Reducing Perceptual Interference Improves Visual Discrimination in Mild Cognitive Impairment: Implications for a Model of Perirhinal Cortex Function

Rachel N. Newsome,^{1*} Audrey Duarte,² and Morgan D. Barense^{1,3}

ABSTRACT: Memory loss resulting from damage to the medial temporal lobes (MTL) is traditionally considered to reflect damage to a dedicated, exclusive memory system. Recent work, however, has suggested that damage to one MTL structure, the perirhinal cortex (PRC), compromises complex object representations that are necessary for both memory and perception. These representations are thought to be critical in shielding against the interference caused by a stream of visually similar input. In this study, we administered a complex object discrimination task to two memory-impaired populations thought to have brain damage that includes the PRC [patients diagnosed with amnesic mild cognitive impairment (MCI), and older adults at risk for MCI], as well as age-matched controls. Importantly, we carefully manipulated the level of interference: in the High Interference condition, participants completed a block of consecutive perceptually similar complex object discriminations, whereas in the Low Interference condition, we interspersed perceptually dissimilar objects such that there was less buildup of visual interference. We found that both memory-impaired populations were impaired on the High Interference condition compared with controls, but critically, by reducing the degree of perceptual interference, we were largely able to improve their performance. These findings, when taken together with convergent evidence from animals with selective PRC lesions and amnesic patients with focal damage to the PRC, provide support for a representational-hierarchical model of PRC function and suggest that memory loss following PRC damage may reflect a heightened vulnerability to perceptual interference. © 2012 Wiley Periodicals, Inc.

KEY WORDS: perirhinal cortex; medial temporal lobe; Alzheimer's disease; mild cognitive impairment; perception; visual discrimination; interference

INTRODUCTION

Mild cognitive impairment (MCI) is a condition that often precedes diagnosis of Alzheimer's disease, and is usually associated with memory impairments. MCI patients have incipient damage to key brain structures known to be vital for memory: namely, the medial temporal lobes

(MTL) (e.g., Loewenstein et al., 2009; Schmidt-Wilcke et al., 2009). Traditionally, the MTL has been thought to exclusively support long-term declarative memory, our conscious memory for events (e.g., Squire and Zola-Morgan, 1991; Eichenbaum and Cohen, 2001). According to this theory, the primary function of the MTL is in memory and not in other aspects of cognition, such as object perception (Clark et al., 2011; Kim et al., 2011; Squire and Wixted, 2011). However, recent reports have challenged this prevailing view that the mechanisms underlying memory and perception are anatomically segregated, suggesting instead that the MTL—in particular the perirhinal cortex (PRC)—is not only important for memory but also essential for certain forms of perception (e.g., Buckley et al., 2001; Bussey andaksida, 2002; Lee et al., 2005a; Bartko et al., 2007b; O'Neil et al., 2009; Barense et al., 2010b; Lee and Rudebeck, 2010; Barense et al., 2011a,b; Murray and Wise, 2012). These findings have led to a representational-hierarchical account of PRC function (Fig. 1), which holds that apparently distinct mnemonic and perceptual functions may arise from common representations and computational mechanisms (Murray and Bussey, 1999; Cowell et al., 2010b; Graham et al., 2010; Saksida and Bussey, 2010; Cowell, 2012). More specifically, recent studies in humans (Barense et al., 2005; Lee et al., 2005b; Barense et al., 2007; Devlin and Price, 2007; O'Neil et al., 2011), monkeys (Bussey et al., 2002; Bussey et al., 2003; Burke et al., 2011), and rats (Bartko et al., 2007a; Burke et al., 2010; McTighe et al., 2010) suggest that the PRC is necessary for processing the complex conjunctions of features comprising objects, during both memory and perceptual tasks. This property of visual discriminations has been termed “feature ambiguity,” meaning that the task is not solvable using single features alone but instead requires a complex conjunction of object features. These findings suggest that the PRC should be considered an extension of the representational hierarchy within the ventral visual stream. When an object is viewed, low-level features are represented in early posterior regions of the ventral visual stream, whereas conjunctions of these low-level features are represented in more anterior regions (e.g., Desimone and Ungerleider, 1989; Tanaka, 1996; Riesenhuber and Poggio, 1999; Martinovic et al., 2008). According

¹Department of Psychology, University of Toronto, Toronto, Ontario; ²School of Psychology, Georgia Institute of Technology, Atlanta, Georgia; ³Rotman Research Institute, Toronto, Ontario

