Conceptual and Perceptual Novelty Effects in Human Medial Temporal Cortex

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ABSTRACT: Medial temporal lobe (MTL) structures often respond to stimulus repetition with a reduction in neural activity. Such novelty/familiarity responses reflect the mnemonic consequences of initial stimulus encounter, although the aspects of initial processing that lead to novelty/familiarity responses remain unspecified. The current functional magnetic resonance imaging (fMRI) experiment examined the sensitivity of MTL to changes in the semantic representations/processes engaged across stimulus repetitions. During initial study blocks, words were visually presented, and participants made size, shape, or composition judgments about the named referents. During repeated study blocks, the initial words were visually re-presented along with novel words, and participants made size judgments for all items. Behaviorally, responses were faster to repeated words in which the same task was performed at initial and repeated exposure (i.e., size→size) relative to repeated words in which the tasks differed (i.e., composition→size and shape→size). fMRI measures revealed activation reductions in left parahippocampal cortex following same-task and different-task repetition; numerically, the effect was larger in the same-task condition. Accordingly, left parahippocampal cortex demonstrates sensitivity to perceptual novelty/familiarity, and it remains unclear whether this region also is sensitive to novelty/familiarity in the conceptual domain. In left perirhinal cortex, a novelty/familiarity effect was observed in the same-task condition but not in the different-task condition, thus revealing sensitivity to the degree of semantic overlap across exposures but insensitivity to perceptual repetition of the visual word form. Perirhinal sensitivity to semantic repetition and insensitivity to perceptual repetition suggests that human perirhinal cortex receives conceptual inputs, with perirhinal contributions to declarative memory perhaps partially stemming from its role in processing semantic aspects of experiences. © 2004 Wiley-Liss, Inc.

KEY WORDS: perirhinal cortex; parahippocampal cortex; medial temporal lobe; episodic encoding; priming

INTRODUCTION

The ability to respond to novelty—or, conversely, familiarity—in the environment yields important processing benefits. In the realm of declarative memory, novelty/familiarity detection aids in the differential allocation of resources to novel stimuli at encoding (e.g., Stern et al., 1996; Tulving et al., 1996; Stark and Squire, 2001; Habib et al., 2003), and at retrieval, familiarity can serve as a signal for explicit recognition, allowing an organism to consciously distinguish previously experienced from novel stimuli (Mandler, 1980; Jacoby, 1991; Yonelinas, 2002). The functional utility of novelty/familiarity signals has motivated efforts to specify the neural processes that are sensitive to this stimulus dimension, and the resulting data have revealed novelty/familiarity effects in the medial temporal lobe (MTL) (e.g., Knight, 1996; Gabrieli et al., 1997; Kirchhoff et al., 2000). The objective of the present event-related functional magnetic resonance imaging (fMRI) investigation was to more precisely characterize novelty/familiarity responses in MTL, using an incidental encoding paradigm that allowed for assessment of the nature of the processes or representations that must be repeated to elicit such responses.

Prior electrophysiological and neuroimaging data indicate that MTL neurons exhibit reduced responses to familiar (i.e., repeated) relative to novel stimuli. For example, in the nonhuman, neurons in perirhinal cortex show lower firing rates during presentation of repeated relative to novel stimuli (e.g., Zhu et al., 1995; Desimone, 1996; Ringo, 1996; Brown and Xiang, 1998; Eichenbaum, 2000; Brown and Aggleton, 2001). In humans, novelty/familiarity effects have been observed in parahippocampal gyrus (including perirhinal and parahippocampal cortices), and, to a lesser extent, in hippocampus (Stern et al., 1996; Gabrieli et al., 1997; Kirchhoff et al., 2000; Grunwald et al., 2003; Henson et al., 2003; Weis et al., 2004), with the typical neuroimaging finding being reduced rCBF or BOLD signals during the processing of repeated relative to novel stimuli.

Given the consistent presence of novelty/familiarity responses in MTL cortex, a fundamental objective is to determine what processes or representations must be repeated to elicit these responses. Insights into the nature of MTL novelty/familiarity responses may partially come from consideration of the inputs to perirhinal cortex (PRc) and parahippocampal cortex (PHc). In infrahuman primates, PRc and PHc receive inputs from unimodal and polymodal association cortices in the temporal, frontal, and parietal lobes (Suzuki and Amaral, 1994), with the majority of input coming from visual association cortex. The predominant inputs to PRc stem from unimodal visual association cortices in laterally adjacent inferior temporal regions—structures that are important

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for the processing of visual objects—whereas the predominant inputs to PHc stem from posterior visual association areas and posterior parietal cortex—structures that represent visuospatial information (Lavenex and Amaral, 2000; for review, see Burwell, 2000).

