State-related and item-related neural correlates of successful memory encoding

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Neuroimaging studies show that the efficacy of long-term memory encoding of a stimulus is indexed by transient neural activity elicited by that stimulus. Here, we show that successful memory encoding is also indexed by neural activity that is tonically maintained throughout a study task. Using functional magnetic resonance imaging (fMRI), transient and sustained neural activity were dissociated with a mixed event-related and blocked design. In a series of short task blocks, human subjects made semantic or phonological decisions about visually presented words. After statistically removing item-related activity, we found that the mean level of activity across a task block was correlated with the number of words subsequently remembered from that block. These correlations were found in inferior medial parietal and left prefrontal cortex for the semantic task, and in superior medial parietal cortex for the phonological task. Our findings suggest that state-related activity in these brain regions is involved in memory encoding.

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With the development of functional neuroimaging, there has been increasing interest in the neural systems responsible for long-term memory encoding[1,2]. In early studies that used blocked designs, the temporal resolution needed to study encoding for individual stimulus events was not available. The advent of event-related fMRI in the mid-1990s[3], however, has made this possible. In the 'subsequent memory' approach, for example, subjects study a series of items while neural activity is recorded, and then they take a memory test for those items. The neural activity recorded during the study period is sorted according to whether items are remembered or forgotten in the subsequent memory test. Brain regions where activity differentiates between subsequently remembered and forgotten items—regions showing transient, item-related activity—are taken as candidate regions for a role in memory formation. Findings from the subsequent memory approach suggest that several cortical regions are involved in encoding[1,4,5].

Previous studies have not, however, addressed the possibility that encoding may rely on tonically maintained activity (state-related activity) in addition to transient neural activity elicited by individual items (item-related activity). For methodological reasons, this is a distinction that cannot be addressed with a conventional blocked ('boxcar') design because the detected activity represents an aggregate of item- and state-related effects that cannot be separated (**Fig. 1**). There is no theoretical reason, however, to assume that state-related neural activity does not influence memory encoding. Indeed, the time course of activity in entorhinal cortex during a memory task indicates that neural activity sustained over a short block of words is associated with the number of words successfully encoded[6]. However, state- and item-related neural activity could not be dissociated in that study.

Here, we used a mixed event-related and blocked experimental design to ask whether state-related activity is associated with episodic encoding. In this design, transient neural responses were varied in time relative to sustained responses, thereby allowing the two types of response to be estimated separately (**Fig. 1**). The same approach has been used in earlier studies to investigate state-related processes in attention[7] and recognition memory[8].

In the present experiment, we obtained whole-brain, blood oxygenation level–dependent (BOLD) contrast images while subjects engaged in a series of 83-s task blocks, which alternated with short rest blocks (**Fig. 1a**). During each task block, a cue instructed subjects to make either animacy or syllable judgments (see Methods) about 12 words presented at random intervals during the block. Fifteen minutes after scanning was completed, subjects were given a recognition memory test for the presented words. Item-related neural correlates of successful encoding were identified by determining where event-related activity varied according to whether items were remembered or forgotten in the subsequent memory test ('item-related subsequent memory effects'). State-related correlates of encoding were identified by determining where, after statistical removal of item-related activity, mean activity across the task blocks correlated with the number of words remembered from each block ('state-related subsequent memory effects'). As we used two study tasks, we were able to determine whether state-related correlates differ according to the type of processing engaged at the time of study, as has been found for the neural correlates of item-related encoding[9].

