Investigating the Mechanisms of Forgetting in Aging Using Eyetracking

by

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Abstract

Recent studies in rodents (McTighe et al, 2010; Burke et al, 2010) have suggested that forgetting is caused by the misidentification of novel stimuli as being familiar, matching the predictions of the representational-hierarchical model of Saksida & Bussey (2010). Here, we tested this idea in humans. Three groups of participants (young, healthy elders, elders at-risk for MCI) viewed novel and repeated stimuli in a continuous viewing task while their eye movements were recorded. According to the eye-movement based memory effect (Ryan et al, 2000) individuals make fewer fixations on items which are perceived as familiar. As interference increased, eye-movements directed to the novel stimuli declined, indicating these novel items were perceived as familiar. This effect was stronger in groups more vulnerable to interference (eg. at-risk elders). These results suggest that forgetting in humans, like rats, is driven by the misidentification of novel items as being familiar.
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1 Introduction

Imagine walking down the street with your grandmother. Suddenly, you notice a marching band (wearing green jackets with smartly polished buttons) jogging by briskly: they are running late to the Christmas parade. The two of you arrive at the parade, find a nice spot to stand, and spend some happy hours watching countless other floats go by. As the two of you are leaving, you ask her: “Grandma, remember that marching band we saw on the way here? They looked so cold that they marched twice as fast as all the others.” She laughs and replies, “Those green jackets aren’t as warm as they look. What was your favorite float today?” Thinking back, you mention that you really liked the one with Santa’s village. She thinks for a moment, then replies: “I’m sorry honey; I don’t remember seeing that one.”

Why does Grandma remember the marching band so well, but can’t remember the floats that followed? Perhaps she can only remember so many items at a time, and so once the parade started, she was unable to encode many of the floats you saw together. Or perhaps she did encode some details about everything she saw, but because there were so many floats, she wasn’t able to tell whether her memories come from one float or many different floats. If the first theory is true, then many floats never entered Grandma’s memory (or they did, but subsequently decayed). If you were to show her your tape of the parade later, she would think that she is seeing those floats for the first time (treating them as novel). This account is closer to the decay theory of forgetting. But if the second theory is true, then while watching your tape, she would feel as though every float looks somewhat familiar, even the ones from a different year’s parade that you accidentally left on the tape. In other words, she would be treating novel items as being familiar, and in a déjà vu like haze, she can’t figure out which floats she actually did see before. This account is closer to the interference theory of forgetting.

Since the work of Jenkins & Dallenbach in 1924, interference theory has been central to accounts of forgetting (Wixted, 2004). It proposes that forgetting is driven by additional learning of other material, especially material similar to the material that one is trying to remember. However, the mechanisms underlying interference remain unclear. The representational-hierarchical model of Saksida & Bussey (2010) provides some fresh insight into what mechanisms might underlie the effects of interference.
1.1 The Representational-Hierarchical Model

An extensive body of work spanning the last five decades has established the central role of the medial temporal lobes (MTL) – consisting of the hippocampus, and the entorhinal, perirhinal and parahippocampal cortices - in forming memories. While one dominant theory argues that the MTL forms a dedicated system for the formation of declarative memory (Squire, Stark & Clark, 2004; Squire & Wixted, 2011), the representational-hierarchical model proposes that MTL structures contain complex representations of objects and scenes, which underlie both mnemonic and perceptual processes (Saksida & Bussey, 2010).

A number of experiments have provided strong evidence that MTL structures may play a role in perception. Eacott, Gaffan & Murray (1994) reported that monkeys with perirhinal cortex lesions were impaired not only in a delayed-matching-to-sample task, but also on a simultaneous-matching-to-sample task, where the target image that the monkeys had to identify was presented simultaneously with the lure images they monkeys had to avoid. Because the images were presented simultaneously, demands on memory were extremely small. Thus, these findings suggested that in addition to its mnemonic role, the perirhinal cortex also played a role in visual perception. However, this effect was found only when trial-unique stimuli were used. A later study by Buckley & Gaffan (1998) provided additional insight into the nature of the perirhinal cortex’s perceptual role. When monkeys were shown a configural learning task in which they learned that certain combinations of letters (e.g., AB) were rewarded, but the individual letters could appear in rewarded or non-rewarded combinations (e.g., AB and BC are rewarded, but AC is not), monkeys with perirhinal cortex lesions took much longer to learn the task than non-lesioned monkeys. This suggested that the perirhinal cortex is responsible for processing conjunctions of stimuli.

Bussey, Saksida & Murray (2002) further clarified the perceptual role of the perirhinal cortex. Monkeys discriminated between objects under varying conditions of “feature ambiguity.” In this concurrent object discrimination task, the monkeys were rewarded for correctly selecting one particular object from a pair of objects. In the minimum feature ambiguity condition, a single feature allowed the monkeys to identify whether an object was the rewarded object or not. However, in the maximum feature ambiguity condition, only the combination of two features would allow monkeys to distinguish which object was rewarded. Thus, in the maximum
ambiguity condition each feature appeared in both a rewarded and a non-rewarded object, whereas in the minimum ambiguity condition the features did not repeat across objects. Perirhinal cortex-lesioned monkeys were unimpaired at the minimum feature ambiguity condition, but were severely impaired at the maximum feature ambiguity condition. This suggested that the perirhinal cortex is necessary to resolve feature ambiguity and to distinguish between objects with overlapping features. Barense et al. (2005) extended these findings to humans: Human patients with lesions that included both the hippocampus and the surrounding cortex (including perirhinal cortex) were impaired at object recognition when feature ambiguity was high, but not when feature ambiguity was low. A control group of patients with focal hippocampal lesions performed similarly to healthy controls across both feature ambiguity conditions. These results suggest that damage to the perirhinal cortex (in the patients with lesions spanning both the hippocampus and the perirhinal cortex) is responsible for the impairments in distinguishing feature ambiguity in objects.

