

RAPID COMMUNICATION

Lag-Sensitive Repetition Suppression Effects in the Anterior Parahippocampal Gyrus

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ABSTRACT: Single-unit recording studies of monkeys have shown that neurons in perirhinal and entorhinal cortex exhibit activity reductions following stimulus repetition, and some have suggested that these “repetition suppression” effects may represent neural signals that support recognition memory. Critically, repetition suppression effects are most pronounced at short intervals between stimulus repetitions. Here, we used event-related functional magnetic resonance imaging (fMRI) to identify repetition suppression effects in the human medial temporal lobe and determine whether these effects are sensitive to the length of the interval between repetitions. Twenty-one participants were scanned while performing a continuous recognition memory task in which the interval between item repetitions was parametrically varied from 2 to 32 intervening items. We found evidence of repetition suppression in the anterior parahippocampal gyrus, but only when the repetition interval was relatively short. Moreover, bilateral hippocampal regions showed lag-sensitive repetition effects. Our results demonstrate that activity in the human medial temporal cortex, like that of monkeys, exhibits repetition suppression effects that are sensitive to the length of the interval between repetitions. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

Results from human (Scoville and Milner, 1957) and animal lesion studies (Gaffan, 1974; Zola-Morgan and Squire, 1990) have established the importance of the medial temporal lobes (MTL) in declarative memory. More recently, it has been suggested that subregions of the MTL support specific aspects of declarative memory. For example, Eichenbaum et al. (1994) argued that the hippocampus (dentate gyrus, CA1–3 fields, and subiculum) supports memory for relationships between individual items, whereas the parahippocampal region (perirhinal, entorhinal, and parahippocampal cortex) supports memory for individual items. Single-unit recording studies of monkeys support this functional

dissociation, showing that neurons responsive to item-repetition are common in perirhinal, entorhinal, and inferotemporal cortex, but are relatively rare in the hippocampus (see Brown and Xiang, 1998). Unlike neurons that enhance their firing rates to actively maintain an item in working memory (Li et al., 1993), these neurons are insensitive to distraction and exhibit repetition suppression, a phenomenon whereby neurons exhibit reduced responses to repeated stimuli relative to novel stimuli.

In contrast to animal studies, human neuroimaging studies have revealed little evidence for repetition suppression effects in the entorhinal and perirhinal cortices, even when activity is observed in other MTL regions. One notable exception, however, is a review of results from four human functional magnetic resonance imaging (fMRI) studies (Henson et al., 2003). Across these studies, a common region in the anterior collateral sulcus (likely corresponding to perirhinal cortex) showed reduced activation for repeated items relative to novel items.

The findings of Henson et al. (2003) suggest that repetition suppression may be a viable mechanism for recognition memory in human perirhinal cortex. However, many other imaging studies of recognition memory from other laboratories have not detected robust repetition effects within the perirhinal or entorhinal cortices. The failure of human neuroimaging studies to find evidence of repetition suppression in this region could be due to the fact that magnetic susceptibility artifacts (Greicius et al., 2003; Ojemann et al., 1997) make it especially difficult to measure the BOLD response in these regions. Alternatively, the magnitude of repetition effects might depend on the “repetition lag,” i.e., the time delay or amount of interference between the first and second presentations of an item. Indeed, most perirhinal and entorhinal neurons that exhibit repetition effects only do so when the repetition lag is on the order of minutes (Xiang and Brown, 1998), and only a small proportion of repetition sensitive cells in these regions are responsive to stimulus repetition at much longer repetition lags (Fahy et al., 1993). Critically, human neuroimaging studies have generally examined recognition memory only after relatively long delays between study and test, leaving open

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the possibility that robust repetition effects might be seen at shorter repetition lags.