Because of a scarcity of data, the inputs to PRc and PHc in humans are less well known. From one perspective, based on the connectivity in infrahuman primates, human PHc is thought to differentially receive visuoperceptual and visuospatial inputs, whereas PRc inputs are thought to partially stem from lateral temporal cortices that represent semantic knowledge in humans. Accordingly, lesions of human PHc yield visuospatial memory deficits (Bohbot et al., 1998; Epstein et al., 1999), and activation of PHc in the healthy brain is reduced during the viewing of repeated relative to novel pictures and words (e.g., Stern et al., 1996; Kirchhoff et al., 2000). By contrast, human PRc may be sensitive to semantic, rather than purely perceptual, aspects of stimuli. Human PRc responds more robustly (1) when making semantic, relative to perceptual, decisions about objects (Ricci et al., 1999); (2) when processing sentences with semantic, relative to syntactic, violations (Newman, 2001), and (3) when processing high-frequency, relative to low-frequency, nouns, the former of which may entail richer semantic elaboration as a result of having more conceptual associations (Fernández et al., 2002). Intracranial electrode recordings from human MTL have also demonstrated an anterior medial temporal cortical field potential that is larger for words with semantic content than for words serving grammatical functions, with this potential declining due to semantic priming at delays of a couple seconds (Nobre and McCarthy, 1995).

The objective of the present fMRI study was to examine the nature of the representations/processes that must be repeated to elicit novelty/familiarity responses in human MTL. Because prior neuroimaging investigations of novelty/familiarity effects in MTL cortex co-varied perceptual and conceptual repetition (i.e., for a repeated stimulus, the perceptual input and the task performed on the stimulus were identical across repetition), extant data do not specify whether repetition-induced signal reductions in MTL cortex reflect memory for perceptual or conceptual information. Accordingly, while holding perceptual repetition constant, we sought to determine whether novelty/familiarity effects in PRc and PHc occur upon perceptual re-encounter with a stimulus (1) regardless of the overlap between the specific conceptual operations performed or semantic features accessed during the initial and repeated encounters, or (2) only when the same semantic processes/representations are engaged during initial and repeated encounter. The former outcome would suggest novelty/familiarity at the perceptual level, whereas the latter would suggest novelty/familiarity at the conceptual level.

MATERIALS AND METHODS

Informed consent was obtained from 21 right-handed native English speakers, aged 18–35 years (9 female), in a manner approved by the institutional review boards of MIT and Massachusetts General Hospital. fMRI data were acquired on a 1.5-tesla (T) Siemens Sonata system, using a gradient-echo echo-planar se-
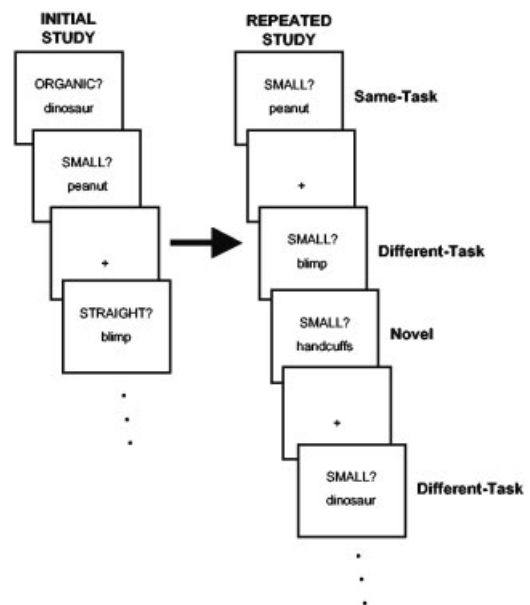
FIGURE 1. **Schematic of the experimental conditions. Words were visually presented in cycles that alternated between "initial study," visual fixation (not shown), and "repeated study" blocks. During initial study blocks, subjects made one of three judgments, i.e., size (small?), shape (straight?), or composition (organic?), about each word. During repeated study blocks, subjects made a size judgment for visually repeated and novel words, yielding Same-Task, Different-Task, and Novel trials. Within each study block, variable duration fixation trials (+) were interleaved between word trials according to an event-related design optimization algorithm.**

quence (repetition time = 2,500 ms, echo time = 30 ms, 21 axial slices aligned parallel to the AC-PC plane, $3.125 \times 3.125 \times 5$ mm, 1-mm interslice skip, 432 volumes per run). Four initial dummy volumes were discarded to allow for equilibration effects. In addition, a high-resolution T1-weighted (MP-RAGE) anatomical volume was collected. Head motion was restricted using a pillow and foam inserts.

