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Interactive report

# fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory[1]

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**Abstract**

Richly detailed memories for particular events depend on processes that bind individual features of experience together. Previous cognitive behavioral research indicates that older adults have more difficulty than young adults in conditions requiring feature binding. We used functional magnetic resonance imaging (fMRI) during a working memory task to identify neural substrates of this age-related deficit in feature binding. For young, but not older, adults there was greater activation in left anterior hippocampus on combination trials (remember objects together with their locations) than on trials in which participants were told to remember only which objects or only which locations occurred. The results provide neuroimaging evidence for an age-related hippocampal dysfunction in feature binding in working memory. 

*Theme:* Neural basis of behavior

*Topic:* Cognition

*Keywords:* Working memory; Feature binding; Aging; Hippocampus; Prefrontal cortex

## 1. Introduction

Creating new associations between the individual features of experience (e.g., colors, locations, objects) is critical for establishing episodic (autobiographical) memories. Recent behavioral evidence suggests that, compared to young adults, older adults show a deficit in remembering combinations of features, even when they show equivalent memory for the individual features [10]. Establishing such associations is presumably facilitated by working memory [3] processes by which people reflect [36] on current experience. That is, the processes by which information is maintained and manipulated in working memory constitute encoding processes that determine later long-term memory [36]. Consistent with the idea that age-related deficits in long-term memory may be related at least in part to encoding deficits, older adults show disruptions in feature binding during working memory tasks [49]. Although the brain regions that play a role in maintaining *individual* features in working memory have received considerable attention [66], neuroimaging studies have only recently begun to explicate the processes mediating the *binding* together of individual features [32,33,54]. Furthermore, the neural correlates of age-related deficits in binding processes remain to be identified.

In order to explore the neural differences that may underlie age-related binding deficits, we used fMRI to investigate neural activity during working memory tasks that did and did not require binding features. Young and older adults were tested in three working memory tasks that required them to hold information in working memory and respond on the basis of memory for either individual features or feature combinations (see Fig. 1). Across conditions, the study stimuli were the same while the instructions and type of test varied. During different blocks of trials, participants were tested on either object, location, or combined object+location information (see Fig. 1).

There have been relatively few neuroimaging studies of memory in normal, older adults. A common strategy in the

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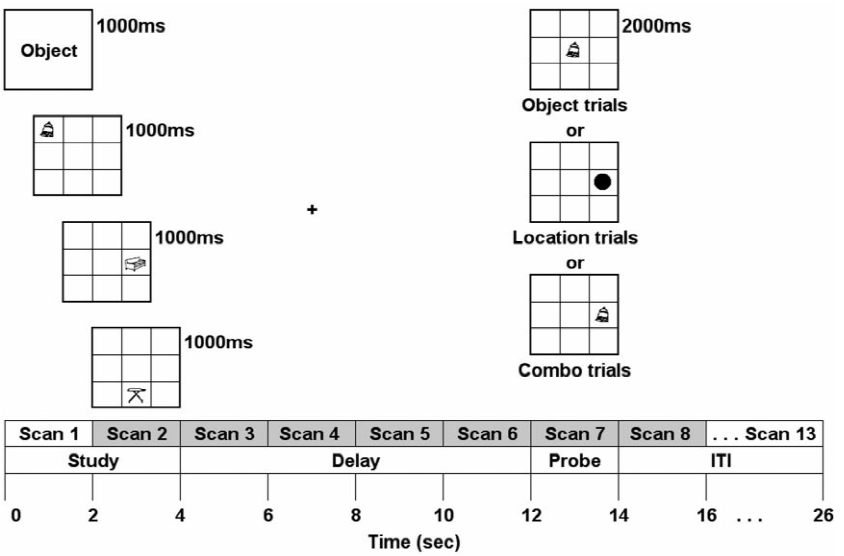


Fig. 1. Schematic of the working memory task (see Materials and methods for details).

available studies is to compare young and older adults on a memory task (e.g., old/new recognition), usually with reference to a non-memory baseline control (e.g. [44]). However, here we are not interested in overall differences in levels of neural activation between young and older adults (i.e., main effect of age), but rather in the relative performance of young and older adults on memory tasks that require binding and memory tasks that do not (i.e., an age by condition interaction). Thus, our analysis was designed to identify areas that were *differentially* active between young and older adults in the combination condition relative to the single feature conditions.

Hippocampus and prefrontal cortex (PFC) regions were of particular interest based on the extensive prior literature suggesting that these regions are involved in feature binding. Damage to the hippocampus and associated structures can produce a profound deficit in episodic memory, and it has been proposed that such amnesia reflects disruption of hippocampally-mediated feature binding processes [13,70]. Consistent with this proposal, amnesics [59], including those with identified hippocampal lesions [43], show a deficit, compared to normal controls, on tasks designed to test binding. Furthermore, recent PET studies indicate that the hippocampus is involved in the formation of semantic and inter-item associations, i.e., binding [32,33]. Damage to PFC usually does not produce marked anterograde amnesia. It can, however, impair source memory (e.g., remembering where an object was seen, what color it was, who said what) more than item memory (e.g., remembering the object or what was said) [64]; furthermore, recent neuroimaging evidence shows areas of PFC that are more active during tests requiring source information than tests requiring only old/new discrimination [35,50,56,61]. Greater PFC activation has also been found during a working memory task in which people maintained integrated feature information versus a task in which they maintained the features separately [54]. In addition, electrophysiological recordings in monkeys during working memory tasks show that some cells in prefrontal cortex code for both object and location [55].

Together, such findings are consistent with the idea that feature binding depends on a frontal-hippocampal circuit in which PFC influences the opportunities for the hippocampal binding critical for long-term episodic memory [8,12,37], for example, by maintaining conjunctions of features and/or modulating hippocampal activity. There is extensive evidence that PFC plays a role in maintaining information in working memory [20], and reciprocal connections between PFC and hippocampus are consistent with such a circuit [29].