In the present study, we used event-related fMRI to examine the sensitivity of MTL regions to repetition, sampling across four short repetition lags. While in the scanner, subjects performed memory judgments on words presented for the first time, or repeated after 2, 8, 16, or 32 intervening words. Based on the single-unit results (Xiang and Brown 1998), we hypothesized that perirhinal and entorhinal activity would be sensitive to repetition lag such that the short lag items would elicit the lowest activation and this activation would gradually increase with longer lags. Moreover, we hypothesized that repeated items would elicit decreased activity relative to new items. In contrast, we did not expect repetition-related activity differences in the hippocampus. Hippocampal neurons are sensitive to repetition during recognition tasks that require configural or relational processing (Wan et al, 1999), but not on tasks requiring simple discriminations between novel and repeated items.

Twenty-one healthy members of the University of California at Davis community participated in this experiment. Participants provided informed consent and were financially compensated for their time. Behavioral and fMRI data were analyzed for the 19 subjects who did not have excessive head movement (14 female, 5 male; aged 18–29; all right-handed native English speakers).

On each trial, a word was presented for 500 ms followed by a 2,000-ms delay. Participants ranked their memory confidence on a scale of 1–6 (1 = very sure old; 6 = very sure new), using a fiberoptic button box (Mag Design and Engineering, <http://www.magconcept.com/index.html>). In the behavioral and imaging analyses we collapsed across these responses, and coded Responses 1–3 as “old” responses and Responses 4–6 as “new” responses. A total of 552 trials were spread across six test blocks, each consisting of randomly interleaved trials of 92 “new” words (40 that never reappeared), and 13 words repeated after each of 2, 8, 16, and 32 intervening words.

Imaging acquisition parameters and preprocessing steps were similar to those described previously (Ranganath et al., 2004), the exceptions being that the echo time (TE) was changed to 45 and one hundred-ninety volumes were acquired for each scan run, each one consisting of twenty-two axial slices. Data were modeled under a general linear model (GLM) in Voxbo (<http://www.voxbo.org>). New words, independent of memory performance, served as the statistical baseline. This allowed for each subject to have an equal frequency and temporal distribution of baseline trials, while still allowing us to test for repetition suppression effects and lag effects in an unbiased manner. Separate covariates were created for each type of correctly identified old word (lag-2, lag-8, lag-16, lag-32), for trials during which no response was made, and for inaccurately identified old words (for which there were very few to analyze). Thus, the lag-2 covariate reflects the magnitude of the repetition effect (repeated vs. novel word) when two words intervened during the repetition interval. BOLD responses to each trial type were modeled by convolving each trial onset with a subject specific hemodynamic response function (Aguirre et al.,

1998; Handwerker et al., 2004). Parameter estimates, reflecting the magnitude of old–new repetition effects for correctly identified old items at each lag, were extracted and entered into a second-level random effects analysis to identify brain regions sensitive to the lag manipulation. Specifically, we performed a voxel-wise one-way analysis of variance (ANOVA), treating subject as a random factor and lag as a fixed effect. The ANOVA results were used to identify areas sensitive to the lag manipulation, irrespective of the direction of the effect. Critically, this analysis was not biased to reject models that falsify our predictions about repetition suppression (e.g., repetition enhancement in perirhinal cortex). The resulting F-map was thresholded at $P < 0.01$, with a spatial extent threshold of at least five contiguous voxels. Our a priori predictions led us to restrict this analysis to the parahippocampal gyrus (i.e., entorhinal cortex, perirhinal cortex, and parahippocampal cortex), and the hippocampus (i.e., the dentate gyrus, CA1–3 fields, and the subiculum). Accordingly, suprathreshold voxels in these regions were further characterized in region-of-interest (ROI) analyses. An exploratory analysis of areas lateral to the MTL was also conducted, but revealed no significant clusters of activity, and will not be discussed further.

Accuracy, as assessed by d' , varied across lags ($F_{(3,54)} = 18.2$, $P < 0.001$) (Table 1), and a linear trend analysis revealed that recognition performance declined with increasing study-test lags ($F_{(1,18)} = 53.5$, $P < 0.001$).

