

Differential Effects of Encoding Instructions on Brain Activity Patterns of Item and Associative Memory

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Abstract

■ Evidence from neuroimaging studies suggests a critical role of hippocampus and inferior frontal gyrus (IFG) in associative relative to item encoding. Here, we investigated similarities and differences in functional brain correlates for associative and item memory as a function of encoding instruction. Participants received either incidental (animacy judgments) or intentional encoding instructions while fMRI was employed during the encoding of associations and items. In a subsequent recognition task, memory performance of participants receiving intentional encoding instructions was higher compared with those receiving incidental encoding instructions. Furthermore, participants remembered more items than associations, regardless of encoding instruction. Greater brain activation in the left anterior hippocampus was observed for intentionally compared

with incidentally encoded associations, although activity in this region was not modulated by the type of instruction for encoded items. Furthermore, greater activity in the left anterior hippocampus and left IFG was observed during intentional associative compared with item encoding. The same regions were related to subsequent memory of intentionally encoded associations and were thus task relevant. Similarly, connectivity of the anterior hippocampus to the right superior temporal lobe and IFG was uniquely linked to subsequent memory of intentionally encoded associations. Our study demonstrates the differential involvement of anterior hippocampus in intentional relative to incidental associative encoding. This finding likely reflects that the intent to remember triggers a specific binding process accomplished by this region. ■

INTRODUCTION

Episodic memory, the remembrance of events situated in time and place, entails the ability to link together elements of an event and to integrate them into a cohesive memory episode (Tulving, 1972). A distinction can be made between memory for individual elements of an episode (i.e., item memory) and memory for the relation between those elements (i.e., associative memory; Davachi, 2006). Generally, individuals perform better in item compared with associative memory tasks (Kamp & Zimmer, 2015; Naveh-Benjamin, 2000), an effect that has been replicated with numerous types of stimuli (e.g., words, faces, names; Old & Naveh-Benjamin, 2008). This performance difference might result from differences in elaborative encoding processes that item and associative memory require. More precisely, associative compared with item memory involves additional cognitive operations, namely, binding, which requires the generation of associations between two or more items and is supported and enhanced by strategic processing (Addis & McAndrews, 2006). According to the levels of processing

model, memory formation occurs as a by-product of perceptual processing and does not require intentional memorization (Craik & Tulving, 1975; Craik & Lockhart, 1972). Support for this model comes from studies investigating item memory. Consistently, memory for incidentally encoded items processed in a deep fashion (i.e., semantically) is equal to memory for intentionally encoded items and exceeds memory for items encoded incidentally but processed in a shallow fashion (e.g., phonologically; Buckner, Wheeler, & Sheridan, 2001; Otten, Henson, & Rugg, 2001; Otten & Rugg, 2001; Walsh & Jenkins, 1973). Studies on associative memory, however, have revealed rather mixed results. Whereas Hyde and Jenkins (1973) observed similar performance for deep incidentally and intentionally encoded associations, others noted a superiority in memory of the latter (Troyer, Hafliger, Cadieux, & Craik, 2006; Wicker & Bernstein, 1969). Hence, although intentional in comparison with deep incidental encoding instructions do not seem to benefit item memory, their modulatory effect on associative memory remains uncertain.

Evidence from neuroimaging studies suggests that, although episodic memory depends on large-scale brain networks (Nyberg et al., 2000), particularly the medial temporal lobe (MTL) and the lateral PFC (Simons & Spiers, 2003), they may differ in their relative involvement in item and associative encoding. Greater activity in the left inferior

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frontal gyrus (IFG) has been observed for associative relative to item encoding (Wong, de Chastelaine, & Rugg, 2013; Murray & Ranganath, 2007; Addis & McAndrews, 2006; Achim & Lepage, 2005). In the MTL, the perirhinal cortex plays a major role in memory for items, whereas the hippocampus is strongly involved in the formation of between-item associations (“domain dichotomy view”; Mayes, Montaldi, & Migo, 2007; Davachi & Wagner, 2002). Although hippocampal binding mechanisms are supposed to be domain general (see Park & Rugg, 2011; Davachi, 2006), a functional differentiation has been proposed along the longitudinal axis of this region. The left anterior part of the hippocampus appears to be more engaged during successful compared with failed encoding of associative information and also relative to retrieval (Chua, Schacter, Rand-Giovannetti, & Sperling, 2007; Prince, Daselaar, & Cabeza, 2005; Jackson & Schacter, 2004). Attempts to specify the neural effects of encoding instructions on item memory revealed that similar regions were associated with successful intentional and successful incidental encoding, including subregions of the MTL (Stark & Okado, 2003) and the left IFG (Buckner et al., 2001; see Henson, 2005). That is, encoding instructions seemed to have little modulatory effect on functional brain activity underlying item encoding. However, most studies on associative memory investigated encoding under either intentional or incidental encoding instructions without directly comparing the two (Park & Rugg, 2011; Chua et al., 2007; Qin et al., 2007; Jackson & Schacter, 2004). Yet, associative compared with item memory requires additional binding and strategic processes that exceed mere semantic processing (Shing, Werkle-Bergner, Li, & Lindenberger, 2008; Kirchhoff & Buckner, 2006) but might be triggered by intentional encoding instructions. Accordingly, the underlying processes of associative binding as indicated by differential hippocampal and IFG recruitment suggest qualitative differences between incidental and intentional associative encoding. However, to date, it remains poorly understood how encoding-related brain activity in associative memory differs according to the nature of instructions.

We investigated similarities and differences in functional brain correlates for item and associative memory as a function of encoding instructions. We used fMRI to compare brain activity during encoding of between-item associations and single items in individuals who received either deep incidental or intentional encoding instructions. Importantly, item stimuli were presented in a fragmented fashion during encoding to equate the visual input between item and associative trials, which enabled comparisons across the two conditions. We hypothesized a stronger modulatory effect of the type of instruction for associative than item memory. Specifically, we expected higher performance for intentional versus incidental encoding of associations, whereas we expected this difference to be less pronounced between encoding groups for item memory. We further expected greater BOLD activity differences between intentional and incidental

associative encoding, primarily located in the anterior hippocampus and left IFG, but that instruction-related differences would be smaller for item encoding. We additionally predicted stronger functional connectivity of the hippocampal region and IFG during encoding of subsequently remembered compared with subsequently forgotten associations (Addis & McAndrews, 2006).

METHODS

Participants

Written informed consent was obtained from 56 healthy, right-handed adults. All participants lived in the area of Stockholm, Sweden, and were paid for participation. Five participants were excluded because of early termination of the experiment or corruption of scanner images. The final sample consisted of 51 adults with normal or corrected-to-normal vision, who were eligible for MRI (27 women; age range = 21–30 years, $M_{\text{age}} = 25.10 \pm 1.58$ years). Of the final sample, 27 participants received intentional encoding instructions (16 women; $M_{\text{age}} = 24.89 \pm 1.63$ years, $M_{\text{education}} = 15.17 \pm 2.09$ years), and 24 participants received incidental encoding instructions (11 women; $M_{\text{age}} = 25.33 \pm 1.52$ years, $M_{\text{education}} = 16.33 \pm 3.13$ years). The two groups did not differ in age, education, or sex distribution ($ps > .05$). The study was approved by the regional ethical review board in Stockholm.

