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A role for the hippocampus in encoding simulations of future events.

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Abstract

The role of the hippocampus in imagining the future has been of considerable interest. Preferential right hippocampal engagement is observed for imagined future events relative to remembered past events, and patients with hippocampal damage are impaired when imagining detailed future events. However, some patients with hippocampal damage are not impaired at imagining, suggesting that there are conditions in which the hippocampus may not be necessary for episodic simulation. Given the known hippocampal role in memory encoding, the hippocampal activity associated with imagining may reflect the encoding of simulations rather than event construction per se. The present fMRI study investigated this possibility. Participants imagined future events in response to person, place and object cues. A post-scan cued-recall test probing memory for detail sets classified future events as either successfully encoded or not. A contrast of successfully versus unsuccessfully encoded events revealed anterior and posterior right hippocampal clusters. When imagined events were successfully encoded, both anterior and posterior hippocampus showed common functional connectivity to a network including parahippocampal gyrus, medial parietal and cingulate cortex, and medial prefrontal cortex. However, when encoding was unsuccessful, only the anterior hippocampus, and not the posterior, exhibited this pattern of connectivity. These findings demonstrate that right hippocampal activity observed during future simulation may reflect the encoding of the simulations into memory. This function is not essential for constructing coherent scenarios and may explain why some patients with hippocampal damage are still able to imagine the future.

\body It is now firmly established that both remembering past experiences and imagining future events rely on a common network of brain regions, including medial prefrontal, medial and lateral parietal, and medial and lateral temporal regions (1-4, for reviews, see 5,6). However, despite this overlap, some regions within this network – particularly the right anterior hippocampus – are preferentially engaged by imagining future events relative to remembering past events (2,7,8). Furthermore, some patients with hippocampal damage, in addition to showing impaired episodic memory, also have difficulty imagining detailed and coherent future events (9-12). These findings suggest that the hippocampus is important for imagining the future, although its involvement is not a reflection of future orientation per se, but rather of the content and phenomenology of episodic simulations (4). Recently, however, an adult developmental amnesic patient (13), a group of developmental amnesic school-aged children (14), as well as a group of patients with bilateral hippocampal damage but spared remote episodic memory (15), were all shown to be unimpaired at imagining detailed future events, implying that a fully intact hippocampus may not be required for episodic simulation. The role of the hippocampus in imagining the future, which has emerged recently as a critical issue in the cognitive neuroscience of memory, future thinking, and imagination (5,6,16), is therefore currently controversial (15,17).

One way to reconcile these conflicting findings is to consider that different regions of the hippocampus may play different roles in the process of simulation. Even though a general function of the hippocampus with respect to memory is to integrate distinct representations of objects and people with contextual information into coherent scenarios (18), the anterior and posterior aspects of the hippocampus may differ in terms of their contributions to this process (19-21). Current models propose that the posterior hippocampus is important for reinstatement of an episode in its original form, whereas the anterior hippocampus is involved in more 'flexible' encoding of associative information (22-25). The involvement of the posterior hippocampus in episodic reinstatement may also be reflected in the processing of familiar spatial contexts and storage of

cognitive maps for the purpose of navigation (26, 27). With respect to episodic simulation, an imagined event is situated within some spatial framework. Without such a platform upon which to build the scenario, the imagined event would lack a vital sense of coherence (9), suggesting that the posterior hippocampus should be critical for episodic simulation in general. This idea is supported by the finding that activity in the posterior hippocampus is modulated by participant ratings of detail – including spatial and contextual details – for both remembered past and imagined future events (28).

However, the anterior aspect of the hippocampus is differentially activated by future events relative to past events (2,7,8). The aforementioned hippocampal models would predict that such activity reflects the binding together of episodic details into novel and flexible arrangements and/or the encoding of these representations, and consistent with this prediction, anterior hippocampal activity has been shown to correlate with the amount of detail comprising a future event (28). Moreover, the disparateness of the details being integrated can modulate engagement of this region. For instance, Weiler, Suchan, & Daum (7) found that right anterior hippocampal activity was associated with simulating unlikely future events for which the degree of 'flexible processing' may be particularly amplified.