To test for lag sensitivity within the MTL, we conducted a map-wise random-effects ANOVA, testing for differences in activity across different repetition lags. Consistent with our hypothesis, activity varied across lags in a region in the left anterior parahippocampal gyrus ($F_{(3,54)} = 7.24$, $P < 0.001$). As shown in Figure 1, activity in this region increased with longer study-test lags. Because the cluster of significantly active voxels appeared to include both the perirhinal and entorhinal cortex, and we were unable to confidently separate activity to perirhinal or entorhinal cortex using the procedures outlined in (Pruessner et al., 2002), we refer to this area as anterior-parahippocampal gyrus (APHG).

To determine whether APHG activity was reduced for repeated items compared with the new items, we contrasted activity for the lag conditions, aggregated into short-lag (lag-2 and lag-8) or long-lag (lag-16 and lag-32) trials, and compared each to the new item baseline. For the APHG ROI, activity in the short-lag conditions was significantly lower than the new

TABLE 1.

Mean Accuracy (d') for Each Lag

	Repetition lag ^a			
	Lag-2	Lag-8	Lag-16	Lag-32
Accuracy	2.68 (0.62)	2.45 (0.71)	2.28 (0.64)	2.16 (0.54)

^aSD in parentheses.

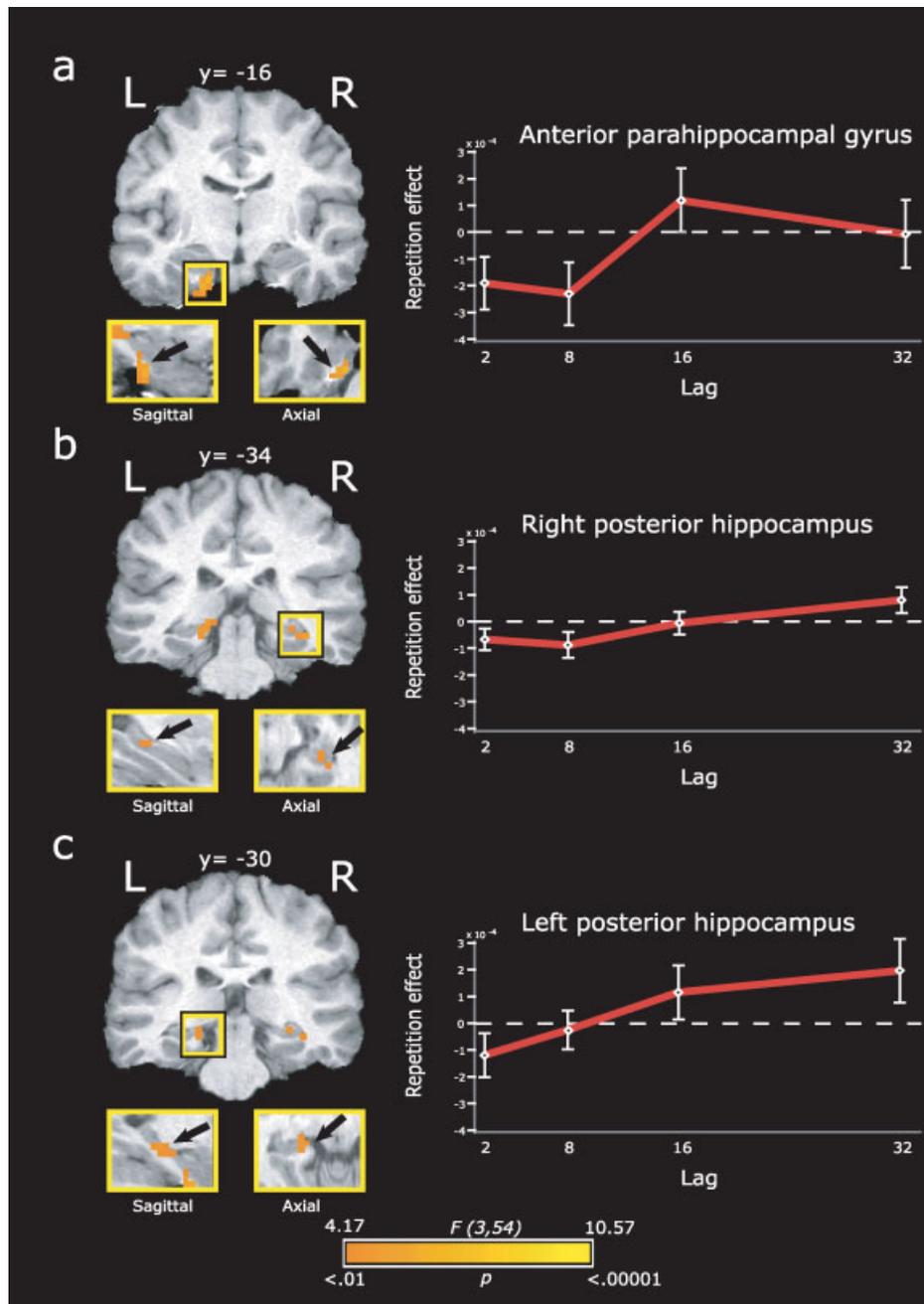


FIGURE 1. Lag-sensitive repetition effects in the medial temporal lobes. Relative locations are shown for three medial temporal lobe regions of interest (ROIs). a: Left anterior parahippocampal gyrus (maxima = $[-19 -15 -34]$). b: Right posterior hippocampus (maxima = $[30 -30 -11]$). c: Left posterior hippocampus (maxima = $[-19 -34 -8]$). Each of these regions exhibited repetition suppression effects that were sensitive to the number of items intervening

between 1st and 2nd presentation of a word (2, 8, 16, or 32). For each ROI, a graph at right shows mean parameter estimates indicating the magnitude of the repetition effect at each lag (negative numbers refer to decreased activation for repeated items). Error bars show the standard error of the mean across subject. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

