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RAPID COMMUNICATION

Establishing a Relationship Between Activity Reduction in Human Perirhinal Cortex and Priming

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ABSTRACT: Perirhinal neurons exhibit reduced firing rates with stimulus repetition, a phenomenon termed "repetition suppression." However, relationships between perirhinal repetition suppression and behavioral expressions of memory remain unclear. We used anatomically constrained functional magnetic resonance imaging (fMRI) to assess relationships between perirhinal activity and priming, a type of implicit memory. Priming was expressed as speeded animacy judgments for old versus new words. Concurrently, old words elicited less neural activity in bilateral perirhinal cortex. The magnitude of the left perirhinal activity reduction selectively predicted the magnitude of behavioral priming in an across-subjects hierarchical linear regression analysis. These findings have implications for considering how perirhinal cortex may contribute to different neurocognitive functions, possibly including both implicit memory and familiarity-based recognition. This study documents the first evidence linking behavioral measures of priming to information processing in perirhinal cortex. © 2009 Wiley-Liss, Inc.

KEY WORDS: priming; perirhinal cortex; implicit memory; familiarity; fMRI

A fundamental challenge for contemporary memory research is to elucidate the functions of subdivisions among structures of the medial temporal lobe or MTL–the hippocampus proper, dentate gyrus, subicular complex, perirhinal, entorhinal, and parahippocampal cortex, and amygdala. The essential role for these structures in declarative memory for facts and events has been acknowledged since seminal descriptions of the amnesic syndrome that results from their damage (Scoville and Milner, 1957; Squire, 2004). The most influential position holds that MTL structures make vital contributions to declarative memory, but that current data are insufficient for demonstrating functional subdivisions within MTL cortical regions that map onto distinct subtypes of declarative memory, such as stimulus-specific familiarity and associative recollection (Squire and Bayley, 2007; Squire et al., 1980, 2004, 2007).

Conceivably, MTL cortical structures act together, along with the hippocampus, to support declarative memory storage. However, experiments in nonhuman animals have shown that neurons in different MTL structures signal repetition in fundamentally different ways. Most perirhinal cortex neurons exhibit lower firing rates for repeated versus novel stimuli, a phenomenon termed "repetition suppression," whereas few hippocampal neurons exhibit these effects (e.g., Brown and Xiang, 1998; Zhu et al., 1995). A prominent position is that perirhinal cortex is central in producing item-specific familiarity, whereas the hippocampus is essential for associative memory processing (Eichenbaum, 2000; Brown and Aggleton, 2001; Eichenbaum et al., 1994, 2007).

Experiments in humans have not provided overwhelming support for this distinction (Squire et al., 2004, 2007). Moreover, despite the large number of functional magnetic resonance imaging (fMRI) studies of memory, reduced perirhinal activity, which might be expected on the basis of findings of repetition suppression, seems remarkably infrequent. It is important to note that current fMRI methods cannot be used to study neuronal repetition suppression, defined as reduced firing rates in individual neurons due to repetition. This is because fMRI is sensitive to metabolic activity and blood flow correlated with input and processing within a population of neurons more so than with firing rates of neurons in that region (Logothetis, 2002). We will therefore use the term "activity reduction" to refer to observed reductions in fMRI activity for old versus new stimuli, leaving open the question of how this activity might relate to repetition suppression in individual neurons.

A meta-analysis of recognition studies reported by Henson et al. (2003) identified reduced activity for repeat versus novel items in a region of anterior temporal cortex that might correspond to perirhinal cortex. Furthermore, O'Kane et al. (2005) found perirhinal activity reduction in priming tests. Priming tests may be sensitive to implicit memory for perceptual information of the sort specifically represented in perirhinal cortex, that is, information concerning visual objects (Burwell, 2000; Lavenex and Amaral, 2000). Priming effects are widely thought to rely on repetition-induced fluency of neural processing within structures in the ventral visual processing stream (Wiggs and Martin, 1998), coupled with fluency of strategic processing in frontal cortex (Schacter et al., 2007). The manner in which perirhinal activity reduction

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relates to behavioral indicators of memory is currently unclear, which complicates interpretations with respect to any of the various theoretical schemes for MTL function (e.g., Eichenbaum et al., 2007; Murray et al., 2007; Squire et al., 2007).