Based on the results of numerous studies (including those mentioned above), Bussey & Saksida (2002, 2010) proposed a representational-hierarchical model of MTL function. According to this model, the MTL forms an extension of the ventral visual stream (VVS), in which each successive region (moving anteriorly in the brain from the primary visual cortex (V1) towards the MTL) contains increasingly complex representations, comprised of conjunctions of more simple representations. These regions form a representational hierarchy, with each level of representations supporting both mnemonic and perceptual functions (See Figure 1 below).
Figure 1- a) The representational-hierarchical model in the brain. Moving anteriorly from V1, successive brain regions contain increasingly complex representations, comprised of conjunctions of simpler representations. b) Simplified diagram of the representational-hierarchical model applied to anterior VVS regions and perirhinal cortex. The perirhinal cortex contains object representations, which are conjunctions of feature representations (in anterior VVS regions). Each object representation comprises a unique conjunction of features, but different objects can include the same features (in this example, features B and C are shared by the two object representations). Note that what exactly constitutes a visual feature has not been fully elucidated. However, representations in the perirhinal cortex are approximately at the level of complexity of an everyday object.

In this model, the anterior regions of the VVS support representations of visual features. The perirhinal cortex supports representations of objects, which are comprised of unique conjunctions of visual features (see Figure 1 above). However, each visual feature represented in the anterior VVS is not unique to any specific object represented in the perirhinal cortex. Rather, a visual feature might be found in many different object representations.

This model explains why perirhinal cortex lesions impair the ability to handle feature ambiguity. An intact perirhinal cortex contains the complex conjunctive representations that indicate which features should be bound into which objects. This allows an individual to uniquely represent distinct objects and distinguish between different objects with many overlapping features. When the perirhinal cortex is damaged, viewers lack these complex object-level representations, and are forced to rely on feature representations processed by anterior VVS regions. Each feature is not necessarily unique to one particular object. Because of the overlap in features among similar objects, damage to the perirhinal cortex impairs the ability to distinguish between perceptually similar objects. Consider the example of distinguishing between a tennis ball and a green apple. With a perirhinal cortex, separate object representations are formed for each item; thus they can easily be distinguished. Without a perirhinal cortex, an individual must necessarily to rely on
feature representations. Because a tennis ball and an apple share many common features (e.g. color, roundness, size, etc.), it is very difficult to distinguish them on the basis of features alone.

One key prediction of this model is that damage to the perirhinal cortex will cause increased vulnerability to interference. When complex object-level representations are not present, it becomes harder to distinguish between similar items. Consider the case where a number of similar items are seen in quick succession (e.g. floats in a parade). With a perirhinal cortex, each float would have its own unique representation, which activates only when that exact exemplar of a float is seen. Later, we can distinguish whether or not we have seen a particular float before. Without a perirhinal cortex, each float would activate a number of feature-level representations. Because floats tend to have many similar features, the same group of representations would be activated many times – even though the individual floats themselves are different. Now, if we are shown another float and asked if we saw it before, the feature-level representations would signal familiarity: even though the entire float is actually novel, the individual lower-level features are familiar. Thus, the representational-hierarchical model suggests that perirhinal cortex damage causes an increased vulnerability to interference because novel items are mistakenly perceived as familiar.

1.2 Forgetting Caused By Perceiving Novel Items as Familiar under High Interference Conditions: McTighe et al. (2010)

McTighe et al. (2010) sought to test the prediction of the representational-hierarchical model that damage to the perirhinal cortex would lead to an impaired ability to handle object-level interference, and that this impairment would be due to perceiving novel items as though they are familiar. They compared the performance of perirhinal cortex-lesioned rats against healthy rats in a modified spontaneous object recognition (SOR) task under conditions of high- and low-interference.

In the modified SOR task, the amount of time a rat spends exploring an object is taken to be a measure of how novel they perceive the stimuli to be (Ennaceur & Delacour, 1988). Rats will spend more time exploring objects they perceive to be novel, and less time exploring objects they perceive to be familiar. An analogous phenomenon can be observed in humans. When shown a stimulus they perceive to be novel, humans direct an increased amount of their viewing time
towards it, and make more visual fixations on the stimulus compared to a stimulus they perceive to be familiar (Althoff, 1998 as cited by Hannula et al, 2010)

Figure 2 - Task from McTighe et al. (2010)

In the initial study phase of McTighe et al (2010), rats were placed into a Y-maze and allowed to explore two identical objects for three minutes (Figure 2) Then, the rats were either returned to their holding cages for one hour (high-interference) or placed in a visually restricted environment (low interference) for the same period of time. During a subsequent test phase, the rats were returned to the Y-maze, and allowed to explore either a pair of novel objects, or the same pair of (repeated) stimuli they had previously explored in the study phase. The dependent measure was the ratio of exploration time of test phase objects to the exploration time of study phase objects. Comparable exploration time at test compared to study was taken to indicate that the rat viewed the test objects as novel. This was indicated by a test:study ratio close to 1. Conversely, reduced exploration time at test compared to study was taken to indicate that the rat viewed the test objects as familiar. This was indicated by a test:study ratio that was much less than 1.