If PFC and hippocampal regions jointly participate in a feature binding circuit, then we would expect to find evidence of disruption in activity in one or both of these regions in older, compared to younger, adults. Interestingly, Grady et al. [30] found hippocampal activation in young but not older adults during encoding of faces — a task that may involve the binding of featural information (e.g., [43], Exp. 2), although the relation between hippocampal binding processes and processes subserved by the fusiform 'face area' [40] remain to be explored. Indirect evidence for the specific role of PFC and hippocampal regions in feature binding comes from studies showing a correlation between older adults' scores on neuropsychological tests used clinically to assess frontal and medial-temporal function and their performance in source identification tasks [18,27,34]. Nevertheless, neuropsychological tests provide only suggestive evidence about underlying brain regions [62]. Thus, more direct evidence about the neural mechanisms that may account for age-related feature binding deficits is needed.

## 2. Materials and methods

The study was approved by the Institutional Review Boards at Princeton University and the University of Pennsylvania and all participants gave written, informed consent. The participants were six, right-handed young adults (*M* age=23.7 yrs, *M* education=17.5 yrs) and six, right-handed, older adults (*M* age=67.0 yrs, *M* education=15.5 yrs). Older adults reported themselves in good health, did not have a history of strokes, seizures, or loss of consciousness, had normal scores on the MMSE, Beck Depression Inventory, and the Geriatric Mood Assessment, and were not taking any psychotropic medications.

Each trial (see Fig. 1) consisted of three 3×3 grids, presented sequentially; each grid contained a different object (colored line drawing) [69] in a different location, excluding the center cell. Conditions were blocked (12 trials per block) and blocks were presented in pseudo-random order so each condition occurred in each third of the experimental session. There were three such orders, each used for two young and two older adults. In all cases, the condition name (instructing participants to remember object or location or both) appeared for 1 s, followed by the three study arrays which appeared for 1 s each, followed by an 8-s retention interval (during which time a '+' appeared). A test probe then appeared for 2 s, followed by a 12-s intertrial interval (ITI). Thus each trial was 26 s including the ITI. On object trials, the test probe was a black and white object in the center of a grid; participants responded (via right-handed button press) 'yes' if it corresponded to a study item on that trial and 'no' (left hand) if it did not. On location trials, the test probe was a black dot in one of the grid cells (other than the center) and participants responded 'yes' if it appeared in a location that an object had occupied on that trial and 'no' if it appeared elsewhere. On combination trials, a black and white object appeared in one of the periphery cells and participants responded 'yes' if the test probe corresponded exactly to a studied object/location pairing and 'no' if it did not. Distractor items in this condition were always re-pairings of objects and locations from the current trial. The objects on each trial were drawn randomly from a set of eight to equate the number of different objects with the number of different locations, with the restriction that each item appear equally often in each condition. Stimuli were presented using PsyScope software [11]. Thirteen volumes were obtained per trial, one every 2 s (see Fig. 1).

Data were acquired at the University of Pennsylvania Medical Center using a 1.5 T Signa scanner (GE Medical Systems). Sagittal and axial T1-weighted anatomical images were obtained for every participant. A gradient echo, echoplanar sequence (TR=2000 ms, TE=50 ms) was used to acquire functional data sensitive to the blood oxygenation level dependent (BOLD) signal [51]. Resolution was 3.75×3.75 mm in plane, and 5 mm between planes (21 axial slices of functional data were acquired).

Data were motion corrected using a 6 parameter automated algorithm (AIR) [73]; images for all participants were co-registered to a common (young adult) reference brain using a 12 parameter automated algorithm (AIR), mean normalized to equate mean global signal intensity across all images over time and between subjects, and spatially smoothed using a 3D gaussian filter (8 mm FWHM). NIS software (developed by the Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh, and the Neuroscience of Cognitive Control Laboratory, Princeton University) was used for the statistical analyses. The raw mean normalized signal values for each voxel were examined using a mixed Analysis of Variance with the following factors: Age (young, old)×Condition (object, location, combination)×Scan (2–8, see Fig. 1)×Cycle (1st, 2nd, and 3rd repetition of each condition), with subject as a random factor. Scans 2–8 were examined to include stimulus encoding and maintenance processes that presumably underlie feature binding. The regions of primary interest were: (a) those that were differentially active between conditions for young and older adults as indicated by a significant Age×Condition interaction (where a region included at least 4 contiguous voxels [25], each of which was significant in the Age×Condition interaction at $P<0.025$) that was not qualified by higher order interactions and in which subsequent planned comparisons showed that activation in the combination condition was greater than both the object and the location conditions ($P<0.025$), and (b) those that showed a main effect of condition (4 contiguous voxels, each at $P<0.025$) that was not qualified by any interaction with age and that showed the combination condition was greater than both feature conditions in subsequent planned comparisons ($P<0.025$). To localize the regions of interest, the data were overlaid on the structural images of the common reference brain (one of the young subjects) which had been transformed to Talairach space [71] using AFNI [17].

## 3. Results

### 3.1. Behavioral data

Consistent with previous findings [49], older adults demonstrated a deficit in accuracy (corrected recognition) in the combination condition (*M* young=0.95 [*SD*=0.05]; *M* older=0.74 [*SD*=0.25]; $t(10)=2.07$, $P=0.06$) but not the object (*M* young=0.95 [*SD*=0.07]; *M* older=0.95 [*SD*=0.05]; $P>0.10$) or location (*M* young=0.93 [*SD*=0.08]; *M* older=0.88 [*SD*=0.14]; $P>0.10$) conditions.

### 3.2. fMRI data

We were interested in areas where an Analysis of Variance showed a condition by age interaction and where subsequent planned comparisons between conditions

showed greater activity in the combination condition than both the object and the location condition for either age group. Areas that showed patterns in the subsequent contrasts in which the combination condition was greater than only object (or only location) were considered likely to be object (or location) processing areas and not specific to feature binding. One region met the criteria for a feature binding area: An area of left anterior hippocampus (see Fig. 2a). In this area, for young adults activation was significantly greater in the combination condition than in both the location and object conditions. This was not the case for the older adults, where activation was lowest in the combination condition (and significantly below that of the object condition). This pattern indicates that, compared to a feature only memory task, a memory task requiring feature binding results in relatively greater hippocampal activation in young, but not older, adults.

