Persistence of hippocampal multivoxel patterns into postencoding rest is related to memory

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The transformation of new experiences into lasting memories is thought to be mediated by postencoding reactivation or the reexpression of activity patterns that characterize prior encoding experiences during subsequent offline periods. Although hippocampal reactivation has been well-described in the rodent, evidence for postencoding persistence of hippocampal encoding patterns has yet to be described in humans. Using functional MRI, we examined the persistence of multivoxel hippocampal encoding patterns into postencoding rest periods. To characterize activity patterns, we computed the pairwise multivoxel correlation structure (MVCS) across hippocampal voxels during two distinct encoding tasks as well as during pre- and postencoding rest periods. We found that the hippocampal MVCS for each encoding task was more similar to the MVCS during immediate postencoding rest periods compared with a preencoding, baseline rest period. Additionally, using a principal component decomposition approach, we found that the strongest encoding patterns showed evidence of preferential persistence into immediate postencoding rest periods. Finally, the extent to which the strongest encoding patterns showed evidence of preferential persistence into immediate postencoding rest significantly correlated with later memory for stimuli seen during encoding. Taken together, these results provide strong evidence for hippocampal reactivation in humans, which was measured by the persistence of hippocampal encoding patterns into immediate postencoding rest periods, and importantly, provide a possible link between this persistence and memory consolidation.

hippocampus | multivoxel pattern analysis | resting state

Our ability to remember a unique episode for days, months, and even years in the future is an impressive biological feat. Converging evidence across multiple species indicates that the hippocampus is essential for the initial formation of an episodic memory trace (1, 2). In addition to memory acquisition, the hippocampus is also thought to play a pivotal role in the postencoding stabilization of memories by restructuring how information is represented across hippocampal–neocortical networks (2–4). Specifically, hippocampal replay or the subsequent reactivation of patterns of hippocampal activity that characterize a prior experience (5–8) is hypothesized to contribute to memory consolidation (3, 6, 9).

In line with these predictions, previous work in rodents has shown that multivariate patterns of hippocampal activity are reactivated during sleep (10–12) and awake periods (13–16). Critical for theories of consolidation, the extent of hippocampal reactivation in rodents has recently been related to spatial memory improvements (17), whereas interference with putative reactivation events leads to impairments in learning (18–20). Prior work in humans using functional MRI (fMRI) has shown that resting connectivity between the hippocampus and encoding-related cortical areas can be modulated by an associative encoding experience (21, 22) and that these experience-related changes are correlated with later memory (21, 23). Additionally, overall changes in activity and connectivity in the hippocampus and cortical regions have been shown to occur during slow-wave sleep and subsequent task performance (24, 25). Although it is informative to know that large-scale changes in brain activation and connectivity can be induced after new learning, univariate measures lack the specificity to show that specific patterns of activity pertaining to distinct encoding experiences show evidence of persistence during postencoding periods, which has been shown in the rodent replay literature.

Here, we test whether specific hippocampal multivoxel blood-oxygen level-dependent (BOLD) patterns show evidence of persistence from encoding to postencoding rest periods. To this end, participants performed two different encoding tasks interleaved with rest periods during fMRI scanning. Critically, we found that the two encoding tasks produced dissociable multivoxel hippocampal correlation patterns that selectively persisted into immediate postencoding rest periods. Furthermore, the preferential persistence of the strongest encoding patterns during immediate postencoding rest was positively related to subjects' later memory for stimuli seen during encoding. These results provide evidence for the persistence of multivariate hippocampal encoding patterns during rest in humans and relate this persistence to subsequent memory, suggesting that postencoding persistence may be a sensitive measure of the initial stages of memory consolidation.

Results

Encoding-Related Hippocampal BOLD Activity. To examine whether hippocampal patterns associated with two different encoding tasks show evidence of persistence into postencoding rest, we needed to establish that the hippocampus (*i*) was active during both tasks and (*ii*) exhibited distinctive encoding patterns associated with the two tasks. We found that the hippocampus was significantly active relative to pretrial baseline during both encoding tasks: object face (OF) and scene face (SF) encoding (area under the curve statistic; OF encoding: $t_{19} = 5.50$, $P < 0.0001$; SF encoding: $t_{19} = 4.11$, $P < 0.001$) (Fig. 1*B*). The overall magnitude of the BOLD response did not significantly differ between the two tasks (OF vs. SF encoding: $t_{19} = -1.03$, $P > 0.31$).