There are four possible outcomes in the SOR paradigm: 1) a novel item is correctly identified as being novel, 2) a novel item is mistakenly identified as familiar, 3) a familiar (repeated) item is mistakenly identified as novel, and 4) a familiar (repeated) item is correctly identified as familiar. The test:study ratio is different for each of these outcomes. A high test:study ratio for a
novel object suggests a correct identification of the object as novel, while a low test:study ratio for a novel object suggests that it is being treated as a familiar object. Likewise, a high test:study ratio for a familiar object suggests that it is being mistakenly identified as a novel object, while a low test:study ratio suggests that it is being correctly identified as a familiar object.

As shown in Figure 3, the control rats showed a significantly higher test:study ratio for the novel high-interference and novel low-interference items, compared to the repeated items. This result suggested that the control rats treated the novel stimuli as novel stimuli, and the familiar stimuli as familiar stimuli. Like the control rats, the rats with perirhinal cortex lesions also showed a significantly higher test:study ratio for the novel low-interference items compared to the repeated items, indicating that they were able to identify the low-interference items as novel. However, under conditions of high interference, this increased test:study ratio disappeared. In fact, they showed a similar test:study ratio for the novel high-interference items as they did for the repeated items.
items, suggesting that they were viewing these novel high-interference items as if they were familiar items.

These results suggest that the perirhinal cortex is critical to normal object memory under conditions of high interference, and that memory impairment following perirhinal lesions is due to novel stimuli being mistakenly identified as familiar. In the low-interference condition, lesioned rats behaved exactly like non-lesioned rats: They demonstrated increased exploration of novel objects and reduced exploration of repeated objects. However, in the high-interference condition, the lesioned rats explored novel objects less than control rats, and about the same amount that both groups explored repeated objects. This suggests that the lesioned rats treated novel stimuli as if they were familiar.

These results are consistent with the predictions of the representational-hierarchical model. When the lesioned rats were returned to their cages in the high-interference condition, their feature representations were activated by the other objects in their surroundings (e.g. food pellets, wood shavings, cage bars). These features overlap with some features of the objects used in the study. When the lesioned rats saw the test objects, some of the same features were re-activated. This led to their mistaken identification of the novel test objects as being familiar. In contrast, when the lesioned rats were placed in the visually restricted environment in the low-interference condition, there were no other objects they could see. As a result, no additional feature representations were activated during the delay. Thus, they were able to use their feature representations of the object they saw during the study phase to correctly identify which object was novel or repeated at test (See Bartko et al., 2010, for similar results using stimuli with greater/lesser degrees of feature overlap).

1.3 Aging & Interference

Interference effects are not limited to rats alone; they can also be found in humans. It is well established that older adults are more vulnerable to the effects of interference than younger adults (Hasher, Lustig and Zacks, 2007). For example, one classic paradigm to assess the effects of interference is the AB-AC paradigm. In this paradigm, participants first learn one list of word pairs (e.g. ant-tree), then subsequently learn a second list of word pairs (e.g. ant-bacon). The first words in both lists are the same, but they are paired with different words in each list, causing interference. Performance of older adults is impaired by both proactive interference – when
something learned earlier reduces memory for something learned later (Ebert & Anderson, 2009) - as well as by retroactive interference – when something learned later reduces memory for something learned earlier (Hedden & Park, 2001).

The vulnerability of older adults to interference extends to visual object recognition as well. Toner et al. (2009) employed a continuous recognition task to test false recognition in elderly participants. Participants first studied a number of images of individual items. In a subsequent test phase, participants were asked to classify whether a particular item was repeated (had been seen in the study phase), novel and dissimilar to any previously viewed items (that is, they shared few common features with previously viewed items, corresponding to the “low-interference” test condition in our study, see Methods below), or novel and perceptually similar to a previously viewed item (sharing many common features with previously viewed items, corresponding to the “high-interference” test condition in our study, see Methods below). While older adults were able to classify items that belonged to the first two categories accurately, they had difficulty correctly classifying items that were novel, but perceptually similar to previously studied items. Instead, they identified these items as being either familiar or novel and perceptually different from previously viewed items. These results suggest that forgetting in older adults under conditions of increased interference could be mediated by confusing novel stimuli as familiar stimuli (as hypothesized by the representational-hierarchical model), especially when the novel stimuli have many features in common with other previously viewed stimuli. However, these results are not very clear, possibly because when asked to make an explicit novelty judgment when they had little confidence, older participants chose one of the three possible classifications randomly.

A recent study by Burke et al. (2010) suggested that interference in aging also arises from the mistaken perception of novel stimuli as being familiar, rather than the other way around. Young and aged rats were tested on a modified SOR paradigm similar to that described in McTighe et al., (2010). Between study and test, the rats were returned to their cages, where they were exposed to other objects which could activate the same feature representations found in the study items (as in the “high-interference” condition of McTighe et al, 2010).
Figure 4 - Re-plotted results from Burke et al. (2010), showing test:study ratio for younger and aged rats exploring repeated and novel test objects. Note that aged rats demonstrated reduced exploration for the novel objects, treating them as familiar objects, just like the PRc lesion rats from McTighe et al. (2010).