While differential engagement of the anterior hippocampus may reflect the process of recombining details to construct a scenario, it may also result from encoding. An inherent characteristic of newly-imagined future events is that they have not occurred (or been imagined) and as such, they are yet to be encoded. If a simulation is to serve a functional role in future behaviour, it must be retained in memory so that it can be referred to if and when the imagined event is occurring. This issue was recognized by Ingvar (29), who suggested that the process of encoding and retaining a simulation of future behavior constituted a "memory for the future". This is a critical aspect of the adaptive significance of episodic simulations, and virtually nothing is known about the processes that support their successful encoding and retention.

If a major function of the hippocampus during simulation is to encode the imagined scenarios, hippocampal damage would not necessarily prevent the events from being constructed initially, which may explain some of the conflicting results found in amnesic patients. Indeed, when children with hippocampal damage are asked to imagine future events, they can do so as well as controls. But when asked to recall these imagined events the next day, they are less accurate than controls at describing the original details (14). Therefore, the exact location of damage within the hippocampus may be critical as to whether the construction of simulations is affected. Based on the literature implicating the anterior hippocampus in associative encoding, and on the fact that some patients with hippocampal damage can still imagine the future but not recall their simulations, we hypothesized that the anterior hippocampus would play a role in encoding imagined events, thereby providing empirical evidence directly relevant to Ingvar's (29) early claim.

To this end, we used a novel approach incorporating both the experimental recombination (30) and subsequent memory (31) paradigms (see Fig. S1 in Supporting Information, SI). In an fMRI session, participants were presented with random recombinations of person, location, and object details extracted from their own memories, and for each, imagined a novel future event involving the 3 details, as per the *experimental recombination* paradigm (30). The amount of detail generated for each simulation was rated on a 4-point scale. In the control task, participants were presented with three common nouns and asked to construct a sentence that ordered the objects in size. Participants completed an unexpected post-scan cued recall test, in which memory for each imagined event was probed by testing recall of the person, location, and object details. We examined hippocampal activity related to successful encoding by contrasting events for which the details were later recalled in the post-scan test with those for which the details were later forgotten. We expected hippocampal activity to be higher for events that were successfully encoded and later-remembered relative to events for which the key details were later forgotten. A partial least squares (PLS) analysis of functional connectivity was also conducted on hippocampal seeds yielded by the

encoding analysis. Our findings provide evidence that both the anterior and posterior aspects of the hippocampus are important for encoding imagined events.

Results

Behavioral Results. The number of trials in the control (*M*=45, *SE*=0), later-remembered (*M*=46.52, *SE*=2.16), and later-forgotten (*M*=43.48, *SE*=2.16) future conditions were not significantly different, $F_{2,48}$=.49, p = .613 suggesting that contrasts between these conditions should be unbiased. Later-remembered future events were rated as significantly more detailed (*M*=2.16, *SE*=.07) than later-forgotten ones (*M*=1.67, *SE*=.09) on a four-point scale (0 = low detail, 3 = high detail). The type of detail tested affected rates of recall, $F_{2,48}$=8.17, p=.001. Pairwise comparisons revealed that the number of successfully-recalled events was significantly lower when participants were cued with the person-location details (*M*=13.92, *SE*=.96) than when they were cued with the location-object (*M*=17.2, *SE*=.90, t_{24}=-3.58, p=.002) or person-object (*M*=16.08, *SE*=.73, t_{24}=2.80, p=.01) details. Recall did not differ significantly for the location-object and person-object cues, t_{24}=-1.44, p=.163. The average temporal distance of future events was one year into the future (SE=.28).

fMRI Results.

Regions engaged by imagining future events. Each fixed-effects model included regressors for 3 conditions of interest: (1) later-remembered and (2) later-forgotten future trials; and (3) control trials. For the two future conditions, we also included linear parametric modulation regressors of detail ratings. A contrast image for each condition was entered into a random-effects flexible factorial ANOVA. To examine whether future simulation activated the common core network (1-4, 30, 32-34), we performed a random-effects contrast of all future simulation trials (irrespective of encoding success) with all control trials. For all whole brain analyses, we applied a voxel-level threshold of p=.005 combined with a spatial extent threshold of 145 voxels, which together yielded a threshold of p<.05, corrected for multiple comparisons (as determined by a Monte Carlo simulation;

see Methods). At this corrected level of significance, this contrast revealed a large bilateral network comprised of the medial prefrontal and parietal cortex, medial temporal lobes (including bilateral hippocampus), bilateral angular gyrus and lateral temporal cortex, and right inferior frontal gyrus (see Table S1 and Fig. S2 in SI).

