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Remembering and imagining differentially engage the hippocampus: A multivariate fMRI investigation

C. Brock Kirwan[1,2], Stefania R. Ashby[1], and Michelle I. Nash[1]

[1]Department of Psychology, Brigham Young University, Provo, USA
[2]Neuroscience Center, Brigham Young University, Provo, USA

It has been proposed that imagining the future depends on the ability to retrieve episodic details from past experiences in order to recombine them into novel possible experiences; consequently, the processes of remembering and imagining rely on similar neural substrates, including the hippocampus. We used fMRI and both univariate and multivariate analysis techniques to test this prediction. Unbiased univariate analysis did not reveal differences in the hippocampus between remembering and imagining; however, multivariate analyses revealed evidence that patterns of activity within the hippocampus distinguish between remembering and imagining. Thus, while the hippocampus seems to be involved in both remembering the past and imagining the future, the pattern of activity within the hippocampus distinguishes between these two different tasks.

Keywords: Memory; Imagining; fMRI; Multi-voxel pattern analysis.

In recent years a growing interest has developed concerning the neural processes that support remembering the past and imagining the future (for reviews, see Addis & Schacter, 2012; Buckner, 2010; Schacter & Addis, 2009; Schacter et al., 2012). Many studies have shown that remembering and imagining utilize the same neural substrates including the hippocampus, and are therefore intricately related. Studies of amnesic patients with hippocampal lesions have demonstrated impairments in imagining the future (e.g., Hassabis, Kumaran, Vann, & Maguire, 2007). However, this impairment is not observed in all cases (e.g., Squire et al., 2010). Similarly, neuroimaging studies have demonstrated both overlapping activation between remembering the past and imagining the future (Schacter, Addis, & Buckner, 2007) as well as distinct patterns of activation (Addis, Wong, & Schacter, 2007; Addis, Pan, Vu, Laiser, & Schacter, 2009).

Previous research using univariate analysis techniques to examine the neural structures involved in remembering and imagining have shown that structures such as the hippocampus are similarly involved in both remembering the past and imagining the future (Addis et al., 2007; Botzung, Denkova, & Manning, 2008; Okuda et al., 2003; Spreng, Mar, & Kim, 2009; Szpunar, Watson, & McDermott, 2007; Viard et al., 2011), although functional differences have been observed (Addis et al., 2007; Okuda et al., 2003). Other studies have used spatiotemporal partial least squares (PLS), a multivariate analysis technique, to examine the overall pattern of brain activity in order to determine functional differences between remembering and

Correspondence should be addressed to: Brock Kirwan, Ph.D. 1001 SWKT, Brigham Young University, Provo, UT, 84602 USA. E-mail: kirwan@byu.edu

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imagining. PLS has greater statistical sensitivity than standard univariate analysis techniques (McIntosh, Chau, & Protzner, 2004), and studies using this approach (Addis et al., 2009; Spreng & Grady, 2010) have identified the hippocampus as playing a similar role in remembering the past and imagining the future. PLS, however, examines patterns of fMRI activity across the whole brain and not within specific brain structures. The aim of the current research, therefore, was to test the idea that activity in the hippocampus alone can distinguish between remembering the past and imagining the future by using multi-voxel pattern analysis (MVPA) to examine the overall pattern of activity in the hippocampus related to the two tasks.

METHODS

Participants

Informed consent was obtained from 15 healthy participants who were recruited from the university community. Research was approved by the Institutional Review Boards of the University of Utah and Brigham Young University. The sample consisted of eight males and seven females between the ages of 18 and 25. All volunteers were right-handed, native English speakers, with no prior history of head injury. One participant was excluded from the fMRI analysis due to excessive head movement, and experimenter error resulted in the loss of part of one functional MRI run for one subject. Consequently, data from this participant were included in the univariate analysis but excluded from the multivariate analysis described below.

Behavioral task

The experiment consisted of three different tasks performed while in the MRI scanner: *Remember*, *imagine*, and a *baseline* measurement task. Prior to scanning, each participant provided 60 personal photographs—taken within the last five years—to be used in the memory task. Personal photographs rather than novel photographs were used to cue memory in order to minimize the potential confound of false memories being generated during the remember trials. Additionally, a survey was administered in which participants were asked about travel and leisure activities in order to establish novel places and activities for the imagine task. This allowed us to choose images of things that the participant had never experienced before in order to minimize memory confounds in the imagine task. Participants were instructed to create the most detailed memories and imaginings possible, and to avoid bringing memory into the imagine trials.

