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A Familiarity Signal in Human Anterior Medial Temporal Cortex?

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The medial temporal lobe (MTL) comprises the hippocampal complex and amygdala, along with distinct cortical regions, including the parahippocampal, entorhinal, and perirhinal cortices. It has been suggested that different components of the MTL support dissociable memory functions (see, e.g., Eichenbaum et al., 1994). Of particular relevance to the present report is evidence from lesion studies in nonhuman primates suggesting that the perirhinal region plays a key role in visual recognition memory (Meunier et al., 1993; Bachevalier et al., 2002). Consistent with this suggestion, electrophysiological studies have identified neurons in perirhinal and nearby cortical areas of the monkey in which object-selective responses decrease after previous exposure to the object (Brown and Xiang, 1998). These repetition-related decreases can be found over intervals of ≤24 h, as might be expected of a neural signal contributing to a form of long-term memory. Together, lesion and single neuron evidence has led to the proposal (Brown and Aggleton, 2001) that perirhinal cortex contributes to recognition memory through the assessment of relative familiarity, and that neuronal response decrements provide one basis for such assessments. In the present study, we report that experimentally familiar items elicit smaller hemodynamic responses in human anterior MTL, consistent with the findings from nonhuman primates.

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Evidence for a role of perirhinal cortex in recognition memory comes almost exclusively from work with experimental animals. There are few data to suggest that the region has an equivalent role in humans (but see Buffalo et al., 1998). We report findings from four memory studies recently conducted in our laboratory using event-related functional magnetic resonance imaging (fMRI). In each case, we found evidence of a reduction in the anterior MTL response to experimentally familiar ("Old") items relative to experimentally novel ("New") items—a "New-Old" effect. These studies were conducted independent of one another and are described in detail in separate publications. With the exception of one study (Rugg et al., 2003), however, the data reported in the present study have not been described elsewhere.

The four experiments, A–D, shared many methodological features, including scanner hardware, data acquisition parameters, and data analysis methods. They differed along a number of psychological dimensions (see Detailed Methods). In three of the studies, participants explicitly discriminated Old from New items; in the remaining study, the repetition of items was task-irrelevant (experiment D). Two studies used words (experiments A and B), one used pictures (experiment C), and one used faces (experiment D). In two of the studies (experiments B and C), the task required retrieval of contextual information associated with the prior presentation of Old items.

The pattern of responses to Old and New items was the same in all cases: Old items elicited a smaller response in anterior MTL than did New items (Fig. 1). The effect