Significance

Memory consolidation is thought to depend on the reactivation of patterns of brain activity that characterize recent experience. Although reactivation has been identified and well-described in the rodent hippocampus, a structure critical for the formation of long-term memories, the persistence of patterns of hippocampal activity has not been investigated in humans. Using functional MRI, we find that patterns of hippocampal connectivity that characterize an encoding experience persist into immediate rest periods. Furthermore, this persistence is related to memory for the preceding representations, suggesting that postencoding measures of persistent activity patterns may contribute to memory consolidation.

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Furthermore, the two tasks activated largely nonoverlapping voxels. Across subjects, 31.2 ± 4.8 and 35.1 ± 5.3 hippocampal voxels were active during OF and SF encoding, respectively (Fig. 1*C*). Of these voxels, however, only 11.6 ± 5.3 were active during both encoding tasks (32.2% and 26.3% of the total active voxel populations for OF and SF encoding, respectively) (Fig. 1*C*).

To characterize multivariate patterns of hippocampal BOLD activity, we computed the multivoxel correlation structure (MVCS) across all hippocampal voxels (*Materials and Methods*). We then asked whether the MVCSs across the two encoding tasks showed evidence of distinctiveness and found that the within-task similarity of the hippocampal MVCS was significantly greater than the between-task similarity (within OF vs. OF–SF similarity: $t_{19} = 5.50$, $P < 10^{-4}$; within SF vs. OF–SF similarity: $t_{19} = 4.11$, $P < 10^{-3}$) (Fig. 1*D*). This relationship was present even when the amount of actual time was equated between the within- and across-task comparisons, suggesting that greater within- vs. across-task similarity was not driven by temporal autocorrelation in the BOLD signal (within OF vs. OF–SF similarity: $t_{19} = 3.81$, $P < 0.005$; within SF vs. OF–SF similarity: $t_{19} = 2.15$, $P < 0.05$).

Persistence of Hippocampal Encoding Patterns During Rest. After establishing that hippocampal activation patterns during the OF and SF encoding tasks were distinct (Fig. 1), we then examined whether these patterns showed evidence of persistence into postencoding rest by measuring the similarity of the encoding MVCS and the MVCS from each rest period (after applying Fisher Z transformation to each MVCS) (Fig. 2*A* and Fig. S1 show example MVCSs). Separate one-way repeated measures ANOVAs were performed on the similarity of each encoding task with the MVCSs during rest with a factor of rest period (baseline, post-OF, and post-SF rest). Significant main effects of rest period revealed differential similarity across rest periods for the OF and SF encoding MVCSs (main effect for similarity with the OF encoding MVCS: $F_{2,38} = 3.27$, $P < 0.05$; similarity with the SF encoding MVCS: $F_{2,38} = 4.09$, $P < 0.03$). Critically, these main effects were driven by significant increases in the similarity of each encoding MVCS with the immediate postencoding rest period compared with baseline rest. Specifically, the OF encoding MVCS was significantly more similar to the MVCS measured during post-OF vs. baseline rest ($t_{19} = 2.36$, $P < 0.03$) (Fig. 2*B*), and the SF encoding MVCS showed greater similarity with the MVCS during post-SF vs. baseline rest ($t_{19} = 2.24$, $P < 0.04$) (Fig. 2*C*). These effects remained when we controlled for the temporal proximity between encoding and rest periods (*SI Results, Similarity of Hippocampal Encoding MVCS with Preceding Rest Period*).

Next, we asked whether the persistence of the encoding MVCS (e.g., the OF encoding MVCS) during postencoding rest was selective to the immediate postencoding rest period (e.g., post-OF rest) or whether increases in similarity with each encoding MVCS were also evident in the other nonimmediate postencoding rest period (e.g., post-SF rest). We did not find evidence that, in general, hippocampal encoding patterns showed evidence of persistence during all postencoding rest periods (Fig. 2 *B* and *C*). Specifically, similarity with the OF encoding MVCS during post-SF rest was not significantly different from baseline rest ($t_{19} = 0.18$, $P > 0.8$) (Fig. 2*B*), and likewise, similarity with the SF encoding MVCS did not change from baseline to post-OF rest ($t_{19} = 1.22$, $P > 0.23$) (Fig. 2*C*). Furthermore, higher similarity was found for immediate vs. nonimmediate rest periods; the OF encoding MVCS was significantly more similar to the post-OF vs. post-SF rest MVCS ($t_{19} = 2.36$, $P < 0.03$), and a marginally significant trend was observed for higher similarity of the SF encoding MVCS with the MVCS during post-SF vs. post-OF rest ($t_{19} = 1.98$, $P < 0.063$). We also examined the similarity with the encoding MVCS during rest as a function of the order of the encoding tasks to ask whether the MVCS for the first encoding task showed evidence for an enhanced presence during the second postencoding rest period. However, we did not find evidence for such an effect (*SI Results, Similarity of Hippocampal Encoding MVCS Based on Encoding Order* and Fig. S2). Together, these results indicate that the hippocampal correlation structure present during each encoding task shows evidence of selective persistence into the immediate postencoding rest period and is not globally more present during all postencoding rest periods. Similar results were found using a partial correlation approach (*SI Results, Partial Similarity of the Encoding and Rest MVCS* and Fig. S3).