These findings (Figure 4) provide a striking replication of deficits observed in rats with perirhinal lesions (McTighe et al., 2010). Like the perirhinal cortex-lesioned rats, the aged rats also explored the novel stimuli less than the younger rats, and at a comparable rate to the repeated stimuli, suggesting that they were perceiving the novel stimuli as being familiar. By comparison, the younger rats showed increased exploration of novel stimuli compared to repeated (familiar) stimuli. This demonstrated that they were able to correctly identify each group of stimuli. These findings provide strong evidence that forgetting in aging is also driven by the mistaken perception that novel items are actually familiar.

Older adults with diagnosed memory disorders - eg. Mild Cognitive Impairment (MCI) or Alzheimer’s Disease (AD) - appear to be more vulnerable to the effects of interference. For example, Ebert & Anderson (2009) reported that elderly participants with amnestic MCI (a diagnosis characterized by greater memory loss than in healthy aging, with a high conversion rate to AD) showed stronger effects of proactive interference (as tested using an AB-AC paradigm) than an age-matched group of healthy elders. Della Sala et al (2005) reported that MCI patients performed much worse at verbal recall after a delay, if that delay was filled with
psychometric tests (high-interference) compared to sitting quietly in a dark room (low-interference). Loewenstein et al. (2004) reported increased proactive and retroactive interference in Alzheimer’s disease (AD) patients and MCI patients on a recall test for everyday objects, compared to healthy elders.

1.4 Perirhinal Cortex Changes in Aging & MCI/AD

Given that increased vulnerability to interference is associated independently with both perirhinal cortex lesions - as detailed in McTighe et al. (2010) – as well as with aging and memory disorders (Burke et al, 2010; Hasher, Lustig, Zacks, 2007; Della Sala et al., 2005), one logical question is whether perirhinal cortex decline is associated with normal aging and with the development of MCI and/or AD.

Studies have not shown a significant reduction in perirhinal cortex volume in healthy aging. However, the older groups in these studies had lower average perirhinal cortex volumes than younger groups (even though the difference between them was not significant). An autopsy study using 15 brains defined the perirhinal cortex by cytoarchitectural analysis and showed that a group of older adults (over 70 years old) had a (non-significant) 4% reduction in perirhinal cortex volume compared to a younger group (Insausti et al., 1998b). In a different study using structural imaging scans, older adults had, on average, less perirhinal cortex volume and less perirhinal cortex surface area, compared to younger adults, but these differences did not reach significance (Dickerson et al., 2009).

In contrast, the association between reductions in perirhinal cortex volume and MCI/AD are well established. Amnestic MCI patients showed reductions in grey matter volume in both the left (Bell-McGuinity et al., 2005) and the right entorhinal and perirhinal cortices (Schmidt-Wilcke et al., 2009). Alzheimer’s disease is also associated with significant volume declines in perirhinal cortex. Volumetric studies have demonstrated volume reductions of 27% bilaterally (Juottonen et al., 1998) and 42% in the right hemisphere and 31% in the left (Teipel et al., 2006). Beyond reductions in volume, Alzheimer’s disease has also been linked to significant cortical thinning in the perirhinal cortex (Dickerson et al., 2009).
1.5 Eyetracking as Measure of Novelty in Humans

To investigate the mechanisms of forgetting in humans, a measure of novelty detection analogous to exploration time in rodents was necessary. Ennaceur & Delacour (1988) suggested that visual preference in primates was similar to exploration time in rodents. When shown a familiar stimulus, humans typically demonstrate an eye-movement based memory effect (Ryan et al., 2000), making more fixations and sampling more regions of interest than when viewing a novel stimulus compared to a familiar stimulus (see Figure 5 below). This effect has been demonstrated widely, in both faces (Althoff, 1998, as cited by Hannula et al., 2010; Heisz & Shore, 2008) and in scenes (Ryan et al., 2000). This effect is analogous to the increased exploration of novel objects seen in rats.

Figure 5 – Reduced viewing (fewer fixations, fewer regions sampled) for repeated scenes, compared to novel scenes. Figure reproduced (with slight alterations) from Ryan et al. (2000)

One noted advantage of using eyetracking, as Hannula et al. (2010) points out, is that “we gain the ability to test memory under circumstances in which behavioral reports may not (or cannot) be reliably obtained” (p. 2). This was useful in the present study, which depended on analyzing how participants would respond to high-interference images, which have a high degree of feature overlap with other images shown in the study. In this situation, verbal report has two disadvantages. Firstly, because these judgments are difficult, participants would have had low confidence in their judgments, leading to increased variability in our results. Secondly, when participants are asked to make a conscious judgment of novelty, additional cognitive and
mnemonic processes may be invoked, changing the nature of the memory trace for the particular image in question. By using eyetracking, we were able to avoid these complications.

Eyetracking studies conducted with MCI and AD patients showed reduced viewing of novel stimuli compared to repeated (familiar) stimuli. In a visual paired-comparison task contrasting a novel and a repeated picture, MCI patients demonstrated reduced viewing of the novel picture if a two-minute delay was introduced between the study and test phases (Crutcher et al, 2009). AD patients also showed reduced viewing of novel visual stimuli compared to healthy controls (Daffner et al., 2009). While the reduced viewing of novel stimuli in these patients was reminiscent of the reduced exploration of high-interference novel stimuli in perirhinal cortex-lesioned rats in McTighe et al. (2010), it is important to note that the visual-paired comparison task does not allow for comparisons to be made between study and test phases (since only one image is presented at study, but at test, a novel and a repeated image are presented together), making it impossible to disentangle whether novel stimuli are being perceived as familiar, or if familiar stimuli are being perceived as more novel.