We tested for relationships between perirhinal cortex processing and priming via an anatomically constrained analysis of fMRI data that were previously collected and published by Maccotta and Buckner (2004), and that we retrieved from the fMRI Data Center (http://www.fmridc.org). This analysis strategy was chosen because we reasoned that many neuroimaging studies might have failed to identify effects in perirhinal cortex because they did not specifically scrutinize this region. Typical analysis procedures identify brain activity that reliably dissociates conditions in a group of subjects after fMRI data from each subject are warped into a standardized stereotactic space. These procedures are problematic for two reasons. Because fMRI signal in anterior MTL regions is usually subject to distortion and degradation due to adjacent magnetic inhomogeneities (Ojemann et al., 1997; Greicius et al., 2003), data from individuals with poor fMRI signal in anterior MTL can obscure group effects there. Furthermore, the spatial layout of MTL structures varies greatly across individuals, leading to improper alignment of MTL structures in standardized stereotactic space, and limiting the ability to observe reliable effects in these regions. Various approaches can help to overcome these limitations by using anatomical information about each subject's MTL to guide fMRI analysis (e.g., Fernandez et al., 1998; Small et al., 1999; Zeineh et al., 2000; Reber et al., 2002; Stark and Okado, 2003; Kirwan et al., 2007). Here, we made use of the anatomical boundaries of distinct MTL regions in each of 54 young healthy subjects.

Prior to fMRI data acquisition, subjects viewed 30 abstract and concrete words, each repeated five times, and discriminated living versus nonliving items via a two-choice button response. Next, fMRI scanning occurred during a priming test that included 25 of the previously viewed words (old words) and new words. Each old word was presented four times and intermixed with 100 new words, in pseudo-randomized order, for a total of 200 word presentations (in two separate runs). Words appeared for 1,600 ms followed by a fixation cross for 288 ms. Word presentations were interspersed with 100 blank trials, which included only the fixation symbol for 1,888 ms. Subjects made living/nonliving decisions to each word. Robust priming was reported, in that animacy decisions to old words were made significantly faster than decisions to new words. Across-subject correlations were then computed using behavioral and fMRI measures. The magnitude of priming was found to correlate with the magnitude of fMRI activity reduction (i.e., less activity for old vs. new words) in left prefrontal cortex. Activity reduction in anterior ventral visual cortex and inferior temporal cortex was also reported, but the magnitude of these effects was not correlated with priming behavior (Maccotta and Buckner, 2004).

To examine fMRI activity, we defined anatomical regions of interest (ROIs) for each subject using the method of Reber et al. (2002). Our a priori hypotheses concerned perirhinal cortex, but to provide a complete analysis of MTL activity, we used 10 ROIs: entorhinal cortex, perirhinal cortex, anterior hippocampus, posterior hippocampus, and parahippocampal cortex, each defined bilaterally based on anatomical landmarks (Amaral and Insausti, 1990; Insausti et al., 1998). The coronal plane of the uncal apex defined the border between anterior structures (entorhinal cortex, perirhinal cortex, and anterior hippocampus) and posterior structures (posterior hippocampus and parahippocampal cortex). Imaging resolution was lower for functional images than structural images, and ROIs were therefore defined on structural images using the functional image resolution, after image coregistration. Each functional voxel belonged to only one ROI, and voxels with weak signal (<20% of mean whole-brain signal intensity) or erratic signal (>30% signal change over one volume) were excluded. After motion correction and conversion of raw fMRI timeseries to percent signal-change values, values were averaged for each ROI to provide spatial smoothing that respected anatomical boundaries. Stimulus-locked estimates of neural activity for old and new items were achieved using deconvolution with a general linear model, and were quantified as the peak (beta value) of a canonical hemodynamic response function. Blank trials were not modeled as a stimulus category in the current analysis. The deconvolution approach thus quantified activity for each condition as the baseline-to-peak difference of the estimated neural response (not as the difference between experimental and baseline conditions). AFNI software was used for fMRI analysis (Cox, 1996). Note that this analysis did not involve transformation to standardized stereotactic space because all structures were defined and measured separately for each individual subject.

