False Positives to Confusable Objects Predict Medial Temporal Lobe Atrophy

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ABSTRACT: Animal models agree that the perirhinal cortex plays a critical role in object recognition memory, but qualitative aspects of this mnemonic function are still debated. A recent model claims that the perirhinal cortex is required to recognize the novelty of confusable distractor stimuli, and that damage here results in an increased propensity to judge confusable novel objects as familiar (i.e., false positives). We tested this model in healthy participants and patients with varying degrees of perirhinal cortex damage, i.e., amnestic mild cognitive impairment and very early Alzheimer’s disease (AD), with a recognition memory task with confusable and less confusable realistic object pictures, and from whom we acquired high-resolution anatomic MRI scans. Logistic mixed-model behavioral analyses revealed that both patient groups committed more false positives with confusable than less confusable distractors, whereas healthy participants performed comparably in both conditions. A voxel-based morphometry analysis demonstrated that this effect was associated with atrophy of the anteromedial temporal lobe, including the perirhinal cortex. These findings suggest that also the human perirhinal cortex recognizes the novelty of confusable objects, consistent with its border position between the hierarchical visual object processing and medial temporal lobe memory systems, and explains why AD patients exhibit a heightened propensity to commit false positive responses with inherently confusable stimuli. © 2013 The Authors. Hippocampus Published by Wiley Periodicals, Inc.

KEY WORDS: perirhinal cortex; object memory; ambiguity; Alzheimer’s disease; declarative memory

INTRODUCTION

Animal research has demonstrated that the perirhinal cortex (PRc) is critically involved in object recognition memory (Meunier et al., 1993; Zola-Morgan et al., 1989), but it remains less clear how it performs this central function. A recent representational-hierarchical account argues that PRc involvement in object recognition depends on the complexity of stimulus representations required to differentiate and correctly identify targets and distractors (Bussey et al., 2005; Cowell et al., 2006; Bartko et al., 2010; Saksida and Bussey, 2010; Barense et al., 2012). Here, we test this hypothesis in humans with varying degrees of PRc pathology, i.e., those with Alzheimer’s disease (AD) and its putative prodrome, amnestic mild cognitive impairment (aMCI) (e.g., Juottonen et al., 1998; Dickerson et al., 2009).

The representational-hierarchical view is grounded in the functional anatomy of the ventral object processing stream which codes for increasingly more complex visual feature combinations from posterior to anterior ventral and anteromedial temporal sites (Ungerleider and Mishkin, 1982; Saksida and Bussey, 2010). At the anterior apex of this system, the PRc is claimed to contain representations of complex visual feature combinations (Bussey et al., 2005; Buckley and Gaffan, 2006). These representations are required to discriminate between confusable objects which share many features with other objects, since such objects cannot be uniquely identified by simple feature combinations coded in more posterior parts of the ventral object processing stream (Bussey et al., 2005; Saksida and Bussey, 2010). This principle is claimed to govern the PRc’s role in delayed-matching-to-sample (DMS) recognition tasks when stimuli shown at delay share many features with other objects (Cowell et al., 2006, 2009). That is, following PRc damage, complex object representations are no longer available to support the unique identification of novel confusable objects, leading to impaired recognition memory performance for these stimuli (see e.g., Bussey et al., 2002; Bartko et al., 2007). Furthermore, since performance must rely on simpler feature configurations coded in more posterior sites (Cowell et al., 2006, 2009), which are more likely to be shared by many other objects in the task, PRc damage is predicted to lead to increased false
The detrimental effect of interference on object recognition performance has received support from a study in rodents (Bartko et al., 2010) and more recently in a study with human participants (Barense et al., 2012). Barense and colleagues (2012) used a perceptual discrimination task in which participants were instructed to decide whether two presented ambiguous, meaningless objects were identical or different from one another. The inter-trial intervals were filled with objects that shared many features with the test stimuli. The authors found that patients with large aMTL lesions encompassing the PRc performed comparably to controls during the first half of the experiment, but that performance dropped in the latter half of the trials, while healthy controls and patients with lesions restricted to the hippocampi performed equally well in both halves of the experiment. Moreover, the performance of the patients with extensive aMTL damage was rescued by changing the interfering stimuli such that they no longer shared features with the trial items, indicating that these patients were susceptible to the interfering effect of shared features. Taken together, the findings from McTighe et al. (2010) and Barense et al. (2012) suggest that patients with damage including the PRc should perform poorer than healthy controls in tasks that require the disambiguation of confusable distractor objects with many shared features.