Encoding-related hippocampal activity. Hippocampal activity related to successful encoding was examined using a random-effects contrast of later-remembered versus later-forgotten future events, applied within the flexible factorial model described above. With the inclusion of detail as a parametric modulation regressor in the fixed-effects model, the contrast images for later-remembered and later-forgotten events entered into the random-effects analysis reflect the effect of these conditions while controlling for any effects of detail, given the hippocampal activity during future simulation has also been linked to increasing detail (28). At the corrected threshold of $p<.05$, this encoding contrast resulted in activity in some regions of the core network, including bilateral precuneus, parahippocampal gyrus and cerebellum, left inferior frontal gyrus and right posterior hippocampus (see Table 1). Because the hippocampus was an *a priori* region of interest, we computed a corrected threshold on the basis of the volume of the bilateral hippocampus (1,878 2x2x2mm voxels): a voxel-level threshold of $p=.005$ combined with a spatial extent threshold of 26 voxels yielded a threshold of $p<.05$, corrected for multiple comparison (see Methods and reference 35). This analysis revealed activity in the right posterior hippocampus, as expected given the identification of this cluster in the whole brain analysis; 54 voxels of the cluster identified in the whole brain analysis were located within the hippocampus itself (*xyz*= 34 -26 -8, voxel-level $p<.001$, $Z = 3.36$, $k = 54$ voxels[1]). Additionally, this regional analysis showed another more anterior cluster of encoding-related activation in the right hippocampus (*xyz*= 20 -12 -16, voxel-level $p<.001$, $Z = 3.34$, $k = 49$ voxels; see Fig. 1a). The opposite contrast of later-forgotten versus later-remembered future events yielded no significant clusters, in either in the whole brain analysis, or the regional analysis.

[1] Note that *k* (number of voxels comprising a cluster) for the hippocampal regional analysis is adjusted to provide only the number of voxels in the cluster that fall within the bilateral hippocampal mask.

Mean percent signal change was extracted from the two hippocampal clusters identified in the encoding analysis; these data for later-remembered and later-forgotten trials are displayed in Fig. 1b for descriptive purposes. Note that these data quantify the effect of the encoding conditions while controlling for any linear effects of detail (due to the inclusion of the parametric regressors in the model). We were interested in whether signal from these encoding clusters would also exhibit an effect of detail[2]. We extracted signal from these clusters during trials rated high in detail (i.e., ratings of 2 and 3) and trials rated low in detail (i.e., ratings of 0 and 1). A detail (high, low) by cluster (anterior, posterior) ANOVA showed a significant overall effect of detail ($F_{1,24}$ = 5.74, p=.03), while the detail by cluster interaction was not significant ($F_{1,24}$=.691, p=.414). Pairwise comparisons revealed that while a numerical difference between high and low detail was evident in both clusters (see Fig 1c), this effect was significant in the anterior (t_{24}=2.42, p=.02) but not the posterior (t_{24}=1.68, p=.11) cluster. **Insert Table 1 and Fig 1**

Seed PLS Results. We conducted a seed PLS analysis to determine whether the two hippocampal clusters exhibited similar patterns of functional connectivity, both within the hippocampus (i.e., between these two seeds) and with the rest of the core network. We also examined whether functional connectivity differed according to encoding success. This analysis identified a significant latent variable (LV), (p=.006) explaining 57.35% of the covariance, that indicated that functional connectivity for these hippocampal regions were modulated by encoding success. The pattern of functional connectivity peaked at TR 3, and results from this TR are reported here (Table 2). When constructing a simulation that was later remembered, both seeds were strongly functionally connected with each other, as well as with the same distributed pattern of activity in regions such as the bilateral parahippocampal gyrus, medial parietal/cingulate cortex, medial prefrontal cortex, left inferior frontal gyrus and left inferior parietal lobule (Fig. 2a). This strong connectivity during successful encoding reflects positive correlations between activity in both

