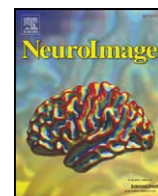




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Does the hippocampus mediate objective binding or subjective remembering?

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ABSTRACT

Human functional magnetic resonance imaging (fMRI) evidence suggests the hippocampus is associated with context memory to a greater degree than item memory (where only context memory requires item-in-context binding). A separate line of fMRI research suggests the hippocampus is associated with “remember” responses to a greater degree than “know” or familiarity based responses (where only remembering reflects the subjective experience of specific detail). Previous studies, however, have confounded context memory with remembering and item memory with knowing. The present fMRI study independently tested the *binding hypothesis* and *remembering hypothesis* of hippocampal function by evaluating activity within hippocampal regions-of-interest (ROIs). At encoding, participants were presented with colored and gray abstract shapes and instructed to remember each shape and whether it was colored or gray. At retrieval, old and new shapes were presented in gray and participants classified each shape as “old and previously colored”, “old and previously gray”, or “new”, followed by a “remember” or “know” response. In 3 of 11 hippocampal ROIs, activity was significantly greater for context memory than item memory, the context memory–item memory by remember–know interaction was significant, and activity was significantly greater for context memory–knowing than item memory–remembering. This pattern of activity only supports the binding hypothesis. The analogous pattern of activity that would have supported the remembering hypothesis was never observed in the hippocampus. However, a targeted analysis revealed remembering specific activity in the left inferior parietal cortex. The present results suggest parietal cortex may be associated with subjective remembering while the hippocampus mediates binding.

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Evidence from single-cell recording and lesion studies in rats and monkeys along with neuropsychological studies in humans suggests a primary function of the hippocampus is to bind previously experienced item and context information to construct detailed item-in-context memories (Squire, 1992; Rolls, 1996; Eichenbaum, 2000). In the last decade, evidence from human functional magnetic resonance imaging (fMRI) has also supported the view that the hippocampus binds item and context information during retrieval (subsequently referred to as the *binding hypothesis*). In one fMRI study (Yonelinas et al., 2001) red or green objects were presented at encoding. At retrieval, old objects were presented in black and participants made context memory judgments where each object was classified as “red” or “green”. In separate runs, the same objects were presented in black at both encoding and retrieval and participants made item memory judgments where each object was classified as “old” or “new”. The contrast of context memory (e.g., a “red” response to a previously red object) versus item memory produced activity in the hippocampus. In a recent fMRI study (Ross and Slotnick, 2008), abstract shapes were presented at encoding to the left or right of fixation. At retrieval, old and new shapes were

presented at fixation and participants classified each item as “old and previously on the left”, “old and previously on the right”, or “new”. In this study, context memory corresponded to accurate old shape recognition and accurate memory for spatial location, an item-hit and context-hit which is subsequently referred to as a hit-hit (e.g., responding “old-left” to a shape previously presented on the left), and item memory corresponded to accurate old shape recognition but inaccurate memory for spatial location, a hit-miss (e.g., responding “old-left” to a shape previously presented on the right). As in the previous study, the contrast of context memory versus item memory produced activity in the hippocampus. The results of these two studies support the binding hypothesis as there was greater activity in the hippocampus during context memory (which required item-in-context binding) than during item memory (where old items were successfully recognized but item-in-context binding was not required or failed). Similarly, fMRI studies have implicated the hippocampus during associative memory versus item memory (Giovanello et al., 2004, 2009) and subsequent context memory versus subsequent item memory (Davachi et al., 2003; Ranganath et al., 2004; Staresina and Davachi, 2008).

While the previous findings support the binding hypothesis, other fMRI studies have focused on the role of the hippocampus during subjective remembering (subsequently referred to as the *remembering hypothesis*). In such paradigms, participants are instructed to

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classify each item at retrieval based on their subjective experience, where “remember” responses reflect memory with specific detail and “know” or familiarity based responses reflect memory without specific detail. In support of the remembering hypothesis, the contrast of “remember” responses versus “know” or familiarity based responses has produced activity in the hippocampus (Eldridge et al., 2000; Yonelinas et al., 2005; Montaldi et al., 2006; Viskontas et al., 2009).

The preceding evidence has linked the hippocampus to either binding or remembering which supports a functional-anatomic dissociation of medial temporal lobe structures (Aggleton and Brown, 1999) where the hippocampus plays a role in recollection (retrieval of specific information) and the perirhinal cortex mediates general familiarity (Eichenbaum et al., 2007). However, the binding hypothesis and remembering hypothesis differ with regard to the specific role the hippocampus plays during recollection, with the binding hypothesis dictating this region mediates objective item-in-context binding and the remembering hypothesis specifying this region reflects the subjective experience of specific detail during retrieval.

The aim of the present investigation was to independently test these hypotheses of hippocampal function. The experimental protocol is illustrated in Fig. 1A. At encoding, colored and gray abstract shapes were presented at fixation. At retrieval, gray old and new shapes were presented at fixation and participants first classified each item as “old

and previously colored”, “old and previously gray”, or “new” and then, for “old” items, made a “remember” or “know” response. In the current paradigm, context memory refers to accurate old shape recognition and accurate context memory (e.g., responding “old and previously colored” to a previously colored shape) and item memory refers to accurate old shape recognition but inaccurate context memory (e.g., responding “old and previously colored” to a previously gray shape). Fig. 1B shows the response rates corresponding to context memory (hit-hit) or item memory (hit-miss) with “remember” or “know” responses. These response rates demonstrate that the processes under investigation are confounded, as context memory is most highly correlated with remembering and item memory is most highly correlated with knowing.