1.6 Study Outline & Hypothesis

The goal of the present study was to investigate how forgetting is mediated in older humans (both healthy elders, and elders thought to be at-risk for MCI). The Montreal Cognitive Assessment Test (MoCA) offers a quick method to test for possible MCI (Nasreddine et al., 2005). Like the Mini-Mental Status Exam (MMSE), the MoCA tests a wide variety of cognitive domains, including memory, spatial perception and attention. More importantly, the MoCA has a much higher sensitivity for detecting MCI (around 90%) compared to the MMSE. Eye movement monitoring was used to provide a measure of whether an object was perceived as novel or familiar. Interference was manipulated by the amount of feature overlap between the images seen at study and the novel test images seen at test, with high-interference images sharing a large number of features with previously studied images and low-interference images sharing fewer features in common with previously studied images. Based on the representational-hierarchical model, we predicted that older humans would confuse novel high-interference stimuli as being familiar, like the perirhinal cortex-lesioned rats of McTighe et al. (2010) and the aged rats in Burke et al. (2010). We further predicted that this effect would be stronger for at-risk elders than healthy elders.
2 Methods

2.1 Participants

Thirteen young participants (12 female, mean age: 20.9 years, range: 19-25) were recruited from the University of Toronto community using flyers. Twenty-four elderly participants (20 female, mean age: 72.8 years, range: 65-80) were recruited from the community using the Adult Volunteer Pool administered by the Psychology Department of the University of Toronto. Elderly participants were tested using the Montreal Cognitive Assessment Test (MoCA), (Nasreddine et al, 2005). Eleven elderly participants scored 26 or above on the MoCA, four elderly participants scored 25 on the MoCA, and nine elderly participants scored 24 or below on the MoCA. The four participants who had a MoCA score of 25 were excluded from this analysis because this score cannot be unambiguously interpreted as evidence of mild cognitive impairment based on the MoCA norms (Nasreddine et al, 2005). One participant from the group which had MoCA scores of 24 or below was excluded because they could not be successfully calibrated on the eyetracker. The remaining participants were classified into two groups on the basis of their MoCA scores. Eleven elderly participants were classified as healthy elders (10 female, mean age = 71.3 years, range = 65-79) and eight participants were classified as at-risk elders (6 female, mean age = 74.9 years, range = 65-80).

All participants were fluent English speakers, and had normal or corrected-to-normal vision, with no color blindness. Participants were screened for neurological disorders or brain damage (from stroke or trauma).

All participants gave informed written consent after being informed about the nature of the experiment and its risks. This research received ethical approval from the Research Ethics Board of the University of Toronto. All participants received monetary compensation for their participation.

2.2 Equipment & Stimuli

The task was run on a Dell Latitude laptop, and presented on a connected 21.2-inch (36x30cm) desktop monitor at a resolution of 1024x768. The task was presented using Experiment Builder (SR Research, Mississauga, ON). Eyetracking measures were recorded using an Eyelink 1000 desktop-mounted eyetracking system, sampling at a rate of 1000 Hz with a spatial resolution of
0.01 degrees. Participants were positioned 55cm away from the monitor, with their heads placed on a chin-rest to limit head motion. Prior to testing, a nine-point calibration was performed. This was repeated until the average gaze error was less than 1 degree, and no point had a gaze error exceeding 1.5 degrees. Prior to every trial, drift correction was performed. Nine-point calibration was repeated if drift exceeded 2 degrees.

144 unique images of single objects were used in this study, but not all images were seen by every participant due to counterbalancing. Some images were seen multiple times (see Figure 6 below). Images were collected from the Hemera Photo Clip Art collection (Hull, QC) or online from Google Image Search (Mountain View, CA), used under the fair dealings clause of the Copyright Act of Canada. All images were of real-world objects, which fell into 12 semantic categories (socks, coffee mugs, heels, lamps, sofas, electric guitars, handbags, engagement rings, teapots, umbrellas, throw pillows and scarves). All images were smaller than 600x600, and except for a few long, thin objects (socks, lamps) at least 250 pixels on the shorter dimension. All images were presented on a grey background.

Data analysis was conducted using SR Research’s DataViewer (Mississauga, ON) to extract the number of fixations/image from the eyetracking data. Subsequent data analysis was performed using SPSS 18 (Somers, NY) and Microsoft Excel (Richmond, WA).

2.3 Task

Participants viewed 172 individual images, sequentially presented individually on a grey background. They were instructed to press the space bar when a target black square appeared on the screen. Of the 172 images, 30 were black squares (approximately 1 black square for every 5.5 normal images). Each image was presented for 5s, with a 1s inter-stimulus interval and drift correction between images.

The images were organized into 6 blocks, each of which consisted of images of individual everyday items that have the same basic-level name (e.g., coffee mugs, electric guitars, engagement rings, handbags, heels, lamps, scarves, socks, sofas, teapots, throw pillows and umbrellas).

Each block was divided into study and test phases. During the study phase, a variable number of items were presented, three times each, with every item presented once before any items were
repeated (see the top half of Figure 6 below). Althoff (1998), as cited by Hannula et al. (2010) noted that at least three repetitions of a studied face were necessary to observe differences in the viewing patterns for novel faces in contrast to repeated faces. Ryan et al. (2000) also used three study viewings. Only in the first presentation of an image were the items completely novel to participants. Thus, this served as our benchmark for how many fixations a novel item should receive. Because our test images were viewed only once each, only these “first-viewing study” images were directly comparable to our test images. Thus only these study images were used for our analyses.