An area of right BA 10 (see Fig. 2b) also showed a significant age by condition interaction. For the young adults, the subsequent contrasts showed that the activation in the combination condition was greater than the location condition but not significantly greater than the object condition. For the older adults, activation in both the combination and location conditions was significantly lower than that in the object condition. Although this area did not meet our criteria for being a binding region in either age group, we present it here because of recent converging results [54]. Prabhakaran et al. [54], looking only at young adults, found a region of right BA 10 that was more active in a working memory task when they presented to-be-remembered features in an integrated fashion than when they presented the features separately. The area in Fig. 2b is in the medial frontal gyrus, a brain region that appears to be included in the Prabhakaran et al. integration area (although Prabhakaran et al. do not provide Talairach coordinates for their activation, visual

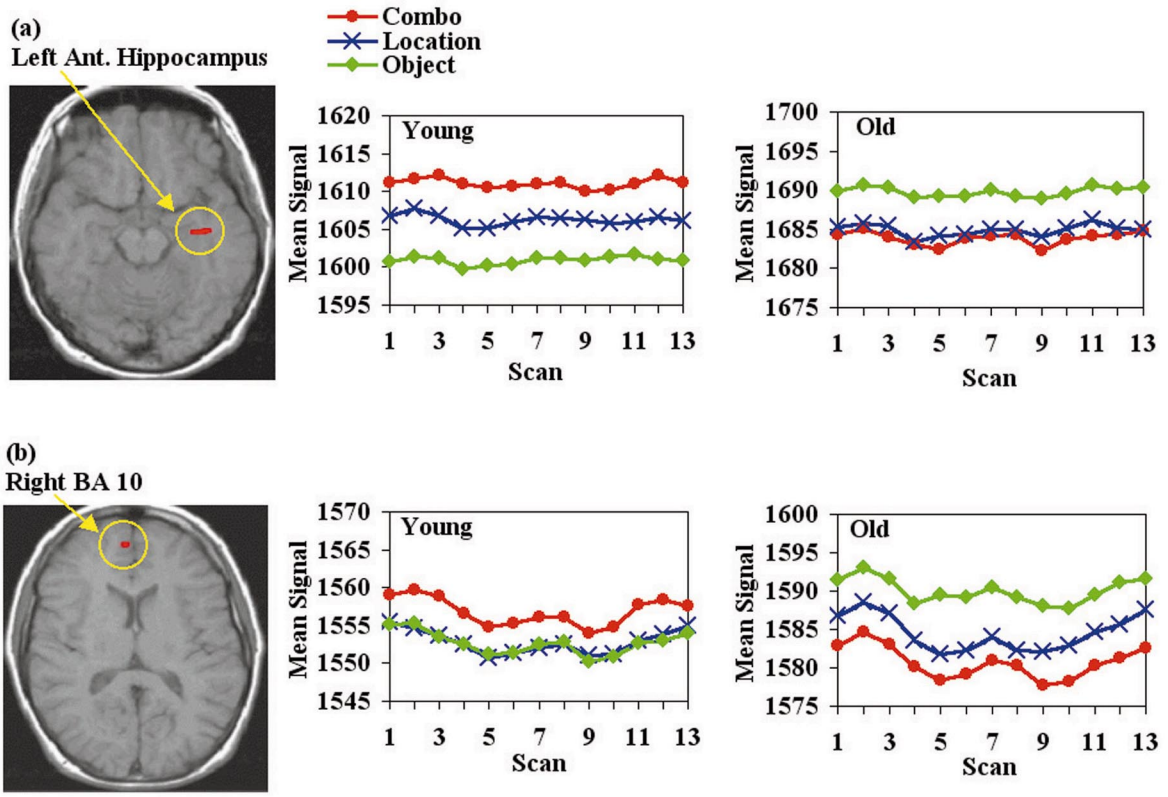


Fig. 2. Hippocampal and prefrontal regions showing age by condition interaction. (a) Area of left anterior hippocampus (Talairach coordinates: $x=-33$, $y=-14$, $z=-11$) that showed an Age×Condition interaction (max. $F$ for the ROI=5.72) and in which the activation in the combination condition was greater than both the object (max. $t$ for the ROI=3.33) and location (max. $t$ for the ROI=3.02) conditions in the young adults. For the older adults, activation in the combination condition was significantly lower than the object condition (max. $t$ for the ROI=2.86). The points on the $X$-axis correspond to scans (2 s each) and the $Y$-axis is mean signal. Only data from scans 2–8 (also see Fig. 1) were included in the ANOVAs but data from the entire trial, including intertrial interval, are presented in the figure. Note that group average activations are mapped onto a single (young) reference brain; the left side of the image shown corresponds to the right side of the brain. (b) Area of right BA 10 (Talairach coordinates: $x=6$, $y=54$, $z=13$) that showed an Age×Condition interaction (max. $F$ for the ROI=6.30) and in which the activation in the combination condition was greater than the location condition (max. $t$ for the ROI=2.69) in the young adults. For the older adults, activation in both the combination (max. $t$ for the ROI=3.08) and location (max. $t$ for the ROI=4.00) condition was lower than the object condition.

inspection suggests that our activation overlaps with, or is adjacent to, their group activation). Furthermore, the pattern shown in Fig. 2b suggests greater relative recruitment of this area in the combination condition (compared to the feature only conditions) for young but not older adults. Together with the Prabhakaran et al. finding, our results suggest that dysfunction in this region may contribute to an age-related binding deficit.

We should note that although activity appears to be greater overall for the older than the young adults in both areas in Fig. 2, this was not the case in all areas. There were regions (not meeting our criteria for binding regions) in which older adults showed lower (e.g., cerebellum, BA 22) or similar (e.g., BA 19/39) levels of activity compared to the young adults.