To test the binding hypothesis and the remembering hypothesis, hippocampal regions-of-interest (ROIs) were first identified and then, within each ROI, activity associated with each event type was extracted. The binding hypothesis predicts greater activity for context memory (hit-hit) than item memory (hit-miss) and the remembering hypothesis predicts greater activity associated with remembering than knowing. It was expected that the pattern of activity in most hippocampal ROIs would not differentiate between these hypotheses due to the aforementioned confound (i.e., context memory with remembering and item memory with knowing). However, when the typically paired events dissociate (i.e., context memory with knowing and item memory with remembering, two middle bars in Fig. 1B; see Hicks et al., 2002), the corresponding pattern of activity in the hippocampus should readily support the correct hypothesis and contradict the incorrect hypothesis. Specifically, if the hippocampus is preferentially associated the item-in-context binding, this should be manifested by significantly greater activity associated with context memory versus item memory, and this difference in activity should be significantly greater than that associated with remembering versus knowing (i.e., a significant interaction). The opposite pattern of activity should be observed if the hippocampus is preferentially associated with remembering, with significantly greater activity associated with remembering versus knowing, and this difference in activity should be significantly greater than that associated with context memory versus item memory. It is possible that both hypotheses are correct, such as if item-in-context binding automatically triggers subjective remembering (which would result in no significant interactions). To compliment the interaction analysis, the dissociated events—context memory with knowing and item memory with remembering—were also directly compared, as the binding hypothesis predicts greater activity during context memory-knowing than item memory-remembering and the remembering hypothesis predicts greater activity during item memory-remembering than context memory-knowing.

Materials and methods

Participants

Twelve participants took part in the study and received \$100 in remuneration. Eleven of these participants (eight females, aged 18.8–32.0) were included in the analysis (one participant was excluded because they did not make any “remember” responses). The protocol was approved by the Massachusetts General Hospital Institutional Review Board and informed consent was obtained.

Stimuli and task

Each participant completed five memory runs. During the encoding phase of each run, 32 abstract shapes spanning 5.5° of visual angle were presented twice at fixation, one set followed by the other, for 2.5 s with an inter-trial-interval of 3.0 s (for details on shape

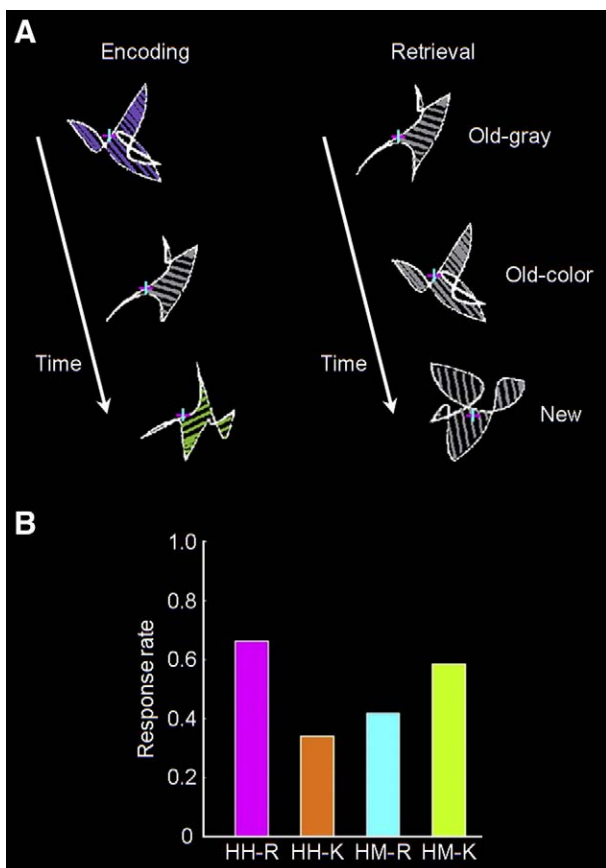


Fig. 1. Task and response rates. (A) At encoding, colored or gray abstract shapes were presented at fixation. At retrieval, gray old and new shapes were presented at fixation and participants classified each shape as “old and previously colored”, “old and previously gray”, or “new” and, for “old” shapes, made a subsequent “remember” or “know” judgment. (B) Response rates corresponding to context memory (item-hit and context-hit referred to as hit-hit) with remembering (HH-R, in magenta) or knowing (HH-K, in orange) and item memory (hit-miss) with remembering (HM-R, in cyan) or knowing (HM-K, in chartreuse). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

construction, see Slotnick and Schacter, 2004). An equal number of shapes had colored internal lines and gray internal lines where the order of shapes for each repetition was random, with the constraint that no more than three shapes of a given type were presented sequentially. During each retrieval phase, the 32 previously presented shapes (old-color, old-gray) and 16 new shapes were presented at fixation for 3.0 s with an inter-trial-interval of 6–10 s in random order, with the constraint that no more than three shapes of a given type were presented sequentially. Sets of shapes (old-color, old-gray, new) were counterbalanced across participants using a Latin Square design. At retrieval, participants pressed response buttons with their left hand to classify each shape as “old and previously colored”, “old and previously gray”, or “new” (while the shape was on the screen) and, for “old” shapes, responded “remember” or “know” to characterize their subjective experience (while the letters R K were presented just above fixation for 2.5 s). Participants had been instructed that a “remember” response meant they consciously recollected specific details about its previous occurrence, such as how it looked on the screen, the way in which it was presented, or even what they were thinking or doing at the time it was shown, while a “know” response meant they were confident the shape appeared but could not recollect any specific

details about its previous occurrence (instructions were taken from Eldridge et al., 2002, and slightly modified to refer to shapes, rather than words). It is important to point out that “remember” responses were not linked to conscious retrieval of color, but could refer to retrieval of any specific detail (e.g., item memory-remembering did not involve retrieval of color information, as the color-gray response was inaccurate).