Materials

Stimuli consisted of 756 grayscale photographs of common objects from 25 categories (e.g., kitchen tools, clothing, animals) that were partly taken from the Bank of Standardized Stimuli (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010; about 430 object images) and partly from freely available pictures on the Internet (326 object images). Images from the Internet were processed in a strict fashion to ensure that image properties from both image sources were identical. More precisely, images from the Internet depicted real objects with no background, shadows, or reflections. Objects depicted both living and nonliving things and were presented once during encoding and once during retrieval. Stimuli were of equal size, grayscaled with identical color filters, and presented on a white background in the upper left and right corners and middle lower part of a squared box (see Figure 1).

Experimental trials belonged to one of two task conditions (i.e., associations, items) and two levels of binding (i.e., two-level binding, three-level binding). These two levels of binding were included in the study to ensure enough variability in associative memory performance and a comparable number of remembered and forgotten trials to conduct subsequent memory analyses. Associative stimuli consisted of 90 trials containing two intact objects (two-level binding) and 90 trials containing three intact

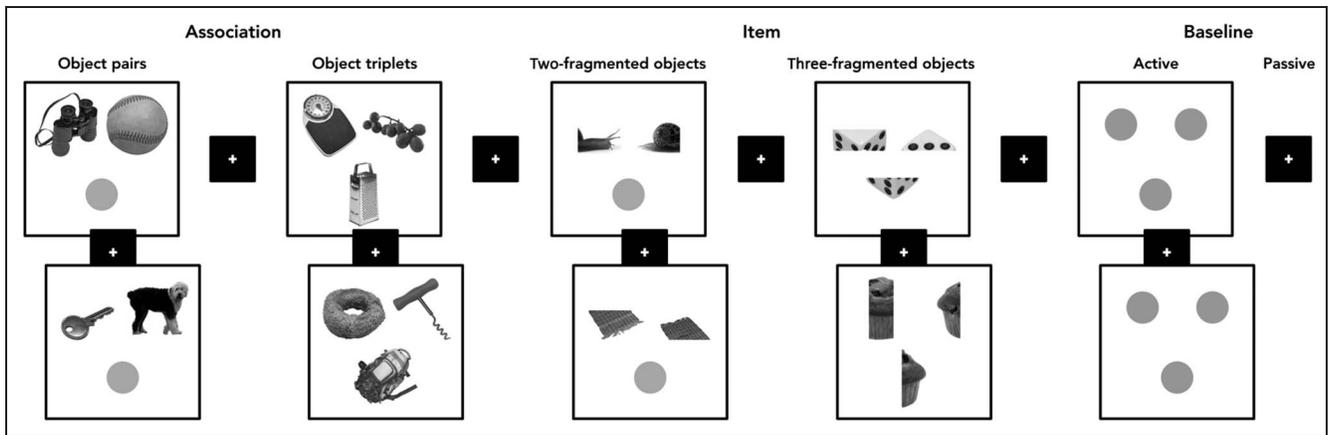


Figure 1. Experimental design and exemplar trials from the in-scanner encoding task. In the three runs, participants were presented with nine blocks of four experimental conditions (i.e., two-level associations, three-level associations, two-fragmented items, three-fragmented items) and six active baseline blocks, each comprising 10 trials. Trials were shown for 3 sec, followed by a fixation cross that lasted between 1.5 and 5.5 sec (mean = 3.28 sec). At the end of each block, a fixation period followed for 16 sec (passive baseline), before instructions for the next condition block appeared on the screen for 2 sec.

objects (three-level binding). Presentation positions were randomly assigned to the stimuli. Items consisted of 90 trials entailing two object fragments (two-level binding), that is, object images were cut into two parts and randomly assigned to one of the upper square corners (following the method of Staresina & Davachi, 2010). Another 90 trials entailed three object fragments (three-level binding) that were randomly placed in the upper corners and middle lower part of the square. Object fragmentation was done to (a) keep the visual input comparable between associative and item trials and (b) induce a low-level perceptual binding process in the item condition to ensure that potential differences between associative and item encoding related to differences in higher-level binding processes and not to differences in the binding of perceptual inputs per se. Object images were cut horizontally if their height exceeded their width (90 object images) and vertically if their width exceeded their height (90 object images). All objects were uniquely labeled, and fragments were unambiguously identified as one object by two independent raters. To keep the visual input stable, all two-level binding trials additionally comprised a gray circle that was presented in the middle lower part of the square. Active baseline trials consisted of three gray circles.

fMRI Design

To identify encoding-related activity, that is, brain activity induced by encoding instructions in general as well as activity related to subsequent memory (Marklund et al., 2007), we used a design that allowed for separate analyses of epoch and event-related effects (Visscher et al., 2003; Donaldson, Petersen, Ollinger, & Buckner, 2001). Epoch-related analyses reveal the sustained engagement of particular brain regions induced by a specific instruction, that is, to intentionally memorize associations or items versus to semantically process those (incidental

encoding) independently of whether an item was successfully remembered (i.e., encoding mode; Marklund et al., 2007). This design also allowed us to investigate transient activation related to encoding success (i.e., activity differences between subsequently remembered and subsequently forgotten trials) for each encoding instruction.

Experimental Procedure

Before fMRI scanning, participants were familiarized with the experimental conditions and performed several practice trials to ensure that they understood the task. For intentional encoding, participants were instructed to memorize single objects and object combinations after a subsequent recognition task. Participants in this group were not provided with any mnemonic strategy but were simply told that they should try their best to memorize single objects and object combinations. For incidental encoding, participants were not informed about a subsequent recognition task but told a cover story that the task was of perceptual nature and that they should perform animacy judgments on the objects presented. Participants in this group were instructed to perform animacy judgments on every object presented on the screen to ensure they processed every item of an object combination.

Encoding

The scanning session consisted of three runs, each lasting for approximately 18 min. Each run entailed three blocks of every experimental condition (i.e., two-level associations, three-level associations, two-fragmented items, three-fragmented items) and two active baseline blocks. The order of blocks was randomized within each run but kept constant across individuals. Each block comprised 10 trials. Trials were shown for 3 sec followed by a white fixation cross, presented on a black background.

The interstimulus fixation varied from 1.5 to 5.5 sec (mean = 3.28 sec). Each block was followed by a passive baseline lasting for 16 sec, before instructions for the next condition block appeared on the screen for 2 sec. The jittering and long fixation intervals between blocks were applied to allow for epoch- and event-related analyses of the fMRI data. Participants in the intentional encoding group were instructed to press one button as soon as an experimental trial appeared on the screen. Participants in the incidental encoding group were instructed to press one of two buttons whenever they identified one of the objects as being alive and the respective other button if none of the objects were alive. The proportion of trials that depicted one or more living objects to trials that depicted only images of nonliving objects was 1:2.5. During the active baseline condition, all participants were instructed to press a button as soon as three circles appeared on the screen. Trials and the presentation order of trials were identical across participants. Button presses were performed with the right index and middle fingers and counterbalanced across participants.