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*Correspondence to: Rachel N. Newsome, 100 St. George Street, Toronto, ON M5S 3G3, Canada. E-mail: rachel.newsome@utoronto.ca

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FIGURE 1. The representational-hierarchical theory. According to this view, the PRC sits at the apex of the ventral visual stream processing pathway, and contains complex representations of objects (Cowell et al., 2010a). The figure shows a lateral view of the human ventral visual stream, and the proposed organization of visual object representations within this pathway. A, B, C, and D represent distinct visual features. Simpler features are represented in posterior regions, and complex conjunctions of features (such as those comprising an entire object) are represented in anterior regions, including PRC. (Figure modified from Murray and Bussey, 1999 and Barense et al., 2012).

to the representational-hierarchical account, the PRC is the apex of this representational hierarchy, representing the most complex conjunctions—perhaps at the level of the whole object (Bussey and Saksida, 2002; Bussey and Saksida, 2007; Murray et al., 2007; Cowell et al., 2010a). In this view, the PRC participates in both perception and memory, and impairments following PRC damage can best be understood in terms of damage compromising high-level conjunctive representations (e.g., those comprising an object), leaving only lower-level representations (e.g., an object's shape or pattern) intact (Cowell et al., 2006; Lee et al., 2012). These impoverished representations will lead to impairments on both mnemonic and perceptual tasks.

Why is it advantageous to maintain representations of complex feature conjunctions? A stream of visual input (such as that encountered over a delay during a memory task) can create interference at the level of individual features, simply because different objects tend to share lower-level features (e.g., shapes, colors). However, the “conjunctive” PRC representations can resolve this interference at the feature level because they are unique to each individual object. Notably, Warrington and Weiskrantz proposed over 40 yrs ago that amnesia may be related to an increased vulnerability to interference (Warrington and Weiskrantz, 1970). Although this theory was later rejected (Warrington and Weiskrantz, 1978), there has been a recent resurgence in the idea (Cowan et al., 2004; Loewenstein et al., 2004; Wixted, 2004; Della Sala et al., 2005; Dewar et al., 2009; Bartko et al., 2010; McTighe et al., 2010). For example, rats with PRC lesions were impaired on a minimal-delay object recognition task when a “perceptually similar” object was introduced either before or after the to-be-remembered object. The rats were not impaired if the interfering item was “perceptually dissimilar” (Bartko et al., 2010). This suggests that in the

absence of the complex object representations contained in PRC, the animals were unable to resolve interference from incidental, irrelevant lower-level object features. In the perceptually similar condition, many lower-level features were shared between the to-be-remembered object and the interfering object. The PRC bound these features into unique objects, and thus, intact animals were able to perform the task. However, when the PRC was lesioned, the intact posterior regions were not sufficient to resolve the perceptual similarity between low-level features. Similarly, the standard object recognition memory impairment observed after PRC lesions was rescued in rats by using a visual restriction procedure that reduced interference (McTighe et al., 2010). This finding was replicated in aged monkeys (Burke et al., 2011), aged rats (Burke et al., 2010, 2011) and in a mouse model of Alzheimer's disease (Romberg et al., 2012).

These findings were recently extended to humans with focal damage to the MTL using a novel perceptual discrimination task designed to tax complex object representations, for which fMRI implicated the PRC (Barense et al., 2012). Whereas amnesic cases whose damage was limited to the hippocampus performed normally, patients with MTL damage that included the PRC were vulnerable to object-based perceptual interference. These cases with PRC damage were impaired at successive complex object discriminations that contained many repeating low-level features, but critically, when we reduced the degree of object-level interference by interspersing perceptually dissimilar objects, we recovered their performance to normal levels (Barense et al., 2012). Healthy controls, who presumably had an intact PRC, performed as well under conditions of High Interference as they did under conditions of Low Interference; it was only the PRC-damaged group who were susceptible to the high levels of visual interference. These findings provide evidence to support the idea that the PRC is critical for representing the complex conjunctions of features that distinguish perceptually similar objects (see also Baxter, 2012; Peterson et al., 2012; Ryan et al., 2012). These PRC representations become essential when repeated presentation of multiple, similar features causes interference at the level of the features represented by intact posterior regions in the ventral visual stream.