Item memory percent correct was computed as the percentage of correctly classified old shapes and new shapes, regardless of context accuracy, weighted by the probability of each item type (Macmillan and Creelman, 2005). Context memory percent correct was computed as the percentage of items in which context was correctly identified, contingent on accurate old item recognition. Item memory and context memory d' values were computed from the corresponding hit and false alarm rates (correctly remembered colored items were classified as hits). These behavioral measures (mean \pm 1 standard error reported) were compared using two-tailed t -tests.

Data acquisition and pre-processing

MRI was conducted using a Siemens 3 Tesla Allegra or Trio Scanner with a standard head coil. Anatomic images were acquired using a magnetization prepared rapid gradient echo sequence (TR = 30 ms, TE = 3.3 ms, flip angle = 40°, field-of-view = 256 \times 256 mm², acquisition matrix = 256 \times 256, slices = 128, slice thickness = 1.33 mm, 1.33 \times 1 \times 1 mm resolution). Functional images were acquired using an echo planar imaging sequence (TR = 2000, TE = 20 ms, flip angle = 90°, field-of-view = 256 \times 256 mm², acquisition matrix = 64 \times 64, slices = 33–35, slice thickness = 4 mm, 4 mm isotropic resolution). Note, while the number of slices varied it was always sufficient for whole-brain coverage. Unless otherwise specified, analysis was conducted using BrainVoyager QX (Brain Innovation B.V., Maastricht, The Netherlands). Pre-processing of functional data included slice-time correction, motion correction, and temporal filtering by removal of linear trends and components below three cycles per run length. Functional and anatomic images were transformed into Talairach space.

ROI identification and analysis

Hippocampal ROIs were identified using separate functional and anatomic procedures. For the functional ROI analysis, a general linear model was used where, on an individual participant basis, the activity associated with each event type was modeled by convolving that event's protocol (defined by the corresponding onsets and durations) with a canonical hemodynamic response. Retrieval event durations were calculated from the time of stimulus onset until the first response. Retrieval events where participants did not respond were modeled separately. There were a sufficient number of trials in all critical conditions to conduct a meaningful analysis (i.e., old-hit-hit = 83.0 \pm 6.3, old-hit-miss = 35.9 \pm 3.2, remember = 73.5 \pm 8.1, know = 45.4 \pm 4.3, old-hit-hit-know = 26.0 \pm 2.8, old-hit-miss-remember = 16.5 \pm 3.2, new-correct rejection = 32.5 \pm 3.8; mean \pm 1 standard error). As is commonly done (Henson, 2005; Spaniol et al., 2009), activity generally associated with retrieval was identified by contrasting accurate item recognition versus correct rejection of new items. A random effect analysis was conducted to identify voxels (ROIs) within the hippocampus that were consistently active across participants at $p < 0.01$ (corrected for multiple comparisons, false discovery rate $p < 0.05$). All contrasts utilized this individual voxel threshold. Based on the known anatomic segmentation of the hippocampus (Pruessner et al., 2000; Bernasconi et al., 2003; Malykhin et al., 2007) and the surrounding cortical areas (Insausti et al., 1998; Pruessner et al., 2002), each activation/ROI was completely confined to the hippocampus. Hippocampal activity was projected onto a

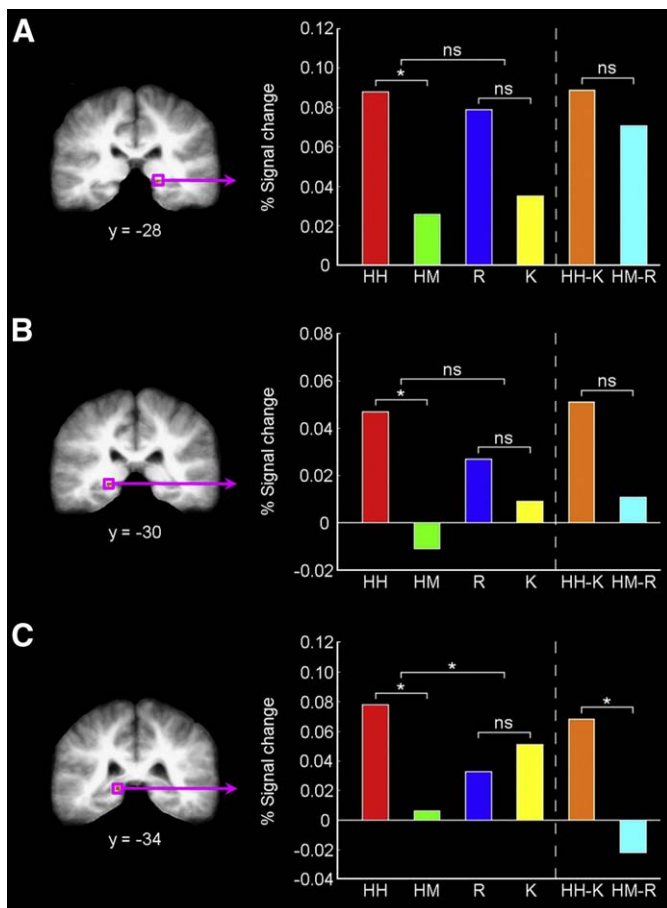


Fig. 2. Recognition memory ROIs and event-related activity. ROIs were identified by contrasting accurate item recognition versus correctly rejected new items. To the left, hippocampal activations/ROIs, demarcated by magenta squares, are shown on coronal images (at the given y-coordinate; left hemisphere is on the left). To the right, activity extracted from each ROI associated with hit-hit (HH, in red), hit-miss (HM, in green), remember (R, in blue), know (K, in yellow), and to the right of the vertical dashed line, hit-hit-know (HH-K, in orange) and hit-miss-remember (HM-R, in cyan). Statistical comparisons are illustrated by white lines with significance level indicated (ns = not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