Group-Level Principal Component Analysis of Hippocampal BOLD Patterns. Thus far, the MVCS has been used to measure patterns of the BOLD signal across all hippocampal voxels during task performance. Here, we adopt a complementary approach by performing principal component analysis (PCA) on the encoding data (26, 27) (*Materials and Methods*). This process results in a data-driven decomposition of the hippocampal encoding MVCS (separately for each encoding task) into distinct multivoxel components or patterns that are ordered based on the amount of variance that they explain in the encoding data (Fig. 3*A* shows a decomposition of data from an example subject). This approach allows us to examine the persistence of multivoxel encoding patterns as a function of their strength during encoding.

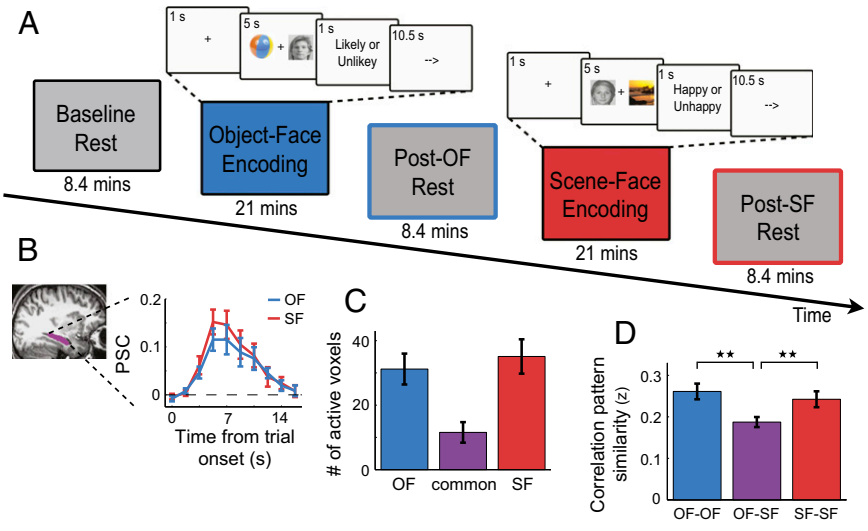

Fig. 1. Experimental design and hippocampal BOLD activity during encoding. (*A*) All subjects performed OF and SF encoding tasks interleaved with rest scans. Each encoding trial consisted of a fixation cue, presentation of a stimulus pair, a decision, and performance of a baseline arrows task. (*B*) Sagittal slice from one subject's anatomical scan showing that subjects' hippocampal mask. Trial-triggered average hippocampal BOLD response during OF encoding (blue) and SF encoding (red) across all hippocampal voxels. Percent signal change (PSC) was calculated relative to baseline (mean signal during first two repetition times). (*C*) The average number of hippocampal voxels labeled as active during OF encoding, SF encoding, and both tasks (common voxels). (*D*) Mean similarity (Fisher Z-transformed correlation coefficient) of multivoxel hippocampal correlation patterns within each encoding task (OF–OF, within OF encoding; SF–SF, within SF encoding) vs. across-task similarity (OF–SF). Error bars indicate mean ± SEM across subjects unless otherwise noted. $^{**}P < 0.001$.