Subjects made semantic decisions about novel and repeated words during scanning. Stimuli were presented over two functional runs using a mixed block/event-related design. Each run comprised two cycles of initial study and repeated study blocks, with 30-s fixation periods interleaved between the study blocks. Within each study block, words were visually presented in a pseudo-randomized order, jittered by variable-duration fixation events.

Each 2.5-s word trial consisted of a 500-ms task cue (straight?, organic?, or small?) that remained on the screen for an additional 400 ms coincident with visual word presentation; a 1,000-ms fixation period followed offset of the cue + word, and trials ended with a 600-ms blanket screen. In each initial study block, participants were presented 48 common nouns, and made a yes/no judgment of size ("Is it smaller than a 13-inch box?"), shape ("Are its edges more straight than curvy?"), or composition ("Is it made of organic material?") for each word (i.e., 16 trials/task; Fig. 1). In each repeated study block, the 48 studied words were re-presented along with 16 novel words. For all words in repeated study blocks, participants made a size judgment. Thus, for repeated words, the

semantic judgment made at repetition was either identical to (Same-Task: size→size) or different from (Different-Task: shape→size, or composition→size) the judgment made at first exposure, with perceptual repetition being identical across the Same-Task and Different-Task conditions (i.e., the orthographic or visual word form input was repeated during both Same- and Different-task trials; Fig. 1). The inclusion of two types of Different-Task trials (shape→size and composition→size) was designed to ensure that any across-task repetition effects were not specific to particular semantic task mappings, thus increasing the likelihood that such effects arise due to perceptual repetition (i.e., ortho-graphic/visual word form repetition).

The fMRI data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London), with standard slice-acquisition timing and motion correction preprocessing procedures (for details, see Davachi and Wagner, 2002). Subsequently, structural and functional images were normalized to the MNI stereotaxic space. Images were re-sampled into 3-mm cubic voxels and spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed using the general linear model. Trials were modeled using a canonical hemodynamic response function and its temporal derivative. Effects were estimated using a subject-specific fixed-effects model, with session-specific effects and low-frequency signal components treated as confounds. Linear contrasts yielded subject-specific estimates that were entered into second-level random-effects analyses. Following others (e.g., Davachi and Wagner, 2002; Strange et al. 2002; Dobbins et al., 2003; Weis et al., 2004), given the lower signal-to-noise often observed in MTL due to susceptibility signal loss (Ojemann et al., 1997; Schacter and Wagner, 1999), a threshold of $P < 0.005$ with a cluster extent of 5 or more voxels was used to identify MTL novelty/familiarity effects. To further characterize these fMRI responses, regions of interest (ROIs) were identified in MTL, functionally defined as described below, and included all significant voxels within 6 mm of each maximum. For each subject, signal was calculated by selectively averaging data with respect to peri-stimulus time per condition (using a toolbox written by R. Poldrack: http://sourceforge.net/projects/spm-toolbox/). The resulting % signal change measures (integrated from 2.5–7.5-s peri-stimulus time) were submitted to analysis of variance (ANOVA).

RESULTS

The critical data come from the repeated study blocks, and constitute comparisons between the Same-Task, Different-Task, and Novel conditions. Behaviorally, reaction times (RT) differed across Conditions [$F(2,40) = 33.67$, $P < 0.001$], as RT declined during Same-Task [$t(20) = -6.15$, $P < 0.001$] and during Different-Task trials [$t(20) = -4.70$, $P < 0.001$] relative to Novel trials (Table 1). The repetition effect on RT was attenuated when there was a change in the semantic task between initial and repeated exposures, as RT during Different-Task trials was slower than that during Same-Task trials [$t(20) = -5.67$, $P < 0.001$]; this pattern is consistent with prior behavioral reports (Vriezen et al., 1995; Thompson-Schill and Gabrieli, 1999; Franks et al.,

Reaction Time and Response Accuracy as a Function of Condition during Repeated Study Blocks

| Condition	Reaction Time (ms)	Proportion Correct
Same-Task	816 (73)	.94 (.06)
Different-Task	859 (86)	.92 (.06)
Novel	891 (100)	.93 (.07)

Note: standard deviations in ().