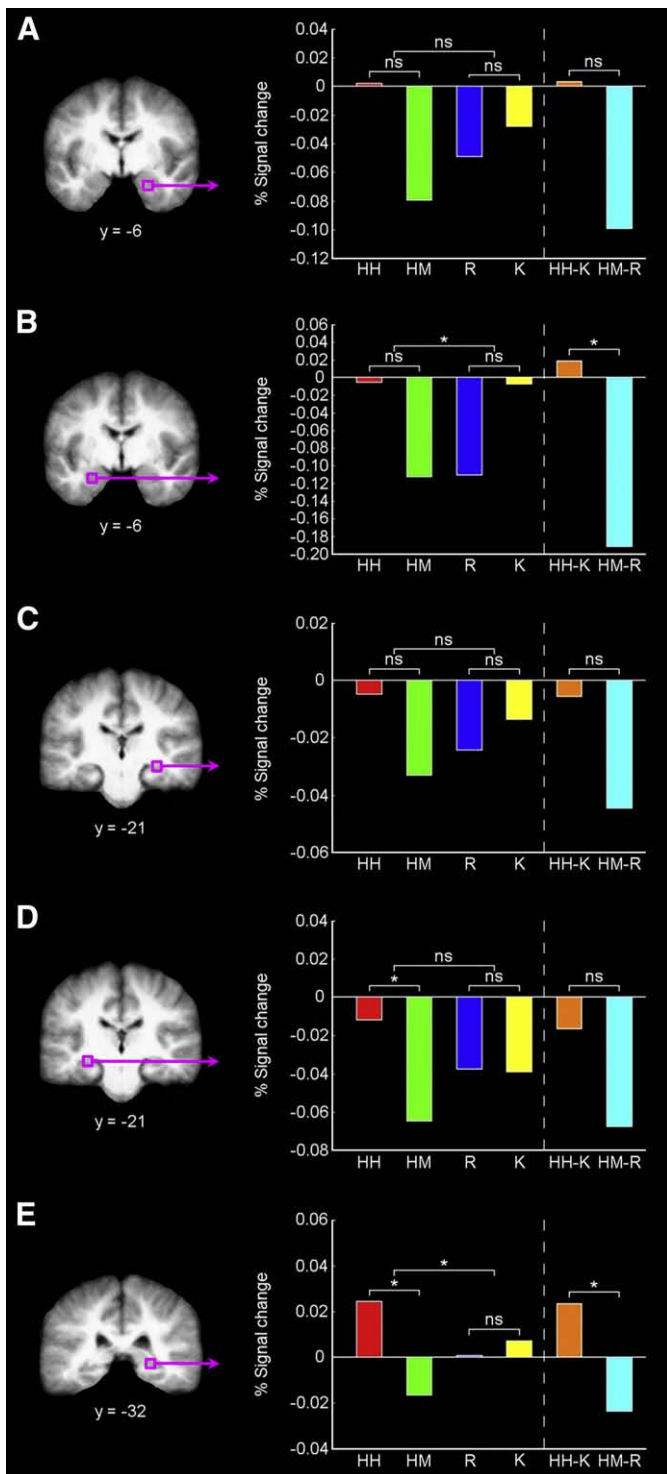


Fig. 3. Anatomic ROIs and event-related activity. ROIs were identified within the head, body, and tail of the hippocampus. To the left, hippocampal ROIs, demarcated by magenta squares, are shown on coronal images (at the given y-coordinate; left hemisphere is on the left). To the right, activity extracted from each ROI associated with hit-hit (HH, in red), hit-miss (HM, in green), remember (R, in blue), know (K, in yellow), hit-hit-know (HH-K, in orange) and hit-miss-know (HM-R, in cyan). Statistical comparisons are illustrated by white lines with significance level indicated (ns = not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

group averaged anatomic volume and cortical activity was projected onto a surface representation of a representative participant (for details on cortical segmentation and reconstruction, see Slotnick, 2005).

Anatomic ROI selection was guided by the y-coordinates of previous hippocampal activity associated with source memory, remembering, and associative retrieval (Eldridge et al., 2000; Yonelinas et al., 2001; Giovanello et al., 2004; Yonelinas et al., 2005; Montaldi et al., 2006; Ross and Slotnick, 2008; Giovanello et al., 2009). The corresponding y-coordinates had a trimodal distribution with means -6.3 ± 1.5 (range -4 to -9), -21.4 ± 0.4 (range -21 to -23), and -32.2 ± 0.7 (range -31 to -35). At these y-coordinates (-6 , -21 , and -32), the center of the hippocampus was identified in each hemisphere of the group averaged anatomic volume. These ROIs were localized to the head, body, and tail of the hippocampus using established anatomic criteria (Malykhin et al., 2007; see also, Bernasconi et al., 2003). Specifically, with reference to coronal slices, “the most posterior slice of the hippocampus head was the first slice where the uncus apex was clearly present” (Malykhin et al., 2007, p. 159) and “the most anterior slice of the hippocampus tail was the first slice where the fornix was clearly seen in full profile, or was separated from the wall of the ventricle, whichever came first” (Malykhin et al., 2007, p. 158). The corresponding y-coordinates of the most posterior right and left hemisphere hippocampus head were -16 and -17 , respectively, and the corresponding y-coordinates of the most anterior right and left hemisphere hippocampus tail were -30 and -32 , respectively. Based on the y-coordinates of previous retrieval studies and anatomic localization procedures described immediately above, the resultant hippocampus head ROI coordinates were $(22, -6, -20)$ and $(-23, -6, -20)$, hippocampus body ROI coordinates were $(29, -21, -8)$ and $(-27, -21, -9)$, and hippocampus tail ROI coordinates were $(23, -32, -1)$ and $(-22, -32, -3)$.