[2] Because these clusters were selected on the basis of an encoding analysis, and moreover that analysis controlled for the effect of detail (achieved by including detail ratings as a parametric modulation regressor), the contrast of interest (the effect of detail) is independent of voxel selection.

seed regions and the whole brain network identified by the LV (anterior seed, *r* = .58; posterior seed, *r* = .85; Fig. 2b). However, when constructing a simulation that was later forgotten, the posterior hippocampal seed region was no longer functionally connected with the anterior hippocampal seed or with the wider network of regions, illustrated by an absence of correlation between posterior hippocampal activity and the whole brain pattern (*r* = -.10; Fig. 2c). However, the connectivity for the anterior hippocampal seed and the wider network was evident irrespective of encoding success (*r* = .50; Fig. 2c). **Insert Table 2, Fig 2**

Discussion

The aim of this study was to establish whether hippocampal activity evident during episodic simulation of the future reflects the events being encoded into memory. Because prior models suggest that the anterior hippocampus is particularly important for the encoding of novel associative combinations (23,24), we hypothesized that the anterior aspect of the right hippocampus would be particularly important for the encoding of imagined events. However, our findings suggest that both the anterior and posterior regions of the right hippocampus contribute to the encoding of imagined future events. In fact, our PLS analysis suggests that connectivity of the posterior hippocampus to the anterior hippocampus and other core autobiographical regions might be most critical to successful encoding.

The finding that the right anterior hippocampus is responsive to successful encoding fits with the encoding-retrieval distinction along the long axis of the hippocampus that was proposed over a decade ago (36, but see also 37). More recently, Spaniol et al. (38) conducted a meta-analysis of 26 studies of encoding success and 30 studies of retrieval success, and confirmed that the anterior hippocampus was more reliably activated during successful encoding than during successful retrieval. Moreover, the anterior hippocampus appears to be particularly responsive to the encoding of associative (21) and novel (39) information, both of which characterize imagined future events.

The posterior hippocampus was also responsive to encoding success, and functional connectivity analyses showed that this region may be particularly critical for subsequent memory of

imagined future events. The connectivity of the posterior hippocampus with the anterior hippocampus and a distributed network of regions was only evident when an imagined future event was successfully encoded. Given that the posterior hippocampus has been shown to be particularly important for the processing of spatial relations (20,27,40,41), the importance of this area for episodic simulation may be in the domain of creating a spatiotemporal context in which to ground the event. Imagining future events requires recall or generation of spatial locations in which to set them, and may also include simulated navigation through these contexts, both of which may be supported by the hippocampus (42).

The posterior hippocampus has also been implicated previously in the successful encoding of future-related representations using a different paradigm. Poppenk et al. (43) had participants view scenes in the scanner and either generate future intentions or present actions associated with the scenes. Post-scan, participants viewed scene cues and recalled whether they were seen in the scanner and if so, under what task conditions (i.e., generating an intention or a present action). Results revealed a right posterior hippocampal activity covaried with overall subsequent memory performance.

The fact that highly-detailed imagined events were more likely to be encoded suggests that detail can influence the process of encoding. Relevant here is that constructing a memorable imagined event will depend to some degree on how well the event details could be retrieved from memory. Since the cues for the imagined future events consisted of familiar people, places, and objects, retrieval of these familiar items was necessary before event construction. The posterior hippocampus has been associated with retrieval (24, 37) and the reinstatement of previous conditions (19, 25). Moreover, according to the constructive episodic simulation hypothesis (44), episodic details need to be retrieved from memory to build a coherent scenario, and the posterior hippocampus has been found to respond to the amount of episodic detail comprising both past and future events (28). Indeed, our behavioral results demonstrate that more detailed events were more likely to be successfully encoded. Activity in regions supporting retrieval of contextual and

visuospatial information, such as the parahippocampal gyrus (45, 46) and the precuneus (47), also exhibited an encoding effect and/or connectivity with the hippocampal seed regions. It is, however, a challenge to tease apart neural activity related to the retrieval of details from episodic memory and the integration of these details into a coherent imagined scenario. Developing paradigms that can disambiguate these processes is an important focus for future research.