In this study, we sought to determine whether these findings would generalize to another group of individuals with documented memory problems—those with MCI. The MTL is one of the earliest structures to show the neuropathological hallmarks of Alzheimer's disease, with the PRC demonstrating significant atrophy (Juottonen et al., 1998; Du et al., 2001; Guilozet et al., 2003; Pennanen et al., 2004; Taylor and Probst, 2008; Loewenstein et al., 2009; Schmidt-Wilcke et al., 2009). MCI patients who later convert to Alzheimer's disease show damage to the MTL (Bell-McGinty et al., 2005), including to the PRC (Mitchell et al., 2002). Interestingly, evidence suggests that MCI and Alzheimer's disease patients show impairments on perceptual tasks, especially when those tasks require complex visuo-perceptual processing of objects (e.g., Alegret et al., 2009, 2010). Alegret et al. found that MCI and Alzheimer's disease patients have visuo-perceptual deficits that may be more subtle than standard visuo-perceptual tests can pick up, yet no study

has investigated their performance on perceptual tasks known to be PRC dependent. To address this, here we administered the same perceptual discrimination task from Barense et al. (2012) to MCI patients. To provide further evidence in a related participant group and to increase our sample size, we also administered the task to older adults at risk for MCI, on the assumption that the integrity of the PRC would already be compromised in the earliest stages of the disorder (e.g., Du et al., 2001; Loewenstein et al., 2009; Schmidt-Wilcke et al., 2009). We identified these individuals at risk for MCI based on the Montreal Cognitive Assessment (MoCA), a brief standardized neuropsychological measure shown to be extremely sensitive in distinguishing controls from MCI patients (Nasreddine et al., 2005; Damian et al., 2011). Consistent with the cut-off scores provided by the developers of the MoCA (Nasreddine et al., 2005), we included older adults who scored below 26/30 on the MoCA as at risk for MCI, and older adults who scored 26/30 or above as a healthy control group. We predicted that MCI patients and individuals at risk for MCI would be impaired at object discrimination under conditions of high perceptual interference, but that we could improve their performance by reducing the degree of object-based perceptual interference.

MATERIALS AND METHODS

Participants

Ten patients with clinically diagnosed amnesic MCI participated in this study. These participants were recruited through the Emory Alzheimer's Disease Research Center, Atlanta, GA. Of these 10, three were excluded on the basis of their near perfect scores on the MoCA (Nasreddine et al., 2005) and Mini-Mental State Exam (MMSE, Folstein et al., 1975), leading us to believe they were "worried well" (Ahmed et al., 2008). Our exclusion criteria were a perfect score on one or both of the MoCA or the MMSE, as well as a passing score on the remaining test (i.e., a perfect score on the MoCA and a passing score on the MMSE, or a perfect score on the MMSE and a passing score on the MoCA). The remaining seven patients (mean age = 68.43 yrs, standard deviation = 8.69, three females) completed a detailed neuropsychological battery (Table 1). Patients were tested in the Memory and Aging laboratory at the Georgia Institute of Technology. All patients provided informed consent, and they were compensated for their time and travel expenses. The patient testing was approved by the Georgia Institute of Technology and the Emory University Institutional Review Boards.

In addition to MCI patients, 29 older adults with no known neurological conditions were recruited from the University of Toronto's Adult Volunteer Panel to participate in the study. Of these, 10 individuals (mean age = 71.11, standard deviation = 6.22, seven females) scored below 26 on the MoCA (mean score = 24.3, standard deviation = 1.05) and were considered to be at risk for MCI (Nasreddine et al., 2005). The remaining 19 individuals (mean age = 71.05 yrs, standard deviation =

5.33, 14 females) scored above 26 on the MoCA (mean score = 27.78, standard deviation = 1.47) and were included as control participants. Participants gave informed consent, and they were compensated for their time. These participants were tested in the Barense laboratory at the University of Toronto. The study was approved by the University of Toronto Ethics Review Board.

Thus, in total, three groups of participants participated in this study: those with MCI, older adults at risk for MCI ("At-risk" group), and older adults not thought to be at risk for MCI (healthy controls). Healthy controls' MoCA scores differed from those of the At-risk group [$t(27) = 6.61$, $p < 0.001$], and from those of MCI patients [$t(14) = 4.21$, $p < 0.001$]. MCI patients' performance on the MoCA was lower than the At-risk group [$t(15) = 2.08$, $p = 0.05$]. Because of scheduling constraints, two of the MCI patients were not administered the MoCA. Importantly, the MoCA was given after the experimental task for all remaining subjects, so the experimenter could not be biased by a participant's MoCA performance on the administration of the task. Age did not differ between controls, MCI patients, or those at risk for MCI ($t < 0.21$, $p > 0.49$).