The magnitude of event-related activity within each ROI was estimated using timecourse analysis (Slotnick, 2005). The center coordinate of each ROI was identified a priori and then the mean event-related activity from -2 to 12 s following stimulus onset was extracted within a cube (spanning 5 mm) centered at this location. Each activation timecourse was then linear trend corrected and baseline corrected from -2 to 0 s following stimulus onset. For each event, the mean activity from 4 to 8 s following stimulus onset was used to conduct statistical comparisons. This time window contained the peak of the activation timecourse generated by averaging hit-hit-remember, hit-hit-know, hit-miss-remember, and hit-miss-know activity in all functional hippocampal ROIs. As the hypotheses under investigation corresponded to previously reported unidirectional differences in magnitude (i.e., hit-hit greater than hit-miss and remember greater than know), one-tailed t -tests were employed. Binomial tests ($p = q = 0.5$) were used to evaluate activity across all hippocampal ROIs.

Results

Behavioral results

Item memory performance and context memory performance were at intermediate levels and did not differ, as measured by percent correct (item memory percent correct = 73.0 ± 1.7 , context memory percent correct = 69.4 ± 2.5 , $t(10) = 1.19$, $p > 0.20$, chance = 50% correct) and d' (item memory $d' = 1.05 \pm 0.14$, context memory $d' = 1.07 \pm 0.15$, $t(10) < 1$). The similarity in context memory and item memory strength suggests differential hippocampal activity was not due to differences in task difficulty.

Recognition memory ROIs

Hippocampal ROIs were first identified by contrasting accurate old item recognition, regardless of context accuracy (hit-hit, hit-miss) or “remember”–“know” response, versus correctly rejected new items. This contrast yielded three hippocampal ROIs, one in the right

hemisphere and two in the left hemisphere (Fig. 2). Fig. 2A shows the right hippocampal ROI (Talairach coordinate 19, -28, -2) where activity was significantly greater during context memory than item memory ($t(10)=1.96, p<0.05$), activity was not significantly greater during remembering than knowing ($t(10)=1.35, p=0.10$), the interaction was not significant ($F(1,10)<1$), and context memory-knowing was not significantly different than item memory-remembering ($t(10)<1$). This pattern of activity provides weak support for the binding hypothesis, as it is also consistent with the remembering hypothesis given the lack of significant interaction and dissociated event difference. In a left hippocampal ROI (Talairach coordinate -21, -30, -4) shown in Fig. 2B activity was significantly greater during context memory than item memory ($t(10)=2.62, p<0.05$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was not significant ($F(1,10)=1.53, p=0.12$), and context memory-knowing was not significantly different than item memory-remembering ($t(10)=1.13, p=0.14$). As in the previous ROI, this pattern of activity provides weak support for the binding hypothesis, as it is also consistent with the remembering hypothesis given the lack of significant interaction and dissociated event difference. Fig. 2C shows the other left hippocampal ROI (Talairach coordinate -14, -34, 1) where activity was significantly greater during context memory than item memory ($t(10)=2.50, p<0.05$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was significant ($F(1,10)=4.59, p<0.05$), and context memory-knowing was significantly greater than item memory-remembering ($t(10)=2.03, p<0.05$). This pattern of activity provides strong support for the binding hypothesis. It should be highlighted that in this ROI know related activity was greater in magnitude than remember related activity (although this difference was not significant), which is in direct opposition to the pattern of activity predicted by the remembering hypothesis.

It is possible that the recognition memory contrast employed above may have had reduced sensitivity because new correct rejections (which served as baseline) might have elicited a novelty response (Habib et al., 2003; Kumaran and Maguire, 2009). However, the magnitude of new correct rejection activity was not significantly greater than zero in any of these ROIs (all $t_s<1$), which indicates new correct rejections did not produce a novelty response. Still, to directly address this issue, hippocampal ROIs were also identified by conducting an omnibus test with events hit-hit-remember, hit-hit-know, hit-miss-remember, and hit-miss-know. This yielded two hippocampal ROIs at precisely the same coordinates as the right hemisphere ROI and more posterior left hemisphere ROI reported above, indicating the use of new correct rejections as baseline in the recognition memory contrast above did not reduce sensitivity.

Anatomic ROIs

Anatomically defined ROIs were identified in the head, body, and tail of the hippocampus at y -coordinates computed from a meta-analysis of previous retrieval studies (see Materials and methods). This yielded six hippocampal ROIs, although to ensure the results were independent the left hippocampal tail ROI (Talairach coordinate -22, -32, -3) was excluded from the analysis due to overlap with a previous left hippocampal ROI (Talairach coordinate -21, -30, -4; these ROIs had 13 mm³ in common). Related to this point, there was no overlap between any of the ROIs analyzed in the present study (i.e., each ROI was compared to all other ROIs in the entire study and there was no overlap). Fig. 3A shows the right hippocampal head ROI (Talairach coordinate 22, -6, -20) where activity was not significantly greater during context memory than item memory ($t(10)=1.32, p=0.11$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was not significant ($F(1,10)=1.35, p=0.14$), and context memory-knowing