item activity ($t(37) = 2.82, P < 0.01$), whereas activity in the late-lag conditions was not different from new items ($t(37) = -0.64, P = 0.26$), indicating the repetition suppression in the APHG was not robust at long lags. Note that an alternative analytic approach is to test directly for repetition suppression effects at short and long lags at the voxel-wise level. This approach revealed similar results to the results from our

ANOVA analysis; specifically, repetition suppression effects were observed at short lags ($t(37) = 3.00, P < 0.01$), but not long lags, in a left anterior parahippocampal region that overlapped the one identified in the ANOVA analysis (local maxima: $x = -22, y = -15, z = -30$ mm). Using this latter approach, no additional medial temporal lobe regions showed repetition suppression for short-lag items.

In addition to the APHG, we also observed lag-sensitive repetition effects in regions of the left ($F_{(3,54)} = 5.11, P < 0.01$) and right ($F_{(3,54)} = 5.39, P < 0.01$) posterior hippocampus. As shown in Figure 1, these regions exhibited increasing activity with increased repetition lag, a finding that parallels what was observed in the APHG. However, unlike the APHG, activity in these hippocampal regions appeared to increase relative to new items at the longest lags. Analyses on the left hippocampal ROI revealed no significant changes from the new-item baseline in the short-lag conditions ($t(37) = 1.39, P = 0.17$), whereas activity in the late-lag conditions was marginally above baseline ($t(37) = 1.98, P = 0.053$). For the right hippocampal ROI, activity in the short-lag conditions was significantly below the new-item baseline ($t(37) = 2.58, P < 0.05$), but activity in the long-lag conditions was not significantly above baseline ($t(37) = 1.14, P = 0.26$).