Retrieval

Immediately after fMRI scanning, participants were brought into a separate room to perform a recognition task that tested memory of the objects and object combinations presented during encoding. The recognition task consisted of three runs, each entailing three blocks with 12 trials from each experimental condition. The associative memory condition included seven old trials, two new trials, and three rearranged trials (i.e., one of the object images from an original encoding combination was alternated with another object image from a different combination). New trials were added to increase the number of “no” trials without decreasing the number of hit trials important for subsequent memory analyses by rearranging objects across them. Object images were only rearranged within the same difficulty level. The positions of the objects within a combination remained the same to ensure that participants would not identify rearranged combinations based on object locations. Item blocks contained 10 old trials and two new trials. Old trials consisted of one intact object previously presented in fragments that was placed in the middle of a square. New trials consisted of an intact but new object that was not shown during encoding. The recognition task contained more old trials than new/rearranged trials as only old trials lead to a production of hits and misses, which allow for subsequent memory analyses. Recognition trials were shown for 3 sec, and participants were instructed to indicate with a button press whether they had seen the object or object combination during encoding. Compliance to follow the instruction was assessed from all participants. Participants from the incidental encoding group reported that they were focusing on the categorization task and that they did not attempt to memorize.

None of the participants reported that they expected a subsequent recognition test. On the contrary, all participants from the intentional encoding group reported trying to memorize the material in preparation for the subsequent recognition task, showing that the behavioral manipulation had worked.

fMRI Data Acquisition and Preprocessing

Participants were scanned with a 3-T GE750 scanner using a 32-channel head coil and a gradient echo pulse sequence (repetition time = 2.2 sec, echo time = 30 msec, flip angle = 70°, field of view = 22, in-plane resolution = 1.72 × 1.72 mm). Forty-six slices (slice thickness = 3 mm) were collected in axial orientation covering the whole brain. Before image acquisition, 10 dummy scans were performed to allow for MR stabilization. In total, 500 volumes were collected for each of the three functional runs. Before fMRI, a T1-weighted MRI scan was collected from each participant using the SAG FSPGR BRAVO sequence (repetition time = 8.20 msec, echo time = 3.22 msec, field of view = 24, in-plane resolution = 0.94 × 0.94 mm, 172 adjacent sagittal slices, slice thickness = 1 mm).

The data were preprocessed and analyzed in SPM12 (Functional Imaging Laboratory, Wellcome Department of Imaging Science, www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB R2014b (The MathWorks Inc., Natick, MA). T1-weighted images were preprocessed using the unified segmentation approach (Ashburner & Friston, 2005) and the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (Ashburner, 2007). Functional images were slice-time corrected and realigned for motion correction with reference to the first slice. Images were coregistered to their respective structural T1 scan, spatially normalized to the group-specific Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra template and to Montreal Neurological Institute space, resampled into 2-mm cubic voxels, and finally smoothed with a Gaussian convolution kernel of 8-mm FWHM. The normalized gray matter images of all participants were averaged to create a binary gray matter mask that was used as an explicit mask in all fMRI group level analyses.

Statistical Analyses

Behavioral Analyses

Recognition performance was measured as the proportion of hits minus false alarms (discrimination index $Pr [p(\text{hits}) - p(\text{false alarms})]$; Snodgrass & Corwin, 1988). New associative foils were excluded from the behavioral analyses, because they could have been identified as foils by relying on item memory. To investigate differences in mean recognition performance in associative and item memory between groups, we conducted a 2 (associations vs. items) × 2 (two- vs. three-level binding) × 2 (intentional vs. incidental encoding instruction) repeated-measures ANOVA. To further

investigate the underlying pattern of recognition performance, we conducted the repeated-measures ANOVAs separately on the proportion of hits and the proportion of false alarms.

Functional Brain Analyses

Analyses were performed within the framework of the general linear model. SPMs were generated using *t* statistics and thresholded at $p < .001$. Results were considered significant at a family-wise error-corrected cluster-extent threshold of $p < .05$. Activations in the anterior hippocampal region and left IFG, for which we had had a priori predictions, were thresholded using small-volume corrections. Masks of the anterior hippocampal region based on the Montreal Neurological Institute (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013) and the left IFG (pars opercularis, pars triangularis, and pars orbitalis) were created using the automated anatomic labeling atlas (Tzourio-Mazoyer et al., 2002).

Analyses of brain activity related to associative and item encoding. For the epoch-related analyses, experimental and control conditions were modeled as a box-car waveform convolved with the hemodynamic response function. Covariates of no interest included six realignment parameters per run to account for motion artifacts. Runs were entered separately in the model, and contrasts were averaged across them. To increase statistical power for the epoch-related analyses, binding levels were pooled within the two experimental conditions (associative encoding blocks and item encoding blocks) and contrasted with baseline conditions (active and passive). Using the full-factorial option in SPM, we performed a whole-brain repeated-measures ANOVA with the within-participant factor Task condition and the between-participant factor Encoding instruction. Three analyses were conducted within this model: We investigated (a) how encoding modes of associations and items differed from each other—therefore, within each encoding group, regions were identified that were reliably more engaged during associative encoding compared with item encoding, and vice versa; (b) if encoding modes for associations and items differed depending on the type of instruction—thus, we compared associative and item encoding blocks between groups and identified regions that showed significantly greater activation under intentional compared with incidental encoding instructions, and vice versa; and (c) the interaction between Task condition and Encoding instruction, that is, determined how incidental differed from intentional associative and item encoding, by identifying areas showing a reliable Task condition \times Encoding instruction interaction. More precisely, we contrasted intentional associative $>$ intentional item encoding with incidental associative $<$ incidental item encoding.

Analyses of brain activity related to successful memory formation. For the event-related analyses, event onsets

were modeled with a stick function and convolved with the hemodynamic response function. Events were specified as occurring at the presentation of the stimuli that participants responded to with a button press and labeled according to task condition (association vs. item), binding level (two vs. three), and subsequent memory in the postscanning recognition task (hit vs. miss). This yielded eight types of events. Trials that were rearranged for the postscanning recognition task and trials that participants did not respond to during encoding were modeled as events of no interest. Because there were too few events in one or more runs (<6 ; Murphy & Garavan, 2005), we concatenated runs treating all three to a single time series (number of trials included per participant and condition: min = 17, max = 52). Covariates of no interest included six realignment parameters to account for motion artifacts and two linear parameters to control for effects between runs. To assess brain regions related to successful memory formation, we performed a subsequent memory analysis. This was done by comparing activity related to the encoding of associations and items that were subsequently remembered with those that were later forgotten (hits $>$ misses; Paller & Wagner, 2002; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998). The subsequent memory analysis served as a follow-up analysis to the epoch-related analysis and was performed separately for encoding groups and task conditions.