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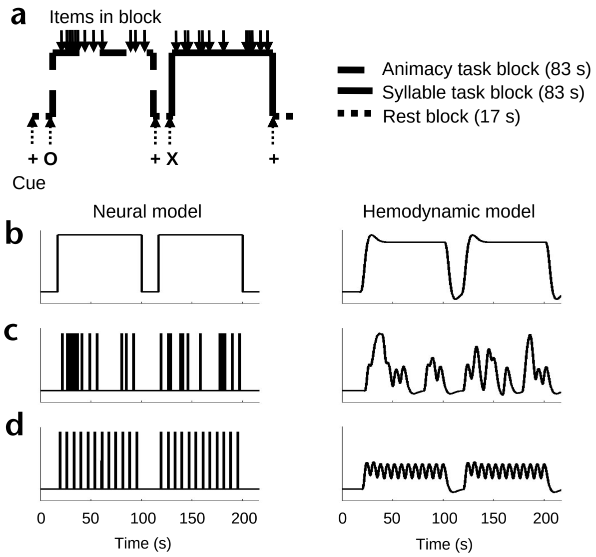

Fig. 1. Methods. (**a**) Experimental design. In the study phase, subjects engaged in short task blocks, during which they made either animacy or syllable judgments about 12 words presented at random intervals, alternating with short rest blocks. A visual cue (**+**, rest; **O**, animacy block; **X**, syllable block) signaled the current block. See Methods for further details. (**b**) State-related neural activity was modeled with boxcar functions representing activity sustained throughout task blocks (neural model, left). These functions were convolved with a standard hemodynamic response function[27] to generate a 'hemodynamic model' (right). This model was one of the regressors within the general linear model that we used to decompose the variance in BOLD signal during the study phase (Methods). (**c**) Item-related neural activity was modeled with delta functions representing word onsets (left). These were also convolved with a hemodynamic response function to provide the regressor for the detection of item-related activity (right). Crucially, the correlation between the item- and state-related regressors was kept relatively low (0.58 in the present example) by pseudorandomly varying the interval between item onsets within each task block. This permits the reasonably efficient estimation of the two classes of neural activity. (**d**) Illustration of the kind of item-related hemodynamic model produced by an experimental design in which items are presented at regular intervals in each task block (as is typical in conventional blocked designs). The model is similar in form to that for the state effect shown in (**b**) above (correlation of 0.9 in the case illustrated here), making the estimation of state and item effects highly inefficient.

RESULTS

Task performance

Animacy and syllable judgments during the study phase were highly accurate (mean, 94% correct in each case). Subjects took longer to respond when a syllable—rather than animacy—judgment was required (mean reaction times of 1,212 and 980 ms, respectively; $t_{15} = 5.32$, $P < 0.001$). In neither task did response times predict whether a word would subsequently be remembered. In addition, there was no relation between serial position (of items within blocks or of blocks within the study phase) and probability of subsequent recognition memory.

Recognition memory accuracy for 'sure' and 'unsure' responses (Methods) was indexed by the discrimination measure calculated by subtracting the probability of a false alarm from the probability of a hit[10] (**Table 1**). For confident (sure) responses, discrimination was significantly greater than zero for words from both study tasks (0.53 and 0.27 for the animacy and syllable tasks, respectively; $t_{15} = 12.48$ and 8.35, both $P < 0.001$). Accuracy was higher for words from the animacy task ($t_{15} = 9.01$, $P < 0.001$). For unconfident (unsure) responses, recognition accuracy was not reliably greater than zero for words from the animacy task, and was only slightly greater than chance for words from the syllable task (0.07, $t_{15} = 3.03$, $P < 0.01$). On the basis of these and previous findings[9,11–13], studied words were categorized as 'remembered' when they received a "confident old" judgment during the subsequent recognition memory test, and 'forgotten' when they were misclassified as new.

State-related activity and episodic encoding

We found state-related subsequent memory effects in three regions (**Table 2; Figs. 2** and **3**). In the animacy task, there were significant effects in inferior medial parietal cortex and left inferior frontal gyrus. In the syllable task, an effect was found in a more superior medial parietal region. We further evaluated this apparent dissociation between tasks with interaction contrasts and found greater state-related subsequent memory effects in the animacy task compared with the syllable task in medial parieto-occipital cortex (Talairach (x, y, z) coordinates –6, –78, 27; $Z = 3.47$) and left inferior frontal gyrus (–48, 24, 0; $Z = 3.64$). These regions overlap with or are adjacent to those identified in the original analysis of effects in the animacy task. We did not find any voxels that showed reliably greater subsequent memory effects in the syllable task.