Although our primary focus here is on age differences in feature binding areas, several 'feature' regions often identified in the working memory literature were found by looking for areas that showed a main effect of condition, not qualified by an interaction with age, and where planned comparisons showed significantly greater activity in the object condition compared to the location condition (e.g., left BA 7/19 [20], left BA 44/6 [68], left BA 32 [67]; see Table 1) or greater activity in the location condition compared to the object condition (e.g., right BA 7 [15,20]; see Table 1). More central to the present interests, we found two 'binding regions' that did not interact with age, that is, areas where main effects of condition followed by subsequent contrasts showed significantly greater activity in the combination condition than in both the object and the location conditions. One was a region of left anterior cingulate cortex (BA 32/24; see Fig. 3a), the other was a region of left precentral gyrus/premotor cortex (BA 6; see Fig. 3b).

## 4. Discussion

### *4.1. An age-related deficit in feature binding: Disruption of a hippocampal-PFC circuit?*

The present results provide the first direct evidence for age-related hippocampal formation dysfunction in a memory task requiring feature binding. The finding of greater activation for young adults in anterior hippocampus in the combination condition (binding) than individual feature conditions (Fig. 2a) supports a recent proposal by Schacter and Wagner that anterior hippocampal activations may be particularly likely when tasks involve relational encoding [63].

With respect to the role of PFC in feature binding, although the greater activation in right BA 10 for younger adults for combination compared to location trials (Fig. 2b) did not fully meet our criteria for a binding region (combination was greater than location but not greater than object), it is consistent with data obtained by Prabhakaran et al. [54]. They compared young adults' working memory for letters and locations presented in a combined format to their working memory for letters and locations presented independently and found greater activity in right BA 10 in their combination condition. Together, these two studies provide converging evidence for a role for right BA 10 in feature binding.

Raz ([57]; see also [58]) recently reviewed neuro-

Table 1
'Feature' areas: areas showing a main effect of condition, not qualified by an interaction with age, and in which subsequent planned comparisons showed (A) Object>Location or (B) Location>Object[a]

| Contrast of interest | BA area | Talairach coordinates ($x$, $y$, $z$) | max $t$ value |
|---|---|---|---|
| (A) Object>Location | Left 10/46 | −25, 52, 16 | 3.30 |
| | Left 47 | −21, 19, −3 | 2.49 |
| | Left 44/6 | −30, 7, 28 | 3.23 |
| | Left 32 | −6, 4, 40 | 2.33 |
| | Left 34 | −15, −6, −15 | 2.81 |
| | Left 7/19 | −29, −52, 34 (extending inferiorly to $z=17$) | 3.75 |
| | Left 19 | −43, −74, 4 | 2.56 |
| | Medial 23/31 | 0, −24, 24 | 5.52 |
| | Right 22/42 | 49, 11, 8 | 4.37 |
| | Right 21/20 | 35, −6, −21 | 3.22 |
| | Right 19/30 | 17, −45, −2 | 4.43 |
| (B) Location>Object | Left 21 | −42, −4, −28 | 2.59 |
| | Left 22/42 | −62, −6, 8 | 3.74 |
| | Right 39 | 39, −62, 28 | 3.70 |
| | Right 7 | 20, −61, 40 | 2.89 |

[a] All areas contained at least four contiguous voxels each of which was significant at $P<0.025$ in both the main effect and subsequent comparisons.

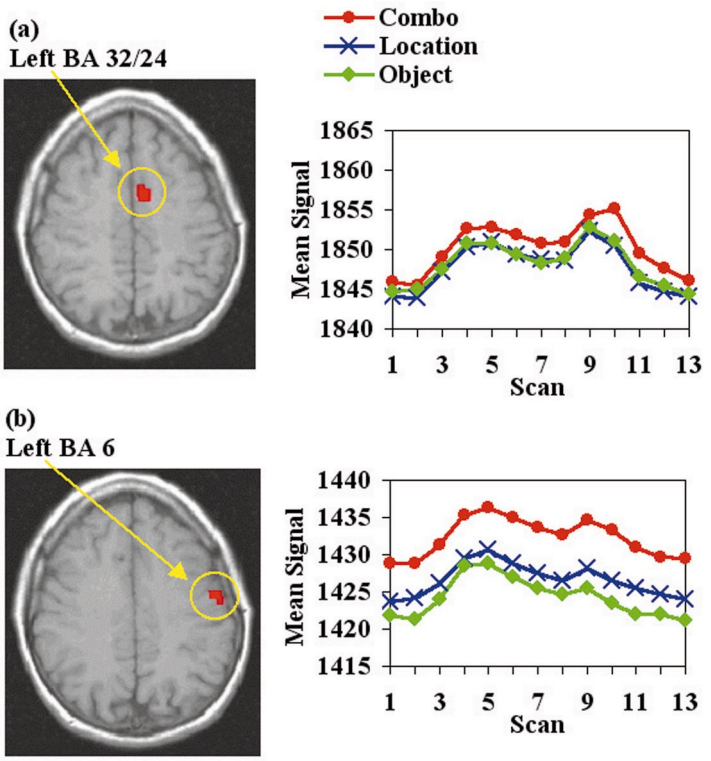


Fig. 3. Anterior cingulate and precentral gyrus/premotor cortex regions showing main effect of condition. (a) Area of left anterior cingulate (BA 32/24; Talairach coordinates: $x=-6$, $y=4$, $z=40$; max. $F$ for the ROI=6.69) in which activation in the combination condition was greater than both the object (max. $t$ for the ROI=3.16) and location (max. $t$ for the ROI=3.44) conditions. (b) Area of left precentral gyrus/premotor cortex (BA 6; Talairach coordinates: $x=-54$, $y=-5$, $z=35$; max. $F$ for the ROI=7.29) in which activation in the combination condition was greater than both the object (max. $t$ for the ROI=4.03) and location (max. $t$ for the ROI=3.56) conditions.

anatomical, neurochemical, and metabolic indicators of aging and concluded that normal aging has a greater impact on prefrontal cortex than on the hippocampal formation (in contrast, atrophy of the hippocampus and the entorhinal cortex may be a pathological feature of Alzheimer's Disease). However, even mild age-related neuropathology in the hippocampal formation may be particularly disruptive when feature binding is necessary and may be exacerbated by frontal dysfunction.