The purpose of the present study was to test whether PRc atrophy in humans is associated with an increased number of false-positive responses to stimuli which are inherently perceptually and semantically confusable relative to less confusable stimuli, i.e., in the absence of an explicit interference condition (cf., McTighe et al., 2010; Barense et al., 2012). We capitalize on findings showing that concrete objects from different domains of knowledge, i.e., living and nonliving things, differ in the degree to which their perceptual and semantic features are shared by other objects and are therefore confusable (Tyler and Moss, 2001; Cree and McRae, 2003; Randall et al., 2004; Taylor et al., 2008, 2012). Specifically, living things are characterized by rich representations with many shared perceptual and semantic features (e.g., has eyes) and few distinctive features (e.g., has an udder), rendering them confusable with respect to basic-level identity (e.g., horse vs. cow). In contrast, nonliving things tend to have fewer features in total with fewer shared features (e.g., made of metal) and more distinctive features (e.g., is serrated), such that these objects are less confusable with respect to their basic-level identity (e.g., a hammer vs. knife; Tyler and Moss, 2001; Randall et al., 2004; Taylor et al., 2007). Thus, upon presentation of an equal number of living and nonliving objects in object memory tasks, as in human experience in general, features of living things are probabilistically repeated more often than those of nonliving things, since living things have a greater number of shared features (Rosch, 1975). In the presence of PRc damage, confusable living distractors are predicted to be judged as falsely familiar because the complex representations required to uniquely identify the objects and thus their novelty are no longer available (Tyler et al., 2004; Moss et al., 2005; Taylor et al., 2006, 2009). However, performance with target objects is not expected to suffer since the familiarity responses can be made on the basis of simpler features coded at the more posterior ventral stream regions (cf., McTighe et al., 2010), i.e., targets do not need to be uniquely identified in order to be judged as familiar.

To test these hypotheses, we developed a delayed recognition task comprised of living and nonliving objects which we presented to normal control participants and patients with varying degrees of PRc atrophy (Taylor and Probst, 2008; Dickerson et al., 2009), i.e., those with AD and its purported prodrome aMCI (Winblad et al., 2004). Previous studies on recognition performance in AD patients have demonstrated that they exhibit a more liberal response bias compared to healthy control participants (Snodgrass and Corwin, 1988; Busdon et al., 2006). This bias is reflected in a lower threshold of judging both novel distractor items and target items as familiar, resulting in an increased number of both false positives and hits, respectively. A similar pattern of recognition performance has been observed in patients with frontal lobe damage; for this reason, AD patients’ positive response bias has been attributed...
to performance monitoring and verification deficits due to frontal lobe dysfunction (Budson et al., 2002, 2006).

In the present study, we measured performance with confusable living distractors and less confusable nonliving distractors, each of which were presented with living and nonliving targets. A mixed-model approach allowed us to examine performance trial-wise to tease apart the effects related to distractor domain and target domain. We then related recognition performance to voxel-based measures of gray matter integrity. To adjudicate between competing accounts of the locus of false positive responses in AD—PRc vs. frontal lobe damage—we performed voxel-based correlation analyses across the whole brain. We predict that the degree of PRc atrophy will be associated with an increasing number of false positive recognition responses to semantically and perceptually confusable living distractors compared to less confusable nonliving distractors.

### MATERIALS AND METHODS

#### Participants

Thirty-nine native Swiss-German or German-speaking adults participated (mean age = 72.9 yrs, SD = 6.7 yrs; mean education = 11.7 yrs, SD = 2.8 yrs; mean Mini Mental State Examination score [MMSE; Folstein et al., 1975 = 27.7, SD = 2.4]). Fourteen individuals were optimally healthy control participants recruited from two longitudinal research studies on aging and dementia at the Memory Clinic, Department of Geriatrics at the University Hospital, Basel. Ten participants were diagnosed with aMCI according to the Winblad et al. criteria (McKhann et al., 1984). This study was approved by the local ethics committee, and informed consent was obtained from each participant.

The group demographics are presented in Table 1. The groups did not differ in mean age ($F_{2,36} = 2.2$, ns), years of education ($F_{2,36} = 1.5$, ns), or the proportion of female participants ($\chi^2_{2} = 2.4$, ns) but did differ with respect to mean MMSE score ($F_{2,36} = 10.6$, $p < 0.0001$), as expected, with both patient groups scoring lower than NC participants, and AD patients lower than aMCI patients. We note that the AD participants were in mild stages of the disease as indicated by the MMSE scores (Monsch et al., 1995). A summary of each diagnostic group’s performance on a comprehensive battery of neuropsychological tests is presented in Supporting Information Table 1.

#### Material

One hundred and twenty realistic color pictures were selected for the DMS task. Half of the pictures were targets from an implicit learning task (see Procedure) and half were novel distractors. Within the target and distractor sets ($n = 60$ each), half of the pictures represented objects from the living and half from the nonliving domain ($n = 30$ each; Fig. 1). Living things consisted of animals and fruits/vegetables and nonliving things of vehicles and tools ($n = 15$ in each target and distractor group). The distractors were paired with the targets according to ‘visual similarity’ such that one-third of the distractors were from the same category and were similar in form and color ($n = 20$; e.g., mouse - guinea pig), one-third of the targets were paired with a distractor from the same category and were visually dissimilar ($n = 20$; e.g., giraffe–hedgehog), and one-third of the distractors were visually similar to the target, but represented objects from a different category ($n = 20$; e.g., telescope–cucumber). In the latter group, animals were paired with vehicles and fruits/vegetables with tools (see Moss et al., 2005). Mean accuracies in each ‘visual similarity’ condition and target/distractor category are presented in Supporting Information Table 2 (see also Supporting Information Table 3). Since visual similarity had no significant effect on performance and did not interact with diagnosis (see Results), data were collapsed across this condition (see Table 3 and VBM analyses).