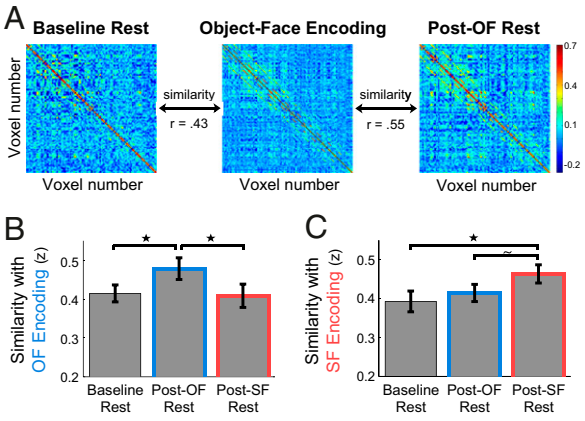

Fig. 2. Persistence of hippocampal correlation structure during immediate postencoding rest periods. (*A*) Hippocampal MVCS for an example subject during baseline rest, OF encoding, and post-OF rest. The color value in each matrix corresponds to the correlation between a voxel pair during each time period. The similarity (correlation) between the Fisher Z-transformed correlation structures during OF encoding and each rest scan is indicated. For illustration purposes, only one-half of the hippocampal voxels are shown. Fig. S1 shows additional MVCSs. (*B*) Mean similarity (Fisher Z-transformed correlation coefficient) between the hippocampal MVCS during OF encoding and the hippocampal MVCS during all rest periods. (*C*) Mean similarity (Fisher Z-transformed correlation coefficient) between the hippocampal MVCS during SF encoding and the hippocampal MVCS during all rest periods. $^{\star}P < 0.05$; $^{\sim}P < 0.10$.

To better understand the dominant principal components (1–8) of the encoding data, we analyzed the profile of their temporal projections (or scores) during encoding trials and determined if the components have differentially weight-specific voxel populations. As illustrated in Fig. 3*B*, high-strength components (i.e., low-index components that account for the most variance in the data) showed reliable trial-related variability similar to the hemodynamic response function. Consistent with this observation, the amount of task-related variance and the preferential weighting of active voxels significantly declined as a function of decreasing component strength/increasing component indices for both encoding tasks (Fig. 3*C*, *SI Results, Group-Level Encoding Analyses of PCs Patterns*, and Fig. S4). We also found that high-strength components preferentially weighted anterior vs. posterior hippocampal voxels (*SI Results, Group-Level Encoding Analyses of PCs Patterns* and Figs. S4 and S5).

Next, we examined whether these principal components showed evidence of persistence into postencoding rest periods at both the group and individual subject levels (see below). At the group level, we asked whether the overall presence of the dominant principal components (1–8) during rest periods was related to component strength. Consistent with our first analysis approach, we found that high-strength/low-index encoding-derived components show an increased presence during immediate postencoding rest periods. We performed two-way rmANOVAs with factors of encoding component index (1–8) and rest period (baseline and the immediate postencoding rest period) on the similarity of encoding components with the hippocampal MVCS during rest (*SI Materials and Methods*). Significant interactions were found between the encoding component index and similarity with baseline vs. the immediate postencoding rest period MVCS for both the OF ($F_{7,133} = 8.06$, $P < 10^{-4}$) and SF encoding data ($F_{7,133} = 5.97$, $P < 10^{-4}$). Specifically, high-strength/low-index OF encoding components showed significantly greater similarity with the hippocampal MVCS during post-OF vs. baseline rest (OF component 1: $t_{19} = 3.49$, $P < 0.003$; OF component 2: $t_{19} = 2.79$, $P < 0.02$; OF component 3: $t_{19} = 3.51$, $P < 0.003$) (Fig. 3*D*), and the first principal component from SF encoding was significantly more similar to the hippocampal MVCS during post-SF vs. baseline rest (SF component 1: $t_{19} = 3.41$, $P < 0.003$) (Fig. 3*E*). However, in contrast to higher-strength encoding components, no significant