was not significantly different than item memory-remembering ($t(10)<1$). This null pattern of activity does not support either hypothesis. In the left hippocampal head ROI (Talairach coordinate -23, -6, -20) shown in Fig. 3B activity was not significantly greater during context memory than item memory ($t(10)=1.75, p=0.055$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was significant ($F(1,10)=5.90, p<0.05$), and context memory-knowing was significantly greater than item memory-remembering ($t(10)=1.93, p<0.05$). The significant interaction and dissociated event difference provides some support for the binding hypothesis, but the non-significant context memory versus item memory difference makes the interpretation of this pattern of activity unclear (so it was not taken to support either hypothesis). Fig. 3C shows the right hippocampal body ROI (Talairach coordinate 29, -21, -8) where activity was not significantly greater during context memory than item memory ($t(10)=1.41, p=0.094$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was not significant ($F(1,10)=1.87, p=0.10$), and context memory-knowing was not significantly different than item memory-remembering ($t(10)=1.18, p=0.13$). This null pattern of activity does not support either hypothesis. In the left hippocampal body ROI (Talairach coordinate -27, -21, -9) shown in Fig. 3D activity was significantly greater during context memory than item memory ($t(10)=2.07, p<0.05$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was not significant ($F(1,10)=1.92, p=0.098$), and context memory-knowing was not significantly different than item memory-remembering ($t(10)=1.18, p=0.13$). This pattern of activity provides weak support for the binding hypothesis, as it is also consistent with the remembering hypothesis given the lack of significant interaction and dissociated event difference. Fig. 3E shows the right hippocampal tail ROI (Talairach coordinate 23, -32, -1) where activity was significantly greater during context memory than item memory ($t(10)=2.48, p<0.05$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was significant ($F(1,10)=3.81, p<0.05$), and context memory-knowing was significantly greater than item memory-remembering ($t(10)=1.87, p<0.05$). This pattern of activity provides strong support for the binding hypothesis.

Context memory versus item memory ROI

The previous procedures may not have been sufficiently sensitive to identify hippocampal ROIs that were specifically associated with context memory versus item memory or remembering versus knowing. To address this, planned contrasts of context memory versus item memory and remembering versus knowing were conducted. It should be noted that the ROIs identified by each contrast were expected to produce the largest differential activity for the events entered into the contrast; however, both contrasts were subjected to the identical analysis so the procedure was balanced overall. Of particular importance is the pattern of activity for events that were not used to identify a given ROI. If the binding hypothesis is correct activity will be greater during context memory than item memory in remember versus know ROIs, but if the remembering hypothesis is correct activity will be greater during remembering than knowing in context memory versus item memory ROIs.

The contrast of context memory versus item memory yielded one hippocampal ROI (Talairach coordinate -15, -36, 4) shown in Fig. 4 where activity was significantly greater during context memory than item memory ($t(10)=3.62, p<0.01$), activity was not significantly greater during remembering than knowing ($t(10)<1$), the interaction was significant ($F(1,10)=13.09, p<0.01$), and context memory-knowing was significantly greater than item memory-remembering ($t(10)=3.68, p<0.01$). This pattern of activity provides strong support for the binding hypothesis.

Remember versus know ROIs

The remember versus know contrast produced two hippocampal ROIs (Figs. 5A, B). Fig. 5A shows the right hippocampal ROI (Talairach coordinate 27, -22, -11) where activity was not significantly greater during context memory than item memory ($t(10)=1.14$, $p=0.14$), activity was significantly greater during remembering than knowing ($t(10)=1.82$, $p<0.05$), the interaction was not significant ($F(1,10)<1$), and item memory-remembering was not significantly different than context memory-knowing ($t(10)<1$). Fig. 5B shows the left hippocampal ROI (Talairach coordinate -16, -31, -3) where activity was not significantly greater during context memory than item memory ($t(10)=1.07$, $p=0.16$), activity was significantly greater during remembering than knowing ($t(10)=2.69$, $p<0.05$), the interaction was not significant ($F(1,10)=1.12$, $p=0.16$), and item memory-remembering was not significantly different than context memory-knowing ($t(10)=1.01$, $p=0.17$). Both remember versus know ROIs had the same pattern of activity which provides weak support for the remembering hypothesis, as it is also consistent with the binding hypothesis given the lack of significant interactions and dissociated event differences. Of importance, the remember versus know contrast produced a greater number of ROIs than the context memory versus item memory contrast, which argues against the possibility that the lack of remembering specific effects in the hippocampus was due to insufficient power.

Although the remember versus know contrast identified two hippocampal ROIs with greater activity associated with remembering than knowing, it is noteworthy that the interactions and dissociated event differences were not significant. As such, the results thus far have not revealed any evidence indicating the hippocampus is associated with remembering per se. Wheeler and Buckner (2004) contrasted remember versus know and reported activity in two left inferior parietal cortex regions (BA 40/39; remember related activity has also been reported in BA 39 by Montaldi et al., 2006). This region was evaluated in the present study with the singular aim of uncovering activity specifically associated with remembering. The remember versus know contrast identified two left lateral inferior parietal activations/ROIs (Fig. 5C), one in the supramarginal gyrus (BA40, Talairach coordinate -52, -54, 34; 5.1 mm from those reported by Wheeler and Buckner, 2004) and the other in the angular gyrus (BA39, Talairach coordinate -48, -67, 28; 6.8 and 13.0 mm from those reported by Montaldi et al., 2006, and Wheeler and Buckner, 2004, respectively). Fig. 5C (top) shows the supramarginal gyrus ROI where activity was significantly greater during context memory than item memory ($t(10)=2.12$, $p<0.05$), activity was