Target and distractor stimuli in each domain were matched as closely as possible on lemma frequency (Baayen et al., 1995) and rated concept familiarity and subjective visual complexity, both of which were collected using 7-point Likert scales in an independent group of 31 healthy mature, native Swiss-German or German-speaking individuals (see Kivisaari et al., 2012 for details). Neither living vs. nonliving targets nor living vs. nonliving distractors differed with respect to these variables (see Table 2). Specifically, we note that the living and nonliving distractors did not differ from their respective targets with respect to word frequency, familiarity, or subjective visual complexity (all $p > 0.1$), and that the targets paired with living and nonliving distractors did not differ with respect to these variables (all $p > 0.4$). Targets and distractors were comparable with respect to all other variables except for familiarity (Table 2). Importantly, although the targets were more familiar than distractors ($F_{3,112} = 4.0$, $p = 0.048$), familiarity did not interact with domain ($F_{1,112} = 0.24$, $p = 0.63$), and thus the key theoretical comparison was not confounded by object familiarity. Moreover, the targets paired with living distractors did not

| TABLE 1. Demographic Characteristics, MMSE Scores, and Overall Accuracy Scores by Diagnostic Status [M (SD)] |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | NC ($n = 14$)   | aMCI ($n = 11$) | AD ($n = 14$)   |
| Demographics                    | M (SD)          | M (SD)          | M (SD)          |
| Gender (female:male)            | 5:9            | 6:5             | 9:5             |
| Age                             | 71.6 (6.1)     | 70.8 (6.3)     | 75.8 (7.05)     |
| Education (years)               | 12.1 (2.2)     | 10.5 (2.4)     | 12.2 (3.3)      |
| MMSE                            | 29.3 (0.7)     | 27.8 (1.3)     | 25.9 (2.9)      |
| Accuracy over all items         | 0.97 (0.02)    | 0.93 (0.8)     | 0.71 (0.2)      |

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statistically differ from the targets paired with nonliving distractors with respect to any of these psycholinguistic variables (all $Fs < 0.6$, all $ps > 0.5$). All psycholinguistic and visual variables were entered as covariates into the behavioral analyses.

To ensure that the living objects in the present stimulus set were more confusable than the nonliving objects, we collected confusability ratings from an independent sample of 15 healthy participants (mean age $= 28.3$ yrs, SD $= 5.26$; mean education $= 17.45$ yrs, SD $= 2.47$, female: male $= 13:2$). These participants rated the degree to which each target and distractor object shared features with other known objects using a 7-point Likert scale. The objects were presented one at a time in the same pseudorandomized order such that there were no more than four consecutive objects from the same domain or same stimulus type (distractor/target). The experiment started and ended with four filler objects that were not included in the recognition task and which were discarded from the confusability analyses. One target item was not included because of experimenter error. Paired-sample $t$-tests revealed that the living distractors were indeed rated as more confusable than the nonliving distractors, and that the living targets were rated as more confusable than the nonliving targets (see Table 2). The mean confusability ratings for living targets vs. living distractors ($t_{14} = 0.84$, $p = 0.41$) as well as nonliving targets vs. nonliving distractors ($t_{14} = 0.39$, $p = 0.70$) did not significantly differ. Thus, these subjective ratings further support findings from large-scale feature norm studies demonstrating that living things tend to have a higher ratio of shared to distinctive features than nonliving things (Tyler and Moss, 2001; Randall et al., 2004; McRae et al., 2005; Taylor et al., 2007, 2008).

**Procedure**

In an implicit learning phase, participants were sequentially presented with the 60 target items on a computer monitor and were instructed to name each pictured object. The participants
were not instructed to memorize the pictures. These data are reported elsewhere (see Kivisaari et al., 2012). After a delay period (mean = 28.0 minutes; SD = 8.6 minutes), the participants completed a forced-choice DMS task. In this task, the target-distractor pairs (see above) were presented next to one another on a computer monitor in a forced-choice DMS task, with the lateral placement of the target counterbalanced across trials. We note that confusable living distractors were paired with both confusable living targets and less confusable nonliving targets, and vice versa (see Fig. 1), allowing us to disentangle the effects of distractor and target domain. The participants were instructed to decide which object they had previously seen among the two given options (Forster and Forster, 2003). The response or time-out was followed by 2000 ms of silence. The picture pair then appeared on the monitor for 5000 ms or until the participant responded. The response or time-out was followed by a 2000-ms inter-trial interval. DMDX software controlled stimulus presentation and the collection of responses (Forster and Forster, 2003).

### Statistical Analyses

Behavioral analyses were performed with R (R development core team, 2007) using the lme4 library (Bates and Sarkar, 2007). A generalized mixed-effects model with a logit-link function (GLMM), optimally suited for categorical data analyses (Jaeger, 2008), tested for the effects of diagnosis and target and distractor domain on performance by considering each trial as a separate event. Omissions were coded as missing values. Mixed-effects models allow trials and participants to be entered in the same model as crossed random effects, and co-variates- and item-specific variables in the same model. Thus, in a mixed models approach, more variance can be explained compared to traditional statistical models, resulting in more valid estimates of the effects of the predictors (Baayen et al., 2008). Mixed logit models additionally control for potential spurious results associated with categorical variables in traditional ANOVAs (Jaeger, 2008). Since the distractor and target domains were crossed (i.e., living distractors occurred with both living and nonliving targets, and nonliving distractors with both nonliving and living targets; see Fig. 1), and each trial was considered a unique event, we were able to disentangle the effects related to the domain of the distractor from the domain of the target, i.e., to examine the variance explained by target and by distractor characteristics separately. The intercept to which all other conditions were compared was defined as trials where both target and distractor were nonliving, and all contrasts are reported with respect to this condition.