To assess whether any of our findings were due to prolonged item-related activity rather than to state-related activity, we computed an analysis model in which additional basis functions were used to estimate item-related activity more comprehensively; this did not affect the state-related findings. To determine the degree to which our state-related findings were influenced by colinearity between item- and state-related activity, we re-estimated both state- and item-related effects after omitting the other effect from the model. This did not change either finding.

We also investigated whether any regions showed task-dependent state-related activity regardless of subsequent memory performance. The animacy task evoked greater activity in left middle temporal gyrus (–60, –36, 3; $Z = 4.20$) and left superior frontal gyrus (–21, 45, 39; $Z = 4.07$); the syllable task evoked greater activity in the left inferior occipital gyrus (–42, –81, –6; $Z = 3.80$) and the left middle frontal gyrus (–39, 45, 21; $Z = 3.80$).

Item-related activity and episodic encoding

In the animacy task, more item-related activity was elicited by subsequently remembered items than by forgotten items in three regions: left inferior frontal gyrus, left inferior temporal cortex and bilateral fusiform gyrus. In the syllable task, we found analogous effects in left inferior frontal gyrus, bilateral fusiform gyrus and

Table 1. Recognition memory performance.

		Recognition judgment			
Word type		Sure old	Unsure old	Sure new	Unsure new
Proportion of responses					
Old					
	Animacy	0.61 (0.17)	0.20 (0.11)	0.05 (0.06)	0.14 (0.08)
	Syllable	0.35 (0.16)	0.27 (0.12)	0.12 (0.11)	0.25 (0.10)
New		0.09 (0.07)	0.19 (0.08)	0.34 (0.18)	0.37 (0.15)

Values are across-subject means (s.d.).

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Table 2. Regions showing state-related subsequent memory effects in the animacy and syllable study tasks.

Location (*x, y, z*)	Peak *Z*-score	Region	Brodmann area	Direction of effect
Animacy study task				
–48, 18, 3	3.88 (13)	Left inferior frontal gyrus	45/47	Negative
–3, –60, 30	4.13 (49)	Medial parietal cortex	7/31	Positive
Syllable study task				
0, –54, 60	3.54 (5)	Medial parietal cortex	7	Negative

Z-scores refer to the peak of the activated cluster, the size of which (number of voxels) is indicated in parentheses. Coordinates refer to the Montreal Neurological Institute reference brain[31]. See text for interactions between tasks.

left lateral parietal cortex (**Table 3**; **Fig. 4**). To further investigate the apparent task dissociation between these item-related effects, we set up interaction contrasts that identified all voxels where subsequent memory effects differed according to task. Voxels showing greater effects in the animacy task were found in left inferior frontal gyrus (ventral, –48, 33, 15; $Z = 4.52$; dorsal, –51, 18, 0; $Z = 3.59$) and bilateral parahippocampal gyrus/fusiform cortex (left, –33, –9, –21; $Z = 3.62$; right, 39, –24, –15; $Z = 3.87$). Effects were greater in the syllable task in left lateral parietal cortex (–24, –63, 45; $Z = 3.73$). These voxels overlapped with, or were close to, those showing subsequent memory effects in the within-task contrasts.

Overlap between state- and item-related effects

We searched for regions where state- and item-related subsequent memory effects overlapped by identifying all voxels where the effects were conjointly reliable (that is, by inclusively masking one contrast with the other). These analyses did not take into account the direction of the subsequent memory effects, and the threshold used for each contrast was $P < 0.01$. Even at this liberal threshold, only one region—the left inferior frontal gyrus—showed overlapping state- and item-related effects (albeit showing opposite relationships with subsequent memory). Centers of mass of the active clusters were at –48, 18, 3 ($Z = 3.88$) and –54, 18, 3 ($Z = 3.72$) for state- and item-related effects, respectively.