Analyses of hippocampal connectivity in successful memory formation. To determine functional hippocampal connectivity during successful encoding, we used psychophysiological interaction (PPI; Friston et al., 1997) implemented in SPM12. For each individual, we applied a general linear model, which consisted of the subsequent memory effect contrast (hits $>$ misses; psychological regressor), a seed region's time course (selected based on the peak voxel location identified in the preceding subsequent memory analysis; physiological regressor), and the interaction term of both (PPI regressor). Voxels significantly related to the latter, indicating regions in which contribution to the hippocampal region was significantly modulated by subsequent successful memory on the individual level. The resulting PPI contrast images were averaged across individuals and used in a second-level one-sample *t* test.

RESULTS

Behavioral Results

In the intentional encoding group, the proportion of correctly remembered trials (hits) was 60% for associations and 63% for items. In the incidental encoding group, participants remembered 53% of associative trials and 53% of item trials. The proportion of false alarms was comparable across groups: 44% for associations and 20% for items (Table 1; Figure 2).

Table 1. Behavioral Results: Mean Proportions of Hits, False Alarms, and Hits–False Alarms of Encoding Groups (*SD*)

Condition		Overall		Two-level Binding		Three-level Binding	
		Intentional	Incidental	Intentional	Incidental	Intentional	Incidental
Association	Hits	.60 (.11)	.53 (.12)	.63 (.12)	.51 (.13)	.56 (.11)	.55 (.13)
	FA	.44 (.16)	.43 (.10)	.41 (.18)	.41 (.12)	.47 (.16)	.45 (.13)
	H-FA	.16 (.15)	.10 (.09)	.22 (.20)	.10 (.09)	.10 (.13)	.09 (.13)
Item	Hits	.63 (.12)	.53 (.12)	.66 (.11)	.55 (.14)	.60 (.14)	.50 (.12)
	FA	.21 (.12)	.18 (.11)	.17 (.13)	.16 (.12)	.25 (.16)	.21 (.14)
	H-FA	.42 (.17)	.34 (.14)	.45 (.16)	.37 (.15)	.39 (.18)	.32 (.14)

FA = false alarms; H-FA = hits–false alarms.

A repeated-measures ANOVA on hits – false alarms revealed a main effect of Encoding instruction, indicating that the overall memory performance was slightly higher in the intentional encoding group compared with the incidental encoding group ($F(1, 49) = 4.89, p < .05, \eta_p^2 = .09$). Furthermore, a main effect of Task condition ($F(1, 49) = 109.51, p < .001, \eta_p^2 = .69$) indicated that, across

both groups, recognition performance of associations was significantly lower than recognition of items. A main effect of Level of binding ($F(1, 49) = 31.46, p < .001, \eta_p^2 = .39$) revealed that recognition of trials from the two-level binding was higher compared with those from the three-level binding. Moreover, the interaction between Level of binding and Encoding instruction reached significance ($F(1, 49) = 8.92, p < .005, \eta_p^2 = .15$), reflecting that the effect of level of binding was more pronounced in the intentional than incidental encoding group. Specifically, recognition performance did not differ between object pairs and object triplets in the incidental encoding group, in contrast to the intentional encoding group (Task condition \times Level of binding \times Encoding instruction; $F(1, 49) = 5.20, p < .05, \eta_p^2 = .10$). However, the interaction of Task condition \times Encoding instruction did not reach significance. Thus, we could not observe that, in comparison with item memory, performance was differentially worse for incidentally compared with intentionally learned associations ($p > .05$).

We conducted separate analyses for hits, as this behavioral measure was of major interest for the subsequent memory analyses. Analyses revealed a main effect of Level of binding ($F(1, 49) = 16.94, p < .001, \eta_p^2 = .26$), reflecting more hits on trials from the two-level binding compared with the three-level binding, and a main effect of Encoding instruction ($F(1, 49) = 8.39, p < .01, \eta_p^2 = .15$), with individuals from the intentional encoding group producing more hits than those from the incidental encoding group. The main effect of Task condition, however, did not reach significance, indicating that, across groups, the proportion of hits did not differ between the recognition of associations and items. The effect of Level of binding was more pronounced in the intentional compared with the incidental encoding group (Level of binding \times Encoding instruction; $F(1, 49) = 10.03, p < .005, \eta_p^2 = .17$), as the number of hits in the incidental encoding group did not differ significantly between object pairs and object triplets (Task condition \times Level of binding \times Encoding instruction; $F(1, 49) = 5.44, p < .05, \eta_p^2 = .10$). Analyses of false alarms revealed a

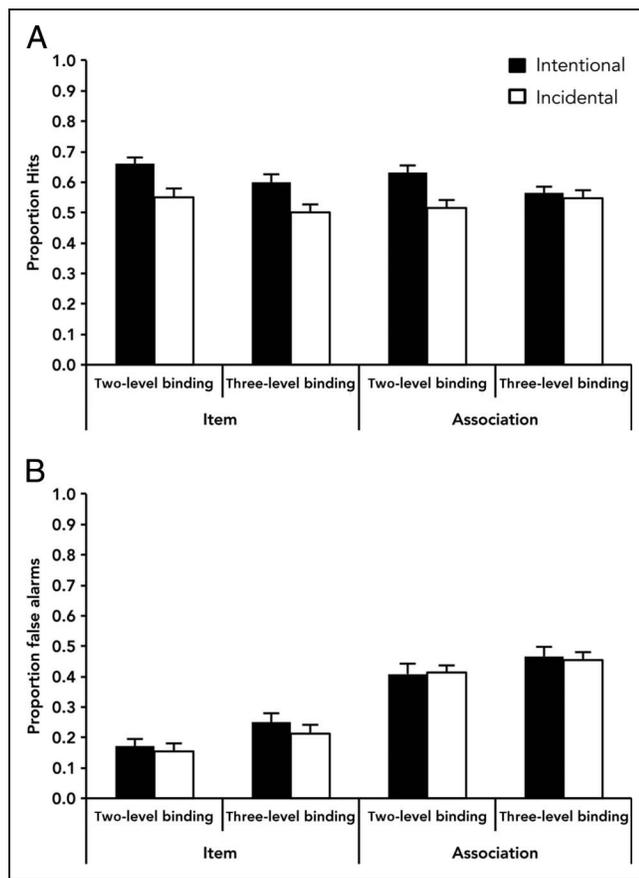


Figure 2. Proportion of (A) hits and (B) false alarms in the recognition task across task conditions (associations and items), binding levels (two- and three-level binding), and encoding groups (intentional and incidental). Error bars represent *SEMs*.