A top-down model selection procedure was adopted for the behavioral analysis, where all the fixed effects and interactions of interest as well as potential covariates (familiarity, lemma frequency and visual complexity of the target and distractor, age and picture naming success (correct/incorrect by trial) of the participant, lateral placement of the target, and presentation order) were entered into an initial model (Verbeke and Molenberghs, 2009). The random effects, i.e., participant variance as well as the variance related to each trial (target-feature pair), were entered one at a time, and the resulting model was compared to the initial model. The model with the smallest Aikake Information Criterion was selected. Only covariates with \( p < 0.15 \) were included in the final model.

The coefficient estimates (\( b \)) resulting from the mixed model analysis indicate the size and direction of the effects and, for the categorical variables, represent the difference in log-odds at one level with respect to a ‘baseline’ or the intercept. For example, assume that NCs are coded as 0 (i.e., baseline), trials with a nonliving distractor are coded as 0 (i.e., baseline), and trials with a living distractor are coded as 1. A coefficient estimate of 0.50 for distractor domain would mean that the log-odds for NCs (coded as 0) in trials with a living distractor (coded as 1) are 0.50 higher than log-odds of correct answer for an NC participant in trials with a nonliving distractor (coded as 0). Therefore, the odds for a correct answer in the former trials are \( e^{0.50} \approx 1.65 \) times higher than in the latter trials. Similarly, the coefficient estimate of \(-1.0 \) (aMCI × distractor living) would mean that the odds that aMCI participants make a correct response to a living distractor are \( e^{-1.0} \approx 0.37 \) times lower than the odds of a aMCI participants giving a correct answer when the distractor domain is nonliving. Note that interaction effects represent effects over and above the main effects and not odds ratios of single cells. The logistic coefficient estimates can be transformed into probabilities for a correct answer using the formula \( P = e^{(coefficient Estimate)}/(e^{(coefficient Estimate)} + 1) \), where \( P \) is the probability of a correct answer and \( e \) is Euler’s number.

### Image Acquisition and Processing

Magnetization-prepared rapid acquisition gradient echo (MPRAGE) images were acquired with a 3T MRI scanner.
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MAGNETOM Allegra, Siemens) at the University Hospital Basel using a headcoil (TI = 1000 ms, TR = 2150 ms, TE = 3.5 ms, flip angle = 7°; rectangular field of view = 87.5%, acquisition matrix = 256 × 224 mm, voxel size = 1.1 mm³). Preprocessing of MPRAGE images was performed with Statistical Parametric Mapping software (SPM8, Welcome Institute of Cognitive Neurology, www.fil.ion.ucl.ac.uk) in Matlab 2010 (Mathworks Inc., Sherborn, MA; USA). The images were segmented using masks of non-brain tissue surrounding the aMTL. A study-specific template was created with DARTEL (Ashburner, 2007).

The individual gray matter segmentations were aligned with the DARTEL template and MNI space using the DARTEL approach, modulated, and smoothed with 6 FWHM Gaussian kernel.

To determine whether susceptibility to confusable distractors is associated with PRC and frontal lobe integrity, we planned a voxel-based-morphometry analysis. The normalized, modulated, and smoothed gray matter volumes were analyzed using the general linear model in SPM8. Behavioral scores were correlated with signal intensities in each voxel across all participants' preprocessed gray matter volumes, i.e., across the entire brain. To determine the neural correlates of susceptibility to false positive responses to confusable (i.e., living) distractors, we calculated two 'proportion commission' scores, one for trials with living distractors and one for trials with nonliving distractors, where the number of errors in one domain was divided by the number of responses in that distractor domain. The commission error rate therefore reflects false positives rather than omissions. We note that these commission scores were pooled across living and nonliving target domains and 'visual similarity' conditions (see Supporting Information Table 3). The regression analyses additionally co-varied age, MMSE score, and total gray matter volume to account for disease stage and related pathology. Based on the group mean coefficient details).

Of all covariates, distractor familiarity ($b = -0.60, z = -2.99, p = 0.003$) significantly predicted performance, reflecting a greater likelihood for a correct answer when the distractor was unfamiliar. The model yielded trends for both distractor visual complexity ($b = -0.41, z = -1.88, p = 0.061$), reflecting a trend toward poorer performance when the distractor was visually complex, and target domain frequency ($b = 0.14, z = 1.66, p = 0.096$), indicating a trend toward a greater likelihood of a correct response when the target was associated with a higher lemma frequency. All other psycholinguistic variables (see Table 2) as well as picture naming success (see Kivisaari et al., 2012), the main effect of 'visual similarity', the 'visual similarity' × diagnosis, and target domain × distractor domain interactions, were eliminated from the model based on the criterion described above (i.e., $p > 0.15$).