DISCUSSION

Using a mixed blocked and event-related design, we identified and dissociated item- and state-related neural correlates of successful episodic memory encoding. Three brain regions showed a predictive relationship between neural activity that is sustained over a task block and long-term memory performance. Thus, the findings strongly support the proposal[6] that the likelihood that a stimulus event will lead to an enduring memory is influenced by both the neural activity recruited as the event is processed 'online', and the neural 'context'—as determined by tonic levels of regional activity—in which the processing occurs.

In previous studies of episodic encoding, state- and item-related neural activity could not be differentiated. Early neuroimaging studies that used blocked designs (for review, see ref. 1) confounded the two kinds of activity, and more recent event-related studies (for review, see ref. 4) have focused exclusively on the detection of item effects. Although state effects similar to those described here may have contributed to previous findings, such effects can only be identified unambiguously using designs that separate hemodynamic signals into item- and state-related components.

Through what mechanisms could state-related activity influence or be associated with episodic encoding? The present findings argue against the possibility that state effects merely index some general determinant of cognitive efficiency, such as arousal. Were this the case, the same state-related subsequent memory effects would have been found in both study tasks. Instead, we found that the regions showing these effects in the two tasks did not overlap. Thus, as is the case for item-related subsequent memory effects[9,14], state-related effects seem to be task-dependent.

In considering how tonic neural activity might influence the processing of a specific stimulus, it is useful to distinguish between state-related effects that co-localize with item effects and those that do not. The former case corresponds with previously reported positive correlations between attention-related modulation of co-localized state- and item-related activity in extrastriate visual cortex[7], and with previous findings of co-localized effects in the frontal operculum[8]. In the present study, out of the three regions showing a state-related subsequent memory effect, only one—inferior prefrontal cortex—also showed an item-related effect. Unlike the aforementioned studies[7,8], the rela-