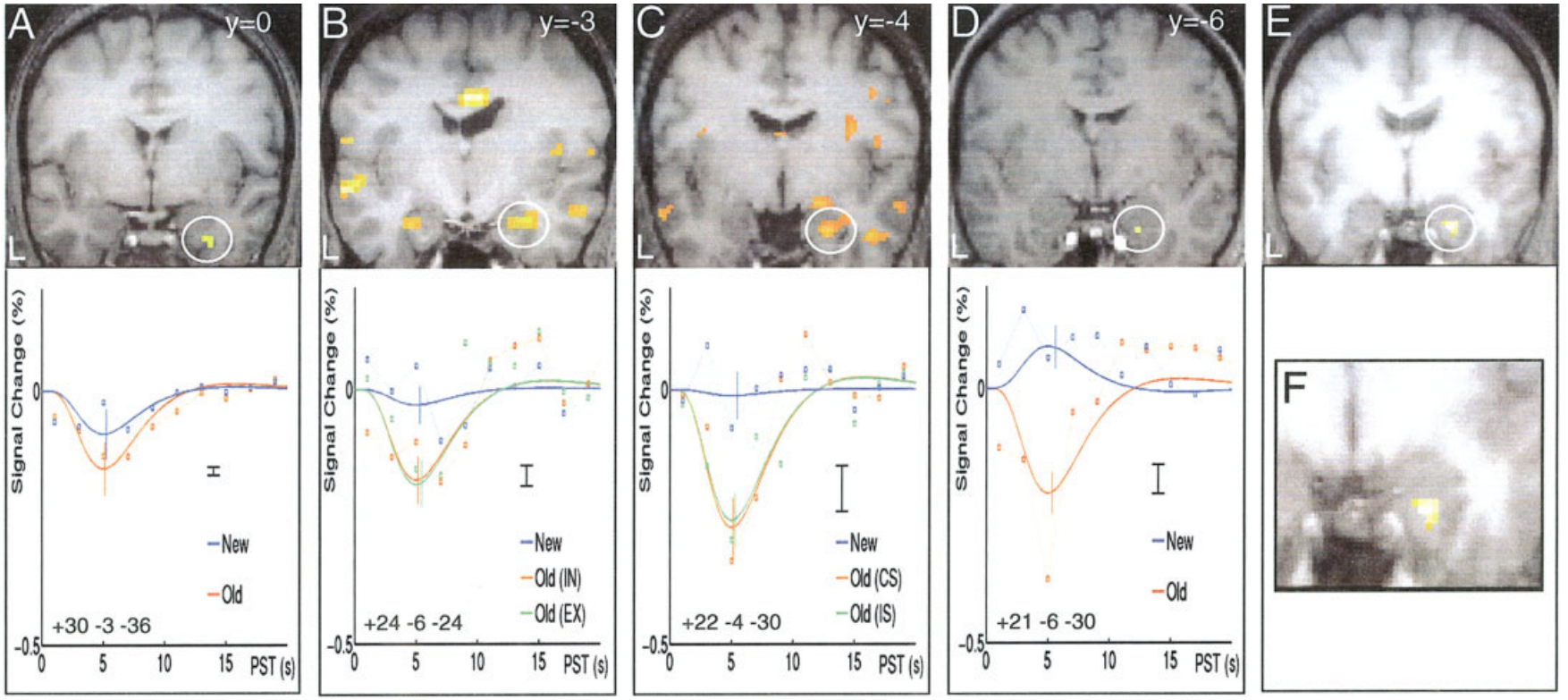

FIGURE 1. New-Old effects in Experiments A–D and common to all four experiments (E,F). Coronal sections in A–D are through normalized T1 images from randomly selected participants, with voxels showing a New-Old effect at $P < 0.001$ in orange (L, left). The section in E is the average of those in A–D; that in F is a magnified portion of the "canonical" MNI brain. Event-related responses in A–D are from the maxima within the circled regions, with stereotactic coordinates from the MNI template. Plots show percent signal change against post-stimulus time (PST) in seconds. Data are averaged every 2 s, using a finite impulse response model; smooth lines are the best-fitting canonical response. Vertical bars at the peak of the fitted responses show the standard error of the response versus baseline; the black bar inset shows the standard error of the New-Old difference. A: Herron et al. (in preparation). B: Rugg et al. (2003). C: Cansino et al. (2002). D: Henson et al. (2000). E/F Center of mass of common region has coordinates +22, −6, −28 (Talairach coordinates +22, −7, −23) and survives $P < 0.01$ in each experiment (combined $P < 6 \times 10^{-6}$, Fisher method). IN, inclusion task; EX, exclusion task; CS, correct source; IS, incorrect source.

varied across the experiments in spatial extent and degree of lateralization but involved a common population of voxels in a region of the right MTL likely encompassing perirhinal cortex (Amaral, 1999), and corresponding in a standard atlas (Talairach and Tournoux, 1988) to the anterior part of Brodmann area 35.

A second feature of the results is evident in the time-courses of the event-related responses, which show that Old items elicited a reduced response relative to the interstimulus baseline (Fig. 1). In the monkey, repetition-related neuronal decrements are observed as a diminution of the excitatory response elicited by an object's first presentation. Thus, whereas the difference in the magnitude of New and Old responses is in the same direction, the repetition-related decrement relative to baseline differs between the present hemodynamic measure and the firing rate measure employed in nonhuman primates. This could reflect a difference in the physiological basis of the two measures, differences in the definition of "baseline," or a species difference. Alternatively, the apparent disparity between human and nonhuman studies may reflect a selection bias in single neuron studies in favor of cells with excitatory object-selective responses. This possibility was proposed by Fried et al. (2002), who in a single-cell recording study in the human MTL, found that most repetition-sensitive cells exhibited a reduction in firing below spontaneous activity, analogous with the present data.

A third feature of the results is that, in the two studies in which the comparison was possible, responses to Old items were insensitive to the amount of contextual information retrieved. Old responses did not differ according to whether the task required explicit retrieval of the study context (experiment B), or whether recognition was accompanied by correct or incorrect context judgments (experiment C). In the latter case, the lack of sensitivity to contextual retrieval contrasts with the greater responses for correct contextual retrieval observed in a more posterior, hippocampal region (Cansino et al., 2002). These data support the proposal (Brown and Aggleton, 2001) that the anterior MTL activity described in the present report contributes to an acontextual familiarity signal, rather than providing information about the context of an object's prior occurrence.

Although the present findings are consistent with the proposal that the human perirhinal region contributes to recognition memory, alternative accounts are possible. Notably, the findings could represent a neural correlate of "priming"—the facilitation of stimulus processing engendered by repetition, often in the absence of conscious memory. Priming has been associated with response decrements in numerous prior functional neuroimaging studies (Schacter and Buckner, 1998). Whereas priming at the perceptual level has generally been associated with response decrements in more posterior cortical regions, it could be argued that the present findings demonstrate that the same phenomenon occurs at higher levels of the visual system. Against this view is the finding that priming is intact after bilateral MTL damage encompassing perirhinal cortex (Hamann and Squire, 1997).