The distractor and target domains were crossed (i.e., living distractors were paired with both living and nonliving targets, and nonliving distractors with both nonliving and living targets; see Fig. 1), and each trial was considered a unique event, and therefore we were able to test the effects associated with the distractor domain and target domain separately. This analysis revealed that aMCI patients performed comparably to the NC participants ($b = 0.23, z = 0.32, p = 0.75$), whereas AD patients performed significantly poorer than NC participants ($b = -2.07, z = -4.00, p < 0.001$) on the baseline condition. NC performance was not significantly affected by distractor domain ($b = 0.37, z = 0.61, p = 0.54$) or target domain ($b = 0.28, z = 0.46, p = 0.64$). However, importantly, both aMCI and AD diagnosis interacted with distractor domain, demonstrating that both the aMCI participants ($b = -2.43, z = -3.06, p = 0.002$) and AD patients ($b = -1.35, z = -2.21, p = 0.027$) performed significantly poorer on trials with living compared to nonliving distractors (see Fig. 2). There were no significant interactions between diagnosis and target domain (aMCI: $b = 1.37, z = 1.81, p = 0.071$, AD: $b = 0.28, z = 0.45, p = 0.65$). These behavioral results suggest that susceptibility to living distractors is indeed associated with early AD-related pathology. Based on the group mean coefficient

**RESULTS**

Two trials were removed from the dataset because fewer than 50% of the NC participants could correctly name the target object in the implicit learning phase (i.e., picture naming task). Thus, 30 living targets, 28 nonliving targets, 29 living distractors, and 29 nonliving distractors remained in the final DMS dataset. The raw accuracy scores and proportion commission scores are reported in Table 3. In the GLMM analysis, we predicted correct answers with diagnostic category, distractor domain, target domain, visual similarity of the distractor and the target, as well as the diagnosis × target domain, diagnosis × distractor domain, and diagnosis × 'visual similarity' interactions. In addition, all psycholinguistic and visual characteristics were included in the model as covariates (see Methods).

![FIGURE 2. Logistic generalized mixed model estimates representing the likelihood of correct answers by diagnostic group and distractor domain (±1 standard error). Higher coefficient estimates reflect a higher probability of a correct answer (see text for details).](Hippocampus)
estimates (see Fig. 2), the likelihood of an aMCI participant to provide a correct answer when the distractor was living or nonliving was 90.7 and 98.7, respectively (NC: 98.9%, 98.4; AD: 74.3%, 88.5%, respectively).

To determine the neural underpinnings of these effects, we correlated the percent commission score for living distractors (i.e., the proportion of errors to living distractors relative to the total number of responses to living distractors) with whole brain gray matter voxel signal intensities. The negative contrast reflecting regions where more false positive responses with living distractors were associated with decreasing signal intensities revealed one significant cluster centered in the left amygdala ($-20$, $-25$, $-13$) with a subpeak in the hippocampal body ($-38$, $-23$, $-13$; Kivisaari et al., in press). Critically, the second subpeak was located on the left PRc ($-26$, $-15$, $-38$; Insauti et al., 1998; Kivisaari et al., in press), with this portion of the cluster extending along the collateral sulcus (i.e., PRc) up to the anterior level $y = 2$ (Fig. 3). Notably, no significant clusters were found in the frontal lobe. This finding indicates that atrophy of the PRc along with the hippocampus and amygdala is indeed associated with increased susceptibility to false positive responding with confusable living distractors but not less confusable nonliving distractors. There were no significant clusters for the analysis of percent commission scores in the nonliving domain testing for regions where decreased signal intensities were associated with an increased number of false positives to nonliving distractors (i.e., the proportion of errors to nonliving distractors relative to the total number of responses to nonliving distractors).

DISCUSSION

The representational-hierarchical view developed in animal studies (Cowell et al., 2006; McTighe et al., 2010; Saksida and Bussey, 2010) is grounded in the ventral occipitotemporal object processing system coding for increasingly more complex combinations of features from posterior to anterior and anterior-lateral temporal sites. This model claims that since the PRc lies at the end of this system, it codes for the most complex feature combinations required to uniquely represent confusable object stimuli (e.g., Buckley and Gaffan, 2006), a prerequisite for disambiguating targets from interfering distractors (Bartko et al., 2010; Saksida and Bussey, 2010; Barense et al., 2012). In this framework, PRc damage generates a tendency to judge novel confusable distractors as familiar (false positive responses), since the recognition decision necessarily depends on simple features shared by many objects coded in posterior ventral stream regions. Consistent with this account, we show that human participants with PRc damage (Braak and Braak, 1991; Taylor and Probst, 2008) indeed committed more errors with inherently confusable compared to less confusable distractor objects, but not target objects, in a DMS task (Bartko et al., 2010; McTighe et al., 2010; Barense et al., 2012; see also Romberg et al., 2012). The representational-hierarchical view is further supported by the present imaging results demonstrating that a disproportionately greater number of false positives to living things but not nonliving things was associated with decreased integrity of the left aMTL. This cluster encompassed a large extent of the PRc (from $y = -16$ to $y = 2$), suggesting that the PRc critically enables novelty detection of confusable distractors (cf., McTighe et al., 2010), thereby supporting object familiarity decisions (Brown and Bashir, 2002; Brown et al., 2010).