Table 2. Brain Regions Showing Significant Activity during Encoding Mode

<i>Contrast</i>	<i>Region</i>	<i>BA</i>	<i>k</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
Task condition × Encoding instruction	Hippocampus	35	89	4.65	-24	-16	-18
Within intentional: association > item	Lingual gyrus	18	1535	6.11	-14	-94	-10
	Lingual gyrus	18		5.98	16	-98	0
	Lingual gyrus	18		4.23	22	-82	-10
	Middle occipital lobe	18		3.79	32	-92	8
	Fusiform gyrus	37	593	5.29	-36	-50	-18
	Fusiform gyrus	19		4.12	-30	-66	-14
	Hippocampus	35	186	5.23	-22	-14	-16
	IFG	47	243	4.22	-46	26	-2
	IFG	45		3.98	-44	22	6
Within incidental: association > item	Inferior occipital lobe	18	633	5.25	-16	-92	-6
Association _{intentional} > association _{incidental}	Paracentral lobule	4	606	4.55	-2	-32	64
	Paracentral lobule	4		4.39	8	-30	62
	Postcentral gyrus	4		4.09	14	-36	68
	Precentral gyrus	4	853	4.45	40	-22	60
	Postcentral gyrus	3		4.32	36	-28	46
	Postcentral gyrus	4		3.92	54	-14	48
	Precentral gyrus	4		3.83	32	-26	56
	Precentral gyrus	6		3.35	28	-14	66
	Hippocampus	35	26	3.75	-24	-18	-18

k = number of voxels; BA = Brodmann area.

main effect of Task condition ($F(1, 49) = 103.01, p < .001, \eta_p^2 = .68$). The recognition of object combinations resulted in more false alarms compared with the recognition of single items and a main effect of Level of binding ($F(1, 49) = 14.08, p < .001, \eta_p^2 = .22$), indicating that the number of false alarms was significantly lower for two-fragmented compared with three-fragmented objects.

Hence, memory performance was overall higher in the intentional compared with the incidental encoding group mainly because of a higher number of hits. Poorer associative relative to item memory primarily stemmed from higher false alarm rates in the associative condition, whereas the effect of level of binding was driven by both more hits and fewer false alarms in two- compared with three-level binding trials.

Imaging Results

Item and Associative Encoding Activity Modulated by Instruction

First, we determined regions that showed greater activation during the encoding of associations relative to items.

This was done separately for the two encoding instruction groups. In the intentional encoding group, the left anterior hippocampus and left IFG were more engaged during associative compared with item encoding. This was also true for the left fusiform gyrus and a cluster in the left and right lingual gyri that extended to the inferior and middle occipital lobes. In contrast, in the incidental encoding group, only one area located in the left lingual gyrus showed significantly greater activation during the encoding of object combinations compared with fragments of single objects. We did not observe any region to be more active during the encoding of items compared with associations in the intentional encoding group or the incidental encoding group (Table 2; Figure 3). We further compared activation related to the encoding of associations and items between the two encoding groups. The two groups did not differ in activity that was related to the encoding of items. However, associative encoding brought about greater activity in the left anterior hippocampus for intentionally compared with incidentally learned associations and also more activity in the bilateral primary motor cortex and right parietal lobe (Table 2). Finally, we identified areas in which

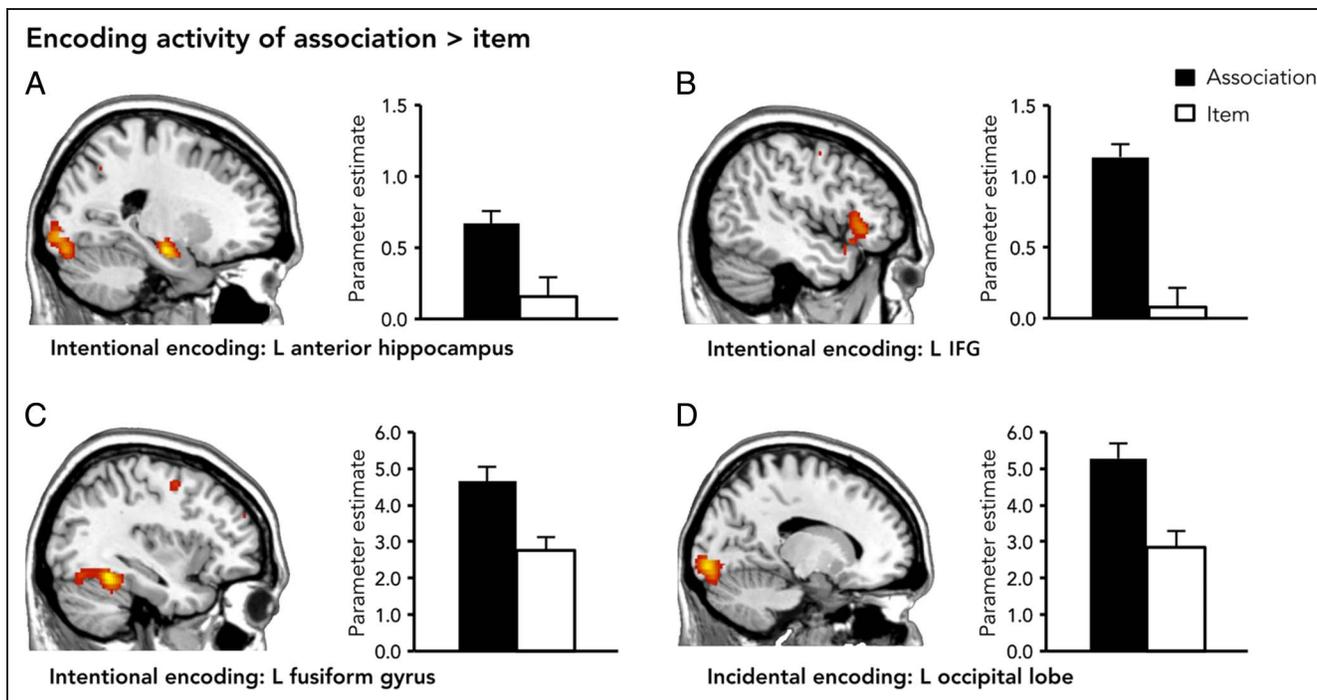


Figure 3. Brain regions significantly activated during encoding of associations relative to items. Mean participant-specific β -weights of voxels within these regions are plotted for experimental conditions separately. Error bars represent *SEMs*. Plots A, B, and C show regions significantly activated within the intentional encoding group, including the left anterior hippocampus, IFG, and fusiform gyrus. Plot D shows the left occipital lobe significantly activated in the incidental encoding group. L = left.

intentional encoding differed from incidental encoding of associations and items (Task condition \times Encoding instruction): The left anterior hippocampus showed greater engagement during intentional relative to incidental encoding of associations compared with intentionally or incidentally encoded items (Table 2; Figure 4). To ensure that differences in brain activity between encoding groups were accounted for by differences in encoding instructions and not subsequent behavioral differences, we repeated the whole-brain ANOVA described above and added memory performance [Pr (p [hits] – p [false alarms])] as a regressor of no interest into the model. The results remained unchanged.