2000; Thompson-Schill and Kan, 2001; see also Wagner et al., 2000a). Finally, comparison of the two types of Different-Task trials (i.e., shape→size and composition→size) revealed that RT did not differ reliably [$t(20) = 1.5$, $P > 0.10$].

Repetition condition also had a significant influence on accuracy [$F(2,40) = 3.92$, $P < 0.05$], reflecting a benefit for Same-Task trials as compared with Different-Task trials (Table 1) [$t(20) = 3.00$, $P < 0.01$]. As with RT, separate analyses performed on the two types of Different-Task trials (i.e., shape→size and composition→size) indicated that these two conditions did not reliably differ ($t < 1$). Given the consistent behavioral pattern observed across the two types of Different-Task trials, these two conditions were collapsed into a single Different-Task condition for the primary fMRI analyses.

fMRI analyses focused on data from the repeated study blocks, where all words were processed under identical task conditions (i.e., a size judgment was performed on all word trials), with words differing in terms of perceptual and conceptual novelty/familiarity across the conditions. The primary question was whether MTL substructures exhibit novelty/familiarity effects that are sensitive to perceptual and/or conceptual repetition. Accordingly, we examined whether repetition-related activation reductions occur (1) in the Same-Task, but not in the Different-Task, condition, or (2) in both conditions. The former outcome would be consistent with a conceptual novelty/familiarity effect, as perceptual repetition was present during the Same-Task and Different-Task conditions; the latter outcome would indicate sensitivity to perceptual novelty/familiarity.

An initial voxel-wise contrast of Novel vs. Same-Task trials revealed one cluster of differential activation in MTL: falling in anterior MTL cortex, at or near left PRc (coordinates of −39, −18, −27; Fig. 2A). Localization of this group-identified region was confirmed at the individual subject level (Insausti et al., 1998; Duvernoy, 1999), with the region consistently corresponding to the anterior collateral sulcus (extending into fusiform gyrus in a subset of subjects). Subsequent ROI assessment of the response pattern in this left PRc region confirmed that the region was highly sensitive to the effect of Condition [$F(2,40) = 8.04$, $P < 0.002$]. As depicted in Figure 2A, left PRc (1) was less active during Same-Task trials relative to Novel trials [$t(20) = -3.41$, $P < 0.004$]; (2) was less active during Same-Task trials relative to Different-Task trials [$t(20) = -2.97$, $P < 0.009$], even though perceptual familiarity/novelty was held constant across these conditions; and (3)
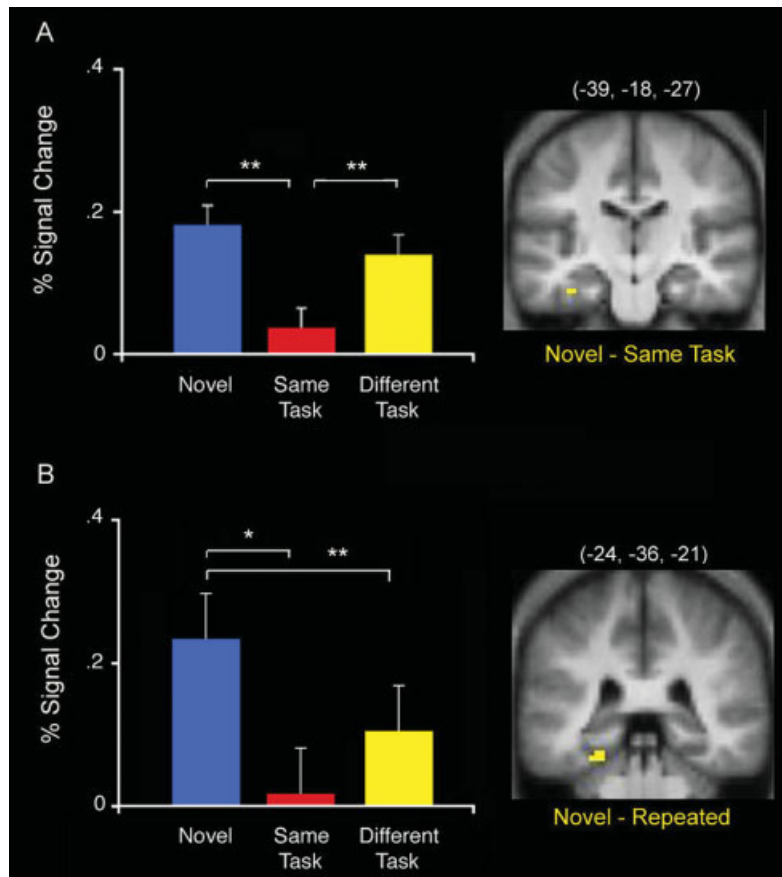
FIGURE 2. Voxel-wise (right) and region-of-interest (left) indices of familiarity/novelty effects in medial temporal lobe (MTL) cortex. A: Voxel-wise map depicting the left perirhinal cortex (PRc) region that demonstrated greater activation during Novel vs. Same-Task trials, with the graph plotting percentage signal change, relative to fixation, for each of the three conditions (N = 21). As shown, left PRc demonstrated a repetition reduction that was selective to the Same-Task condition. B: Voxel-wise map depicting the left parahippocampal cortex (PHc) region that demonstrated greater activation during Novel vs. Repeated trials (collapsed across the Same-Task and Different-Task conditions), with the graph demonstrating that a repetition reduction was observed in this region during both Same-Task and Different-Task trials (N = 18); activation in the two repetition conditions did not reliably differ. *$P < 0.05$; **$P < 0.01$; error bars reflect the standard within-subject error term. [Color figure can be viewed in the online issue, which is available at www.interscience. wiley.com.]