Object recognition memory performance associated with PRc atrophy appears to be driven primarily by the characteristics of distractor and not target stimuli (cf., McTighe et al., 2010). Since living distractors were paired with both living and nonliving targets, and nonliving distractors with both nonliving and living targets, and since we used a mixed-model approach that modeled the effects of distractor and target domain in

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each trial independently, the effects of distractor domain could be assessed while accounting for the variance related to the target domain. This analysis demonstrated that while target domain had no significant effect on performance, distractor domain significantly predicted trial outcome. Thus, these results demonstrate that the domain of the distractor, but not that of the target, drove DMS performance. The lack of a significant interaction between diagnosis and target domain is expected since simpler representations, coded at posterior sites carry the information that a given feature conjunction was previously seen (Cowen et al., 2006, 2009). That is, while PRc is putatively involved in the unique identification of confusable target objects (e.g., Tyler and Moss, 2001; Tyler et al., 2004; Taylor et al., 2006, 2009; Kivisaari et al., 2012) and is required for the unequivocal disambiguation of confusable distractors, the PRc is not deemed necessary for judging the familiarity of targets since these do not require unique object identification, i.e., familiarity information at posterior sites suffices for a correct recognition decision (Cowen et al., 2006, 2009; McTighe et al., 2010). However, we speculate that target confusability may subtly affect performance. That is, relatively distinctive targets (e.g., nonliving things) with fewer shared features than confusable targets (e.g., living things) may elicit a weaker familiarity response throughout the ventral stream, corresponding to fewer hits to distinctive (e.g., nonliving) than confusable targets (e.g., living things). The trend toward poorer aMCI participants performance with nonliving compared to living targets tentatively supports this speculation.

The present findings account for a better understanding of the liberal response bias documented in the context of AD (e.g., Snodgrass and Corwin, 1988; Watson et al., 2001; Budson et al., 2006; Gold et al., 2007). False positive responding in AD has been suggested to be due to insufficient response inhibition and retrieval monitoring due to frontal lobe dysfunction (Budson et al., 2002) and a failure to form sufficiently detailed memory representations of presented items due to semantic memory impairment (Snodgrass and Corwin, 1988; Budson et al., 2000). According to this view, AD patients may succeed in forming a ‘semantic gist’ of the presented items, but they fail to encode items at a more specific level. Reliance on general-level gist-information together with frontal lobe dysfunction would then lead to false positive responding. The present findings are consistent with the claim that AD patients fail to generate sufficiently detailed item representations, but specifies this impairment to perceptually and semantically confusable objects (e.g., living things). However, the present voxel-based correlation findings do not support the hypothesized central role of the frontal lobe dysfunction in false positive responding (Budson et al., 2002, 2006), but instead pinpoint the root of this impairment to the aMTL including the PRc.

The network of aMTL areas involved in rejecting confusable distractor stimuli included the hippocampus and amygdala. Hierarchical, connectivity-based models stress that information processed in the PRc is forwarded to the ERC, and further on to the hippocampus (Kivisaari et al., in press; Mishkin et al., 1997; Witter, 2007), with an increasing amount of converging information and a higher level of associativity at each stage (Lavenex and Amaral, 2000). Thus, the significant association between hippocampal integrity and susceptibility to false positives with confusable distractor stimuli may reflect the additional contextual detail required to process these stimuli. In a similar vein, the amygdala receives convergent input from the aMTL, as well as many subcortical structures and high-level sensory cortices, most notably the ventral visual processing stream (Young et al., 1994; Price, 2003). This convergence of input putatively enables the amygdala to code for the emotional significance of in particular biologically relevant visual stimuli (LaBar and Cabeza, 2006; Pessoa and Adolphs, 2010), such as conspecifics and animals, which have indeed been shown to engage the amygdala (e.g., Mormann et al., 2011). Thus, a hierarchical, connectivity-based approach can account for the relationship between heightened false positive responses to confusable living things in terms of the associative, contextual detail and emotional significance attributed to confusable living stimuli by the hippocampus and amygdala, respectively.

The present findings demonstrate that the inherent properties of the distractor items, i.e., their confusability, significantly influence recognition memory performance. Although there was a trend toward poorer performance when the distractor was visually complex, the effect of distractor domain could not be accounted for by visual complexity alone. This pattern of results resembles that found in studies using explicit pro- or retroactive interference stimuli during recognition tasks (Bartko et al., 2010; Barense et al., 2012). Consistent with these findings, aMCI and AD patients’ memory performance has been shown to be vulnerable to interfering stimulation (Loewenstein et al., 2004; Ebert and Anderson, 2009; Hanseew et al., 2012), and these patients’ memory performance has been shown to benefit from the reduction of interference during the delay period (Cowan et al., 2004; Della Sala et al., 2005). Taken together, these findings suggest that the aMTL network is critical not only for the consolidation of new information, but also for representing complex meaningful concepts, thereby rendering the system resistant to the distracting effects of incidentally learned related information that is irrelevant to the task (see also Warrington and Weiskrantz, 1970; Bartko et al., 2010; Barense et al., 2012).

These results are consistent with the representational-hierarchical account whereby the PRc supports complex object representations required for both novelty detection and identification of confusable objects, and extend this model to account human object recognition impairments with confusable and less confusable meaningful objects. Since the neurofibrillary pathology in AD starts in the transentorhinal cortex, i.e., medial portion of the PRc, before spreading to the rest of the cortex (Braak and Braak, 1991; Taylor and Probst, 2008), these results further suggest that a domain discrepancy in false positive responses may serve as a sensitive marker of incipient AD.