Although visual inspection of Fig. 2 suggests that there may be differences between age groups in the pattern of activity on feature only trials, it is unlikely that the age-related binding deficit is the result of an age-related feature memory deficit. Older adults' performance in the object and location conditions did not differ significantly from that of young adults. In addition, we also found age-related binding deficits but no age-related object or location feature deficits in two ($N=48$ and 32, respectively) other behavioral working memory studies using this procedure [49]. Thus, we have no evidence that the apparent differences in brain activity in the feature only conditions had behavioral consequences in the short term. It is possible that older adults' apparent difficulty recruiting these regions in the location condition, relative to the object condition, indicates problems with location binding more generally (e.g., binding locations to the experimental context) and that this might help explain older adults' long-term location memory deficits [10]. This possibility remains to be explored. What is clear from Fig. 2a and b, however, is that, with respect to the proposed frontal-hippocampal binding circuit, older adults showed a relative lack of engagement of BA 10 and anterior hippocampus in the binding condition, compared to young adults. Whether the identified regions are uniquely involved in binding objects and locations, or whether they play a more general role in binding, remains to be established.

It is worth noting that both young and older adults showed a tonic (sustained) pattern of hippocampal activation in which overall levels did not clearly track the separate within-trial periods (stimulus presentation, retention interval, and test probe) and for which differences between conditions persisted during the intertrial interval. This is in contrast, for example, to the clear phasic (transient) pattern of the ACC and BA6 activation shown in Fig. 3a and b. The tonic hippocampal pattern is consistent with recent evidence that the hippocampus may show longer sustained response (90+ s) than other regions (e.g., auditory cortex, Broca's area) [41]. Kato et al. [41] suggest that such sustained activation is consistent with the presumed role of the hippocampus in the transition from working memory to long term memory function. Kato et al. also reported sustained response in the parahippocam-

pus and Fernández et al. [23] recently found greater tonic activity in entorhinal cortex during study of short lists of words that were subsequently well remembered compared to those that were poorly remembered. However, more transient, within-trial phasic activity in hippocampus [24] and parahippocampus [7,72] has been reported in studies investigating the encoding of individual items. It seems likely, therefore, that both tonic and phasic activation of the hippocampus play important roles in memory.

Inspection of Fig. 2b suggests that tonic effects were also evident in PFC, although like the hippocampus, these tonic effects may be superimposed on phasic effects of within task events. One type of function that would not necessarily be tied to specific trial events but rather to the overall task structure would be a circuit in which a region modulates another area in one or more conditions. The present findings would be consistent with a circuit in which PFC directly or indirectly facilitates hippocampal processing.

We will need additional experiments to isolate the exact role of right PFC in feature binding. Note that the BA 10 region shown in Fig. 2b is consistent with the location of the BA 10 activation found in Prabhakaran et al.'s [54] integration condition but different from the ventral (BA 44, 45, 47) and dorsolateral (BA 9, 46) PFC areas associated with maintenance or manipulation of various types of information in working memory [6,8,16,22,66]. The BA 10 region in Fig. 2b is also different from the right PFC areas (BA 8, 9, 44, and 46) [53] or middle frontal gyrus areas [46] that have been associated with simple vigilance or sustained attention, arguing against the idea that older adults were simply less able to sustain attention during the combination than the feature conditions.

Nor can the present results be explained simply in terms of 'task difficulty.' No doubt, to the extent that binding requires additional processes, it is more difficult than the feature conditions. However, behavioral findings from our lab show that under conditions similar to those of the present study, memory for individual features was not adversely affected in either young or older adults by encoding instructions that encouraged participants to remember combinations of features on all trials ([49, Exp. 2]). Thus, there is no behavioral evidence that intentional binding in and of itself leads to generalized memory decrements for features, as one might predict if combinations were more difficult simply because of increased load. More important, neither this area of BA 10 nor the hippocampus appear to show a sensitivity to increasing working memory load [45] or other manipulations of task difficulty [4,21,31,39,42]. The more general point is that 'difficulty' is not a satisfactory explanatory concept, rather it is something to be explained. That is, different types of difficulty arise from different types and combinations of component cognitive processes. Therefore, we would not expect all types of difficulty to activate exactly the same areas [56]. Consideration of the component processes giving rise to various kinds of 'difficulty' will help specify the function(s) of brain regions.

### *4.2. Other feature binding areas*

There were two regions in this experiment where activity was greater in the combination condition than both the object and location conditions and where condition did not interact with age. One was a region of anterior cingulate cortex (ACC; BA 32/24). Botvinick et al. [5], have suggested that ACC may respond to cognitive conflict (e.g., conflict between representations or between tasks; see also [56]) and may modulate activity in other regions (e.g., PFC). Consistent with this idea, the pattern of activity shown in Fig. 3a may reflect the greater potential for conflict among features in the binding condition. In addition, D'Esposito and colleagues [21] found increased ACC activity in a dual-task condition that required participants to perform both a semantic and spatial task at the same time compared to either task alone. It is possible that trying to remember both objects and locations in our study may have been similar to trying to perform a dual-task.

We also saw a region of left BA 6 activity that was greater in the combination condition than either of the feature only conditions (Fig. 3b). Left BA 6 is often active in both verbal [2,6,19,39] and location-based working memory tasks [15,52]. It has been suggested that this region is part of a subvocal rehearsal circuit [2,39,65] or is involved in spatial attention [1,14,26]. In addition, left premotor activity has been implicated during the generation of images representing concrete words [48] and bilateral premotor activity has been associated with internally-guided shifts of attention ([14,60]; see also [28]). Together, this suggests that premotor activation during the combination condition may be associated with imaging objects in their location during rehearsal, or with shifts in spatial attention during combined spatial and verbal rehearsal.

The fact that the relative activation levels across conditions in ACC and BA 6 did not interact with age suggests that some of the component processes recruited in the combination condition were operating similarly in both young and older adults. Thus the behavioral decrement of the older adults in the combination condition presumably reflects disruption of processes subserved by other regions, particularly binding processes subserved by anterior hippocampus and, perhaps, BA 10.