did not exhibit a reliable repetition reduction during Different-Task relative to Novel trials, even though perceptual novelty was present in the latter condition [$t(20) = -1.23$, $P > 0.20$; signal during Different-Task trials was 0.68 of a standard error lower than that for Novel trials]. Comparison of the two types of Different-Task trials (shape→size and composition→size) revealed comparable activation ($t < 1$). Collectively, these data indicate that left PRc demonstrated a novelty/familiarity effect that depended on repetition of the specific task—and, by inference, the specific semantic processes/features— engaged during initial encounter.

We next examined whether any MTL substructures showed novelty/familiarity responses that were sensitive to perceptual repetition (i.e., repetition reductions that generalized across tasks). A voxel-wise comparison of Novel vs. Repeated trials (collapsed across Same-Task and Different-Task conditions), revealed one MTL cluster—falling in posterior MTL cortex, at or near left PHc (coordinates of -24, -36, -21; Fig. 2B) and well posterior to the perirhinal region that exhibited a task-specific repetition effect. Confirmation that this group-identified region fell in PHc in the

individual subjects (Duvernoy, 1999) revealed that this region included both banks of the collateral sulcus in 18 of the 21 subjects, with localization in a minority of these subjects also including a portion of fusiform gyrus. In the remaining 3 subjects, this region fell exclusively in fusiform gyrus; data from these latter subjects were excluded from the subsequent ROI analysis.

ROI analysis confirmed an effect of Condition in this left PHc region [$F(2,34) = 4.27$, $P < 0.05$], with activation being significantly lower during Same-Task trials [$t(17) = -2.27$, $P < 0.05$] as well as during Different-Task trials [$t(17) = -4.07$, $P < 0.005$] compared with Novel trials. Thus, left PHc showed both within-task and across-task repetition reductions, revealing a sensitivity to perceptual novelty/familiarity. As with PRc, the mean magnitude of the repetition reduction was numerically larger for Same-Task than for Different-Task trials, although a direct comparison revealed that the magnitude of the repetition reduction did not reliably differ between Different-Task and Same-Task trials [$t(17) = -1.08$, $P > 0.20$]. This latter outcome may reflect the greater variance observed in PHc. Finally, as with PRc, the two types of

Different-Task trials elicited comparable activation (t < 1). In sum, left PHc showed a repetition reduction that reliably declined whenever perceptual repetition was present; there also was a unreliable signal decline from Different-Task to Same-Task trials raising the possibility that this region also is sensitive to novelty in the conceptual domain, although strong conclusions either way are not warranted given the present observations.

To confirm the semantic specificity of the novelty/familiarity effect in PRc and that novelty/familiarity in PHc at least partially generalizes across semantic processes/representations, we conducted a final voxel-wise analysis to identify MTL regions that showed a novelty/familiarity effect in the Different-Task condition. The only MTL region showing reduced activation for Different-Task trials relative to Novel trials was the left PHc cluster discussed above that also elicited a reduction during Same-Task repetition (i.e., the region observed in the Novel > Repeated contrast). Accordingly, both voxel-wise and ROI analyses revealed that novelty/familiarity effects in left PRc depend on conceptual processes/representations, whereas such effects in left PHc at least partially depend on perceptual processes/representations. Importantly, although caution is warranted when interpreting the apparent divergence in the sensitivity of PRc and PHc to conceptual novelty/familiarity, as a reliable Region × Condition interaction was not obtained when including Novel, Same-Task, and Different-Task levels of the Condition factor [F(2,34) = 1.09, P > 0.30], a Region × Condition analysis that was restricted to the Novel and Different-Task levels confirmed the differential sensitivity of PHc to perceptual novelty/familiarity [F(1,17) = 5.73, P < 0.05].