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REFERENCES

American Psychiatric Association (APA), 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Washington, DC: American Psychiatric Association.

Ashburner J. 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38:95–113.

Baayen RH, Piepenbrock R, Gulikers L. 1995. The CELEX Lexical Database (CD-ROM). Linguistic Data. University of Pennsylvania.

Baayen RH, Piepenbrock R, Gulikers L. 1995. The CELEX Lexical Database (CD-ROM). Linguistic Data. University of Pennsylvania.

Bartko SJ, Cowell RA, Winters BD, Bussey TJ, Saksida LM. 2010. Heightened susceptibility to interference in an animal model of amnesia: Impairment in encoding, storage, retrieval – or all three? Neuropsychologia 48:2897–2899.

Bates D, Sarkar D. 2007. lme4: Linear mixed-effects models using S4 classes, R package version 0.99875-6.

Braak H, Braak E. 1991. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259.

Brown MW, Bashir ZI. 2002. Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. Philos Trans R Soc B 357:1083–1095.

Brown MW, Warburton EC, Aggleton JP. 2010. Recognition memory: Material, #processes, and substrates. Hippocampus 20:1228–1244.

Buckley MJ, Gaffan D. 2006. Perirhinal cortical contributions to object perception. Trends Cogn Sci 10:100–107.

Budson AE, Daffner KR, Desikan R, Schacter DL. 2000. When false recognition is unopposed by true recognition: Gist-based memory distortion in Alzheimer’s disease. Neuropsychology 14:277–287.

Budson AE, Sullivan AL, Mayer E, Daffner KR, Black PM, Schacter DL. 2002. Suppression of false recognition in Alzheimer’s disease and in patients with frontal lobe lesions. Brain 125:2750–2765.

Budson, AE, Wolk, DA, Chong, H, Waring, JD. 2006. Episodic memory in Alzheimer’s disease: Separating response bias from discrimination. Neuropsychologia 44:2222–2232.

Bussey TJ, Sakaida LM, Murray EA. 2002. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur J Neurosci 15:365–374.

Bussey TJ, Sakaida LM, Murray EA. 2005. The perceptual-semantic/feature conjunction model of perirhinal cortex function. Q J Exp Psychol B 58:269–282.

Cowan N, Beschin N, Della Sala S. 2004. Verbal recall in amnesics under conditions of diminished retroactive interference. Brain 127:825–834.

Cowell RA, Bussey TJ, Sakaida LM. 2006. Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. J Neurosci 26:12186–12197.

Cowell RA, Bussey TJ, Sakaida LM. 2009. Functional dissociations within the ventral object processing pathway: Cognitive modules or a hierarchical continuum? J Cogn Neurosci 22:2460–2479.

Cree GS, McRae K. 2003. Analyzing the factors underlying the structure and computation of the meaning of chipmunk, cherry, chisel, cheese, and cello (and many other such concrete nouns). J Exp Psychol Gen 132:163–201.

Della Sala S, Cowan N, Perini M. 2005. Just lying there, remembering: Improving recall of prose in amnesic patients with mild cognitive impairment by minimising interference. Memory 13:435–440.

Dickerson BC, Feczko E, Augustinack JC, Pacheco J, Morris JC, Fischl B, Buckner RL. 2009. Differential effects of aging and Alzheimer’s disease on medial temporal lobe cortical thickness and surface area. Neurobiol Aging 30:432–440.

Ebert PL, Anderson ND. 2009. Proactive and retroactive interference in young adults, healthy older adults, and older adults with amnestic mild cognitive impairment. J Int Neuropsych Soc 15:83–93.

Folstein MF, Folstein SE, McHugh PR. 1975. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. J Psychiat Res 12:189–198.

Forster K, Forster J. 2003. DMDX: A Windows display program with millisecond accuracy. Behav Res Methods 35:116–124.

Gold CA, Marchant NL, Koutstaal W, Schacter DL, Budson AE. 2007. Conceptual fluency at test shifts recognition response bias in Alzheimer’s disease: Implications for increased false recognition. Neuropsychologia 45:2791–2801.

Hanseew Bj, Saren X, Ivanoua A. 2012. Increased sensitivity to proactive and retroactive interference in amnestic mild cognitive impairment: New insights. Brain Cogn 80:104–110.

Insauti R, Juottonen K, Soininen H. 1998. Volumes of the entorhinal and perirhinal cortices. Am J Neuroradiol 19:659–671.

Jaeger TF. 2008. Categorical data analysis: Away from ANOVAs (transformation or not) and towards logit mixed models. J Mem Lang 59:434–446.

Juottonen K, Laakso MP, Insausti R, Lehtovirta M, Pitkänen A, 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.

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Loewenstein DA, Acvedo A, Luis C, Crum T, Barker W, Duara R. 2004. Semantic interference deficits and the detection of mild Alzheimer's disease and mild cognitive impairment without dementia. J Int Neuropsychol Soc 10:91–100.

McKhan G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944.

McRae K, Cree GS, Seidenberg MS, McNorgan C. 2005. Semantic feature production norms for a large set of living and nonliving things. Behav. Res. Methods Instruments Comput 37:547–559.

McTighe SM, Cowell RA, Winters BD, Bussey TJ, Saksida LM. 2010. Paradoxical false memory for objects after brain damage. Science 330:1408–1410.