The task consisted of three blocks of 20 remember trials, 20 imagine trials, and 60 baseline trials in a pseudorandom order (order counterbalanced across participants). Each block was approximately 12 minutes. The structure and timing of the remember and imagine tasks were the same (Figure 1). First,

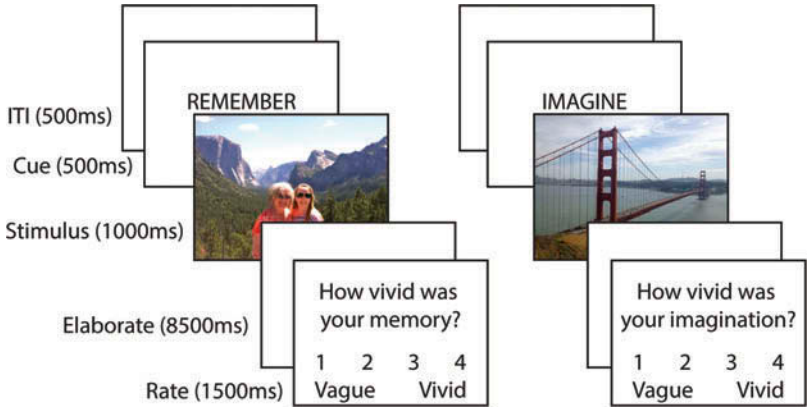

Figure 1. Example of remember and imagine trials. Both remember and imagine trials began with a 500 ms inter-trial interval (ITI) followed by a 500 ms cue screen that indicated the task for that trial (either remember or imagine). The stimulus was presented for 1000 ms. Stimuli for the remember condition were photographs provided by the participant that depicted events from within the last five years. Stimuli for the imagine condition were chosen by the experimenters based on self-reports of activities never performed or locations never visited. Participants had 8500 ms in which to elaborate either their recollection or their imagined scene. Participants then had 1500 ms in which to rate their memory/imagining.

participants were presented with a cue word, either "remember" or "imagine", for 500 ms via a mirror and back-projection screen. Following the cue word, a photograph—either participant-provided for all of the remember conditions or a novel stimulus for all of the imagine conditions—was shown for 1000 ms. Following the presentation of the photograph, participants had 8500 ms to retrieve and elaborate on their memories, or generate and elaborate on a new imagination. After this elaboration phase, participants rated the vividness of their elaboration using a fiber-optic response system. Participants were given 1500 ms in which to make their rating responses on a scale from 1–4, with 1 being extremely vague to 4 being extremely vivid, followed by a 500 ms inter-trial interval (see Figure 1). The average vividness rating was 2.83 (*SD* = 0.32) for the imagine trials and 3.40 (*SD* = 0.42) for the remember trials.

The baseline task consisted of a series of static noise images. First, the participant was shown the prompt ("Do you see an 'x' in the following image?") for 500 ms, followed by a static noise image for 3500 ms. Participants indicated with a button press whether or not they were able to detect the target. Targets were present in 80% of static noise images. The target contrast was varied in order to maintain participant engagement in the task (mean percent correct on the detection task = 90%). Prior to the start of scanning, participants viewed a sample target detection trial and several remember and imagine trials in order to familiarize them with the timing of the tasks.

MRI acquisition and analysis

Imaging was performed on a 3T Siemens scanner at the Imaging and Neurosciences Center at the University of Utah. Functional images were acquired using a gradient-echo, echo planar, T2*-weighted pulse sequence (TR = 2000 ms; 360 TRs/run; TE = 30 ms; flip angle 75°; matrix size = 64 × 64; field of view 22 cm). The first four TRs acquired were discarded to allow for T1 equilibration. Thirty-three oblique coronal slices (slice thickness = 3.3 mm) were acquired parallel with the corpus callosum and covering the whole brain. Structural MRI images were acquired using a T1-weighted MP-RAGE sequence (165 × 220 mm field of view; flip angle 12°; TE 2.58 ms; 128 slices; 1 mm slice thickness; matrix size 144 × 192; voxel size 1.46 × 1.45 × 1 mm).