During the test phase, three types of images are presented: 1) repeated images, which were identical to images in the study phase (of the same block), 2) high-interference images, which were novel images that shared many features with images previously viewed in the study phase, and 3) low-interference images, which were novel images that did not share many features with images in the study phase (See Figure 6 below). All three types of test images were interspersed together during the test phase. The number of images in each category of the test phase was equal to half the number of unique study images. For example, in a block with 2 unique study images, the study phase contained 6 images: those 2 images repeated three times each. The test phase consisted of 3 images: 1 repeated image, 1 high-interference image and 1 low-interference image.

Figure 6 - Example block, showing the study phase (with three repetitions of each unique study image) and the test phases (with repeated, high-interference, and low-interference trials).
To manipulate the degree of interference across blocks, block length varied from 18 images in total (4 unique study images) to 36 images in total (8 unique study images). To simplify the findings of this study, data reported below is collapsed across the different block lengths.

There were two different versions of the task. In each version, six different categories of items were shown, to minimize the possibility that any effects observed were caused by the selection of particular categories of items used. The order of images presented was pseudo-randomized. Among each age group (young and elderly), half of the participants received one version of the task and the other half received the other version.

2.4 Data Analysis

Using DataViewer (SR Research, Mississauga, ON), the number of fixations per image was computed. Fixations were separated by saccades, which were defined as any eye movement with a velocity $\geq 30^\circ/s$, an acceleration $\geq 8000^\circ/s^2$ and a movement of at least $0.1^\circ$. A region of interest was drawn to include the body of each image, with an additional 15-pixel margin; all fixations outside this region of interest were ignored for the purposes of this analysis. The average number of fixations per image category (first-viewing study, repeated, low-interference, high-interference) was computed for each participant. Only the first viewing of each study image was considered, because only at that viewing is each image entirely novel. This makes it possible to compare the viewing of novel stimuli at study with novel stimuli at test (in the low-interference and high-interference image categories). The number of fixations for the test image categories (repeated, low-interference, and high-interference) was divided by the average number of fixations for the first-viewing study image category, giving a test:study ratio for each of the three test image categories. Normalizing by the number of fixations in study allowed comparisons between participants who differed in how many fixations they made overall. The relative proportion of fixations directed at each type of image provided a measure of how novel images in a particular category are perceived to be. These test:study ratios served as the dependent variable for our analyses.

We performed a repeated-measures ANOVA with image category (repeated, low-interference, and high-interference) as a within-subjects factor and participant group (young, healthy elders, at-risk elders) as a between-subjects factor. If the interaction between image category and participant group is significant, we planned to investigate how viewing of low-interference and
high-interference stimuli compared to repeated stimuli (by conducting paired-samples t-tests) and first-viewing study stimuli (by conducting one-sample t-tests) in each participant group separately. We also planned to investigate how viewing of stimuli in each image category differed across groups using independent-samples t-tests.

3 Results

3.1 Predictions

According to the representational-hierarchical model of Saksida & Bussey (2010), impairments in recognition memory are mediated by the false identification of novel stimuli as familiar (i.e. like repeated stimuli). In contrast, a decay hypothesis would suggest that impairments in recognition memory are mediated by the false identification of familiar (repeated) stimuli as novel. Measurement of the eye-movement based memory effect allows us to judge between these two hypotheses. A decrease in viewing to novel stimuli would indicate they are being viewed as though they are familiar (consistent with the representational-hierarchical model). By contrast, an increase in viewing to repeated stimuli would indicate that familiar stimuli are being viewed as though they are novel (consistent with a decay hypothesis).

In this study, interference was manipulated across our image category, and the ability to handle interference changed across groups (with the young participants being more able to handle interference than the healthy elders, who are more able to handle interference than the at-risk elders). As a result, both the representational-hierarchical model and the decay hypothesis predict that there will be a significant interaction of image category (repeated, high-interference, low-interference) by experimental group (young, healthy elders, at-risk elders). However, they differ in their predictions for t-tests that comprise that interaction. These are outlined in turn below.

The young participant group should have no memory impairments. Since they have intact perirhinal cortices, they should be least vulnerable to interference. Both hypotheses suggest that they should be able to identify the repeated test images as being familiar, and the high-interference and low-interference test images as being novel. Thus, we predict that the test:study ratio will be much less than 1 for the repeated test images, but not significantly different from 1 for the high- and low-interference test images. Further, there should be a significant difference
between the test:study ratios for the repeated test images (which are perceived as familiar) and the high- and low-interference test images (which are perceived as novel).

The at-risk elder group has the most impaired object recognition ability of our three participant groups. The representational-hierarchical model suggests that their impairment is caused by the misidentification of high-interference novel items as being familiar. This model predicts that the test:study ratio for high-interference items should be significantly less than 1 (indicating that it is not being viewed as a novel item), while the test:study ratios for repeated and low-interference items should remain the same as in the young participant group. (Since low-interference items have few features in common with the study items, they should still be identified correctly as novel items). Further, this model predicts that repeated items should have a similar test:study ratio as high-interference items (arguing that the latter are being confused for familiar items), but should have a significantly lower test:study ratio than low-interference items (which are still perceived as novel). These predictions are illustrated on the left hand side of Figure 7.