Meunier M, Bachevalier J, Mishkin M, Murray EA. 1993. Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. J Neurosci 13:5418–5432.

Mishkin M, Suzuki WA, Gadian DG, Vargha–Khadem F. 1997. Hierarchical organization of cognitive memory. Philos Trans R Soc B 352:1461–1467.

Monsch AU, Foldi NS, Ermini-Fünfschilling DE, Berres M, Taylor KL, Seifritz E, Stähelin HB, Spiegel R. 1995. Improving the diagnostic accuracy of the Mini-Mental State Examination. Acta Neurol Scand 92:145–150.

Mormann F, Dubois J, Korblith S, Milosavljevic M, Cerf M, Ison M, Tsuchiya N, Kraskov A, Quiroga RQ, Adolphs R, Fried I, Koch C. 2011. A category-specific response to animals in the right human amygdala. Nat Neurosci 14:1247–1249.

Moss HE, Rodd JM, Stamatakis EA, Bright P, Tyler LK. 2005. Anteromesial temporal cortex supports fine-grained differentiation among objects. Cereb Cortex 15:616–627.

Pessoa L, Adolphs R. 2010. Emotion processing and the amygdala: from a "low road" to "many roads" of evaluating biological significance. Nat Rev Neurosci 11:773–783.

Price JL. 2003. Comparative aspects of amygdala connectivity. Ann NY Acad Sci 985:50–58.

Randall B, Moss HE, Rodd JM, Greer M, Tyler LK. 2004. Distinctiveness and correlation in conceptual structure: behavioral and computational studies. J Exp Psychol Learn Mem Cogn 30:393–406.

Romberg C, McIntghe SM, Heath CJ, Whitcomb DJ, Cho K, Bussey TJ, Saksida LM. 2012. False recognition in a mouse model of Alzheimer's disease: Rescue with sensory restriction and memantine. Brain 135:2103–2114.

Rosch E. 1975. Cognitive representations of semantic categories. J Exp Psychol Gen 104:192–233.

Saksida LM, Bussey TJ. 2010. The representational-hierarchical view of amnesia: Translation from animal to human. Neuropsychologia 48:2370–2384.

Snodgrass JG, Corwin J. 1988. Pragmatics of measuring recognition memory: Applications to dementia and amnesia. J Exp Psychol Genera 117:34–50.

Taylor KL, Probst A. 2008. Anatomic localization of the entorhinal region of the perirhinal cortex. Neurobiol Aging 29:1591–1596.

Taylor KL, Moss HE, Stamatakis EA, Tyler LK. 2006. Binding cross-modal object features in perirhinal cortex. Proc Natl Acad Sci USA 103:8239–8244.

Taylor KL, Moss HE, Tyler LK. 2007. The conceptual structure account: A cognitive model of semantic memory and its neural instantiation. In: Hart J, Kraut MA, editors. Neural Basis of Semantic Memory. Cambridge, UK: Cambridge University Press. pp 265–301.

Taylor KL, Salamoura A, Randall B, Moss HE, Tyler KL. 2008. Clarifying the nature of the distinctiveness by domain interaction in conceptual structure: comment on Cree, McNorgan, and McRae (2006). J Exp Psychol Learn Mem Cogn 34:719–725.

Taylor KL, Stamatakis EA, Tyler LK. 2009. Crossmodal integration of object features: Voxel-based correlations in brain-damaged patients. Brain 132:671–683.

Taylor KL, Deveerux BJ, Tyler LK. 2012. Conceptual structure: Towards an integrated neuro-cognitive account. Lang Cogn Process 26:1368–1401.

Tyler LK, Moss HE. 2001. Towards a distributed account of conceptual knowledge. Trends Cogn Sci 5:244–252.

Tyler KL, Stamatakis EA, Bright P, Acres K, Abdallah S, Rodd JM, Moss HE. 2004. Processing objects at different levels of specificity. J Cogn Neurosci 16:351–362.

Ungerleider LG, Mishkin M. 1982. Two cortical visual systems. In: Ingle DJ, Goodale M, Mansfield RJW, editors. Analysis of Visual Behaviour. Cambridge, MA: MIT Press. pp 549–586.

Verbeke G, Molenberghs G. 2009. General guidelines for model building. In: Verbeke G, Molenberghs G, editors. Linear Mixed Models for Longitudinal Data. New York: Springer Verlag. pp 121–134.

Warrington EK, Weiskrantz L. 1970. Amnesic syndrome: Consolidation or retrieval? Nature 228:628–630.

Watson JM, Balota DA, Sergent-Marshall SD. 2001. Semantic, phonological, and hybrid veridical and false memories in healthy older adults and in individuals with dementia of the Alzheimer type. Neuropsychology 15:254–268.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arau H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. 2004. Mild cognitive impairment—Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256:240–246.

Witter MP. 2007. The perforant path: Projections from the entorhinal cortex to the dentate gyrus. In: Scharfman HE, editor. The Dentate Gyrus: A Comprehensive Guide to Structure, Function, and Clinical Implications. Amsterdam, The Netherlands: Elsevier. pp 43–61.

Young MP, Scannell JW, Burns GA, Blakemore C. 1994. Analysis of connectivity: Neural systems in the cerebral cortex. Rev Neurosci 5:227–250.

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. 1989. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9:4355–4370.