Brain Activity Related to Successful Associative Memory Formation

To further investigate whether hippocampal and IFG activation during associative encoding in the intentional encoding group was related to encoding success, we performed event-related subsequent memory analyses. Contrasting successfully remembered to forgotten associations across binding levels, significant activation in the left anterior hippocampus, along with activation in the left fusiform gyrus (Table 3; Figure 5), was observed. As we observed poorer memory for object triplets than object pairs, we performed the analysis separately for two- and

Figure 4. Region in the left anterior hippocampus showing a significant Task \times Instruction interaction. Mean participant-specific β -weights of voxels within this region are plotted separately for encoding groups and experimental conditions. Error bars represent *SEMs*. L = left.

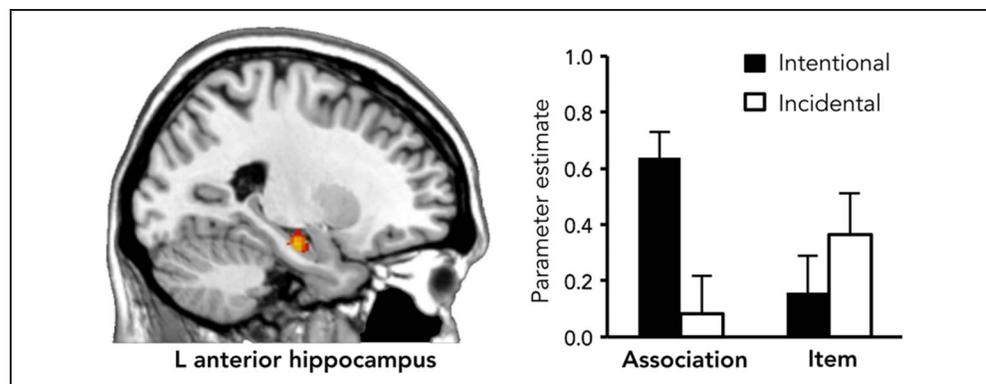


Table 3. Brain Regions Showing Significant Activity during Successful Intentional Encoding of Associations

Contrast	Region	BA	<i>k</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
Across binding levels: hit > miss	Inferior occipital lobe	19	552	4.81	-44	-74	-14
	Inferior occipital lobe	37		4.67	-46	-66	-12
	Fusiform gyrus	37		4.66	-38	-54	-14
	Hippocampus	35	16	3.92	-20	-12	-16
	Hippocampus	35		3.89	-18	-8	-18
Two-level binding: hit > miss	Inferior occipital lobe	37	1173	5.86	-48	-66	-12
	Lingual gyrus	18		5.11	-28	-96	-16
	Fusiform gyrus	19		4.54	-38	-84	-20
	Fusiform gyrus	37		3.68	-32	-50	-22
	Hippocampus	35	68	5.06	-20	-10	-18
	IFG	44	215	4.65	-50	18	34
	IFG	48		4.44	-52	20	24
IFG	45		4.13	-48	24	18	

k = number of voxels; BA = Brodmann area.

three-level binding events to obtain a more fine-grained signal of subsequent memory performance. Although there was no subsequent memory effect for object triplets, activity in the left anterior hippocampus, left IFG, and left

fusiform gyrus was associated with encoding success for object pairs (Table 3; Figure 5). Activity in these regions was not related to successful incidental associative encoding or successful item encoding in either encoding group.

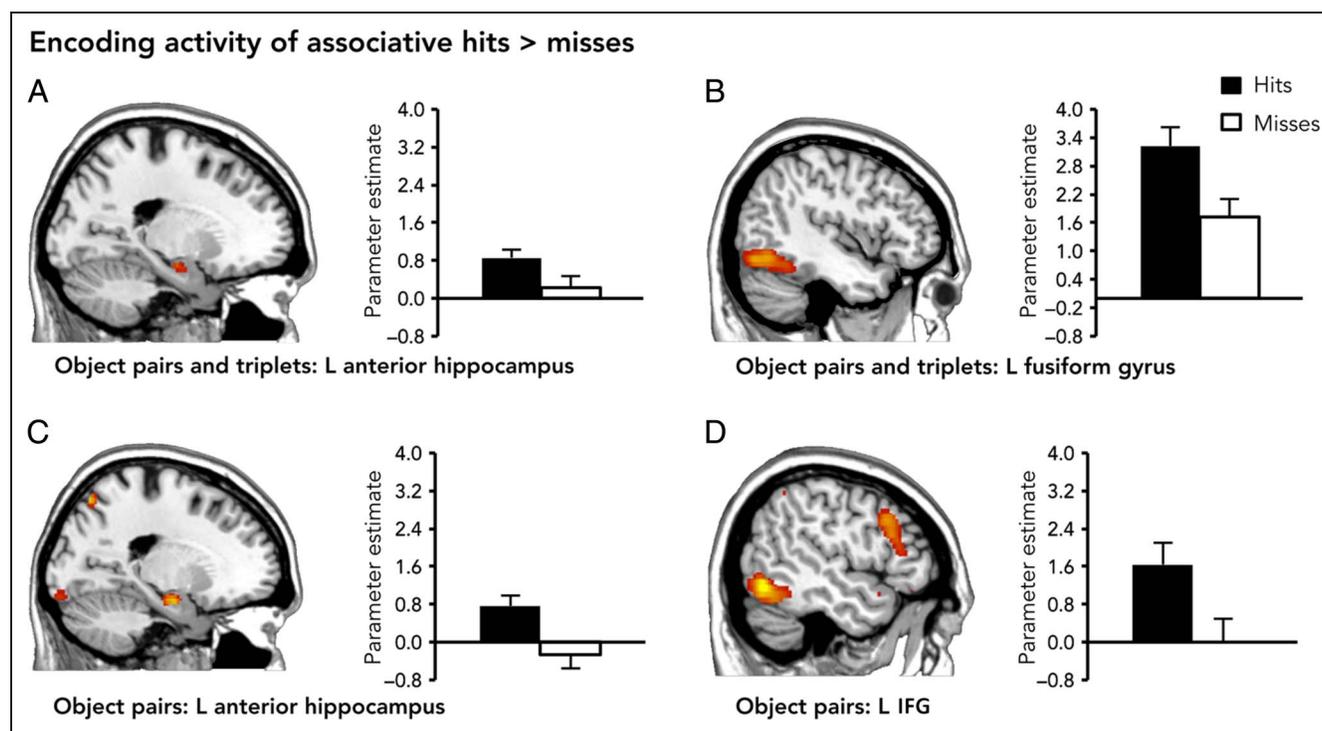


Figure 5. Brain regions significantly activated during intentional encoding of subsequently remembered relative to forgotten associations. Mean participant-specific β -weights of voxels within these regions are plotted for hits and misses separately. Error bars represent *SEMs*. Plots A and B show the left anterior hippocampus and fusiform gyrus activated during successful encoding of all associative trials including object pairs and triplets. Plots C and D show the left anterior hippocampus and IFG activated during successful encoding of object pairs only. L = left.