Preprocessing of MRI data was accomplished using the AFNI suite of programs (Cox, 1996). Functional data were coregistered in three dimensions to the whole-brain anatomical data, slice-time corrected, and coregistered to reduce effects of head motion. Initial spatial normalization was accomplished using each participant's structural MRI scan to transform the data to the atlas of Talairach and Tournoux (1988). Further spatial normalization was carried out using the Advanced Normalization Tools (ANTs) (Avants, Epstein, Grossman, & Gee, 2008; Klein et al., 2009; Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Motley & Kirwan, 2012; Yassa et al., 2010), which uses diffeomorphic mapping to calculate a transformation from an individual participant to a model based on the grayscale structural MRI scan. Functional time series data were transformed to Talairach space and then resampled to 3 mm^3 before being aligned to the template with ANTs.

Anatomical masks were created by defining hippocampus, temporopolar cortex, perirhinal cortex, entorhinal cortex, and parahippocampal cortex on the ANTs model directly using techniques described previously (e.g., Insausti et al., 1998; Kirwan & Stark, 2004). A whole-brain anatomical mask was also defined to encompass the cerebrum of the ANTs model brain.

We first conducted univariate analyses by creating six behavioral vectors that coded trial type (imagine or remember) and the phase of each trial (image presentation, elaboration phase, and rating). In order to control for differences in vividness ratings between the remember and imagine conditions, we excluded imagine and remember trials with low vividness ratings (ratings < 3; mean 17.9 imagine trials and 8.3 remember trials excluded per participant) from all analyses. The behavioral vectors and six additional vectors that coded for motion (three for translations and three for rotations) were used in the deconvolution analysis of the fMRI time series data in which a canonical hemodynamic response was convolved with the behavioral vectors. In order to isolate the elaboration phase of the experiment from the cue and response phases, separate regressors were constructed for these phases of each trial. The duration of the hemodynamic response varied according to the phase of the trial, with image presentation modeled as an event of 1500 ms (cue and stimulus presentation), elaboration (synced with the beginning of the elaboration phase) modeled as an event of 8000 ms, and rating modeled as an event of 2000 ms. The resultant fit coefficients (β coefficients) represent activity versus baseline in each voxel for a given time point and each of the trial types. The visual detection task was used as a baseline against

which to estimate the hemodynamic response. Large motion events, defined as TRs in which there was >0.3° of rotation or 0.6 mm of translation in any direction, were excluded from the deconvolution analysis by censoring the excluded time points (mean of 0.13 events per participant). We also excluded the TR immediately before and after the motion-contaminated TR. We set *a priori* activation thresholds at $p < .05$ (FDR corrected) and >30 voxels (810 mm^3) spatial extent.

To exclude any influence of novelty processing due to the use of novel pictures as prompts for the imagine condition (Stark & Squire, 2001; Stern et al., 1996), we first identified voxels that had a greater response to the novel pictures than to the familiar pictures and setting a liberal voxel-wise threshold of $p = .01$ with no small-volume correction. This contrast identified notable areas of activation in bilateral posterior hippocampus and several midline cortical structures. These voxels were excluded from the MVPA analysis by subtracting them from the anatomical masks described above.

Multi-voxel pattern analysis (MVPA) was carried out using the Princeton MVPA toolbox for Matlab (http://code.google.com/p/princeton-mvpa-toolbox/). The MVPA method has been described in detail elsewhere (for review, see Haynes & Rees, 2006; Norman, Polyn, Detre, & Haxby, 2006). Regressors coding for the elaboration phase of remember and imagine trials as well as for baseline trials were convolved with a canonical hemodynamic response and then thresholded in order to select TRs for each of the conditions of interest that were time shifted to match the hemodynamic response. Time course data were *z*-scored and then entered into a regression analysis in order to select the most informative voxels. The MVPA analysis was performed on fMRI data from the whole brain, and then repeated first on data restricted to the medial temporal lobe (MTL; including hippocampus, temporopolar cortex, perirhinal cortex, entorhinal cortex, and parahippocampal cortex), and then on data restricted to the hippocampus only. In each case, the top 10% most informative voxels were identified by computing a general linear model (using AFNI's 3dDeconvolve command) and selecting the voxels with the highest *F*-values for the overall regression model (6071 voxels for the whole brain mask; 218 voxels for the MTL mask; 47 voxels for the hippocampus mask). Based on the selected voxels, we first trained a linear support vector machine (SVM) classifier for task trials (collapsed across remember and imagine tasks) and for baseline trials. Classifier training was performed on the data for 2.5 runs and the classifier was then tested on the remaining data. This process was then repeated leaving out a different subset of the data for a total of six iterations per participant. Chance performance was determined by shuffling the regressor labels for each TR and training/testing the SVM. The classification score was then tested against chance performance. We then performed a parallel set of analyses for the classification of remember versus imagine trials at the whole brain, MTL, and hippocampal levels.