Interference Task

Participants performed a visual discrimination task described previously as Experiment 4 by Barense et al. (2012). Importantly, assessment of eye movements demonstrated that this task required a high degree of conjunctive processing (Experiment 1, Barense et al., 2012) and fMRI indicated that it recruited the PRC but not the hippocampus (Experiment 2, Barense et al., 2012). On each trial, participants determined if two stimuli were identical (a match) or different (a nonmatch). Each stimulus was presented in one of two invisible boxes ($\sim 9^\circ \times 9^\circ$) positioned in the center of the screen, separated by 0.30° . The task was presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA), and participants made their responses by using a button box connected through a USB port. The buttons were labeled such that participants could always see which button corresponded to which answer. Trials were self-paced, and stimuli were presented on screen until a response was made, for a maximum of 15 s for each trial. All participants completed a practice block with feedback after every trial until they felt comfortable with moving on to the experimental task.

The task was administered under two conditions (High Interference and Low Interference), with a short break between conditions. The key trials in both conditions were high ambiguity object discriminations involving abstract blob-like objects (similar to the blobs in Barense et al., 2005, 2012). These objects consisted of three distinct features: an inner shape, outer shape, and a fill pattern (Figs. 2a–c). Although low-level features (shapes, colors, and fill patterns) repeated across trials, all objects were trial-unique. On each trial, two objects were presented simultaneously, and all objects were rotated between 15° and 165° to discourage a simple feature matching strategy. On match trials, all three features were identical (e.g., ABC vs.

TABLE 1.

Neuropsychological Test Results, Z-Scores in Parentheses

Measures	MCI 1	MCI 2	MCI 3	MCI 4	MCI 5	MCI 6	MCI 7
Age (yrs)	65	68	61	78	55	76	76
Gender	F	M	F	M	M	F	M
Education (yrs)	14	15	12	16	18	18	16
Diagnosis subtype	Amn Lang	Amn	Amn Lang	Amn Exec fx	Amn Lang Exec fx	Amn Lang	Amn
MMSE	24	23	28	28	30	30	29
MoCA	–	–	23	25	25	25	19
CDR	0.5	0.5	0.5	0	0.5	0.5	0.5
GDS	1	7	2	2	3	–	–
Beck Depression Inventory	4	–	1	–	12	–	–
JOLO	16	–	20	22	24	–	22
Logical memory I	15 (–0.16)	5 (–2.70)	14 (0.26)	11 (–0.78)	9 (–1.96)	14 (–0.33)	8 (–1.57)
Logical memory II	13 (–0.33)	4 (–2.39)	12 (0.12)	10 (–0.67)	8 (–1.82)	13 (–0.23)	6 (–1.64)
BVMT-R total recall	16 (–1.10)	–	25 (0.40)	15 (0.90)	13 (–2.00)	–	18 (–0.40)
BVMT-R delay recall	5 (–1.50)	–	9 (0.20)	5 (–1.10)	5 (–1.90)	–	9 (0.50)
CVLT word list memory delay	2 (–3.69)	3 (–1.71)	5 (–1.81)	5 (–0.30)	6 (–0.48)	7 (–0.05)	–
WAIS-R similarities	20 (0.33)	–	17 (0.00)	19 (0.33)	19 (0.00)	–	13 (–0.67)
Trails A	46 (0)	34 (–0.4)	52 (–1.20)	48 (–1.00)	15 (1.90)	27 (0.70)	56 (–1.40)
Trails B	117 (0)	171 (–1.80)	162 (–1.90)	102 (–0.10)	43 (1.10)	53 (1.3)	95 (–0.10)
Verbal fluency: FAS	23 (–1.90)	–	30 (–0.80)	24 (–1.50)	47 (0.10)	–	30 (–0.80)
Category fluency: animals	19 (–0.30)	17 (–0.20)	16 (–0.80)	10 (–2.30)	34 (2.30)	18 (–0.5)	10 (–2.30)
WAIS-R digit symbol	45 (0.00)	36 (0.00)	66 (1.33)	37 (0.00)	64 (1.00)	59 (2.00)	41 (0.33)
Boston naming test (no cue)	25 (–1.60)	30 (2.40)	21 (–1.80)	25 (–0.90)	25 (–1.80)	18 (–2.40)	–
Digit span: forward	6 (–0.92)	10 (1.41)	7 (–0.39)	9 (–0.33)	11 (1.55)	11 (2.33)	–
Digit span: backward	5 (–0.50)	6 (0.25)	4 (–0.99)	3 (–0.33)	10 (1.65)	9 (2.33)	–
Clock drawing	11 (0.52)	12 (1.63)	13 (2.74)	8 (–0.69)	13 (3.48)	13 (1.54)	–