Table 4. Brain Regions Showing Significant Functional Connectivity with the Left Anterior Hippocampus during Successful Intentional Encoding of Associations

<i>Contrast</i>	<i>Region</i>	<i>BA</i>	<i>k</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
Two-level binding: hit > miss	Insula	48	622	5.23	40	4	-8
	Insula	48		5.01	50	-2	2
	IFG	45		4.48	56	24	0
	Superior temporal lobe	38		4.15	58	10	-10
	IFG	45		4.13	52	18	-2
	IFG	45		4.03	46	26	6
	Superior temporal lobe	38		3.98	54	14	-8
	Superior temporal lobe	48		3.91	52	-14	2
	Fusiform gyrus	30	631	4.83	28	-26	-20
	Hippocampus	30		4.49	20	-26	-6
	Fusiform gyrus	37		4.45	44	-50	-24
	Lingual gyrus	27		4.11	6	-34	-4
	Cerebellum	19		4.58	32	-66	-28

k = number of voxels; BA = Brodmann area.

Hippocampal Connectivity Related to Successful Associative Memory Formation

To further investigate which brain areas interacted with the left anterior hippocampus during successful intentional encoding of two-level associations, we applied a functional connectivity analysis using PPI. The peak voxel location in the left anterior hippocampus cluster that showed greater engagement during successful associative formation of object pairs than items ($x = -20, y = -10, z = -18$) was used as a seed ROI. This region exhibited increased functional connectivity during subsequently remembered relative to subsequently forgotten

object pairs with two areas; one cluster was located in the right IFG and extended to the right superior temporal lobe and right insula, whereas the other involved the right posterior hippocampal and parahippocampal region as well as a region in the right FFG that extended to the lingual gyrus and cerebellum (Table 4; Figure 6). Moreover, we observed a cluster in the left IFG that extended to the left superior temporal lobe and left insula (peak voxel coordinates: $x = -42, y = 6, z = -2$; cluster size = 517 voxels) that only slightly failed to reach conventional significance (family-wise error-corrected $p = .059$).

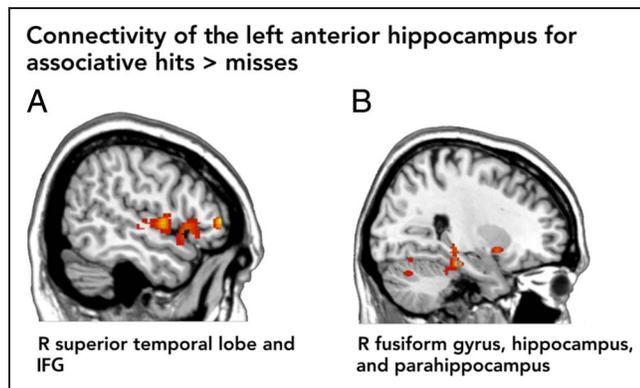


Figure 6. Brain regions including the right superior temporal lobe and IFG as well as the right hippocampal region and fusiform gyrus, showing significant functional connectivity with the left anterior hippocampus during intentional encoding of subsequently remembered relative to forgotten associations (region resulting from subsequent memory analysis located at $x = -20, y = -10, z = -18$). R = right.

DISCUSSION

To our knowledge, this is the first study that investigated differences in functional brain correlates for item and associative memory as a function of encoding instruction (intentional vs. incidental). First, we found that memory performance in the intentional encoding group was higher compared with that in the incidental encoding group. Furthermore, memory performance was higher for item compared with associative memory, regardless of encoding instruction. Second, and in line with previous work, greater activity in the left anterior hippocampus and left IFG was observed for intentional associative encoding compared with item encoding. With regard to our main research question, we observed greater activity in the left anterior hippocampus during intentionally compared with incidentally encoded associations, whereas we could not observe activity differences in this region between intentionally and incidentally encoded items. Moreover, anterior hippocampal and IFG mean BOLD activity, as

well as between-region functional connectivity, was related to subsequent memory for intentionally encoded associations.

Behavioral Performance

In line with past research, individuals performed better in the item compared with the associative recognition task (independent from encoding instruction), and this effect primarily stemmed from higher false alarm rates in the latter condition (Naveh-Benjamin et al., 2009). However, unlike previous studies that compared item and associative memory, the presentation of items in the current study was manipulated such that, during encoding, items were presented as fragments. This manipulation aimed to benefit comparisons of item and associative encoding by matching the visual input, whereby it added a perceptual binding demand to items not present in traditional item associative memory paradigms. It remains open whether this manipulation affected participants' item memory performance and limits the comparison with other studies investigating differences between item and associative memory. Moreover, intentional encoding instructions resulted in higher associative recognition performance compared with incidental encoding instructions. This likely resulted from associative encoding strategies participants used to intentionally encode object combinations, as compared with semantic encoding triggered by animacy judgments in the incidental encoding group. Surprisingly though, the same was true for encoding of items, that is, recognition performance was higher for intentionally than incidentally encoded objects. As such, our data do not support the levels of processing model of memory (Craik & Lockhart, 1972) according to which item memory encoding processes arise even when the task does not require intentional memorization but happen as a by-product of perceptual processing.

In addition to performance differences between the two encoding groups, group-specific effects of level of binding on associative, but not item memory likely reflect differences in underlying encoding processes. In the intentional encoding group, associative recognition was higher for object pairs compared with object triplets. This binding level difference is sensible as the encoding of object pairs required the generation of fewer associations between objects compared with object triplets, hence resulting in enhanced memory performance (Addis & McAndrews, 2006). However, in the incidental encoding group, the level of binding did not affect associative recognition performance, likely reflecting that participants did not actively generate associations between objects during incidental encoding. In contrast, the two encoding groups did not differ in the effect of level of binding on item recognition. Although we did not expect fragmentation level to affect memory performance, as this manipulation was primarily used to control for the visual input between associative and item trials, in both

encoding groups, recognition performance was higher for items presented as two compared with those presented as three fragments. A possible explanation for this pattern is that the integration of three relative to two fragments into a unified item was perceptually more demanding and thus resulted in poorer memory performance. Behavioral results, however, should be interpreted with some caution, as item recognition might be biased because of an imbalanced ratio of old and new trials. Moreover, memory performance in both groups was generally very low, likely because of a high number of trials needed to ensure a sufficient number of hits and misses used in the subsequent memory analysis.