The decay hypothesis suggests that the impairment of the at-risk elder group are caused by the misidentification of repeated stimuli (which are familiar) as being novel. This hypothesis predicts that the test:study ratio for repeated test items should not be significantly different than 1 (that is, they are being perceived as novel). In addition, the high- and low-interference novel stimuli should also be perceived as novel, and their test:study ratios should also not be significantly different than 1. Because all stimuli are perceived as novel, there should be no significant difference between the three image categories. These predictions are illustrated on the right hand side of Figure 7.
Figure 7 - Predicted results, according the representational-hierarchical model (at risk participants see high-interference items as familiar instead of novel) and the decay hypothesis (at-risk participants see repeated items as novel instead of familiar). For clarity, predictions for healthy elders were excluded from this figure.

All hypotheses were directional (there were only predictions that viewing in some image categories or participant groups are less than or equal to viewing in other image categories or participant groups, and no predictions that depended only on differences in viewing). Thus, all statistical tests are one-tailed.

3.2 Main Effects and Interactions

The test:study ratio for each group and each image category are shown in Figure 7. A 3 (image category, within-subjects, with three levels: repeated, high-interference, low-interference) x 3 (participant group, between-subjects, with three levels: young, healthy elder, at-risk elder) repeated-measures ANOVA was conducted. This yielded a main effect of image category (F(2,58) = 16.058, p < 0.001), but no significant main effect of participant group (F(2,29) = 1.248, p = 0.15). Critically, as predicted, there was a significant interaction of image category by participant group (F(4,58) = 2.161, p = 0.042).
3.3 Comparisons Across Image Categories within Each Participant Group

To investigate the interaction between image category and participant group, our sample was first divided by participant group. Within each participant group, one-sample t-tests were conducted using the test:study ratios of each image category to see if they are perceived as significantly different than first-viewing study images (see Figure 8), which form our benchmark for novel images. Since we have normalized by the number of fixations to first-viewing study images, these one-sample t-tests compare the test:study ratios of each image category to 1. Additionally, we conducted paired-samples t-tests comparing the test:study ratios of the three test image categories (repeated, high-interference, low-interference) to see if they differed significantly from each other (see Figure 9).

Figure 8 - Test:Study ratio for each image category (repeated, high interference, low interference) for each participant group (young, healthy elders, at-risk elders). Note how at-risk elders show significantly reduced viewing of high-interference images compared to young participants. Error bars represent SEM. Asterisks indicate that image category has a test:study ratio significantly less than 1 (i.e. is not perceived as novel) ** p < 0.01    * p < 0.05
Figure 9 - Test:Study ratio for each image category (repeated, high interference, low interference) for each participant group (young, healthy elders, at-risk elders). Note how at-risk elders show significantly reduced viewing of high-interference images (which is comparable to viewing repeated images) compared to young participants. Horizontal bar represents viewing of first-viewing (novel) study items. Error bars represent standard error of the mean. Only t-tests between repeated items and high/low interference items shown. * p < 0.05, ** p < 0.01

One sample t-tests were conducted to determine if young participants had test:study ratios significantly less than 1 in each image category (or in other words, viewed those categories as familiar instead of novel). Only repeated images showed a test:study ratio significantly less than 1 for young participants (t(12) = 6.63, p < 0.001). There was no difference in test:study ratios between first-viewing study images and either high-interference novel images (t(12) = 1.16, p = 0.26) or low-interference novel images (t(12) = 1.74, p = 0.10). Young participants were able to correctly identify the repeated images as being familiar and the high- and low-interference images as being novel.
Further, paired-samples t-tests to compare viewing across image categories indicated that repeated images had a lower test:study ratio than both high-interference novel images (t(12) = 6.10, p < 0.001) and low-interference novel images (t(12) = 4.54, p < 0.001). There was no difference between high- and low-interference novel images (t(12) = 1.62, p = 0.13). These results match the predictions of both the representational-hierarchical model and the decay hypothesis: The intact brain is able to resolve interference (and/or resist decay), and thus, novel images (from both high and low interference conditions) were viewed more than familiar images.

For healthy elders, one-sample t-tests indicated that the study: test ratio was significantly less than 1 for repeated images (t(10) = 4.26, p = 0.004), high-interference test images (t(10)=3.19, p = 0.02) and low-interference test images (t(10) = 2.91, p = 0.02). This indicated that all three image categories were viewed as being more familiar than the original study images. Paired-samples t-tests across image categories indicated that repeated test images had a lower test:study ratio than high-interference novel images (t(10) = 2.89, p = 0.02), as well as low-interference novel images (t(10) = 3.70, p = 0.004). There was a trend towards significance in the reduction of test:study ratio of high-interference novel images compared to low-interference novel images (t(10) = 1.85, p = 0.09). These data suggest that while all three image categories are viewed as more familiar than the original study images, the repeated images are viewed as more familiar than the novel test images.