“Amn” means single-domain amnesic, “Lang” means amnesic plus language, “Exec fx” means amnesic plus executive function. Individual cells for each patient represent raw data scores, parentheses reflect Z-scores. “–” indicates no data is available for that patient on that test. Neuropsychological tests: BVMT-R, Benton Verbal Memory Test—Revised (Benton et al., 1983); CDR, Clinical Dementia Rating (Morris, 1993); CVLT, California Verbal Learning Test (Delis et al., 2000); GDS, Global Deterioration Scale (Reisberg et al., 1982); the Beck Depression Inventory (Beck et al., 1961); JOLO, Judgment of Line Orientation (Benton et al., 1978); Logical Memory I and II (Wechsler, 1945); MMSE, Mini Mental Status Exam (Folstein et al., 1975); MoCA, Montreal Cognitive Assessment (Nasreddine et al., 2005); WAIS-R, Wechsler Adult Intelligent Scales—Revised (Wechsler, 1981), Boston Naming Test (Kaplan et al., 1983); Digits Forward; Digits Backward; and a Clock Drawing Test.

ABC; letters represent individual features). Critically, for non-match trials, only one feature differed (e.g., ABC vs. ABD; whether inner shape, outer shape, or fill pattern differed was fully counterbalanced). This high degree of feature ambiguity placed demand on high-level conjunctive representations and analysis of the object as a whole (Barens et al., 2012). The High Interference condition contained 88 consecutive trials of high ambiguity object discriminations (44 match and 44 non-match trials, intermixed in a pseudorandom sequence; Fig. 2b). Each Low Interference block also contained 88 trials, but unlike the High Interference condition, these blocks contained 30 high ambiguity object trials (15 match, 15 non-match) that were each interspersed with two trials containing photographs of easily discriminable everyday objects (58 trials, 29 match, 29 nonmatch; Figs. 2a,c). Importantly, the stimuli presented on photograph trials shared minimal features with the blob-like objects (i.e., they were color photographs of everyday objects, not black and white line-drawings) and thus, the degree of accumulated perceptual interference was much lower in the Low Interference condition. As such, we predicted that the

MCI patient group and the At-risk group would perform better on the Low Interference condition relative to the High Interference condition. We administered two blocks of the Low Interference condition, one before and one after the High Interference condition, to ensure that any observed deficits were specific to the buildup of interfering features and not fatigue or generic task-practice effects.

Control Task: Difficult Size

Following the completion of the interference task, participants were administered a control task that did not require conjunctive processing, but was matched in terms of difficulty to the High Interference condition (control task used previously in Barens et al., 2012). The procedures for the control condition were identical to the interference task described above except the stimuli were squares and participants indicated if they were identical (match) or different (nonmatch) (Fig. 2d). For nonmatch trials, the length of each side of the square was randomly varied from 67 to 247 pixels. The difference between

FIGURE 2. Participants indicated whether two simultaneously presented stimuli were a match or a nonmatch. All objects were rotated, and participants decided whether the objects were identical (a match) or different (a nonmatch). The critical trials were high ambiguity object discriminations involving blob-like objects. These objects were defined by three features: inner shape, outer shape, and fill pattern. For high ambiguity nonmatch trials, only one of these three features differed, and thus, these trials placed a demand on high-level conjunctive representations and analysis of the object as a whole. (a, c) For the Low Interference condition, a high ambiguity object trial was always followed by two trials involving perceptually distinct, colored objects (30 high ambiguity object trials in total).