Our finding of lag-sensitive repetition suppression in the APHG parallels the response suppression effects that have been reported in both monkey perirhinal and entorhinal cortex. Single-unit recordings suggest these repetition suppression effects occur as a relatively automatic consequence of prior exposure (Li et al., 1993), and are robust to distracting stimuli (Fahy et al., 1993). Accordingly, Brown and Xiang (1998) have suggested that lag-sensitive neurons that exhibit repetition suppression may provide a neural signal useful for judging the prior occurrence, or familiarity, of an individual item). How lag effects relate to recognition is unclear from the current study; although subjects' recognition accuracy decreased with lag, we did not have a sufficient number of relevant trials to determine whether activity differences reflected retrieval success (hits vs. misses) or accuracy (hits vs. false alarms). This leaves open the possibility that activity differences reflect a short-term form of priming. For example, in a recent study examining lag effects on an implicit priming task, Henson et al. (2004) found repetition suppression for short, but not long, lags in occipitotemporal areas and parahippocampal areas lateral and posterior to the ROIs currently examined. Note that recognition and priming explanations are not mutually exclusive. Although recognition and priming are traditionally viewed as depending on distinct neural substrates (Keane et al., 1995), some have postulated that familiarity-based recognition judgments depend on resources common to those used on some implicit memory tasks (Yonelinas, 2001). Thus, it is possible that repetition suppression is a general mechanism that contributes to performance on implicit priming tasks as well as recognition tasks that demand conscious awareness of stimulus repetition (Ranganath and Rainer, 2003).

Although the BOLD repetition suppression effects observed in the APHG are similar to the neural repetition suppression effects observed in monkey single-unit recording studies, these parallels should be interpreted with some caution. As mentioned earlier, our old–new differences became negligible with relatively short lags and numbers of intervening items (16) between the first and second presentation. Most repetition sensitive cells in APHG exhibit memory spans that are somewhat longer (i.e., on the order of minutes), and a smaller proportion of neurons exhibit repetition suppression effects even across 72 hour retention intervals (Brown and Xiang, 1998). Such differences could

reflect intrinsic sensitivity differences between BOLD fMRI and single-unit recording, or they could reflect differences in MTL function between humans and monkeys. Clearly, further work must be done to address this question.

In addition to the APHG, we observed lag-sensitive repetition effects in the hippocampus. Although these results were not predicted on the basis of the single-unit studies, numerous human neuroimaging studies investigating recognition memory have reported decreased activity for repeated compared to new items in the human hippocampus (Ranganath and D'Esposito, 2001; Stern et al., 2001; Yonelinas et al., 2001). Additionally, Klimesch et al. (in press), recently reported results from an event-related potential (ERP) study that are consistent with our findings. Approximately 400–600 ms after the onset of a repeated stimulus, these investigators identified a lag-sensitive deflection in the ERP waveform. Subsequent analyses using the Low Resolution Tomography (LORETA) source localization technique placed the focus of activation in the posterior MTL.

The pattern of lag-dependent activity changes in the hippocampus is open to a number of potential interpretations. One possibility is that, rather than solely reflecting memory retrieval signals, these activity changes might have reflected differential engagement of encoding processes. Indeed, although our task clearly tapped retrieval-related activity, it is highly likely that we observed concurrent activity related to encoding of new and repeated items as well (Stark and Okado, 2003). Accordingly, in the present study, the hippocampus might have exhibited activity related to re-encoding items at long, but not short, lags (c.f. Greene, 1989). An encoding explanation is consistent with results indicating that increased hippocampal activity at encoding predicts subsequent recollection (Davachi et al., 2003; Ranganath et al., 2004).

In summary, the current results indicate that lag-sensitive repetition suppression can be observed in the human APHG during recognition memory. Although fMRI studies using longer repetition lags (Henson et al., 2003) have observed repetition suppression in the APHG, our results demonstrate that repetition suppression effects are maximal at short study-test lags. This pattern of results is largely consistent with repetition suppression effects reported in electrophysiological studies of monkeys, and suggests a mechanism that potentially supports the role of the APHG in recognition memory.