No Observed Instruction-specific Activity in Item Encoding

In line with previous neuroimaging studies (Stark & Okado, 2003; Buckner et al., 2001), no differences in brain activity between intentional and incidental item encoding were observed. Previous studies compared intentional encoding with unspecific incidental encoding instructions, that is, the study designs did not allow conclusions about the level of processing (i.e., deep or shallow; Stark & Okado, 2003; Buckner et al., 2001). In contrast, the current task design allowed for a direct comparison between deep incidental and intentional encoding. Still, we did not observe the brain processes related to item encoding to be influenced by the type of instruction. A likely explanation for this is that our incidental encoding instruction contained a semantic categorization (i.e., animacy judgments), which has been shown to be an effective memory strategy for item information (Craik & Lockhart, 1972). Although we found slightly better performance after intentional compared with incidental item encoding, this deep incidental encoding instruction might not be too different with regard to the level of processing elicited by spontaneously applied strategies among participants from the intentional encoding group. Specific cognitive operations that could differentiate incidental from intentional encoding were not specified in this study, which could have resulted in more variability during intentional than incidental encoding. However, after study completion, participants were asked if and what kind of memory strategy they used during encoding: All participants who received intentional encoding instructions reported the use of either deep (e.g., sentence generation or visual imagery; 50% of the participants) or shallow (30% of the participants) strategies (see Dunlosky & Hertzog, 1998, for categorization). Although the level of specificity in these reports may not be sufficient for a detailed analysis of encoding strategies, it supports the notion that young adults self-initiate a set of memory strategies to learn new information, without the explicit instruction to do so (Kirchhoff, Gordon, & Head, 2014).

Instruction-specific Activity in Associative Encoding

In line with our behavioral results, we found greater activity in the left anterior hippocampus during intentional compared with incidental encoding of associations. This activity difference likely reflects differences in encoding processes prompted by the two types of instructions. Previous studies on associative memory have investigated the effects of semantic elaboration in intentional encoding (Hawco, Armony, & Lepage, 2013; Park, Uncapher, & Rugg, 2008). Results showed greater activity in the left anterior hippocampus for items processed semantically relative to those processed phonologically. Although this indicated that a certain level of processing that exceeded the intent to remember modulated anterior hippocampal activity, it raises the question of whether activity in this region is triggered primarily by semantic elaboration. However, we did not observe anterior hippocampal activity related to semantic incidental encoding, but to intentional encoding only. Thus, our data provide evidence that semantic elaboration alone is insufficient but that intention to remember is important for hippocampal activity to occur. Conceivably, intent to memorize triggers a binding mechanism subserved by the anterior hippocampus. In line with our findings, Park and Rugg (2008) presented participants with pairs of unrelated words and provided these under either a semantic or phonologic incidental encoding instruction. Their results showed that neither a semantic nor phonologic instruction during associative encoding prompted anterior hippocampal activity related to associative memory, suggesting that intentional memorization may be a prerequisite for anterior hippocampal engagement to occur. Our findings indicate that intention to remember prompts a binding process in the left anterior hippocampus, although previous findings suggest that the hippocampus is involved in rather automatic binding of items (Eichenbaum, 2001). Specifically, the anterior portion of the hippocampus was related to the deliberate binding of items. This finding supports the specific architecture of the hippocampus and the functions its anterior and posterior portions are suggested to serve. The anterior hippocampus is specialized in the encoding of novel events and conceptual processing, which involves the formation of associations between random items. Thus, the anterior hippocampus may play an important role in collating information through pattern completion, that is, the generation of global representations of relations among units (Moscovitch, Cabeza, Winocur, & Nadel, 2016; Poppenk et al., 2013). Future studies should investigate if item–item binding processes in the anterior hippocampus can be triggered by incidental encoding instructions that involve creating a semantic link between two or more items (Troyer et al., 2006).

We did not find differences in frontal activation between intentionally and incidentally encoded associa-

tions. This was unexpected, given previous work reporting PFC engagement during episodic memory encoding (Habib, Nyberg, & Tulving, 2003). Furthermore, PFC is known to support binding in the hippocampus through strategic and cognitive control mechanisms (Qin et al., 2009; Murray & Ranganath, 2007; Addis & McAndrews, 2006). One possible explanation for this nonobserved effect is that the semantic categorization in the incidental encoding condition triggered strategy-based frontal activations similar to those individuals receiving intentional encoding instructions applied.

Differences in Item and Associative Encoding Modulated by Instruction

A direct comparison of item and associative memory within incidental encoding revealed differences in brain activity in the visual cortex, suggesting that individuals processed more visually distinctive input during associative relative to item encoding. The lack of activity differences in memory-related brain regions (i.e., MTL and PFC) may suggest that the incidental instruction did not trigger elaboration of item relations during associative encoding. Rather, individuals processed objects unconnectedly during incidental associative encoding, whereas encoding of between-object relations was induced only by the intent to memorize. Accordingly, we identified greater activation in the left anterior hippocampus and left IFG during intentional associative encoding compared with item encoding (Qin et al., 2009; Chua et al., 2007; Murray & Ranganath, 2007; Davachi & Wagner, 2002). Importantly, this difference was of qualitative not quantitative nature, as activity in these regions during item encoding did not significantly differ from zero (see Figure 3). Moreover, our study provides evidence for the involvement of anterior hippocampus and IFG, particularly in the binding of items rather than a general binding process as we observed differential activity for item–item binding relative to fragmented items that required a unitization process that did not elicit activity in these regions.

Hippocampal and IFG Contributions to Successful Associative Memory Formation

Results of our subsequent memory analysis provide further evidence that the hippocampus and IFG underlie successful encoding of between-item associations (Qin et al., 2009; Blumenfeld & Ranganath, 2006). In addition, we found activity in the left fusiform gyrus that was related to subsequent memory performance. This region has been implicated in the encoding of associative pictorial materials (for a review, see Kim, 2011). Studies on associative memory have almost exclusively investigated hippocampal and IFG involvement in encoding success. The current study design enabled separate analyses for associative memory activation related to sustained processes

engaged during encoding (i.e., mode) and transient processes involved during successful encoding. Our findings provide new evidence that the hippocampus and left IFG are involved in both successful encoding of associative information and sustained processes related to attempts to remember associative information.

The functional connectivity analysis of the anterior hippocampus revealed that the successful encoding of object pairs was facilitated by increased connectivity with the right IFG, superior temporal lobe, and insula as well as the right FFG and hippocampal and parahippocampal regions. Connectivity with the left IFG, superior temporal lobe, and insula almost reached conventional levels of significance. These findings fit well with the neuroanatomical linkage of hippocampus with these regions (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005). They further support observations on the functional importance of this linkage in successful associative memory formation (Gagnepain et al., 2011; Addis & McAndrews, 2006). This fits well with the influential idea that encoding aspects of an event are processed in neocortical areas and then bound in the hippocampus to support relational memories (Eichenbaum & Cohen, 2001). Moreover, both hemispheres of the IFG have been associated with the processing of pictorial information (Kirchhoff, Wagner, Maril, & Stern, 2000; Kelley et al., 1998) that might have been transferred to the hippocampus during associative encoding.

To conclude, this study demonstrates the differential involvement of the left anterior hippocampus in intentional relative to incidental encoding of between-item associations, thereby extending previous work on the effect of instruction on item memory. Moreover, the data provide further evidence regarding the interaction of anterior hippocampus and IFG during intentional encoding of between-item associations and reveal insights on successful encoding of those associations, as the magnitude of activity and functional connectivity in the same regions predicted subsequent memory.

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