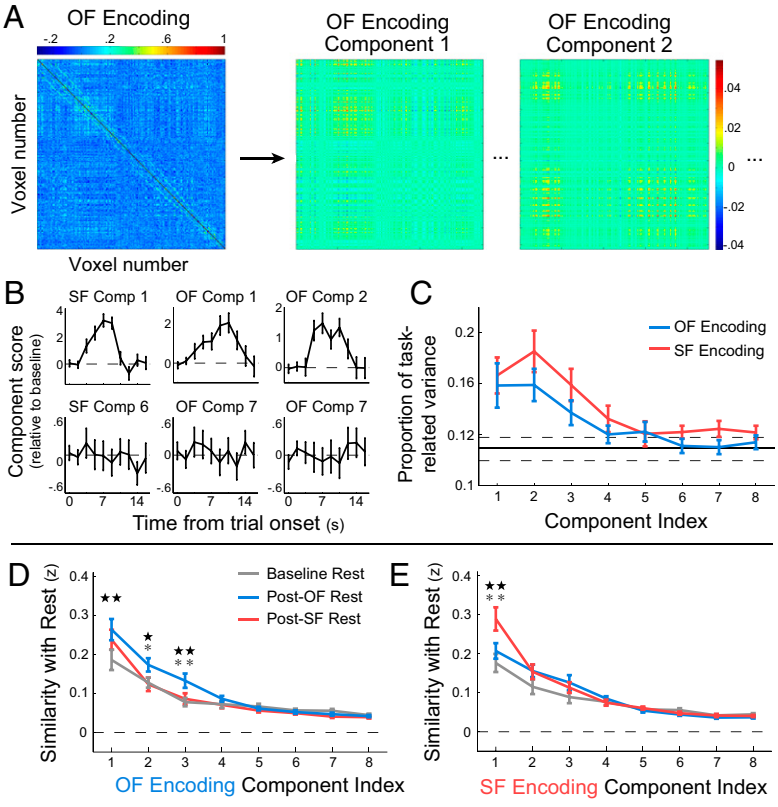

Fig. 3. Principal component decomposition of hippocampal BOLD encoding data and presence of encoding components during rest. (*A*) Illustration of the decomposition procedure for one subject. (*Left*) The correlation structure across all hippocampal voxels during OF encoding is shown and decomposed into a series of components that are ordered by the amount of variance accounted for in a descending fashion. The matrix shown for each component is the outer product of each principal component with itself. (*B*) Mean component score across trials during encoding for example individual components computed relative to baseline. *Upper* shows scores for components with high indices, showing signal modulation across the trial. *Lower* shows scores for components with lower indices. Error bars indicate mean ± SEM across trials. (*C*) The mean proportion of task-related variance for principal components 1–8 derived from OF (blue) and SF (red) encoding (*Materials and Methods*). The black line is the mean proportion of task-related variance derived from noise components, and the dotted black lines are the 95% confidence intervals across noise components. (*D*) Mean similarity (Fisher Z-transformed correlation coefficient) of each OF encoding component with the MVCS during each rest period. $^{\star\star}P < 0.005$; $^{\star}P < 0.05$ for post-OF vs. baseline rest. $^{**}P < 0.005$; $^{*}P < 0.05$ for post-OF vs. post-SF rest. (*E*) Mean similarity (Fisher Z-transformed correlation coefficient) of each SF encoding component with the MVCS during each rest period. $^{\star\star}P < 0.005$ for post-SF vs. baseline rest. $^{**}P < .005$ for post-OF vs. post-SF rest.

increases in the presence of lower-strength encoding components were found during immediate postencoding rest periods (OF and SF encoding components 4–8: all P values > 0.2) (Fig. 3 *D* and *E*). The same pattern of results was observed when we computed the amount of variance accounted for by the encoding components during rest (*SI Results, Group-Level Encoding Component Analyses Using Proportion of Variance Measure* and Fig. S6 *A* and *B*). Additionally, we replicated our prior findings that the persistence of hippocampal encoding patterns was selective for immediate rest periods (*SI Results, Group-Level Similarity of Encoding Components with Nonimmediate Postencoding Rest Periods*).

Strength-Dependent Persistence of Individual Subject-Level Hippocampal Encoding Patterns Is Related to Memory. We next examined the postencoding persistence of individual subject-level hippocampal encoding decompositions and whether this persistence was related to memory (*Materials and Methods*). Mirroring our group-level analyses, we found a significant correlation between the strength of individual encoding components and the presence of those components during immediate postencoding rest periods. Example data from an individual subject (Fig. 4 *A* and *B*) depict the similarity between rest and encoding hippocampal MVCSs separately for each encoding component as a function of the strength of that component during encoding. Example data are shown for each rest period separately (Fig. 4*A*) as well as the change in similarity from baseline rest to the immediate post-encoding rest period (Fig. 4*B*). Across subjects, higher correlations were observed between encoding signal component strength and the similarity with the hippocampal MVCS during immediate postencoding rest vs. baseline rest (OF encoding signal component strength correlations: $t_{19} = 3.24$, $P < 0.005$; SF encoding signal component strength correlations: $t_{19} = 1.80$, $P = 0.087$) (Fig. 4*C*). Encoding signal component strength was also significantly related to the increase in similarity of signal components from baseline to immediate postencoding rest periods (OF encoding signal strength correlations: $t_{19} = 4.97$, $P < 10^{-4}$; SF encoding signal strength correlations: $t_{19} = 4.21$, $P < 0.001$) (Fig. 4*D*). The same effects were observed for the variance accounted for by each encoding component in the rest data (*SI Results, Individual Subject-Level Encoding Component Analyses Using Proportion of Variance Measure* and Fig. S6 *C* and *D*).