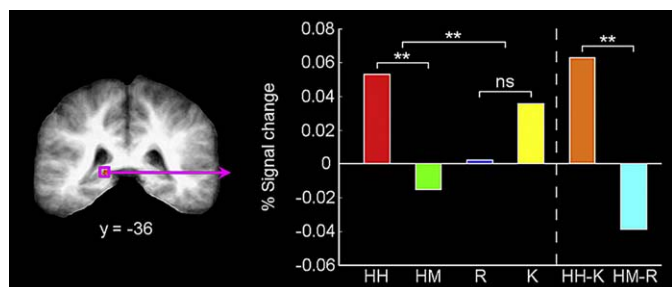


Fig. 4. Context memory versus item memory ROI and event-related activity. The ROI was identified by contrasting context memory (hit-hit) versus item memory (hit-miss). To the left, the hippocampal activation/ROI is shown on a coronal image (at the given y-coordinate; left hemisphere is on the left). To the right, activity extracted from the ROI associated with hit-hit (HH, in red), hit-miss (HM, in green), remember (R, in blue), know (K, in yellow), hit-hit-know (HH-K, in orange) and hit-miss-remember (HM-R, in cyan). Statistical comparisons are illustrated by white lines with significance level indicated (ns = not significant, $*p<0.05$, $**p<0.01$, $***p<0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significantly greater during remembering than knowing ($t(10)=3.77$, $p<0.01$), the interaction was not significant ($F(1,10)<1$), and item memory-remembering was not significantly different than context memory-knowing ($t(10)=1.06$, $p=0.16$). Fig. 5C (bottom) shows the angular gyrus ROI where activity was not significantly greater during context memory than item memory ($t(10)<1$), activity was significantly greater during remembering than knowing ($t(10)=4.95$, $p<0.001$), the interaction was significant ($F(1,10)=5.59$, $p<0.05$), and item memory-remembering was significantly greater than context memory-knowing ($t(10)=2.47$, $p<0.05$). The latter pattern of activity, which was never observed in the hippocampus, suggests remembering may be preferentially associated with the left inferior parietal cortex. It is notable that these significant remember greater than know effects in left inferior parietal cortex were driven by event-related decreases, which is consistent with previous findings (Wheeler and Buckner, 2004; Montaldi et al., 2006).

Discussion

Four distinct patterns of activity were observed in the 11 hippocampal ROIs evaluated (Table 1). In three of the ROIs, there were no significant context memory versus item memory or remembering versus knowing differences which does not support either hypothesis (Figs. 3A, B, C). In two of the ROIs, activity was significantly greater for remembering than knowing providing weak support for the remembering hypothesis, as the interactions and dissociated event differences were not significant (Figs. 5A, B). In three of the ROIs, activity was significantly greater for context memory than item memory providing weak support for the binding hypothesis, as the interactions and dissociated event differences were not significant (Figs. 2A, B, and 3D). In the other three ROIs, the pattern of activity provided strong support for the binding hypothesis, as activity was significantly greater for context memory than item memory, activity was greater for knowing than remembering (in opposition to that predicted by the remembering hypothesis), and the interactions and dissociated event differences were significant (Figs. 2C, 3E, and 4). The pattern of activity across the full set of hippocampal ROIs provided additional support for the binding hypothesis, as activity was only greater for remembering than knowing in 5 of 11 ROIs, which does not differ from chance ($p>0.20$; Binomial test), while activity was greater for context memory than item memory in all 11 ROIs ($p<0.001$; Binomial test).

It should be highlighted that the three ROIs where activity was significantly greater for context memory than item memory with significant interactions and dissociated event differences were all located in the tail of the hippocampus (Figs. 2C, 3E, and 4; Table 1). By comparison, in the body of the hippocampus ROI activity was significantly greater for context memory than item memory (Figs. 2A, B, and 3D) or significantly greater for remembering than knowing (Figs. 5A, B), but the interactions and dissociated event differences were not significant. These results suggest a functional processing distinction, where the hippocampus tail is associated with binding and the hippocampus body is associating with both binding and remembering. While this model of hippocampal function is speculative, it compliments previous processing distinctions across the long axis of the hippocampus (encoding versus retrieval, Lepage et al., 1998; Schacter and Wagner, 1999; Prince et al., 2005; exact versus flexible associated retrieval, Giovanello et al., 2009).

While the hippocampus appears to mediate binding of information during retrieval, cortical regions may be associated with subjective aspects of retrieval. In a recent fMRI study, Kirwan, Wixted, and Squire (2008) found that when subsequent item memory confidence was held constant, prefrontal cortex activity was linearly correlated with subsequent context memory confidence. Although these context memory results are seemingly at odds with the present findings, the linear trend analysis used in that study relied on a disproportional