(b) The High Interference condition was a straight block of 88 consecutive high ambiguity object trials. To avoid confounding effects of fatigue, the order of testing conditions was Low Interference 1, High Interference, and Low Interference 2. We compared performance on high ambiguity trials only. All objects were trial-unique, though the individual features (e.g., shape segments, fill patterns) repeated across trials. (d) In the Difficult Size control task, participants decided if two rotated squares were the same size. This condition could be solved on the basis of a single feature and did not tax conjunctive object representations. Healthy control participants found this condition to be more difficult than the High Interference condition. (Figure modified from Barense et al., 2012.)

the lengths of the squares varied between 9 and 15 pixels. For match trials, the two rotated squares were identical in size.

Planned Analysis: Interference Task

To examine performance on the interference task, we calculated a discriminability measure (d'), where correct responses of “different” to images that were different were designated as hits, and incorrect responses of “different” to images that were the same were designated as false alarms (MacMillan and Creelman, 1991). Scores of 100% or 0% for Hits and False Alarms were subjected to a standard correction whereby half a trial was either subtracted or added, respectively, to the actual number of trials that were designated Hits or False Alarms. Importantly, when calculating d' , we analyzed only the high ambiguity discrimination trials and did not include the photo object trials (for which performance was at ceiling). Thus, our critical trials were 88 trials in the High Interference condition and 30 trials in each Low Interference condition. These data were subjected to a 3×3 -repeated measures ANOVA with a within-subject factor of condition (Low Interference 1, High Interference, Low Interference 2) and a between-subject factor of group (MCI patients, At-risk group, healthy controls). We predicted that MCI patients and the At-risk group would be impaired on the High Interference, but not Low Interference, conditions, compared with controls. Given our directional hypotheses, all statistical tests on the experimental data were one-tailed unless stated otherwise.

Planned Analyses: Control Tasks

We calculated d' for the difficult size task in the same manner as described above. We then performed independent t -tests

to compare performance of MCI patients and those at risk for MCI to healthy controls. We predicted no significant differences in performance across groups.

RESULTS

Interference Task

Data from the interference task are shown in Figure 3. The results of our 3×3 repeated measures ANOVA (interference condition $\times$ group) revealed main effects of interference [$F(2, 66) = 15.79, p < 0.001$] and group [$F(2, 33) = 3.07, p = 0.03$], and an interference $\times$ group interaction [$F(4, 66) = 1.99, p = 0.05$]. Follow up t -tests showed that, as predicted, both the MCI patients and the At-risk group were impaired on the High Interference condition, compared with healthy controls [$t > 2.20, p < 0.02$], with no differences between the MCI patients and the At-risk group ($t(15) = 0.73, p = 0.48$, two-tailed). In contrast, by reducing the degree of perceptual interference, we were largely able to improve performance in both groups: neither group was impaired on the first Low Interference condition [$t < 0.81, p > 0.21$] nor were the MCI patients impaired on the second Low Interference condition [$t(24) = 0.80, p = 0.22$]. Unexpectedly, the At-risk group was impaired on the second Low Interference condition [$t(27) = 1.99, p = 0.03$]. Because the analyzed trials from the Low Interference condition still contained objects with low-level features (e.g., shape segments, fill patterns) that had repeated from previous conditions, a potential explanation for this impairment is that these At-risk participants were unable to recover from

FIGURE 3. d' scores for each group. MCI patients and the At-risk group were impaired on the High Interference condition, but their performance was largely rescued by reducing the degree of interference. There were no differences in performance on the Difficult Size control task, suggesting that the observed deficits are not driven by task difficulty. Error bars denote standard error of the mean. * $P < 0.05$ (comparisons of the MCI patient group and At-risk group relative to healthy controls).

the interference experienced in the previous High Interference condition. Future work is needed to establish the time course of these interference effects.

Reaction time data and proportion correct split according to match and nonmatch trials are shown in Table 2.

Control Task: Difficult Size

We compared performance of the At-risk group and MCI patients to healthy controls using independent t -tests and found that neither group was impaired [$t < 0.94$, $p > 0.18$] (Fig. 3). A paired t -test showed no evidence that control participants found the Difficult Size control as difficult as High Interference condition [$t(18) = 1.40$, $p = 0.18$, two-tailed]. Thus, the intact performance of the memory-impaired groups on the Difficult Size discriminations indicates that their impairment on

the High Interference condition was not simply due to fatigue from performing consecutive difficult discriminations. Table 2 shows the reaction time and proportion correct for match and nonmatch trials.