If the postencoding persistence of hippocampal BOLD patterns is important for memory consolidation, then subjects' later memory for encoding experiences should be positively related to measures of this persistence. After scanning, subjects' memory for all presented stimuli seen during OF and SF encoding was assessed; memory performance was significantly above chance for stimuli from both encoding tasks (mean OF overall memory = 58.0 + 3.5, $t_{19} = 16.65$, $P < 10^{-10}$; SF overall memory = 34.3 + 3.3, $t_{19} = 10.36$, $P < 10^{-8}$). Specifically, we asked whether, within a given subject, the relative persistence of encoding components into immediate postencoding rest based on their strength (the individual data points in Fig. 4*D*) was related to that subjects' later memory (total number of stimuli remembered). Critically, we found a correlation between subsequent memory and the persistence of the hippocampal encoding components during immediate postencoding rest as a function of their encoding strength for both the OF and SF encoding tasks (OF encoding data correlation: $r = 0.49$, $t_{17} = 2.33$, $P < 0.02$, one-tailed test; SF encoding data correlation: $r = 0.41$, $t_{17} = 1.84$, $P < 0.05$, one-tailed test) (*Materials and Methods* and Fig. 4*E*). Similar correlations with memory performance were observed when we measured the correlation between encoding component strength and the increase in the amount of variance explained by encoding signal components during immediate postencoding vs. baseline rest (OF encoding data correlation: $r = 0.43$, $t_{17} = 1.96$, $P < 0.04$; SF encoding data correlation: $r = 0.40$, $t_{17} = 1.79$, $P < 0.05$). In addition to asking whether the differential or relative persistence of encoding patterns based on their strength was related to memory performance, we also asked whether the persistence of the strongest encoding component of each subject's data was related to

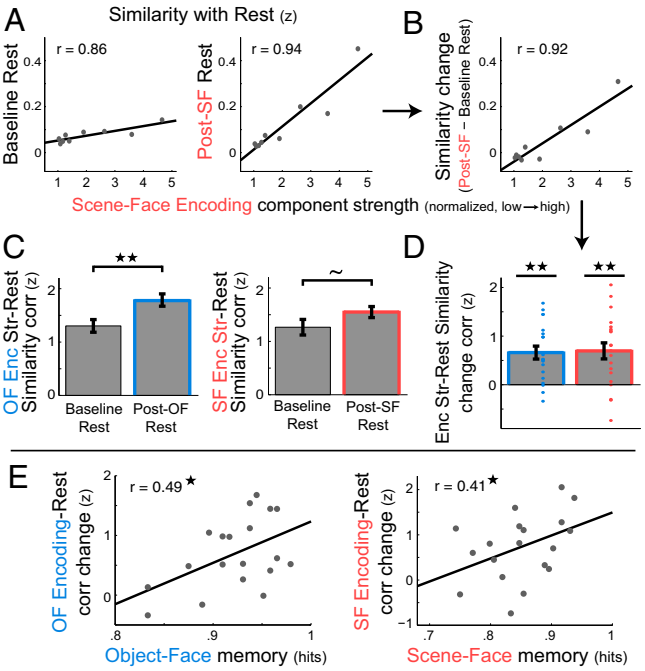

Fig. 4. Individual subject-level analysis of encoding strength–rest similarity and its relation to later memory performance. (*A*) Example subject data showing the relationship between the normalized strength of individual SF encoding components and the similarity (Fisher Z-transformed correlation coefficient) with the MVCS during (*Left*) baseline rest and (*Right*) post-SF rest. (*B*) For the same subject as in *A*, the change in similarity from baseline to post-SF rest of individual SF encoding components is shown as a function of the normalized strength of these components. (*C*) Group data showing the mean encoding strength–rest similarity correlation for (*Left*) OF encoding and (*Right*) SF encoding. The encoding strength–rest similarity correlation for each encoding task is the correlation (Fisher Z-transformed) between encoding component strength for that task and the similarity of those components with the rest data (correlation values shown in *A*). $^{\star\star}P < 0.005$; $^{\sim}P < 0.10$. (*D*) Group data showing the correlation between encoding component strength and the change in similarity from baseline rest to the immediate postencoding rest period (the correlation value shown in *B*) for OF encoding and post-OF minus baseline rest (blue) and SF encoding and post-SF minus baseline rest (red). Individual blue and red dots correspond to values for each subject. $^{\star\star}P < 0.005$. (*E*) Across-subjects relationship between memory performance (total hits) and the encoding strength–rest similarity correlation change (the within-subject Z-transformed correlation between encoding component strength and the change in similarity from baseline rest to the immediate postencoding rest period; individual data points from *D*) for (*Left*) OF encoding and (*Right*) SF encoding. Each gray dot represents data for each individual subject. Significant correlations were found for both OF and SF encoding tasks. $^{\star}P < 0.05$ (one-tailed).

better memory performance. We found that the increase in similarity of the strongest encoding component with the hippocampal MVCS from baseline to the immediate postencoding rest period was also positively correlated with later memory for the OF data ($r = 0.45$, $t_{17} = 2.07$, $P < 0.03$) and marginally correlated for the SF data ($r = 0.34$, $t_{17} = 1.49$, $P = 0.078$). Taken together, these results suggest that the persistence of the strongest hippocampal BOLD patterns into postencoding rest periods may contribute to memory consolidation.