RESULTS

A univariate voxel-based analysis comparing remember versus imagine conditions revealed significant clusters in bilateral retrosplenial cortex, left anterior cingulate cortex, and left parahippocampal cortex (Figure 2) where fMRI activation was greater for the remember condition than the imagine condition. Voxel coordinates for these clusters and for clusters where activation was greater for the imagine condition than remember

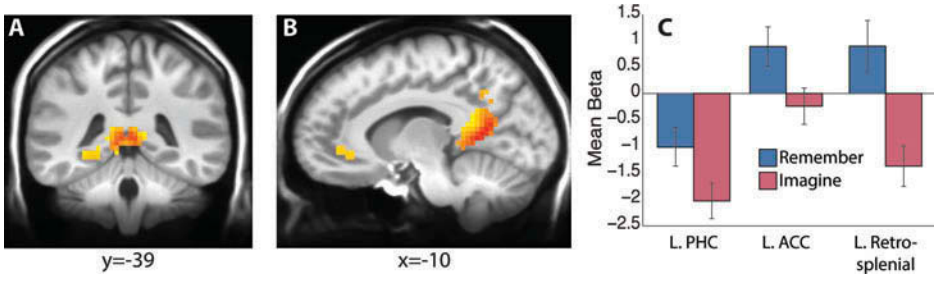

Figure 2. Results of the univariate analysis of remember and imagine trials. A contrast of remember > imagine resulted in significant clusters in left parahippocampal cortex (A) bilateral retrosplenial cortex (A-B) and anterior cingulate cortex (B). Mean fMRI activation for each cluster (C).
Notes: L = left; PHC = parahippocampal cortex; ACC = anterior cingulate cortex; error bars are ±SEM.

TABLE 1
Report of voxel coordinates and cluster extent for regions that were found to have significant activation during univariate analysis for two contrasts: Remember greater than imagine and imagine greater than remember

			Peak activation		
Contrast	*Label*	*#Voxels*	*x*	*y*	*z*
Remember > Imagine					
	B. Retrosplenial	439	8	−56	15
	L. Parahippocapal Cortex	40	−23	−41	−7
	L. Anterior Cingulate Cortex	38	−5	38	−7
Imagine > Remember					
	R. Middle Frontal Gyrus	398	38	56	−1
	R. Inferior Parietal Lobule	354	44	−47	51
	L. Inferior Parietal Lobule	205	−47	−41	54
	L. Inferior Frontal Gyrus	163	−53	17	−4
	L. Middle Frontal Gyrus	124	−50	32	18
	L. Cerebellum	63	−41	−53	−25
	R. Superior Frontal Gyrus	53	20	17	60
	R. Superior Frontal Gyrus	39	20	59	24

(*L* = left; *R* = right; *B* = bilateral).

condition are listed in Table 1. There were no voxels from either contrast that overlapped with our hippocampal anatomical region of interest. We next examined the mean activity in the remember and imagine conditions for all voxels in our hippocampal mask segmented into anterior and posterior sections at the level of the uncus (Talairach X coordinate = 18; Figure 3). A 2 (remember vs. imagine) × 2 (anterior vs. posterior) repeated measures ANOVA for activation in the left and right hippocampus revealed a main effect of anterior/posterior in both left ($F(1, 13) = 78.02$, $p < .001$) and right ($F(1, 13) = 18.33$, $p < .01$) hippocampus, but no main effects of task or task × anterior/posterior interactions. Activation was greater than baseline in the left anterior hippocampus for the remember condition ($t(13) = 2.42$, $p < .05$) and marginally for the imagine condition ($t(13) = 2.05$, $p = .06$). In the posterior hippocampus, activation was less than baseline on the left for both remember ($t(13) = 2.27$, $p < .05$) and imagine ($t(13) = 3.18$, $p < .01$) conditions. Similarly, activation in the right posterior hippocampus was less than baseline for the remember condition ($t(13) = 2.45$, $p < .05$) (Figure 3). Thus, while univariate analyses revealed that regions such as the retrosplenial cortex and parahippocampal cortex distinguish between remember and imagine conditions, they do not reveal any differential activation between remember and imagine conditions in the hippocampus.