DISCUSSION

In this study, we tested amnesic MCI patients, older adults at risk for MCI, and healthy older adult controls on an object discrimination task that has been shown to recruit the PRC and to emphasize processing conjunctions of features (Barense et al., 2012). We administered the task under conditions of high perceptual interference (many repeating similar visual features shown across trials) and low perceptual interference (visually dissimilar features interspersed across trials). MCI patients and those at risk for MCI were impaired under conditions of High Interference, but critically, when we minimized perceptual interference by reducing the number of similar features viewed across trials, their performance improved. Notably, the deficits could not be attributed to generic task difficulty, as both MCI patients and At-risk participants performed normally on a single-feature discrimination task that was matched in difficulty to the High Interference condition. This study reveals striking convergence with findings in amnesic patients whose focal MTL lesions included the PRC (Barense et al., 2012) (see Supporting Information Fig. 1 for a direct comparison), and suggests that memory disorders involving the MTL may reflect a heightened vulnerability to visual interference.

These findings, when considered together with research in humans with focal MTL damage (Barense et al., 2012) and animals with selective PRC lesions (McTighe et al., 2010), provide support for the view that the PRC represents the conjunctions of features necessary to distinguish perceptually similar objects. In the Low Interference conditions, the MCI patients may have successfully used a single-feature strategy supported

TABLE 2. Reaction Time and Accuracy (Proportion Correct) for Each Participant Group

	Low Interference 1	High Interference	Low Interference 2	Difficult Size Control Task
Accuracy: match trials				
Controls	0.82 (0.13)	0.83 (0.11)	0.90 (0.07)	0.81 (0.17)
At-risk	0.79 (0.15)	0.73 (0.17)	0.90 (0.07)	0.79 (0.16)
MCI patients	0.81 (0.10)	0.78 (0.14)	0.90 (0.08)	0.78 (0.09)
Accuracy: nonmatch trials				
Controls	0.72 (0.21)	0.83 (0.11)	0.79 (0.12)	0.76 (0.13)
At-risk	0.71 (0.16)	0.75 (0.10)	0.71 (0.09)	0.71 (0.12)
MCI patients	0.69 (0.14)	0.74 (0.13)	0.71 (0.07)	0.75 (0.05)
Reaction times: all trials				
Controls	5,925.27 (2,002.27)	5,995.20 (1,277.71)	6,130.72 (1,788.44)	3,017.81 (1,091.72)
At-risk	6,639.39 (1,550.92)	6,695.56 (1,347.78)	6,724.54 (1,370.30)	2,858.29 (967.05)
MCI patients	7,551.99 (1,656.85)	7,396.72 (999.79)	7,089.37 (1,493.05)	2,970.14 (562.85)

Standard deviations shown in parentheses.

by intact regions upstream in the ventral visual stream (by definition, objects in the discrimination of ABC vs. ABD differed by a single feature: C vs. D, see Fig. 1). However, the repeated administration of multiple low-level object features (e.g., shapes, fill patterns)—as was the case in the High Interference condition—created massive interference at the level of the representations for these individual features. Under these conditions, a more complex representation that binds the features into unique objects is necessary to resolve the interference from repeating features. Put differently, when a constant stream of visual information creates large-scale feature-level interference from irrelevant features processed on previous trials, a more elaborate object-level representation will be resistant to the feature-level interference. We propose this more complex object-level representation to be contained within PRC. In addition to processing the complex conjunction of features comprising the object, recent research suggests that the PRC may also protect from visual interference by “suppressing” the representation of the lower-level features represented in earlier regions of the visual stream (Peterson et al., 2012).

These results complement a growing body of evidence suggesting that memory impairments following MTL damage may be due to an increased vulnerability to interference (Cowan et al., 2004; Loewenstein et al., 2004; Della Sala et al., 2005; Dewar et al., 2009). For example, one study found that recall of a story in patients with MCI was increased by a remarkable 35% under conditions of Low Interference (during the delay participants reclined in a dark, quiet room) compared with recall under standard interference (a 1-h delay filled with psychometric tasks) (Della Sala et al., 2005). A similar result was reported for amnesics with focal brain damage (Cowan et al., 2004). The interference in these studies may have been from interfering mental activity and memory formation (Wixted, 2004), and/or it may have been due to interference from similar visual information processed during the psychometric tasks. Consistent with the latter idea of visual interference from perceptually similar information, sensory restriction rescued an object recognition memory deficit in rats with perirhinal lesions (McTighe et al., 2010), aged rats (Burke et al., 2010), and in a mouse model of Alzheimer’s disease-typical amyloid- β pathology (the tgCRND8 mouse, Romberg et al., 2012). The present results extend these findings from the mnemonic domain to the visual discrimination of trial-unique stimuli.