Importantly, to determine the specificity of these correlations with memory for recently seen stimuli, we performed a partial correlation analysis to see if the observed relationships for each task remain when holding constant memory performance on the other task. We found a significant relationship between the differential persistence of OF encoding patterns during post-OF rest based on their strength during encoding (individual data points in Fig. 4*D*) and OF memory when controlling for SF

memory ($r = 0.43$, $t_{17} = 1.95$, $P < 0.04$). A marginal relationship was found between the differential persistence of SF encoding patterns during post-SF rest (individual data points in Fig. 4*D*) based on their component strength and SF memory when controlling for OF memory ($r = 0.37$, $t_{17} = 1.67$, $P = 0.063$). Thus, these results suggest that the differential persistence of encoding patterns during postencoding rest is related to memory for stimuli just encountered in the immediately preceding encoding task and does not seem to be reflective of more general, trait-level memory.

Discussion

Offline reactivation of patterns of activity representing recent experience is thought to be a critical mechanism underlying memory consolidation. Although work in rodents has provided evidence for hippocampal reactivation and its relationship to spatial memory, little work has examined the persistence of hippocampal patterns of activity in humans. Here, we provide evidence for a role of the persistence of hippocampal BOLD activity patterns in humans in memory processing. First, we found that two different encoding tasks elicited dissociable patterns of hippocampal BOLD activity: largely distinct populations of voxels were activated by the two tasks, and greater within- vs. across-task similarity was found in the hippocampal BOLD correlation structure. Second, we found that the correlation structure across all hippocampal voxels present during each encoding task selectively persisted into the immediate postencoding rest period. Third, using a data-driven PCA approach, we showed that the strongest hippocampal patterns present during encoding showed evidence of persistence into subsequent postencoding rest periods. Fourth, we found that, across subjects, the extent to which the strongest encoding patterns differentially persisted into postencoding rest was related to subsequent memory. Together, these results show that specific hippocampal BOLD encoding patterns persist during postencoding rest and that the preferential persistence of the strongest patterns present during encoding is related to future memory performance.

Two complementary analysis approaches were used to identify hippocampal encoding patterns associated with distinct tasks and provide evidence for their selective persistence into postencoding rest periods. First, using an approach that includes and equally weights activity from all hippocampal voxels, we found that the pairwise MVCS in the hippocampus associated with each encoding task was more similar to the correlation structure during an immediate postencoding rest period compared with baseline rest. Second, rather than assuming that all voxels are equally informative to patterns of connectivity, we used PCA to decompose the hippocampal correlation structure into distinct activity patterns or principal components that vary as a function of their strength during encoding. Interestingly, at the group level, we found that the strongest encoding patterns differentially weighted voxels located in the anterior (and mid) portions of the hippocampus and voxels that tended to show reliable trial-evoked responses. Moreover, the strongest components showed evidence of persistence during immediate postencoding rest periods compared with lower-strength components that did not show substantial trial-related signal changes or differential weighting of anterior vs. posterior hippocampal voxels. Taken together, these complementary approaches suggest that the hippocampal correlation structure as a whole shows evidence of persistence during immediate postencoding rest periods, but that this persistence is preferentially driven by anterior (and mid) hippocampal voxels showing trial-related modulation of the BOLD signal (refs. 28–30 discuss anterior vs. posterior differentiation of the hippocampus).

These findings extend previous human neuroimaging studies of postencoding activity and its potential relationship to memory consolidation in two ways. First, prior studies have focused on measuring univariate BOLD activity, finding that hippocampal regions active during a spatial navigation task were again active during postlearning sleep and subsequent awake periods (24, 25). Furthermore, overall levels of hippocampal–cortical connectivity have been shown to increase after learning (21, 24, 31). However, it is unclear whether univariate changes in activity and connectivity reflect the persistence of specific multivariate patterns that emerge during preceding experiences. Thus, the present findings provide critical evidence that distinct hippocampal patterns characteristic of recent encoding experiences persist into immediate postencoding rest periods. This result is an important advance as it allows us to conclude that not only, after encoding, some of the same brain structures are engaged but also that similar kinds of information are present. Second, prior work examining postencoding changes in hippocampal activity has often used multitrial learning designs with a substantial spatial component (24, 25, 32, 33). The present findings add to this work by showing that hippocampal patterns can be modulated after trial-unique, nonspatial episodic-like encoding experiences.