Activity in both the anterior and posterior hippocampal clusters was modulated by participant ratings of event detail, though this effect only reached significance in the anterior cluster. This finding suggests that the contribution of these hippocampal regions to encoding success might depend, at least in part, on the ability to construct a detailed and therefore memorable simulation. A right anterior hippocampal response to detail recombination was also found by Staresina and Davachi (48), who observed that a right anterior hippocampal cluster was more responsive when participants had to integrate spatiotemporally-separated details than when details were presented in a combined form. A key component of our study is the integration of event details taken from disparate times and locations into a coherent future simulation, and its similar findings bolster the idea the hippocampus is involved in detail integration.

Our results have important implications for the debate on whether hippocampal damage disrupts the ability to imagine the future (9-15, 17). It is possible that with a damaged hippocampus, the ability to construct detailed scenarios may remain intact while encoding of these representations is disrupted. This appears to be the case both for the children with hippocampal damage who were less accurate in later recalling their imagined events (14), and for the patients with hippocampal damage whose imagined events were described as repetitive, as if they could not recall the portions of the event that they had already constructed (15). Depending on the nature and location of damage – whether it is confined to the anterior/posterior regions identified here, whether it affects the entire hippocampus, and whether it is confined to the hippocampus or also affects other neighboring regions – differential impairments may be seen in tasks that require the generation of imagined episodic details, the encoding of imagined events, or both.

In summary, this study provides a more comprehensive understanding of hippocampal contributions to the construction and encoding of detailed future simulations. We have localized two regions of the right hippocampus involved in this process: one anterior, and one posterior, with the connectivity between these and with other parts of the core autobiographical network being particularly necessary for successful encoding. Furthermore, hippocampal activity was modulated by event detail, suggesting that the generation of episodic details and their storage into memory may be related processes. Future thinking confers an adaptive benefit: simulating solutions to potential obstacles increases chances for success and survival (49). Thus, being able to generate detailed simulations and encode these for later use are important aspects of this ability.

Methods

Participants. Twenty-nine young adults (12 males, aged 18-35) were recruited; all were right-handed, fluent in English and did not meet exclusionary criteria (neurological/psychiatric conditions, ferromagnetic implants, psychotropic medication use). Four participants (1 male) were excluded due to neurological abnormalities, excessive movement and task non-compliance; data from 25 participants were analyzed.

Procedure. We employed an adapted version of the episodic recombination (30) and subsequent memory (31) paradigms (see Fig. S1) consisting of three phases: a pre-scan session in which the memory details were collected, a scan session in which participants imagined future events, and a post-scan cued recall test for the future event details.

Pre-scan session. Participants described 110 personal episodic events from the past 10 years. For each event, three main details were isolated: a person and object that featured in the event and the specific location of the event. To ensure each detail was distinct, participants could not duplicate details across different events; extensive piloting confirmed that young participants could generate this many details. The memory details were then randomly recombined, resulting in 110 recombined detail sets containing a person, location, and object, each from a different memory.

These recombined sets of details were used as cues for the imagined future events during the scan session.

Scan session. Participants were presented with three types of trials: *future, re-imagine,* and *control*. During the 90 future trials, participants were shown the recombined sets of memory details for 8 *s* (the average time needed to construct a future event (2)) and instructed to imagine (from a field perspective) specific future events that integrated all 3 detail cues. This was followed by a detail rating scale shown for 4 *s* (0 = low detail; 3 = vivid detail). In the 45 trials of the control task (30), participants had 8 *s* in which to incorporate 3 presented nouns into a sentence of the form "X is bigger than Y is bigger than Z", making relative size judgments in the process. They then rated task difficulty (0 = no difficulty; 3 = extreme difficulty). During the scanning session, 45 re-imagine trials were also presented; see SI for more information. One fifth of scan time was composed of jittered null (fixation-cross) trials (ranging 4 to 16 *s*). Optseq2 (50) was used to determine the optimal sequence of experimental and null trials for estimation of the hemodynamic response function.