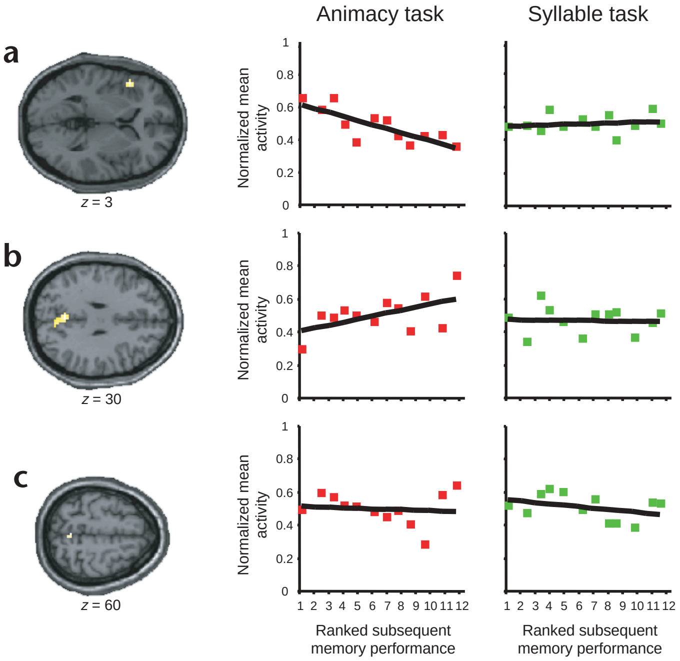

Fig. 2. State-related subsequent memory effects. Left, regions showing state-related neural activity associated with subsequent memory performance (see Methods for details of fMRI data analysis). Significant clusters of activated voxels ($P < 0.0005$) are rendered onto the MNI normalized canonical brain[31] (Talairach z-coordinate given below each image; see **Table 2** for all coordinates). Right, normalized state-related activity plotted against task blocks ranked according to subsequent memory performance (1, worst; 12, best). Data points averaged over subjects. Note that these plots depict the relation between state-related activity and performance, but they do not form the basis of the statistical inferences reported in the text (Methods). (**a**) In the animacy task, mean activation in left inferior frontal gyrus correlated negatively with the number of words subsequently remembered from the block. (**b**) In the animacy task, mean activation in inferior medial parietal cortex correlated positively with the number of remembered words. (**c**) In the syllable task, mean activation in superior medial parietal cortex correlated negatively with the number of remembered words.

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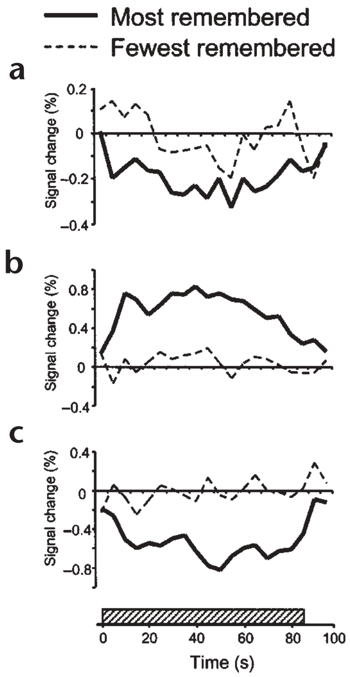

Fig. 3. Time courses of state-related activity related to episodic encoding. For each of the regions showing a state-related subsequent memory effect, two finite impulse response models[32] were estimated for the peak voxel after removing item-related activity. For each subject and session, these were derived from the two study blocks yielding the highest, and the two blocks yielding the lowest, levels of subsequent memory. Thick bar on the *x*-axis represents duration of task block. The *y*-axis represents percent signal change (relative to grand mean over voxels) versus fixation baseline. (**a**) Across-subject average of activity during animacy task blocks in left inferior frontal gyrus. (**b**) Average activity in animacy task blocks in inferior medial parietal cortex. (**c**) Average activity during syllable task blocks in superior medial parietal cortex. See **Table 2** for coordinates.

tionship between the two effects was reciprocal: larger item-related responses were associated with better subsequent memory (consistent with other findings[1,4,5]), whereas the opposite relation held for state-related activity. This pattern suggests a trade-off or competition between the two classes of neural activity. In light of evidence that inferior prefrontal cortex is involved in phonological processing[15], the present findings may reflect a trade-off between phonological resources used to encode items in the animacy task and resources allocated to other activities, such as maintaining an internal narrative or commentary during the intervals between items. Regardless of the validity of this account, taken together with previous work, our results indicate that co-localized state- and item-related activity can be both negatively and positively related.

State-related subsequent memory effects in the absence of co-localized item effects were identified in two medial parietal regions, one in each study task. These regions may influence memory encoding by modulating item-related activity in other areas, or perhaps by altering the efficiency with which encoded information is consolidated into memory. As these effects were task-specific, an account framed in terms of some very general effect on, say, synaptic plasticity, can be ruled out. Indeed, the opposite relationships between state-related activity and subsequent memory in the two medial parietal regions (positive in the animacy task, negative in the syllable task) indicate that activity in these regions influenced memory through qualitatively distinct mechanisms.

Medial parietal activation has been reported in previous studies (both blocked[16,17] and event-related[18,19]) of memory encoding, although the functional significance of these findings remains unclear. These encoding-related effects were reported in regions close to[16], or overlapping with[17–19], the more inferior of the medial parietal regions identified here. Although these observations do not elucidate the state-related subsequent memory effects reported here, they converge with the present findings to suggest a role for this region in encoding across a range of study tasks and materials. The same cannot be said for the more superior medial parietal area that showed a negative relation between state-related activity and subsequent memory in the syllable task; we are unaware of any previous evidence indicating a role for this region in encoding. A possible clue to understanding these effects arises from the observation that the region is one of several sites on the medial cortical surface that show relatively greater activity at rest than during task-engagement[20]. It has been proposed[20] that task-related medial parietal 'deactivations' reflect the role of this region in monitoring the external environment. Perhaps, therefore, the present findings indicate the benefit to nonsemantic episodic encoding of the disengagement of these monitoring operations, and the concomitant freeing up of processing resources. We acknowledge, however, that this represents only one of the many accounts of