Data from 22 subjects were unsuitable for fMRI analysis due to marked signal dropout in entorhinal and perirhinal cortex (25% or greater voxel loss due to weak or erratic signal for entorhinal or perirhinal cortex was used as the exclusionary criterion). Data from 32 subjects remained for analysis (an average of 2.4% of total voxels, range 0–11%, were excluded from all ROIs for included subjects). Response times provided evidence for reliable priming in these subjects. Responses were 121 ms faster, on average, for old versus new words [old mean = 790 ms, $t(31) = 15.6$, $P < 0.001$].

Results for each ROI are summarized in Table 1, including the average volume of included voxels and estimates of neural activity for old and new words. Primary analyses focused on neural activity in left and right perirhinal cortex, with left and right entorhinal cortex included due to physical proximity to perirhinal cortex that could produce correlated activity. Estimated activity differences between old and new items were subject to repeated-measures analysis of variance (ANOVA) including ROI as a factor. Old vs. new activity differences varied by ROI [$F(3,93) = 3.1$, $P = 0.03$], and post hoc comparisons indicated that differences were reliable for left and right perirhinal cortex [$t(31) = 3.6$, $P = 0.001$ and $t(31) = 2.1$, $P = 0.04$, respectively], but not left or right entorhinal cortex [$t(31) = 0.04$, $P = 0.96$ and $t(31) = 1.2$, $P = 0.22$, respectively]. Activity differences were negative for left and right perirhinal cortex, indicating that activity for old words was significantly less than for new words.

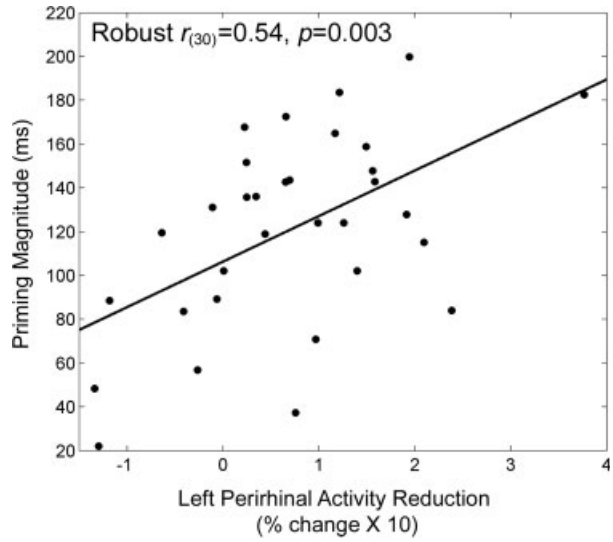

FIGURE 1. Activity reduction in left perirhinal cortex predicts behavioral priming. The correlation between the magnitude of behavioral priming (response-time difference for new minus old words) and activity reduction (fMRI activity difference for new minus old words) was obtained via robust regression.

To assess relationships between MTL activity and priming, we performed a series of across-subjects hierarchical linear regressions of behavioral priming (old minus new response time difference) on activity reduction values (old minus new fMRI activity differences). All values were standardized prior to analysis. The primary analysis included perirhinal and entorhinal cortex, for the reasons noted above (four ROIs, each entered as a single variable in a separate step). The magnitude of activity reduction in left perirhinal cortex predicted the magnitude of behavioral priming ($\beta = -0.59$, $t = -3.3$, $P = 0.003$), whereas activity estimates from the other three ROIs were not significant predictors of response time differences (P-values > 0.52). The scatterplot for left perirhinal activity and behavioral priming is shown in Figure 1. The correlation value is derived from a robust regression analysis (Huber, 1981) to account for the potential influence of outlier values.