Post-scan session. Ten minutes after scanning, participants completed an unexpected cued-recall task that followed the format of Jones's (51) procedure for testing memory for events with multiple components. Participants were presented with two of the details from each *future* trial event imagined in the scanner and recalled the missing detail. As participants were instructed to integrate all three details into an event, memory for the three integrated details gives an indication of the extent to which they were bound and encoded into a coherent scenario. The particular detail tested (person, location, or object) was counterbalanced. This subsequent memory task yielded approximately equal numbers of remembered and forgotten trials, ideal for a subsequent memory analysis. Based on this test, each future trial from the scan session was classified as either successfully or unsuccessfully encoded.

MRI Acquisition, Pre-Processing and GLM Analysis. Full 3T scanning parameters are provided as SI. MRI data were pre-processed in SPM8 using a standard protocol, including slice

timing correction, realignment and unwarping, spatial normalization (resampled at 2x2x2mm voxels), spatial smoothing (8mm Gaussian kernel), high-pass filtering (128 s cut-off), correction for serial correlations). Each event was modelled by SPM8's canonical hemodynamic response function (i.e., a stick function) applied at stimulus onset. Trials were modelled as stick functions to capture early activity reflecting the construction phase of future simulation, and to be consistent with previous studies identifying construction-related right hippocampal activity (e.g., 2, 8). Each fixed-effects models comprised (1) five regressors of interest: *later-remembered future events, later-forgotten future events,* parametric modulation regressors for each of these conditions (detail ratings, modelled linearly), and *control trials;* and (2) two regressors of no interest (*re-imagine* condition; rating task). Importantly, with the inclusion of the detail regressors in the model, the contrast images for the later-remembered and later-forgotten conditions quantify the effect of these conditions while controlling for any linear effects of detail. Contrast images for each regressor of interest (relative to implicit baseline) were entered into a random-effects flexible factorial model with two factors, *condition* and *subject*. Two contrasts were computed: all imagine future trials > control trials; and later-remembered > later-forgotten future events.

For whole brain analyses, a combined voxel-wise threshold of p=.005 and a spatial extent threshold of 145 voxels was employed to achieve an α of .05, corrected for multiple comparisons. The minimum cluster size required for corrected significance was determined using a Monte Carlo simulation (10,000 iterations) implemented using AFNI's 3dClustSim program to estimate the overall probability of false positives within the 3D whole brain search volume (178,888 2x2x2mm voxels). We also computed the required cluster size for the correction of multiple comparisons within our *a priori* region of interest - the bilateral hippocampus (35). Using an anatomical mask of the bilateral hippocampus (generated using MARINA; 52) with a search volume of 1,878 2x2x2mm voxels, the Monte Carlo simulation (10,000 iterations) indicated that a voxel-wise threshold of p=.005 combined with a spatial extent threshold of 26 voxels was required to correct for multiple comparisons at

p<.05. Information regarding localization and visualization of activation (including extraction of percent signal change) are provided in SI.

Functional Connectivity: Seed PLS Analysis. Two significant clusters within the right hippocampus emerged in the encoding analyses: one anterior (*xyz* = 20 -12 -16) and one posterior (34 -26 -8). We were interested in whether these regions exhibited similar patterns of functional connectivity, both with each other and with the rest of the core network, and whether functional connectivity differed according to encoding success. We used spatiotemporal PLS (53; for more detail, see SI) to assess functional connectivity over an 18 *s* temporal window. We used the mean percent signal change extracted from these regions as "seeds"; correlations were computed between signal in each seed and all other voxels for each condition across subjects. The resulting correlation maps were stacked and analyzed with singular value decomposition, producing a set of orthogonal LVs, each containing a linear contrast between the seeds and the conditions (coding for the effect depicted by voxels) and a singular image of voxel weights that are proportional to the covariance of activity with the linear contrast. The statistical significance of each LV was assessed using permutation tests (500 iterations) with a threshold of *p*<.05. The reliability of the voxel saliences was computed using bootstrap estimation of the standard errors (300 iterations). Clusters of 5 or more voxels in which bootstrap ratios were greater than ±4.5 (roughly equal to *p*<.0001), were considered reliable.