DISCUSSION

The current study demonstrates that at least one MTL subregion, the left PRc, is sensitive to the degree of overlap between the conceptual features processed across initial and repeated exposures to a stimulus, but is insensitive to perceptual repetition. When participants semantically processed the same word on two different occasions, repetition of the identical semantic judgment at re-encounter resulted in a robust novelty/familiarity effect in left PRc. In contrast, making a different semantic judgment upon re-encounter resulted in a level of PRc activation that did not reliably differ from that elicited when making the judgment about a novel word, even though perceptual novelty/familiarity differed between these conditions.

The observed novelty/familiarity effect in left PRc parallels previously reported behavioral repetition effects, wherein response times (1) are facilitated when an initial semantic judgment targets the same semantic information that is targeted upon re-encounter, but (2) are not facilitated or are facilitated to a lesser degree when initial semantic judgments target semantic representations that are different from those targeted upon re-encounter (e.g., Vriezen et al., 1995; Thompson-Schill and Gabrieli, 1999; Thompson-Schill and Kan, 2001) (see also Table 1). Such effects have been interpreted as revealing that prior semantic processing "sculpts" an item's conceptual representation in favor of recently accessed se-

mantic features, thus resulting in facilitation when those features are to be retrieved in the future (e.g., Fletcher et al., 2000; Badre and Wagner, 2002). Following this inferential logic, the present fMRI data are consistent with the hypothesis that left PRc receives conceptual inputs from lateral neo-cortical regions, and demonstrates novelty/familiarity effects that depend on mnemonic changes stemming from the specific conceptual representations or operations engaged during initial stimulus encoding.

Extant behavioral data further indicate that across-task RT facilitation can occur when the initial and repeated tasks target the same semantic attribute (e.g., visual→visual semantics or functional→functional semantics), suggesting that behavioral facilitation follows prior processing of particular semantic features irrespective of the task context that leads to this processing (e.g., Vriezen et al., 1995; Thompson-Schill and Gabrieli, 1999). In the present experiment, such a pattern was not obtained in left PRc. Specifically, the two types of Different-Task conditions (shape→size and composition→size) gave rise to similar magnitudes of left PRc activation, even though the shape and size tasks might both appear to tap visual semantics whereas the composition task might appear to tap more abstract semantics. Taken together with the prior behavioral literature, this finding suggests that the shape and size tasks, while appearing to tap common visual semantics, may nevertheless access distinct visual semantic features or alternatively may differentially draw on more abstract semantics. Although future research is required to clarify this divergence between left PRc activation reductions and prior behavioral facilitation effects, the present data unambiguously indicate that reductions in human left PRc activation are particularly sensitive to task repetition and thus, by inference, conceptual novelty/familiarity, but are insensitive to visual perceptual repetition.

Beyond left PRc, a cluster in left PHc exhibited a generalized novelty/familiarity response, wherein the activation elicited when making a novel semantic judgment about a visually repeated word (Different-Task trials) was less than that elicited when making a novel semantic judgment about a visually novel word (Novel trials). Activation in this region did not reliably differ between Different-Task and Same-Task trials, although the magnitude of the repetition reduction was quantitatively larger in the latter condition. Collectively, this pattern of left PHc activation suggests at least three possible interpretations. First, this region may be selectively involved in conceptual processing, but may be insensitive to variations in the particular dimensions of semantic information probed. This would appear unlikely, however, given other evidence implicating human PHc in visuoperceptual and visuospatial mnemonic processes (e.g., Bohbot et al., 1998; Epstein et al., 1999; Kirchhoff et al., 2000; Cabeza et al., 2001). Second, this region may not contribute to conceptual processing, but rather may selectively process visual information. In the present experiment, repetition of orthographic/visual word form input was identical in the Same-Task and Different-Task conditions while the level of conceptual repetition differed across these conditions. This interpretation would be consistent with prior imaging data in humans, and with neuroanatomical evidence that, in infrahuman primates, PHc receives input from posterior visual association areas and posterior parietal cortex (Burwell, 2000; Lavenex and Amaral,

2000). A third possibility is that, in addition to being sensitive to visuoperceptual novelty/familiarity, left PHc may also receive some conceptual inputs and thus may demonstrate some sensitivity to conceptual novelty/familiarity. Weak evidence to this effect may stem from the quantitative decline in PHc activation between the Different-Task and Same-Task trials. Although this decline was not statistically reliable ($P > 0.20$), the raw magnitude of the decline was similar to that seen in PRc, thus motivating future research that aims to determine whether left PHc demonstrates conceptual novelty/familiarity in addition to the presently observed sensitivity to perceptual novelty/familiarity.