### *4.3. Potential advantages of event-related blocked designs*

Early fMRI studies using blocked designs that did not analyze for time periods within trials could not observe phasic effects. More recent event-related designs provide information about within-trial phasic effects but might be insensitive if expectations about the time the hemodynamic

response takes to return to baseline are based on estimates from visual, motor, or auditory tasks [41]. Also, tonic effects produced by a sustained neural response to an event (e.g., reverberating neural circuits) that is greater in one condition than another might be missed if researchers analyze only differences in activation between the event and the intertrial interval. As the present findings demonstrate, direct comparisons between conditions, each of which may include activation during events that does not differ from the intertrial interval, can be informative. The present findings also point to an advantage of combining event-related designs with blocking by condition. Such event-related blocked designs allow one to simultaneously observe both within-trial phasic effects (e.g., Fig. 3) and across-trial tonic effects (e.g., Fig. 2) that might result from, for example, higher-order cognitive processes associated with sets, goals, or strategies that are established and sustained across similar trials within a block. For example, the present results are consistent with the idea that ACC is responding to trial-by-trial conditions of conflict [5] whereas the BA 10 activity is related to set or strategy effects [56]. Furthermore, as shown by a recent event-related potential (ERP) study demonstrating processing differences induced by blocked vs. randomized trials [38], manipulating trial designs to influence strategies provides another potentially fruitful way of investigating the neural correlates of various higher-order strategic processes and their interaction with more transient processing effects that occur trial by trial.

## 5. Conclusions

In short, the present study provides evidence that there is an age-related disruption in hippocampal function during feature binding in working memory. It is reasonable to suppose that an age-related dysfunction of hippocampal processing may play a significant role in age-related deficits in tasks requiring feature binding, for example, long term episodic memory for the context or source of information. The extent to which hippocampal dysfunction reflects neuropathology in this region or is secondary to neuropathology in other regions (e.g., PFC) is an important issue for future research. Furthermore, the generality or specificity of anterior hippocampal activity across different feature combinations remains to be determined. Another central question is whether the tonic hippocampal activity shown in Fig. 2a reflects long lasting phasic activity to specific within trial events [41] or activity related to strategies adopted for a block of trials involving the same task, resulting perhaps from an interaction with PFC. Additional studies exploring the functional connectivity [9,47] between hippocampal regions and other areas (e.g., BA 10, ACC, BA 6) by examining correlations of activity among these regions under different binding conditions would be particularly useful.

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## References

[1] E. Awh, J. Jonides, Spatial working memory and spatial selective attention, in: R. Parasuraman (Ed.), The Attentive Brain, MIT Press, Cambridge, MA, 1998, pp. 353–380.
[2] E. Awh, J. Jonides, E.E. Smith, E.H. Schumacher, R.A. Koeppe, S. Katz, Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography, Psychol. Sci. 7 (1996) 25–31.
[3] A. Baddeley, Working memory, in: M.S. Gazzaniga (Ed.), The Cognitive Neurosciences, The MIT Press, Cambridge, MA, 1995, pp. 755–764.
[4] D.M. Barch, T.S. Braver, L.E. Nystrom, S.D. Forman, D.C. Noll, J.D. Cohen, Dissociating working memory from task difficulty in human prefrontal cortex, Neuropsychologia 35 (1997) 1373–1380.
[5] M. Botvinick, L.E. Nystrom, K. Fissell, C.S. Carter, J.D. Cohen, Conflict monitoring versus selection-for-action in anterior cingulate cortex, Nature 402 (1999) 179–181.
[6] T.S. Braver, J.D. Cohen, L.E. Nystrom, J. Jonides, E.E. Smith, D.C.A. Noll, A parametric study of prefrontal cortex involvement in human working memory, Neuroimage 5 (1997) 49–62.
[7] J.B. Brewer, Z. Zhao, J.E. Desmond, G.H. Glover, J.D.E. Gabrieli, Making memories: brain activity that predicts how well visual experience will be remembered, Science 281 (1998) 1185–1187.
[8] R.L. Buckner, W.M. Kelley, S.E. Petersen, Frontal cortex contributes to human memory formation, Nat. Neurosci. 2 (1999) 311–314.
[9] R. Cabeza, A.R. McIntosh, E. Tulving, L. Nyberg, C.L. Grady, Age-related differences in effective neural connectivity during encoding and recall, NeuroReport 8 (1997) 3479–3483.
[10] B.L. Chalfonte, M.K. Johnson, Feature memory and binding in young and older adults, Memory and Cognition 24 (1996) 403–416.
[11] J. Cohen, B. MacWhinney, M. Flatt, J. Provost, PsyScope: An interactive graphic system for designing and controlling experiments in the psychology laboratory using Macintosh computers, Behav. Res. Meth. Instru. Comput. 25 (1993) 257–271.
[12] J.D. Cohen, R.C. O'Reilly, A preliminary theory of the interactions between prefrontal cortex and hippocampus that contribute to planning and prospective memory, in: M. Brandimonte, G.D. Einstein, M.A. McDaniel (Eds.), Prospective Memory: Theory and Applications, Erlbaum, Mahwah, NJ, 1996, pp. 267–295.
[13] N.J. Cohen, H. Eichenbaum, Memory, Amnesia, and the Hippocampal System, The MIT Press, Cambridge, MA, 1993, 330 pp.
[14] M. Corbetta, Functional anatomy of visual attention in the human brain: Studies with positron emission tomography, in: R. Parasuraman (Ed.), The Attentive Brain, MIT Press, Cambridge, MA, 1998, pp. 95–122.
[15] S.M. Courtney, L.G. Ungerleider, K. Keil, J.V. Haxby, Object and spatial visual working memory activate separate neural systems in human cortex, Cereb. Cortex 6 (1996) 39–49.
[16] S.M. Courtney, L.G. Ungerleider, K. Keil, J.V. Haxby, Transient and sustained activity in a distributed neural system for human working memory, Nature 386 (1997) 608–611.
[17] R.W. Cox, AFNI: software for analysis and visualization of functional magnetic resonance neuroimages, Comput. Biomed. Res. 29 (1996) 162–173.
[18] F.I.M. Craik, L.W. Morris, R.G. Morris, E.R. Loewen, Relations