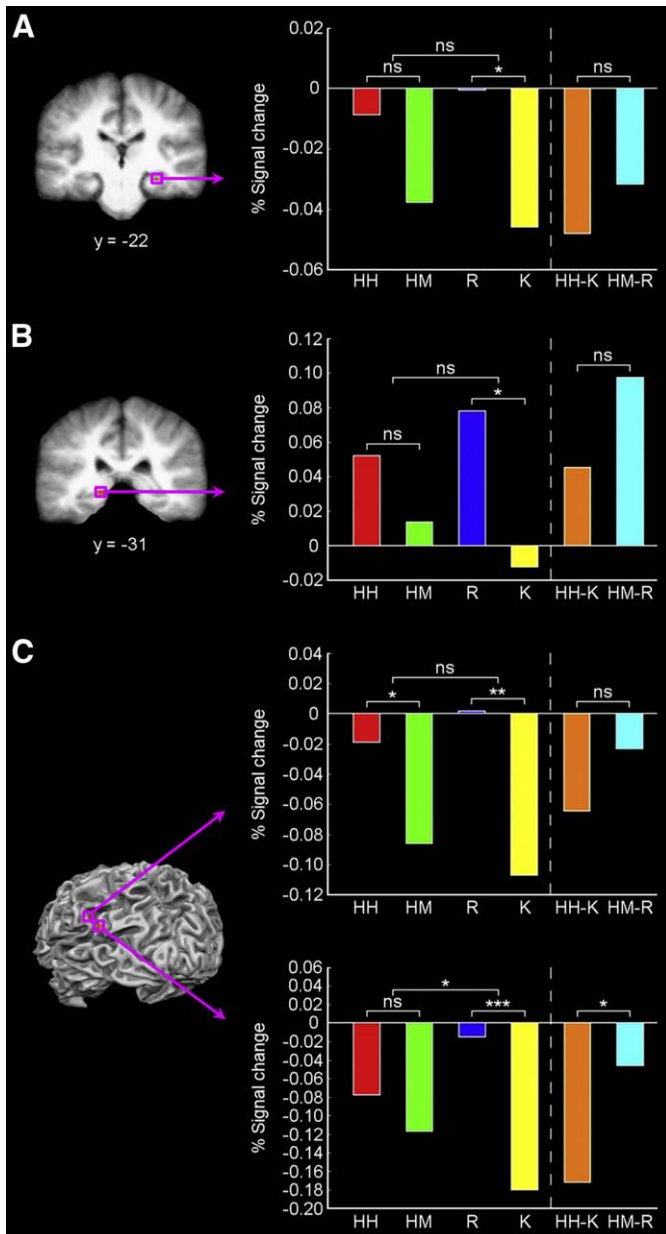


Fig. 5. Remember versus know ROIs and event-related activity. ROIs were identified by contrasting remember versus know. To the left in (A) and (B), hippocampal activations/ROIs are shown on coronal images (at the given y-coordinate; left hemisphere is on the left). To the left in (C), left inferior parietal activations/ROIs are shown on a cortical surface representation (lateral-posterior view; gyri and sulci are in light and dark gray, respectively). To the right, activity extracted from each ROI associated with hit-hit (HH, in red), hit-miss (HM, in green), remember (R, in blue), know (K, in yellow), hit-hit-know (HH-K, in orange) and hit-miss-remember (HM-R, in cyan). Statistical comparisons are illustrated by white lines with significance level indicated (ns = not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

number of accurate (higher confidence) context memory ratings. As such, hippocampal activity in that study should arguably be of relatively constant magnitude across (accurate) context confidence, rather than linearly increasing, due to successful binding of item and context information. Based on this, the prefrontal cortex activity reported by Kirwan et al. may have been associated with context memory confidence rather than memory accuracy. In support of this possibility, there is evidence that the prefrontal cortex is preferentially associated with memory confidence while the medial temporal lobe is preferentially associated with memory accuracy (Chua et al.,

Table 1
Hippocampal ROI results.

Identification method	Talairach coordinates			Region	Support for hypothesis	
	x	y	z		Binding	Remembering
Recognition > N-CR	19	-28	-2	Body	Weak	None
Recognition > N-CR	-21	-30	-4	Body	Weak	None
Recognition > N-CR	-14	-34	1	Tail	Strong	None
Anatomic	22	-6	-20	Head	None	None
Anatomic	-23	-6	-20	Head	None	None
Anatomic	29	-21	-8	Body	None	None
Anatomic	-27	-21	-9	Body	Weak	None
Anatomic	23	-32	-1	Tail	Strong	None
Hit-hit > Hit-miss	-15	-36	4	Tail	Strong	None
Remember > Know	27	-22	-11	Body	None	Weak
Remember > Know	-16	-31	-3	Body	None	Weak

N-CR = new-correct rejection.

2004; Kao, Davis, and Gabrieli, 2005). Considered in conjunction with the present and previous results suggesting the left inferior parietal cortex is associated with remembering to a greater degree than knowing (Wheeler and Buckner, 2004; Montaldi et al., 2006), prefrontal and parietal cortex may be associated with the subjective experience relating to memory (as measured by confidence ratings or remember-know judgments, as described above, or as manifested by perceived oldness; Wagner et al., 2005; Cabeza et al., 2008). In contrast, objective binding of memorial information appears to be mediated by the hippocampus. These characterizations are further supported by evidence suggesting the prefrontal cortex is associated with relatively slow post-retrieval monitoring (Schacter et al., 1997; Goldmann et al., 2003) while the hippocampus mediates rapid item-in-context binding (Rolls et al., 1989; Slotnick, 2009).

Squire and colleagues have proposed that context memory and item memory similarly depend on the hippocampus (Manns et al., 2003; Gold et al., 2006; Squire et al., 2007). The present results support this view to some degree, as assessment of activity across all hippocampus ROIs was not only significantly greater for context memory than item memory ($t(10) = 8.06$, $p < 0.001$) but was also significantly greater for item memory as compared to new correct rejections ($t(10) = 1.93$, $p < 0.05$; although activity did not differ between item memory and old misses, $t(10) < 1$). A similar pattern of results has been reported based on single-cell recording in the human hippocampus (Rutishauser et al., 2006; Rutishauser et al., 2008). These findings suggest the hippocampus is associated with both context memory and item memory. Still, the present and previous results (Yonelinas et al., 2001; Davachi et al., 2003; Giovanello et al., 2004; Ranganath et al., 2004; Ross and Slotnick, 2008; Staresina and Davachi, 2008; Giovanello et al., 2009; Viskontas et al., 2009) indicate the hippocampus is preferentially associated with context memory. It may be that the hippocampus can mediate binding of any item attribute during retrieval, including the individual features that comprise an item or the context(s) in which it was presented. This would predict an increasing level of hippocampal activation as this region binds increasing amounts of information, as has been recently reported (Staresina and Davachi, 2008).

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