We next employed a multivariate analysis to determine if the overall pattern of activation differentiated remember trials from imagine trials or task from baseline. Our first analysis investigated classifier accuracy for task (both remember and imagine) versus baseline considering voxels across the whole brain, restricted to the MTL, and again restricted to the hippocampus. Classifier accuracy at each of these levels is depicted in Figure 4 and all statistics reported below are corrected for multiple comparisons using the Bonferroni method. For the task versus baseline classification, chance accuracy was determined to be 0.787 by training/testing the SVM with scrambled regressors. Classifier accuracy was significantly above chance at the whole brain (mean(*SD*) = 0.97(0.01); $t(12) = 44.5$, $p < .0001$) and MTL (0.85(0.04); $t(12) = 6.70$, $p < .0001$) levels. However, when restricting the analysis to the hippocampus, classifier accuracy for task versus baseline was not different from chance (0.79(0.05); $t(12) = 0.47$, $p = .65$). This lack of differentiation between the baseline and task may be due to collapsing across distinct activation patterns for remember versus imagine trials, as suggested by the

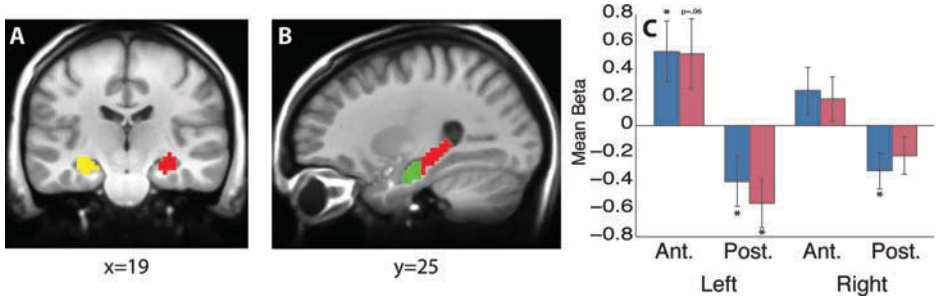

Figure 3. Anatomical masks for the hippocampus (A) were divided into anterior and posterior sections at the level of the uncus (B). There was a main effect of anterior-posterior region on fMRI activation (C) for both left and right hippocampus, but no main effect of task (remember vs. imagine) or task × anterior-posterior interaction.
Notes: Ant. = anterior; Post. = posterior; * indicates $p < .05$; error bars are ±SEM.

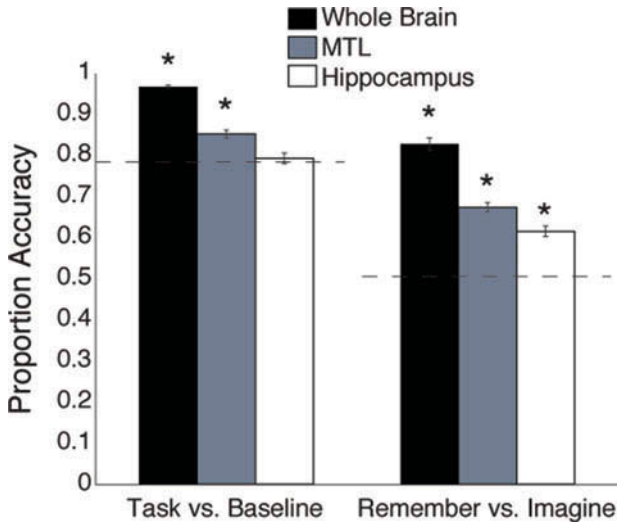

Figure 4. Mean accuracy scores for the MVPA classifier on the task (both remember and imagine) versus baseline classification and the remember versus imagine classification with three different anatomical masks: Whole brain, MTL, and hippocampus only.
Notes: Chance performance is indicated with dashed lines; * indicates $p < .0001$; error bars are ± SEM.

differing results of the univariate analysis in the anterior and posterior hippocampus. Our next analysis examined the differential patterns for remember and imagine trials. For the remember versus imagine classification, chance accuracy was determined to be 0.522. In this comparison, accuracy was significantly above chance at the whole brain (0.83(0.06); $t(12) = 19.9$, $p < .0001$), MTL (0.67(0.06); $t(12) = 13.4$, $p < .0001$), and hippocampal level (0.62(0.05); $t(12) = 7.2$, $p < .0001$), indicating that the pattern of activation across voxels in the hippocampus distinguishes between remembering the past and imagining the future.