between source amnesia and frontal lobe functioning in older adults, Psychol. Aging 5 (1990) 148–151.
[19] B. Crosson, S.M. Rao, S.J. Woodley, A.C. Rosen, J.A. Bobholz, A. Mayer, J.M. Cunningham, T.A. Hammeke, S.A. Fuller, J.R. Binder, R.W. Cox, E.A. Stein, Mapping of semantic, phonological, and orthographic verbal working memory in normal adults with functional magnetic resonance imaging, Neuropsychology 13 (1999) 171–187.
[20] M. D'Esposito, G.K. Aguirre, E. Zarahn, D. Ballard, R.K. Shin, J. Lease, Functional MRI studies of spatial and nonspatial working memory, Brain Res. Cogn. Brain Res. 7 (1998) 1–13.
[21] M. D'Esposito, J.A. Detre, D.C. Alsop, R.K. Shin, S. Atlas, M. Grossman, The neural basis of the central executive of working memory, Nature 378 (1995) 279–281.
[22] M. D'Esposito, B.R. Postle, D. Ballard, J. Lease, Maintenance versus manipulation of information held in working memory: an event-related fMRI study, Brain and Cognition 41 (1999) 66–86.
[23] G. Fernández, J.B. Brewer, Z. Zhao, G.H. Glover, J.D.E. Gabrieli, Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate, Hippocampus 9 (1999) 35–44.
[24] G. Fernández, A. Effern, T. Grunwald, N. Pezer, K. Lahnertz, M. Dümpelmann, D. Van Roost, C.E. Elger, Real-time tracking of memory formation in the human rhinal cortex and hippocampus, Science 285 (1999) 1582–1585.
[25] S.D. Forman, J.D. Cohen, M. Fitzgerald, W.F. Eddy, M.A. Mintun, D.C. Noll, Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold, Magn. Reson. Med. 33 (1995) 636–647.
[26] D.R. Gitelman, A.C. Nobre, T.B. Parrish, K.S. LaBar, Y.-H. Kim, J.R. Meyer, M.-M. Mesulam, A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls, Brain 122 (1999) 1093–1106.
[27] E.L. Glisky, M.R. Polster, B.C. Routhieaux, Double dissociation between item and source memory, Neuropsychology 9 (1995) 229–235.
[28] P.S. Goldman-Rakic, Toward a circuit model of working memory and the guidance of voluntary action, in: J.C. Houk, J.L. Davis, D.G. Beiser (Eds.), Models of Information Processing in the Basal Ganglia, MIT Press, Cambridge, MA, 1995, pp. 131–148.
[29] P.S. Goldman-Rakic, L.D. Selemon, M.L. Schwartz, Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey, Neuroscience 12 (1984) 719–743.
[30] C.L. Grady, A.R. McIntosh, B. Horwitz, J.M. Maisog, L.G. Ungerleider, M.J. Mentis, P. Pietrini, M.B. Schapiro, J.V. Haxby, Age-related reductions in human recognition memory due to impaired encoding, Science 269 (1995) 218–221.
[31] C.L. Grady, B. Horwitz, P. Pietrini, M.J. Mentis, L.G. Ungerleider, S.I. Rapoport, J.V. Haxby, Effect of task difficulty on cerebral blood flow during perceptual matching of faces, Hum. Brain Mapp. 4 (1996) 227–239.
[32] K. Henke, A. Buck, B. Weber, H.G. Wieser, Human hippocampus establishes associations in memory, Hippocampus 7 (1997) 249–256.
[33] K. Henke, B. Weber, S. Kneifel, H.G. Wieser, A. Buck, Human hippocampus associates information in memory, Proc. Natl. Acad. Sci. USA 96 (1999) 5884–5889.
[34] L.A. Henkel, M.K. Johnson, D.M. De Leonardis, Aging and source monitoring: Cognitive processes and neuropsychological correlates, J. Exp. Psychol. Gen. 127 (1998) 251–268.
[35] R.N.A. Henson, T. Shallice, R.J. Dolan, Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis, Brain 122 (1999) 1367–1381.
[36] M.K. Johnson, MEM: Mechanisms of recollection, J. Cogn. Neurosci. 4 (1992) 268–280.
[37] M.K. Johnson, S. Hashtroudi, D.S. Lindsay, Source monitoring, Psychol. Bull. 114 (1993) 3–28.
[38] M.K. Johnson, S.F. Nolde, M. Mather, J. Kounios, D.L. Schacter, T. Curran, The similarity of brain activity associated with true and false recognition memory depends on test format, Psychol. Sci. 8 (1997) 250–257.
[39] J. Jonides, E.H. Schumacher, E.E. Smith, E.J. Lauber, E. Awh, S. Minoshima, R.A. Koeppe, Verbal working memory load affects regional brain activation as measured by PET, J. Cogn. Neurosci. 9 (1997) 462–475.
[40] N. Kanwisher, J. McDermott, M.M. Chun, The fusiform face area: a module in human extrastriate cortex specialized for face perception, J. Neurosci. 17 (1997) 4302–4311.
[41] T. Kato, P. Erhard, Y. Takayama, J. Strupp, T.H. Le, S. Ogawa, K. Ugurbil, Human hippocampal long-term sustained response during word memory processing, Neuroreport 9 (1998) 1041–1047.
[42] T. Klingberg, B.T. O'Sullivan, P.E. Roland, Bilateral activation of fronto-parietal networks by incrementing demand in a working memory task, Cereb. Cortex 7 (1997) 465–471.
[43] N.E.A. Kroll, R.T. Knight, J. Metcalf, E.S. Wolf, E. Tulving, Cohesion failure as a source of memory illusions, J. Memory and Language 35 (1996) 176–196.
[44] D.J. Madden, T.G. Turkington, J.M. Provenzale, L.L. Denny, T.C. Hawk, L.R. Gottlob, R.E. Coleman, Adult age differences in the functional neuroanatomy of verbal recognition memory, Hum. Brain Mapp. 7 (1999) 115–135.
[45] D.S. Manoach, G. Schlaug, B. Siewert, D.G. Darby, B.M. Bly, A. Benfield, R.R. Edelman, S. Warach, Prefrontal cortex fMRI signal changes are correlated with working memory load, NeuroReport 8 (1997) 545–549.
[46] G. McCarthy, A. Puce, R.T. Constable, J.H. Krystal, J.C. Gore, P. Goldman-Rakic, Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI, Cereb. Cortex 6 (1996) 600–611.
[47] A.R. McIntosh, L. Nyberg, F.L. Bookstein, E. Tulving, Differential functional connectivity of prefrontal and medial temporal cortices during episodic memory retrieval, Hum. Brain Mapp. 5 (1997) 323–327.
[48] E. Mellet, N. Tzourio, M. Denis, B. Mazoyer, Cortical anatomy of mental imagery of concrete nouns based on their dictionary definition, NeuroReport 9 (1998) 803–808.
[49] K.J. Mitchell, M.K. Johnson, C.L. Raye, M. Mather, M. D'Esposito, Aging and reflective processes of working memory: Binding and test load deficits, Psychol. Aging (in press).
[50] S.F. Nolde, M.K. Johnson, M. D'Esposito, Left prefrontal activation during episodic remembering: an event-related fMRI study, NeuroReport 9 (1998) 3509–3514.
[51] S. Ogawa, D.W. Tank, R. Menon, J.M. Ellerman, S.-G. Kim, H. Merkle, K. Ugerbil, Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging, Proc. Natl. Acad. Sci. USA 89 (1992) 5951–5955.
[52] A.M. Owen, A.C. Evans, M. Petrides, Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study, Cereb. Cortex 6 (1996) 31–38.
[53] J.V. Pardo, P.T. Fox, M.E. Raichle, Localization of a human system for sustained attention by positron emission tomography, Nature 349 (1991) 61–64.
[54] V. Prabhakaran, K. Narayanan, Z. Zhao, J.D.E. Gabrieli, Integration of diverse information in working memory within the frontal lobe, Nat. Neurosci. 3 (2000) 85–90.
[55] S.C. Rao, G. Rainer, E.K. Miller, Integration of what and where in the primate prefrontal cortex, Science 276 (1997) 821–824.
[56] C.L. Raye, M.K. Johnson, K.J. Mitchell, S.F. Nolde, M. D'Esposito, fMRI investigations of left and right PFC contributions to episodic remembering, Psychobiology (in press).
[57] N. Raz, Aging of the brain and its impact on cognitive performance:

Integration of structural and functional findings, in: F.I.M. Craik, T.A. Salthouse (Eds.), The Handbook of Aging and Cognition, 2nd Edition, Erlbaum, Mahwah, NJ, 2000, pp. 1–90.
[58] N. Raz, F.M. Gunning-Dixon, D. Head, J.H. Dupuis, J.D. Acker, Neuroanatomical correlates of cognitive aging: Evidence from structural magnetic resonance imaging, Neuropsychology 12 (1998) 95–114.
[59] M.T. Reinitz, M. Verfaellie, W.P. Milberg, Memory conjunction errors in normal and amnesic subjects, J. Memory and Language 35 (1996) 286–299.
[60] A.C. Rosen, S.M. Rao, P. Caffarra, A. Scaglioni, J.A. Bobholz, S.J. Woodley, T.A. Hammeke, J.M. Cunningham, T.E. Prieto, J.R. Binder, Neural basis of endogenous and exogenous spatial orienting: A functional MRI study, J. Cogn. Neurosci. 11 (1999) 135–152.
[61] M.D. Rugg, P.C. Fletcher, P.M.-L. Chua, R.J. Dolan, The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study, NeuroImage 10 (1999) 520–529.
[62] T.A. Salthouse, N. Fristoe, S.H. Rhee, How localized are age-related effects on neuropsychological measures?, Neuropsychology 10 (1996) 272–285.
[63] D.L. Schacter, A.D. Wagner, Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval, Hippocampus 9 (1999) 7–24.
[64] A.P. Shimamura, Memory and frontal lobe function, in: M.S. Gazzaniga (Ed.), The Cognitive Neurosciences, The MIT Press, Cambridge, MA, 1995, pp. 803–813.
[65] E.E. Smith, J. Jonides, Working memory: A view from neuroimaging, Cognit. Psychol. 33 (1997) 5–42.
[66] E.E. Smith, J. Jonides, Storage and executive processes in the frontal lobes, Science 283 (1999) 1657–1661.
[67] E.E. Smith, J. Jonides, R.A. Koeppe, Dissociating verbal and spatial working memory using PET, Cereb. Cortex 6 (1996) 11–20.
[68] E.E. Smith, J. Jonides, R.A. Koeppe, E. Awh, E.H. Schumacher, S. Minoshima, Spatial versus object working memory: PET investigations, J. Cogn. Neurosci. 7 (1995) 337–356.
[69] J.G. Snodgrass, M. Vanderwart, A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity, J. Exp. Psychol. Hum. Learn. Mem. 6 (1980) 174–215.
[70] L.R. Squire, S. Zola-Morgan, The medial temporal lobe memory system, Science 253 (1991) 1380–1386.
[71] J. Talairach, P. Tournoux, Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging, Thieme Medical Publishers, New York, 1988, 122 pp.
[72] A.D. Wagner, D.L. Schacter, M. Rotte, W. Koutstaal, A. Maril, A.M. Dale, B.R. Rosen, R.L. Buckner, Building memories: remembering and forgetting of verbal experiences as predicted by brain activity, Science 281 (1998) 1188–1191.
[73] R.P. Woods, S.R. Cherry, J.C. Mazziotta, Rapid automated algorithm for aligning and reslicing PET images, J. Comput. Assist. Tomogr. 16 (1992) 620–633.