Recently, attention has focused on human anterior MTL cortex, perhaps corresponding to PRc, as mediating novelty/familiarity responses during incidental encoding/priming paradigms and during explicit recognition tasks (e.g., Henson et al., 2003; Weis et al., 2004). As with these prior paradigms, the present size judgment task corresponded to an incidental encoding paradigm that, in theory, could have been affected by nondeclarative (priming) and/or declarative (explicit) memory for a stimulus's initial encounter. A noted aspect of prior neuroimaging findings from incidental encoding/priming and explicit recognition tasks is that, in addition to demonstrating decreased activation during the processing of repeated relative to novel stimuli, activation in anterior MTL cortex can also extend below that observed during the low-level baseline (e.g., visual fixation; Henson et al., 2003). Although interpreting baseline levels is often challenging (e.g., Stark and Squire, 2001), and across study consideration of baselines is likely particularly suspect, in the present incidental encoding task, activation levels in left PRc exceeded the fixation-baseline during Novel and Different-Task trials and fell to, but not below, baseline in the Same-Task condition.

In contrast with studies exploring novelty/familiarity effects at stimulus repetition, investigations of encoding activation during stimulus encounter have shown that greater responses in anterior MTL cortex predict superior subsequent stimulus familiarity (e.g., Davachi et al., 2003; Ranganath et al., 2004; Kirwan and Stark, 2004), with these responses also often falling above a low-level baseline. Taken together with the present left PRc pattern, one might speculate that re-encoding will further enhance subsequent stimulus familiarity to the extent that novel conceptual features are processed upon stimulus re-encounter. This possibility is consistent with the encoding variability hypothesis (e.g., Martin, 1968; see also Wagner et al., 2000b), as well as with evidence indicating that stimulus familiarity is sensitive to conceptual elaboration (e.g., Toth, 1996; Wagner et al., 1997). Accordingly, the present characterization of the nature of MTL cortical responses sets the stage for future understanding of how novelty/familiarity at re-encoding impacts subsequent memory performance.

Acknowledgments

REFERENCES

Badre D, Wagner AD. 2002. Semantic retrieval, mnemonic control, and prefrontal cortex. Behav Cogn Neurosci Rev 1:206–218.

Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L. 1998. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 36:1217–1238.

Brown, MW, Aggleton, JP. 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2:51–61.

Brown MW, Xiang JZ. 1998. Recognition memory: neuronal substrates of the judgment of prior occurrence. Prog Neurobiol 55:149–189.

Burwell RD. 2000. The parahippocampal region: corticocortical connectivity. Ann NY Acad Sci 911:25–42.

Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL. 2001. Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci USA 98:4805–4810.

Davachi L, Wagner AD. 2002. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol 88:982–990.

Davachi L, Mitchell JP, Wagner AD. 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source. Proc Natl Acad Sci USA 100:2157–2162.

Desimone R. 1996. Neural mechanisms for visual memory and their role in attention. Proc Natl Acad Sci USA 93:13494–13499.

Dobbins IG, Rice HJ, Wagner AD, Schacter DL. 2003. Memory orientation and success: separable neurocognitive components underlying episodic recognition. Neuropsychologia 41:318–333.

Duvernoy HM. 1999. The human brain: sufface, blood supply, and three-dimensional sectional anatomy. New York: Springer-Verlag.

Eichenbaum H. 2000. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 1:41–50.

Epstein R, Harris A, Stanley D, Kanwisher N. 1999. The parahippocampal place area: recognition, navigation, or encoding? Neuron 23:115–125.

Fernández G, Klaver P, Fell J, Grunwald T, Elger CE. 2002. Human declarative memory formation: segregating rhinal and hippocampal contributions. Hippocampus 12:514–519.

Fletcher PC, Shallice T, Dolan RJ. 2000. "Sculpting the response space"—an account of left prefrontal activation at encoding. NeuroImage 12:404–417.

Franks JJ, Bilbrey CW, Lien KG, McNamara TP. 2000. Transfer-appropriate processing (TAP) and repetition priming. Mem Cogn 28:1140–1151.