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Figure Legends

Figure 1: (a) A subsequent memory analysis revealed clusters in anterior right hippocampus (left panel, *xyz* =20 -12 -16) and posterior right hippocampus (right panel, 34 -26 -8). Activations are corrected for multiple comparison (p<.05), and are shown at a voxel-wise threshold of p< .005 uncorrected (masked to only show voxels within the bilateral hippocampus). (b) For illustrative purposes, percent signal change is shown for later-remembered and later-forgotten trials (note that error bars are not included as this effect is not independent of voxel selection). (c) Percent signal change is broken down according to the level of detail of the simulations (high vs. low). Error bars show *SEM*. *p<.05.

Figure 2: (a) A Seed PLS analysis showed that two hippocampal seed regions (see Methods for coordinates) exhibited functional connectivity with each other and with a distributed pattern of brain regions at TR 3. Warm colors indicate regions significantly correlated with the seeds and the

whole brain pattern, and represent the relative strength of this correlation (thresholded at $p<.0001$). (b) Both seeds exhibited connectivity during successful encoding, as indicated by strong positive correlations between seed activity and brain scores (a weighted average of activation across regions exhibiting significant functional connectivity). (c) During unsuccessful encoding, the anterior seed continued to show this connectivity pattern but the posterior seed did not. %SC=percent signal change.

Table 1: Regions activated by the successful encoding of future events

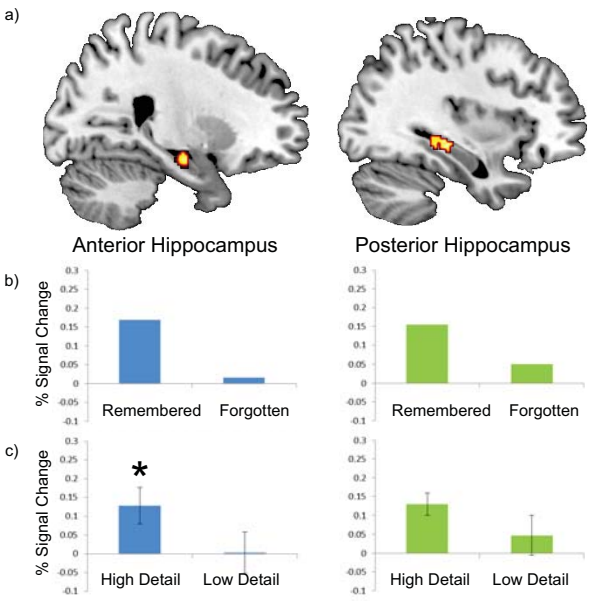
Cluster size*	Brain Region	MNI co-ordinates			*Z*-score	*p*-value**
		x	*y*	*z*		
706	R Precuneus (BA 31)	22	-58	20	3.91	<.001
	R Retrosplenial cortex (BA 30)	10	-50	18	3.24	.001
694	L Parahippocampal gyrus (BA 30)	-18	-48	-2	3.71	<.001
	L Parahippocampal gyrus (BA 36)	-26	-44	-8	3.22	<.001
	R Parahippocampal gyrus (BA 36)	36	-34	-14	3.27	.001
	R Fusiform gyrus (BA 37)	28	-44	-16	2.84	.002
375†	L Inferior frontal gyrus (BA 47)	-20	32	-12	3.97	<.001
	L Anterior cingulate cortex (BA 32)	-12	34	-10	3.71	<.001
214	L Precuneus (BA 31)	-16	-58	16	3.48	<.001
189	R Hippocampus	34	-26	-8	3.36	<.001
173	L Cerebellum	-24	-48	-30	3.98	<.001
149†	R Cerebellum	6	-48	-32	3.09	.001

Note: All clusters are significant at $p<.05$, corrected for multiple comparisons. *Cluster size (*k*) indicates the number of voxels comprising the cluster; only clusters with a minimum extent of 145 voxels are reported. **Voxel-level *p* value is provided. †Cluster extends bilaterally. BA = Brodmann area; L=left; R=right.