An additional across-subjects hierarchical regression was used to assess relationships for other ROIs. Response-time priming was regressed on fMRI differences between old and new stimuli using a model incorporating the 10 ROIs (each entered as a single variable in a separate step). No relationships were identified for any ROI except left perirhinal cortex ($\beta = -0.72$, $t = -2.8$, $P = 0.01$; all other P-values > 0.25).

There were thus three chief results. First, behavioral priming was indicated by faster responses to old versus new words. Second, fMRI activity reduction was evident as less activity for old versus new words in left and right perirhinal cortex. Third, the magnitude of activity reduction in left (but not right) perirhinal cortex predicted the magnitude of behavioral priming.

Preferential left-hemisphere contributions may be due to the use of verbal material. Indeed, O'Kane et al. (2005) found

TABLE 1.

Summary of fMRI data for medial temporal regions of interest

	Perirhinal cortex		Entorhinal cortex		Anterior hippocampus		Posterior hippocampus		Parahippocampal cortex	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Volume (mm^3)	654 (51)	633 (44)	671 (46)	626 (44)	2,095 (120)	1986 (134)	2025 (73)	2071 (69)	1357 (62)	1230 (56)
Old activity (% change × 10)	17.6 (0.6)	8.9 (1.8)	11.0 (1.7)	10.9 (1.8)	17.0 (1.1)	14.0 (1.0)	17.6 (0.6)	11.8 (1.9)	16.6 (0.8)	16.9 (0.5)
New activity (% change × 10)	18.3 (0.5)	9.7 (1.9)	11.0 (1.6)	11.8 (1.9)	16.6 (0.8)	14.2 (1.0)	17.6 (0.5)	11.7 (1.8)	16.9 (0.6)	16.9 (0.5)
Old minus new activity difference	−0.71[a](0.19)	−0.75[b] (0.35)	−0.02 (0.56)	−0.85 (0.69)	0.31 (0.58)	−0.14 (0.28)	0.01 (0.34)	0.12 (0.53)	−0.28 (0.27)	−0.04 (0.27)

ROI volume was computed for each subject in native anatomical space based on the voxels used for data analysis, and thus excluded voxels with noisy fMRI data. Voxel size was 3.75 × 3.75 × 8.0 mm^3. For old versus new pairwise differences, $P > 0.2$ unless otherwise indicated. SE is indicated in parentheses.

[a]Old versus new pairwise difference $P = 0.001$.

[b]Old versus new pairwise difference $P = 0.04$

activity reduction in left perirhinal cortex when the same categorization decision was repeated from study to test, but not when different decisions were required, indicating a greater sensitivity to semantic rather than perceptual information processing (see also Taylor et al., 2006). It is possible that right perirhinal activity reduction in the current data reflected fluent perceptual information processing that contributed less to the categorization task used to measure priming than did fluent processing indexed by left perirhinal activity reduction. Further investigation is needed to elucidate these apparent hemispheric differences in perirhinal contributions to memory.

These results are consistent with the notion that different MTL regions make different contributions to novelty/familiarity detection (Brown and Xiang, 1998), but are not problematic for the hypothesis that MTL structures operate as a functional unit to accomplish declarative memory. That is, distinct MTL regions that perform distinct operations, as appears here to be the case for perirhinal cortex vs. other MTL structures, could nonetheless operate in a concerted fashion to accomplish declarative memory (Squire et al., 2004, 2007).

