examined discrimination between successfully recognized and forgotten pairs, strong age-related and flexibility-related effects were found in the entire hippocampus, despite overall stronger memory effects in the body and tail regions compared to the head. Specifically, younger participants showed memory-related effects only for same-location trials (i.e., trials which presented strong contextual reinstatement of the studied episode), and younger children recruited the hippocampus significantly less than the other age groups for trials that required flexible retrieval. These patterns held across female and male participants, and when controlling for behavioral performance.

This finding is consistent with our prediction of age-related differences in hippocampal activation as a function of demand for flexible retrieval, but since this pattern was strongly evident in the entire hippocampus, it is not consistent with our expectation that age-related patterns of activation would differ along the hippocampal anterior-posterior axis. Strong hippocampal involvement with associative recognition has been documented (Kirwan and Stark, 2004; Prince et al., 2005; Giovanello et al., 2009; Dennis et al., 2014), with evidence that left anterior hippocampal regions may be preferentially engaged when more flexible retrieval is required (e.g., Giovanello et al., 2004, 2009). Thus, we had predicted that age differences between

children and adults would be strongest in the left hippocampal head.

Interestingly, even though activation discrimination between successfully recognized and forgotten pairs was not restricted to the hippocampal head at the trial level, an individual difference analysis in activation showed that only individual differences in contrast values for flexible retrieval in the more anterior portions across the entire sample were associated with creative thinking. Indeed, left hippocampal head and body activations discriminating between correctly recognized and forgotten trials in the flipped condition were associated with a higher number of descriptions of unusual object uses, an indicator of divergent and creative thinking. It is interesting to note that although as a group 8-year-olds were more likely to recruit the hippocampus to recognize pairs presented in the same location, the extent to which individual children showed stronger activation for hit > miss across flipped-location trials predicted, as for the other age groups, creativity. This suggests that, although emerging, the extent of flexibility effects in these anterior regions is also beneficial in these younger children.

The current association between activation during flexible retrieval and creative thinking suggests that the flexibility of hippocampal representations to combine and recombine features is critical for episodic memory, but also for other cognitive functions. There is emerging support for this notion in the literature. For example, Zeihamova et al. (2012) have demonstrated that the hippocampus contributes to the ability to make inferences on the basis of recently learned events. There have also been demonstrations of deficits in creative thinking in amnesic patients with hippocampal lesions (Duff et al., 2013). Our results extend these previous demonstrations in amnesic patients because the association between hippocampal activation and creative thinking was found across flipped-location trials only, thereby making a direct and specific connection between memory flexibility and flexibility in other domains such as creativity, imagination, and exploration (Rubin et al., 2014).

This individual difference result was not the only finding implicating anterior hippocampal regions. Evidence of age differences along the hippocampal axis was found when we restricted our analysis to the most specific contrast examining activation for correct recognition of flipped- versus same-location studied pairs. An interaction between age, sex, and hippocampal sub-region, revealed that among females, but not males, 8-year-olds and 10-year-olds recruited the left head more strongly for same- versus flipped-location trials compared to adults who did not exhibit this bias towards exact reinstatement. In contrast, only 8-year-olds showed more activation for same- versus flipped-location trials in the tail; 10-year-olds and adults were undistinguishable in this sub-region. An intermediate pattern was evident in the left body.

These findings are in part consistent with earlier structural (DeMaster et al., 2014) and functional (DeMaster et al., 2013) studies suggesting that episodic retrieval depends more strongly on the anterior hippocampus in adults compared to children. Results also point to stronger reliance on the hippocampal tail

in older children, garnering some additional evidence for a potential developmental shift from more posterior to more anterior hippocampal regions. This possibility is intriguing in light of some evidence that hippocampal connectivity during embryonic development also follows a posterior-anterior direction (Bayer and Altman, 1987), and that the volume of the hippocampal head corresponds to a larger proportion of the entire hippocampus in humans compared to primates (Strange et al., 2014), inviting the speculation of a correspondence between ontogeny and phylogeny. However, whether the developmental differences reported here truly correspond to a gradual shift from reliance on more posterior to more anterior hippocampal regions can only be determined by examining within-individual change over time. Additional research will also offer the opportunity to further investigate whether the sex differences observed here reflect a meaningful difference in associative recognition and its neural substrates, as suggested by some work in aging (Bender et al., 2010). Moreover, flexibility effects along the hippocampal axis likely depend on several task-related factors. The type of material used (e.g., objects, scenes, or words) likely affects the extent of anterior versus posterior recruitment beyond flexibility demands. For example, the use of verbal materials may accentuate recruitment of anterior hippocampal regions even when flexibility manipulations are not included (e.g. Duarte et al., 2011). Additional flexibility manipulations are also warranted given that recruitment of posterior hippocampal regions has also been found in adults in tasks requiring flexible inferences (Zeithamova and Preston, 2010).

Finally, the hippocampus is structurally heterogeneous, comprising the CA subfields, dentate gyrus and subiculum (Duvernoy, 2005); these sub-regions are differentially distributed along the anterior-posterior axis (Duvernoy, 2005), follow different developmental trajectories (Lee et al., 2014), and are differentially associated with episodic memory (e.g., Bakker et al., 2008; Yassa and Stark, 2011). Thus, future investigations that provide more precise characterizations of subfield contribution to memory may help elucidate anterior-posterior differences and help paint a more consistent picture about the nature of these differences.

In conclusion, the present study revealed developmental differences in hippocampal contribution to retrieval and new evidence that flexibility demands contribute to these differences. Young children as a group failed to recruit the hippocampus for flexible retrieval favoring instead, unlike the other age groups, conditions of contextual reinstatement. The associations between flexibility and creative thinking underscore the implications of these findings not only for the development of episodic memory, but also for other forms of flexible cognition.

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