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REFERENCES

- Aguirre GK, Zarahn E, D'Esposito M. 1998. The variability of human, BOLD hemodynamic responses. *NeuroImage* 8:360–369.
- Brown MW, Xiang JZ. 1998. Recognition memory: neuronal substrates of the judgement of prior occurrence. *Prog Neurobiol* 55:149–189.

- Davachi L, Mitchell JP, Wagner AD. 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc Natl Acad Sci USA* 100:2157–2162.
- Eichenbaum H, Otto T, Cohen NJ. 1994. Functional components of the hippocampal memory system. *Behav Brain Sci* 17:449–472.
- Fahy FL, Riches IP, Brown MW. 1993. Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Exp Brain Res* 96:457–472.
- Gaffan D. 1974. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *J Comp Physiol Psychol* 86:1100–1109.
- Greene RL. 1989. Spacing effects in memory—evidence for a 2-process account. *J Exp Psychol Learn Mem Cogn* 15:371–377.
- Greicius MD, Krasnow B, Boyett-Anderson JM, Eliez S, Schlaggar AF, Reiss AL, Menon V. 2003. Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. *Hippocampus* 13:164–174.
- Handwerker DA, Ollinger JM, D'Esposito M. 2004. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *NeuroImage* 21:1639–1651.
- Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD. 2003. A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 13:301–304.
- Henson RN, Rylands A, Ross E, Vuilleumier P, Rugg MD. 2004. The effect of repetition lag on electrophysiological and haemodynamic correlates of visual object priming. *NeuroImage* 21:1674–1689.
- Keane MM, Gabrieli JD, Mapstone HC, Johnson KA, Corkin S. 1995. Double dissociation of memory capacities after bilateral occipital-lobe or medial temporal-lobe lesions. *Brain* 118(Pt 5):1129–1148.
- Klimesch W, Hanslmayr S, Sauseng P, Gruber W, Brozinsky CJ, Kroll NEA, Yonelinas A, Doppelmayr M. Oscillatory EEG correlates of episodic trace strength. *Cerebral Cortex* (in press).
- Li L, Miller EK, Desimone R. 1993. The representation of stimulus familiarity in anterior inferior temporal cortex. *J Neurophysiol* 69:1918–1929.
- Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE. 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *NeuroImage* 6:156–167.
- Pruessner JC, Kohler S, Crane J, Pruessner M, Lord C, Byrne A, Kabani N, Collins DL, Evans AC. 2002. Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. *Cereb Cortex* 12:1342–1353.
- Ranganath C, D'Esposito M. 2001. Medial temporal lobe activity associated with active maintenance of novel information. *Neuron* 31:865–873.
- Ranganath C, Rainer G. 2003. Neural mechanisms for detecting and remembering novel events. *Nat Rev Neurosci* 4:193–202.
- Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M. 2004. Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia* 42:2–13.
- Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurochem* 20:11–21.
- Stark CE, Okado Y. 2003. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *J Neurosci* 23:6748–6753.
- Stern CE, Sherman SJ, Kirchoff BA, Hasselmo ME. 2001. Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. *Hippocampus* 11:337–346.
- Wan H, Aggleton JP, Brown MW. 1999. Different contributions of the hippocampus and perirhinal cortex to recognition memory. *J Neurosci* 19:1142–1148.
- Yonelinas AP, Hopfinger JB, Buonocore MH, Kroll NE, Baynes K. 2001. Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study. *NeuroReport* 12:359–363.
- Xiang JZ, Brown MW. 1998. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology* 37:657–676.
- Zola-Morgan SM, Squire LR. 1990. The primate hippocampal formation: evidence for a time-limited role in memory storage. *Science* 250:288–290.