As indicated earlier, a recent framework suggests that priming effects in the visual modality are supported by two neural mechanisms: facilitated perceptual processing in ventral visual cortex, and facilitated strategic processing in left prefrontal cortex (Schacter et al., 2007). Only the strategic effects are thought to relate directly to behavior, possibly via interactions with the information that is conveyed by facilitated neural processing by visual cortex. Indeed, this pattern was uncovered in the original report of the current data, in that the magnitude of left prefrontal response reductions was correlated with priming, whereas response reductions in visual cortex were not (Maccotta and Buckner, 2004). Our results extend this model of priming by showing that processing in perirhinal cortex is strongly associated with priming. Given that perirhinal cortex receives the majority of its input from object-sensitive cortex in the ventral visual stream, it is possible that perirhinal cortex is instrumental in relating signals of facilitated processing from earlier visual cortex to task demands determined by frontal cortex. Indeed, Halgren et al. (2006) characterized word processing in perirhinal cortex as comprising rapid, feedforward input from earlier visual cortex, followed by feedback input from higher cortical regions. The current results are consistent with this characterization, and suggest that perirhinal cortex is involved in the interface between bottom-up signals from earlier visual cortex and the context in which these signals are interpreted; in this case, these signals influenced decisions in a priming test. It will be intriguing to determine whether similar mechanisms contribute to the subjective experience of fluent processing that can influence many complex decision-making processes (e.g., Oppenheimer, 2008).

Are these fluency operations—repetition-induced processing facilitation—relevant only for implicit memory? Fluency operations performed in perirhinal cortex might also play a role in explicit memory. Indeed, a prominent view is that perirhinal cortex supports familiarity-based recognition, which is an expression of explicit memory (Eichenbaum et al., 2007). Intriguingly, MTL activity reductions in perirhinal cortex similar to the current effects have been identified during recognition tests (e.g., Brozinsky et al., 2005; Danckert et al., 2007), and specifically linked to familiarity-based recognition (Gonsalves et al., 2005). Moreover, encoding activity in perirhinal cortex has been shown to predict later familiarity-based recognition (e.g., Davachi et al. 2003). Priming and familiarity may both rely on repetition-induced processing fluency (Verfaellie and Cermak, 1999; Whittlesea and Williams, 2000; Yonelinas, 2002), despite the fact that they can be dissociated behaviorally (Wagner et al., 1997) and neuroanatomically (Stark and Squire, 2000). If this were the case, then associations between the magnitude of perirhinal response reduction and the magnitude of both priming (as in the current results) and familiarity-based recognition (as in Gonsalves et al., 2005; Henson et al., 2005) could arise because fluent visual cortex processing can promote both memory phenomena.

It is possible that perirhinal cortex is instrumental in producing signals of facilitated visual processing that are used in different ways depending on current behavioral goals. In one context, overt retrieval processing may predominate, whereas in the context of a priming test, some other process is stressed. Nevertheless, perirhinal response reductions might play a parallel role for recognition and for priming.

Conversely, perirhinal activity reductions identified during recognition tests could reflect processing that does not promote recognition but that does promote priming that occurs incidentally during recognition tests, given that neural correlates of priming and familiarity can co-occur during explicit memory testing (Paller et al., 2007). In some cases, processing that tends to produce good recognition might be confounded with processing that tends to drive priming. Furthermore, as argued by Voss and Paller (2008), because of the co-occurrence of processing pertaining to both implicit and explicit memory, behavioral measures of both types of memory are needed to convincingly associate these sorts of neural measures with a specific memory function. The perirhinal activity described in this article could conceivably be attributed to recognition processing given the following two assumptions: (1) differential perirhinal activity for old and new items contributed to covert recognition experiences that were not at all required of the subjects, and (2) subjects with greater differential perirhinal activity and thus with greater covert recognition tended to be the same subjects who showed larger priming effects. However, the second assumption goes against common dissociations between recognition and priming. A more likely explanation for the demonstrated relationship between priming magnitude and left perirhinal activity is that this activity systematically influenced the extent to which a given subject exhibited priming. Our results thus establish evidence for the role of perirhinal cortex in priming. Additional approaches will be necessary to determine if perirhinal cortex contributions to familiarity and priming differ. Further data are also needed to determine the nature of hemispheric differences in perirhinal contributions to memory.

In conclusion, detailed anatomical information is clearly helpful when scrutinizing contributions from anterior medial temporal structures to memory using fMRI. Our findings constitute the first to establish a relationship between the magnitude of perirhinal activity reductions and the magnitude of a behavioral expression of repetition-induced processing fluency. This brain-behavior correlation highlights perirhinal contributions to novelty signals that can yield priming effects in certain types of implicit memory test.

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