Table 3. Regions where item-related activity was greater for subsequently remembered than forgotten items in the two study tasks.

Study task	Location (*x, y, z*)	Peak Z-score	Region	Brodmann area
Animacy				
	–48, 33, –15	4.09 (94)	Left inferior frontal gyrus	47
	–45, 27, 15	3.97 (44)	Left inferior frontal gyrus	45
	–54, 18, 3	3.72 (8)	Left inferior frontal gyrus	45/47
	–45, 6, –39	3.38 (5)	Middle temporal gyrus	20/21
	–33, –6, –42	5.09 (48)	Inferior temporal gyrus	20
	33, –18, –27	4.05 (22)	Parahippocampal/Fusiform gyrus	36/20
	–42, –48, –3	3.65 (9)	Superior temporal sulcus	21/22
Syllable				
	–57, 9, 15	3.39 (5)	Left inferior frontal gyrus	44
	–45, 0, 24	3.46 (10)	Left inferior frontal gyrus	9/44
	–45, –45, –24	3.72 (7)	Left fusiform gyrus	37
	–27, –51, 63	3.72 (19)	Left lateral parietal cortex	7
	–42, –60, –9	4.55 (29)	Left fusiform gyrus	19/37
	12, –60, –9	3.57 (6)	Right fusiform gyrus	19

Z-scores refer to the peak of the activated cluster, the size of which (number of voxels) is indicated in parentheses. Coordinates refer to the Montreal Neurological Institute reference brain[31]. See Results for interactions between tasks.

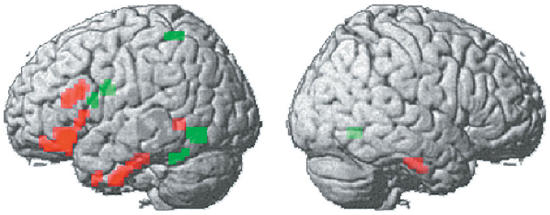

Fig. 4. Item-related subsequent memory effects. Highlighted regions are where item-related activity was greater for subsequently remembered than for forgotten items in each study task. Significant clusters of activated voxels ($P < 0.001$) in the animacy task (orange) and syllable task (green) are rendered onto the cortical surface of the MNI normalized canonical brain[31]. In the animacy task, item-related fMRI signals were greater for words that were subsequently remembered versus forgotten in left prefrontal and bilateral temporal regions; in the syllable task, this pattern was found in left prefrontal and posterior regions. There were no areas of overlap in the effects for each task. See **Table 3** for coordinates.

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this finding that are possible given the current level of understanding of task-dependent, state-related neural activity.

In addition to the state-related effects discussed above, item-related subsequent memory effects were evident in both encoding tasks. Other considerations aside, this result highlights the robustness of these effects; the experimental design adopted here, with its high proportion of relatively lengthy inter-stimulus intervals, is not optimal for the detection of differential item-related activity[21]. Notably, and in a pattern consistent with previous findings[9,14], the regions showing item-related effects in the animacy and syllable tasks did not overlap. Together with the task-specificity of the state-related effects, this result further supports the proposal that the cortical regions supporting the episodic encoding of a stimulus event differ according to how the event is processed[9,22].

Several regions showed task differences in state-related activity that were independent of subsequent memory performance. None of these overlapped with the regions showing subsequent memory effects, suggesting (unsurprisingly perhaps) that some aspects of task-dependent state-related activity support processes that are independent of those modulating memory encoding (for example, processes necessary for the maintenance of different 'task sets'[23]).