Although we prefer to consider these results in terms of impoverished object representations impairing perception, it is worth noting that there is a working memory component to the task. Although the objects were displayed simultaneously, the discriminations required a series of eye movements and comparisons across objects. Thus, it is possible that the observed deficit could be related to problems with working memory. There has been a recent surge of research indicating that short-term memory may be impaired following MTL damage (e.g., Hannula et al., 2006; Nichols et al., 2006; Olson et al., 2006; Warren et al., 2010; although see Jeneson et al., 2010), with evidence suggesting that the MTL is important in online processing of highly similar visual objects (Warren et al.,

2011a,b). We are certainly not opposed to the notion that MTL structures are important for working memory. Indeed, it seems highly likely that the conjunctive representations processed by PRC are essential for online maintenance of information while shifting attention from one object to the other (see also Barense et al., 2012). We would additionally argue, however, that these representations are critical for any cognitive task that requires them, which includes long-term memory, working memory, and complex object perception. In support of this, other studies have demonstrated perceptual deficits on tasks with no working memory component (i.e., perception of single objects and figure-ground perception of familiar object configuration), suggesting that the deficits observed here reflect a more fundamental deficit in representing complex objects (Lee and Rudebeck, 2010; Barense et al., 2011b).

It is important to note that due to the unavailability of structural MRI scans of participants in the current study, we cannot conclusively localize the observed deficits to PRC pathology. It is very well established that the hippocampus and entorhinal cortex are affected very early, likely even first, in MCI (Wakabayashi et al., 1994; Harris et al., 2010; Devanand et al., 2012). The PRC is heavily connected to these structures (e.g., Suzuki and Amaral, 1994), and is part of the neural circuit affected early in MCI (Mitchell et al., 2002; Bell-McGinty et al., 2005; Schuff and Zhu, 2007; Zhang et al., 2012). Thus, it is not surprising that PRC function would be compromised. Consistent with this, the profile of performance in both the MCI patients and those at risk for MCI is remarkably consistent with findings from research that allows more precise localization of the PRC: (1) animal studies that have demonstrated object discrimination deficits and interference effects after precise, localized PRC lesions (Buckley et al., 2001; Bussey et al., 2002, 2003; Bartko et al., 2010; McTighe et al., 2010), and (2) functional neuroimaging revealing PRC activity in healthy participants during the discrimination task reported here (Barense et al., 2012) and other tasks taxing complex object perception (Devlin and Price, 2007; Lee et al., 2008; O’Neil et al., 2009; Barense et al., 2010a, 2011a). In addition, based on the intact performance of amnesic patients with focal hippocampal damage (Barense et al., 2012; Supporting Information Fig. 1), we can localize our deficits to nonhippocampal structures.

One notable finding of the present study is that although the At-risk participants do not have diagnosed MCI, their performance suggests that a clinical exam might lead to an MCI diagnosis. However, now, they appear to be “unworried unwell.” In other words, these volunteers from the community presented with no subjective memory complaint, but had an objective cognitive deficit. The subjective memory complaint in question is a vital component of diagnosis using the original Peterson criteria (Peterson et al., 1999), and it remains to be seen whether these participants would be diagnosed with MCI. Nonetheless, the MoCA has been identified as a sensitive brief measure in detecting cognitive impairment (Nasreddine et al., 2005; Markwick et al., 2012). Additionally, the present study indicates that and those who fall below norms on the MoCA are vulnerable to visual interference. In fact, an additional

correlational analysis investigating performance across all groups on all tasks showed that MoCA scores predicted performance on the High Interference task ($r(33) = 0.54, p < 0.01$, Bonferroni corrected), but not the other three conditions [$r(33) < 0.29, p > 0.09$, Bonferroni corrected]. We are currently following up the At-risk participants on a number of cognitive and physiological longitudinal assessments.

In conclusion, these data illustrate that reducing perceptual interference improves performance on a discrimination task in MCI patients and those at risk for MCI. Furthermore, these data add additional support to the idea that damage to the complex, conjunctive representations processed by PRC causes an increased susceptibility to object-based perceptual interference, which leads to deficits in both memory and perception.

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