Table 2: Regions showing significant functional connectivity with the hippocampal seed regions.

Cluster size*	Brain Region	MNI co-ordinates			BSR	*p*-value
		x	*y*	*z*		
8044	L Medial parietal/cingulate cortex (BA 29) †	-12	-50	10	15.62	<.001
753	R Inferior occipital gyrus (BA 19)	50	-76	-6	14.75	<.001
290	L Precentral gyrus (BA 6)	-38	-2	26	11.89	<.001
221	L Superior temporal gyrus (BA 22)	-48	-12	-12	14.19	<.001
137	R Inferior temporal gyrus (BA 20)	46	-14	-24	9.12	<.001
126	L Medial frontal gyrus† (BA 10)	-4	66	-2	10.13	<.001
123	R Thalamus†	0	-10	6	7.45	<.001
119	L Cerebellum	-32	-34	-32	8.14	<.001
104	L Middle frontal gyrus (BA 8)	-40	16	58	8.96	<.001
93	R Parahippocampal/inferior temporal gyrus (BA 20/36)	36	-14	-26	6.16	<.001
82	R Fusiform gyrus (BA 20)	48	-34	-22	6.84	<.001
78	L Middle frontal gyrus (BA 8)	-28	16	42	9.39	<.001
72	L Thalamus	-12	-30	6	8.90	<.001
71	L Inferior frontal gyrus (BA 47)	-38	30	-14	9.62	<.001
68	R Middle frontal gyrus (BA 10)	38	54	30	8.43	<.001
42	L Inferior parietal lobule (BA 40)	-42	-38	32	9.06	<.001
40	L Cerebellum†	-6	-40	-22	5.95	<.001
37	L Precentral gyrus (BA 4)	-54	-10	56	6.16	<.001
33	L Parahippocampal gyrus (BA 36)	-22	0	-38	7.85	<.001
24	R Cerebellum	16	-56	-34	6.10	<.001
23	R Hippocampus	30	-30	-8	5.60	<.001

Note: Only clusters evident during the peak timepoint (TR 3) with a bootstrap ratio of greater than +/- 4.5 (roughly equivalent to a p-value of $p < .0001$) are reported. *Cluster size (*k*) indicates the number of voxels comprising the cluster; only clusters with a minimum extent of 20 voxels are reported. BA = Brodmann area; BSR = Bootstrap ratio; L = left; R = right. †Cluster extends bilaterally.


a)
Anterior Hippocampus
Posterior Hippocampus
b)
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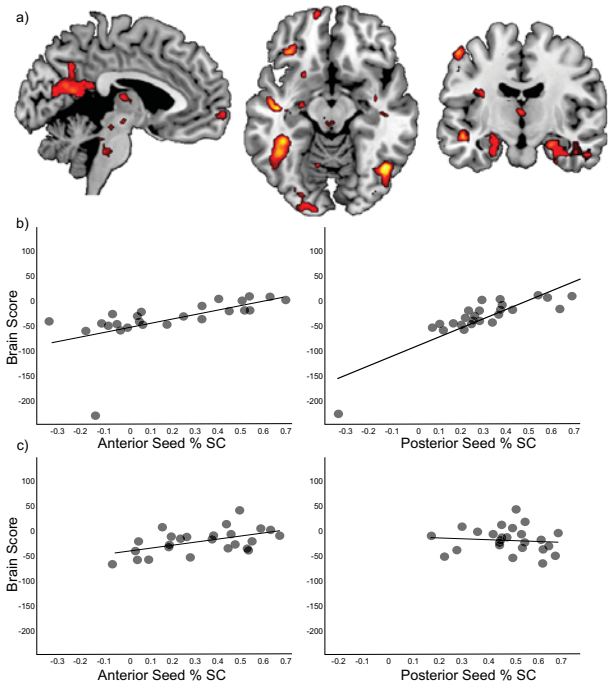
a)
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Brain Score
Anterior Seed % SC
Posterior Seed % SC
c)
Brain Score
Anterior Seed % SC
Posterior Seed % SC