Taken together, our results suggest that the postencoding persistence of hippocampal encoding patterns may be relevant for and a marker of the initial stages of memory consolidation. However, it is important to note that, in the current paradigm, delays of only ~40–50 and 70–80 min occurred between encoding and memory testing, respectively (for the second and first encoding blocks, respectively). Thus, although our findings provide important initial evidence that the persistence of encoding patterns during postencoding rest may be relevant for consolidation, it will be critical for future studies to determine whether these findings relate to extended measures of long-term memory and examine how long these neural measures of persistence are detectable (an example is given in ref. 34). Furthermore, future work can address what aspects of an experience modulate postencoding persistence. In the current study, distinct features of the encoding experience, including bottom-up sensory differences in the stimulus content and top-down processes (reflecting different instructions and decisions across the tasks) (35–37), could have contributed to the distinctive hippocampal patterns seen during OF and SF encoding.

In conjunction with other recent work (13–17, 20, 21, 23, 38, 39), our findings highlight the notion that postencoding processes occurring in the awake state and not just during sleep are potential contributors to memory consolidation. Specifically, it has been hypothesized that time periods that engender a reduction in environmental stimulation may allow for the expression of physiological mechanisms underlying memory consolidation (3, 40). Additionally, robust and reliable patterns of connectivity are known to occur during awake rest (41, 42), and several recent studies have shown that overall univariate measures of blood flow, BOLD responses, and BOLD connectivity during awake rest may be modulated in a manner consistent with memory consolidation (21–25). Here, we extend these results by showing that multivariate encoding-related hippocampal BOLD patterns persist into awake rest periods and that this persistence is related to future overall memory for prerest experiences.

Materials and Methods

Subjects and Procedures. Twenty-four subjects were scanned using fMRI during the performance of two different encoding tasks and rest periods before and after each encoding task (Fig. 1*A*); 4 of 24 participants were excluded from the analyses because of excessive motion. During the fMRI session, subjects were first scanned during a baseline rest period, allowing us to measure baseline patterns of resting BOLD activity across the hippocampus. Participants then performed two encoding tasks during separate functional scans: OF encoding and SF encoding. After each encoding task, a postencoding rest scan was administered: post-OF rest after OF encoding and post-SF rest after SF encoding. The order of the encoding tasks was counterbalanced across subjects. During both tasks, subjects viewed pairs of items presented in a slow event-related manner and were instructed to make a decision about the two items interacting (Fig. 1*A*). After the scanning session, subjects were given a surprise memory test to assess their memory for stimuli seen during both encoding tasks. Full procedures and MRI data acquisition and processing details can be found in *SI Materials and Methods*.

Hippocampal MVCS Analyses. The hippocampus was anatomically defined, and additional preprocessing was performed to remove nuisance signals from the BOLD data (*SI Materials and Methods*). To characterize multivoxel hippocampal patterns during encoding and rest periods, we computed the MVCS separately for each time period by calculating the zero-lag correlation between all pairs of hippocampal voxels using the entire time course of the BOLD signal (similar to previous methods) (43–46). This process results in a separate multivoxel BOLD correlation structure or MVCS for each encoding task and rest period (Fig. 2*A* and Fig. S1 show example MVCSs). To determine whether the MVCS was distinctive between the OF and SF encoding tasks, we computed the similarity of the hippocampal MVCS both within and across the two tasks by dividing the data from each 21-min encoding task into six 3.5-min blocks. We then computed the MVCS separately for each 3.5-min block and measured the similarity of the Fisher Z-transformed MVCSs across blocks. *SI Materials and Methods* has details about how we equated the time between the within- and across-task estimates of MVCS similarity.

Decomposition of Hippocampal Encoding Data. PCA was performed on the hippocampal BOLD data from each encoding task. To examine the presence of encoding components during rest periods, two measures were used: the similarity of each encoding component with the MVCS during rest and the proportion of variance associated with each component during rest (*SI Materials and Methods* shows full descriptions of these measures). To assess individual subject decompositions of the hippocampal encoding data, we computed the normalized strength for each principal component in each subject based on its eigenvalue and the results of noise simulations (details in *SI Materials and Methods*). This process allowed us to examine the presence of signal components (i.e., nonnoise components with normalized strength >1) during rest, in order to ask whether the specific values of encoding component strength predicted the enhanced presence of these components during postencoding rest within a subject. Critically, we then asked if the relationship between encoding component strength and evidence of persistence during postencoding rest was positively related to memory performance (*SI Materials and Methods*).

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