Gabrieli JDE, Brewer JB, Desmond JE, Glover GH. 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276:264–266.

Grunwald T, Pezer N, Münte TF, Kurthen M, Lehnertz K, Van Roost D, Fernández G, Kutas M, Elger CE. 2003. Dissecting out conscious and unconscious memory (sub)processes within the human medial temporal lobe. NeuroImage 20:S139–S145.

Habib R, McIntosh AR, Wheeler MA, Tulving E. 2003. Memory encoding and hippocampally-based novelty/familiarity discrimination networks. Neuropsychologia 41:271–279.

Henson RNA, Cansino S, Herron JE, Robb WGK, Rugg MD. 2003. A familiarity signal in human anterior medial temporal cortex. Hippocampus 13:301–304.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkänen A. 1998. MR volumetric analysis of the human

entorhinal, perirhinal, and temporopolar cortices. Am J Neuroradiol 19:659–671.

Jacoby LL. 1991. A process dissociation framework: separating automatic from intentional uses of memory. J Mem Lang 30:513–541.

Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000. Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 20:6173–6180.

Kirwan CB, Stark CEL. 2004. Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus 14:919–930.

Knight RT. 1996. Contribution of human hippocampal region to novelty detection. Nature 383:256–259.

Lavenex P, Amaral DG. 2000. Hippocampal-neocortical interaction: a hierarchy of associativity. Hippocampus 10:420–430.

Mandler G. 1980. Recognizing: the judgment of previous occurrence. Psychol Rev 87:252–271.

Martin E. 1968. Stimulus meaningfulness and paired-associate transfer: an encoding variability hypothesis. Psychol Rev 75:421–441.

Newman AJ. 2001. An event-related fMRI study of syntactic and semantic violations. J Psycholinguist Res 30:339–364.

Nobre AC, McCarthy G. 1995. Language-related field potentials in the anterior-medial temporal lobe. II. Effects of word type and semantic priming. J Neurosci 15:1090–1098.

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.

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.

Ricci PT, Zelkowicz BJ, Nebes RD, Meltzer CC, Mintun MA, Becker JT. 1999. Functional neuroanatomy of semantic memory: recognition of semantic associations. NeuroImage 9:88–96.

Ringo JL. 1996. Stimulus specific adaptation in inferior temporal and medial temporal cortex of the monkey. Behav Brain Res 76:191–197.

Schacter DL, Wagner AD. 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9:7–24.

Stark CE, Squire LR. 2001. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci USA 98:12760–12766.

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 93:8660–8665.

Strange BA, Otten L, Josephs O, Rugg MD, Dolan RJ. 2002. Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. J Neurosci 15:523–528.

Suzuki WA, Amaral DG. 1994. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol 350:497–533.

Thompson-Schill SL, Gabrieli JDE. 1999. Priming of visual and functional knowledge on a semantic classification task. J Exp Psychol Learn Mem Cogn 25:41–53.

Thompson-Schill SL, Kan IP. 2001. Perceptual and conceptual sources of priming on a word generation task. Mem Cogn 29:698–706.

Toth JP. 1996. Conceptual automaticity in recognition memory: levels-of-processing effects on familiarity. Can J Exp Psychol 50:123–138.

Tulving E, Markowitsch HJ, Craik FEM, Habib R, Houle S. 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 6:71–79.

Vriezen, ER, Moscovitch M, Bellos SA. 1995. Priming effects in semantic classification tasks. J Exp Psychol Learn Mem Cogn 21:933–946.

Wagner AD, Gabrieli JD, Verfaellie M. 1997. Dissociations between familiarity processes in explicit recognition and implicit perceptual memory. J Exp Psychol Learn Mem Cogn 23:305–323.

Wagner AD, Koutstaal W, Maril A, Schacter DL, Buckner RL. 2000a. Process-specific repetition priming in left inferior prefrontal cortex. Cereb Cortex 10:1176–1184.

Wagner AD, Maril A, Schacter DL. 2000b. Interactions between forms of memory: when priming hinders new episodic learning. J Cogn Neurosci 12(suppl 2):52–60.

Weis S, Klaver P, Reul J, Elger CE, Fernández G. 2004. Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. Cereb Cortex 14:256–267.

Yonelinas, AP. 2002. The nature of recollection and familiarity: a review of 30 years of research. J Lang Mem 46:441–517.

Zhu XO, Brown MW, Aggleton JP. 1995. Neuronal signaling of information important to visual recognition memory in rat rhinal and neighboring cortices. Eur J Neurosci 7:753–765.