In conclusion, we have demonstrated that variability in the episodic encoding of discrete stimulus events is expressed in both the neural activity elicited by the events themselves, and in sustained activity unrelated to the processing of any particular event. More specifically, our findings indicate that a full understanding of the neural determinants of successful memory encoding will require investigation of both item- and state-related correlates of subsequent memory performance. Therefore, methodological and conceptual developments will be needed to bring these two classes of neural activity together within a common framework.

METHODS

Subjects. Sixteen volunteers (mean age 24 years, range 18–32, ten women) were paid to participate in the experiment. All volunteers reported themselves to be native speakers of English, right handed, with no neurological or psychiatric histories. All gave informed consent before the experiment; procedures were approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology joint Medical Ethics Committee.

Tasks and procedure. The experiment took the form of an incidental study phase followed by a surprise recognition memory test. The study phase was carried out in the MRI scanner. To separate state- and item-related neural activity, the study phase used a mixed event-related and blocked design (**Fig. 1a**). Task blocks (83-s duration) were alternated with rest blocks (17-s duration). A visual cue (+, rest; **O** or **X** for task blocks) signaled the current block. Rest blocks consisted of the presentation of a fixation point alone. Each task block consisted of the presentation of 12 words, displayed one at a time. The intervals between the words were jittered pseudorandomly between 2.4 and 31.6 s, such that the correlation between the regressors used to estimate item- and state-related activity did not exceed 0.5. The type of cue presented during a task block indicated the type of decision that had to be made about all words in the block. When an **O** was presented, volunteers decided whether or not each word in that block was animate or referred to a property of a living entity. When an **X** was presented, they decided whether the number of syllables in the word was odd or even. One of two buttons was pressed according to each decision. Both speed and accuracy were stressed. Responses were given with the left and right hands (responding hand counterbalanced across volunteers). Animacy and syllable blocks alternated to maximize sensitivity of detecting differences related to type of study task. Half of the subjects started with an animacy block, and half with a syllable block. Before entering the scanner, subjects received an explanation about the study tasks and performed a practice list. The study phase proper consisted of 12 animacy and 12 syllable task blocks interleaved with 26 rest blocks, and was presented in two halves.

Approximately 15 min after completion of the study phase, the memory test was administered. All 144 animacy- and 144 syllable-judged words from the study phase were re-presented, along with 144 new words. By pressing one of four keys, volunteers made old/new recognition judgments and at the same time indicated whether they were sure or unsure about their judgment. Both speed and accuracy were stressed. Subjects received a short practice list, followed by four blocks of 108 trials each.

Experimental stimuli were presented visually in a white uppercase Helvetica font in central vision on a black background. For the study phase, the words were projected onto a mirror in direct view of the reclining volunteer. Each word was presented for 300 ms, and subtended an approximate vertical visual angle of 0.9° and a horizontal visual angle ranging between 2.5 and 6°. The task and rest cues measured 0.9 × 0.8° of visual angle and were presented continuously throughout a block, except when words were presented. For the test phase, each word was presented on a computer monitor for 300 ms. The time between successive word onsets was 4.8 s. Each test word was preceded for 2 s by a warning stimulus (a cross).

Word lists. The stimulus lists were created from a pool of 552 words (4–9 letters in length, 1–4 syllables, 1–30 occurrences per million)[24]. Three sets of 144 words each were chosen pseudorandomly from this pool with the restrictions that the distribution of word lengths were equivalent across sets, half of the words in each set were animate and half contained an odd number of syllables. Across subjects, these sets were rotated across the three conditions: animacy, syllable and new. An additional 36 words were selected from the word pool to create practice lists.