DISCUSSION

We collected fMRI data as participants engaged in remembering the past and imagining the future. Our univariate analyses revealed a number of regions that distinguished the remembering and imagining conditions from one another, including the retrosplenial cortex and parahippocampal cortex. However, we did not observe activation differences in the hippocampus between remember and imagine conditions with either a voxel-based analysis or an anatomical region of interest analysis. In contrast, when we used MVPA to examine the overall pattern of activation within the hippocampus, we found that the patterns of activation within the hippocampus discriminate between remembering and imagining when considering the voxels in the hippocampus separately from the rest of the brain.

Addis and Schacter (2012) propose that the hippocampus is necessary in the early phase of constructing possible future scenarios due to the need to retrieve details of past experiences in order to form novel recombinations. This is consistent with the proposed role of the hippocampus in forming novel and flexible expressions of past experiences (Eichenbaum & Cohen, 2001). Addis and Schacter (2012) further propose that the posterior hippocampus is involved in retrieval while the anterior hippocampus is involved in the recombination and re-encoding of these details in an imagining condition (Schacter & Wagner, 1999; Spaniol et al., 2009). Addis et al. (2007) have demonstrated that the anterior right hippocampus was more active for imagining the future than for remembering the past in the early phase of the task, but that this differential activity was reduced in later phases (see also Addis et al., 2009; Addis, Cheng, Roberts, & Schacter, 2011). Our analysis did not separate the early and late phases of the elaboration phase and thus cannot be entirely explained in terms of the temporal differences between imagining and remembering. Moreover, the novelty-responsive voxels in the hippocampus were predominantly in the posterior hippocampus (Stern et al., 1996). The activity pattern differences observed in our data nevertheless could be due to spatiotemporal differences in the two conditions as suggested by these authors. Additionally, our results are consistent with those of

Weiler, Suchan, and Daum (2010) who observed greater right anterior hippocampal activation for imagined events that had a low probability of occurring in the upcoming holidays relative to higher-probability events. In our study, some of the stimuli in the imagine condition might be considered "highly improbable" for some of our participants (e.g., skydiving). This level of novelty or likelihood of an event happening may have influenced activity in the hippocampus. Future studies may wish to control for the likelihood of imagine events in order to account for any additional variance in hippocampal activity occasioned by subjective likelihood.

The use of personal photographs to cue memories and novel photographs to cue imagination in the current experiment was meant to control for false memories in the remember condition and veridical memory retrieval in the imagine condition. This manipulation, however, introduced important differences between the two task conditions, such as the relative familiarity of the cue images. To control for novelty effects, voxels deemed to be responding to the novelty of the imagine photographs were not included in the MVPA and only TRs during the elaboration phase were included in the MVPA. However, because of the sensitivity of multivariate analysis, it is possible that sub-threshold novelty activity could be affecting our results. Future studies may wish to control for such novelty effects at the level of task design in addition to excluding novelty-activated voxels from their multivariate approach. Further, the emotional content of the cue images may have influenced neural responses. While the emotional content of the photographs provided by the participants was generally high (and almost uniformly positive), the photographs used in the imagine condition were also emotionally charged. For example, in the imagine condition participants were explicitly instructed to imagine themselves directly participating or interacting with the scene that was being viewed. Many of the photographs shown during the imagine condition depicted highly emotional contents, such as skydiving or disaster photos after a tsunami. Future studies will be needed to rule out any possible influence of emotional content on neural responses in these two conditions.

The above results suggest that while the hippocampus is involved in both remembering the past and imagining the future, the pattern of activity for these two activities is distinct. A univariate analysis using an unbiased selection technique (anatomical masking) resulted in undifferentiated activation for the remember and imagine conditions, though the activation did differ along the anterior-posterior axis of the hippocampus. Importantly, these anterior-posterior differences were similar for both remember and imagine conditions, as indicated by the lack of task by anatomical regions interactions. This anterior-posterior difference in activation may also account for our failure to observe significant task versus baseline discrimination in the MVPA analysis since our MVPA mask collapsed over the entire hippocampus to avoid having too few voxels in the analysis. Our results are consistent with other studies that have observed effects using MVPA that were not apparent with traditional univariate analyses (e.g., Haynes & Rees, 2005; Polyn, Natu, Cohen, & Norman, 2005). When we considered the overall pattern of activity across voxels within the hippocampus in the multivariate analysis, we observed that the hippocampus significantly differentiates between remembering and imagining while our univariate analyses failed to observe any such difference.

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