Another possibility is that the New-Old effects reported in the present work constitute further evidence of a role for the anterior MTL in memory encoding (Fernandez et al., 1999; Strange et al., 2002). By this argument, the effects reflect the tendency for encoding operations to be engaged to a greater extent by novel than by familiar stimulus events (the "novelty/encoding hypothesis"; Tulving et al., 1996). Arguing against this possibility is the finding (Fig. 1) that in only one of the four experiments (experiment D) did New items elicit a response above baseline. The absence of a consistent anterior MTL activation for New items seems inconsistent with the proposal that these items preferentially engage encoding operations, although we acknowledge that this argument holds only to the extent that inter-stimulus activity constitutes an appropriate baseline against which to assess item-related responses (Stark and Squire, 2001). In any case, the proposal that anterior MTL New-Old effects are a correlate of relative familiarity, and the proposal that they reflect preferential encoding of novel events, are not mutually exclusive. There seems no reason why the same mechanism could not both provide information supporting recognition judgments, and lead to the differential engagement of encoding operations.

The present findings are foreshadowed by those from a previous event-related fMRI study of recognition memory (Henson et al., 1999), in which old judgments were segregated into "Remember" and "Know" responses, corresponding to recognition with and without contextual retrieval respectively. Relative to Old items attracting either class of response, New items elicited greater activity bilaterally in an area tentatively identified as amygdala, but which, in retrospect, may also include anterior MTL cortex. Since these data were obtained using different methods for image acquisition and spatial normalization from those employed in the studies described in the present report, they have not been included in the analyses presented above. In other fMRI studies employing blocked designs, it was reported that trial blocks containing experimentally novel stimuli elicit greater MTL activity than do blocks of familiar stimuli in "encoding" tasks (e.g., Stern et al., 1996; Gabrieli et al., 1997; Rombouts et al., 1999; see also Habib, 2001). In these studies, however, familiar stimuli were presented repeatedly during the course of the experiment, and differential activity was found in MTL regions posterior to those described in the present report. More relevant to the present findings, in an event-related fMRI study of recognition memory for pictures, Rombouts et al. (2001) reported greater activity in bilateral parahippocampal cortex for New than for Old items (but see Stark and Squire, 2000). While located somewhat posterior to the effects illustrated in Fig. 1 (left and right y's of -18 and -13, respectively), it is possible that this New-Old effect is a further example of the same phenomenon.

In summary, the present findings indicate that across a variety of stimulus materials, whether stimulus repetition is task-relevant or incidental, and regardless of level of contextual retrieval, the human anterior MTL is sensitive to whether a visual stimulus is experienced in an experimental context for the first or second time. The response decreases for Old relative to New items bear a striking resemblance to repetition-related decreases in neuronal firing rate in monkey perirhinal cortex. To the extent that differential neural activity in the perirhinal cortex of the monkey supports recognition memory, the present findings imply a similar role for this region in the human brain.

DETAILED METHODS

T2*-weighted transverse echoplanar (EPI) images were acquired on a 2T Siemens Vision system, using blood oxygenation level-dependent (BOLD) contrast. Analysis was performed with Statistical Parametric Mapping (SPM99, http://www.fil.ion.ucl.ac.uk/spm.html), normalizing to an EPI template derived from gray matter priors from the Montreal Neurological Institute (MNI). Event-related responses were modeled by a canonical hemodynamic response function. All events were confined to correct responses. Statistical inferences were made for New versus Old event-types, using a random effects model thresholded at $P < 0.001$:

Experiment A: Herron et al. (in preparation). Twelve participants underwent three study-test cycles, in each case first studying 77 words, and subsequently performing a yes/no recognition test. Different ratios of Old to New items were presented in each test cycle. The present data are averaged across the Old-to-New ratio, which did not interact with the New-Old effect in anterior MTL.

Experiment B: Rugg et al. (2003). Twelve participants underwent four study-test cycles, first studying either 40 or 100 words, and then at test either responding yes to any Old item (Inclusion task) or only to Old items studied in a specific color and spatial position (Exclusion task). The present data are averaged across length of study list, which did not interact with other effects. New items are averaged across Inclusion and Exclusion tasks; Old items are shown separately for each task.

Experiment C: Cansino et al. (2002). Seventeen participants studied 90 color pictures of everyday objects, presented in one of four spatial positions. The test task required participants to classify each test item as New or, if Old, to classify it according to its study location. The present data are shown for New items, Old items with correct study classification (Correct Source) and Old items with incorrect classification (Incorrect Source).

Experiment D: Henson et al. (2000); experiment 1. Six participants observed a sequence of faces, responding only to a pre-specified target. One-half of the faces were famous, one-half unfamiliar; each face was repeated once at a random interval. The present data are collapsed over face familiarity.

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