Image acquisition. A 2-T Siemens Vision system (Erlangen, Germany) was used to acquire both T1-weighted structural images and T2*-weighted echoplanar (EPI) images (64 × 64; 3 × 3 mm pixels; echo time (TE), 40 ms) with BOLD contrast. Each volume comprised 26 axial slices (2.5 mm thick, separated by 2 mm), positioned to cover all but the cerebellum and the most superior region of the brain. Scanning started with a 15-min structural scan. Functional scans were then acquired during two sessions, each comprising 622 volumes, corresponding to the two halves of the study phase. Volumes were acquired continuously with an effective repetition time (TR) of 1.98 s per volume. The first five volumes in each session were discarded to allow for T1 equilibration effects.

Data analysis. fMRI data were analyzed using SPM99 software (http://www.fil.ion.ucl.ac.uk/spm/spm99.html)[25]. Volumes were realigned, corrected for different slice acquisition times, normalized to a standard EPI template based on the Montreal Neurological Institute

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(MNI) reference brain in Talairach space[26], and smoothed with an isotropic 8-mm, full-width, half-maximum Gaussian kernel. The volumes acquired during the two sessions were treated as separate time series. For each series, the variance in BOLD signal during the study phase was decomposed with a set of regressors in a general linear model. Variance was decomposed into components associated with item-related activity, state-related activity and memory effects on item- and state-related activity, separately for each study task. Because item- and state-related activity were modeled simultaneously, each set of regressors only accounts for variance unique to either item- or state-related activity. The relatively low correlation between each set allowed item- and state-related activity to be estimated reasonably efficiently (**Fig. 1**).

All item- and state-related effects were modeled separately for each study task. Item-related activity was modeled with a delta (stick) function representing stimulus onsets, convolved with a canonical hemodynamic response function[27]. Item-related subsequent memory effects were assessed by modeling subsequently remembered and subsequently forgotten words separately. State-related activity was modeled with boxcar and exponential decay functions representing activity sustained throughout task blocks and activity showing decay within blocks, respectively, each convolved with a canonical hemodynamic response function. The decay function did not add meaningful information (not shown, available on request). State-related subsequent memory effects were assessed by modeling a linear parametric modulation of the height of the boxcar regressor by the mean-corrected number of words remembered from each block[28]. Thus, for a given session, this modulatory regressor was positive for blocks from which more than the average number of words were remembered for that session, and negative for blocks in which fewer than the average number of words were remembered, the degree of positive/negative modulation being proportional to the difference from the mean. The modulatory regressor models the extent to which the scan-by-scan BOLD signal expressed such a memory-related fluctuation around the mean block activity (modeled by the state-related boxcar function). These regressors, together with regressors representing residual movement-related artifacts and the mean over scans, comprised the full model for each session. The data and model were high-pass filtered to a cut-off of 1/120 Hz.

Parameter estimates for each regressor were calculated from the least mean squares fit of the model to the data. Effects of interest were estimated with one-sample t-tests of linear contrasts of parameter estimates averaged across the two sessions per subject[29]. Images were transformed into statistical parametric maps (SPMs) of the Z statistic. With one exception, inferences were based on all 16 subjects. Inferences about item effects in the animacy task were based on 15 subjects, as one subject forgot less than 12 words. Item-related subsequent memory effects were thresholded at $P < 0.001$. These contrasts identified regions where activity was greater for remembered items, consistent with most previous studies[1,4,5] (the reverse contrast was also conducted to ascertain whether regions showing the opposite effect[30] co-localized with state-related effects). Because there were no pre-experimental predictions with respect to the direction of state-related subsequent memory effects, contrasts were performed bi-directionally with a threshold in each case of $P < 0.0005$, corresponding to a two-tailed threshold of $P < 0.001$. Only activations involving contiguous clusters of at least five voxels are reported here. All analyses were confined to study trials associated with correct animacy or syllable decisions. Stereotactic coordinates are reported in Talairach space and correspond to the standard MNI normalized canonical brain[31].

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Competing interests statement

The authors declare that they have no competing financial interests.

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