For at-risk elders, one-sample t-tests indicate that repeated images had a test:study ratio significantly less than 1 (t(7) = 4.26, p = 0.004), as did high-interference test images (t(7) = 3.19, p = 0.02), suggesting that these two image categories were not perceived as being novel. However, low-interference test images did not have a test:study ratio that differed from 1 (t(7) = 1.06, p = 0.32), indicating that they were perceived as novel. When viewing was compared across image categories, we found no significant difference between the test:study ratio of repeated test images and high-interference test images (t(7) = 0.79, p = 0.46). In contrast, there was a significant reduction in test:study ratio for repeated test images compared to low-interference test images (t(7) = 2.55, p = 0.04). There was a trend towards significance in the reduction of test:study ratio towards high-interference test images, compared to low-interference test images (t(7) = 2.15, p = 0.07). These data suggest that the repeated and high-interference novel items are being perceived as equally familiar, while the low-interference items are being perceived as novel, which supports the predictions of the representational-hierarchical model.
4 Discussion

4.1 Conclusions

In this study, we demonstrated that at-risk elders, like the perirhinal cortex-lesioned rats in McTighe et al. (2010) confused high-interference novel items as familiar items. However, they were able to correctly identify low-interference novel items as being novel. These data support an interference-based account of forgetting, as predicted by the representational-hierarchical model.

Our younger participants, like the control rats in McTighe et al. (2010), were able to correctly identify repeated stimuli as being familiar and the high- and low-interference novel stimuli as being novel. Their test:study ratio was significantly lower for the repeated stimuli compared to the novel test stimuli and the images seen during the study phase.

In contrast, the at-risk elders confused high-interference novel items as being familiar. They showed a test:study ratio for high-interference novel items that was similar to their test:study ratio for repeated items, which are familiar. Further, their test:study ratio for high-interference novel items was much less than for novel images seen during the study phase. However, they were able to correctly identify the repeated items as being familiar (as demonstrated by their test:study ratio in this image category that is significantly less than 1), and low-interference items as being novel (as demonstrated by their test:study ratio in this image category that is not significantly less than 1).

Data from the healthy elders indicates that they too confused high-interference novel items as being familiar, but not to the same degree as the at-risk elders. While their test:study ratio for high-interference novel items was significantly less than 1 (indicating they did not perceive these items as being entirely novel), it was also significantly greater than their test:study ratio for repeated items (indicating that they did not perceive the high-interference items as entirely familiar either, unlike the at-risk elders).

These data suggest that forgetting is mediated by interference. Specifically, as interference increases, groups with impaired interference handling abilities (eg. our two elder groups) increasingly perceive novel stimuli as being familiar. As a result it becomes difficult to distinguish which stimuli are truly familiar, leading to impairments in memory.
4.2 Future Directions

The findings of this study agree with the prediction of the representational-hierarchical model of Saskida & Bussey (2010), and provide a human analogue to the findings of McTighe et al. (2010) and Burke et al. (2010). These results are also consistent with other models of interference. For instance, the model of Hasher, Lustig and Zachs (2007) argues that interference arises from a lack of inhibitory mechanisms to focus attention. Our finding that interference arises from the viewing of novel stimuli as familiar is consistent with this account of interference. The inhibitory mechanisms of Hasher, Lustig and Zachs (2007) could be hypothesized to control implicit familiarity signals; their weakening would lead to the viewing of novel stimuli as being familiar. A different model of forgetting proposed by Wixted (2004) argues that interference arises from disturbances in the process of consolidation (which is hypothesized to be hippocampus dependent). This model expresses no preference for how interference would cause us to view novel and familiar stimuli, which means that our results would remain consistent with this model as well.

While studies have shown that MCI is associated with declines in perirhinal cortex grey matter volume (Bell-McGuinty et al., 2005; Schmidt-Wilcke et al., 2009), and our study shows that participants at risk for MCI have impaired interference handling abilities, leading to the mistaken perception of novel items as familiar ones, no studies directly connect perirhinal cortex damage to the effects seen in this study in humans. One way of testing this directly would be to apply this paradigm to two lesion groups: one with circumscribed hippocampal lesions and one with more extensive MTL lesions, following the example of Barense et al. (2005). If the group with focal hippocampal lesions show interference effects that are identical to controls, while the group with more extensive MTL lesions show stronger interference effects, this would provide strong evidence for a perirhinal cortex role in interference handling in humans.

To deal with potential criticisms that patients in lesions studies may not have well-defined lesions or might have benefitted from cortical reorganization, imaging studies in healthy populations would provide corroborating evidence for either account of forgetting. One approach would be to compare performance on this task with volumetric measures obtained through structural imaging. For instance, performance on this task could be correlated with the volume of the perirhinal cortex, quantified using the tracing methods of Insausti et al. (1998a). Diffusion
tensor imaging could be employed to look at the perirhinal cortex’s white matter connectivity to other brain regions, and how this might relate to interference handling.

Functional imaging could also give complementary evidence for the role of the perirhinal cortex in handling interference, as well as give some insight into the mechanisms supporting it. It would be possible to compare perirhinal cortex activity during viewing of each type of test stimuli, and see how perirhinal cortex activity might change as interference built up. It would also be possible to compare how the perirhinal cortex might respond differently across groups with different interference handling capabilities. Another avenue would be to explore how functional connectivity with other brain regions changes across our image categories, interference conditions and experimental groups.

One shortcoming of this paradigm is that it does not try to clarify which features are causing interference, but assumes that based on semantic similarity, there should be overlapping features between items shown. By careful selection of stimuli, it would be possible to explore feature overlap in a systematic way. It could be possible to look at very simple features (eg. colors, shapes) which are expected to be minimally overlapping. Alternatively, stimuli could be found which change in spatially restricted regions (for instance, the fribbles of Williams and Simons (2000)), allowing eyetracking analysis of those regions to determine if interference is global or part-based.

Figure 10 – An example of a fribble (Williams & Simons, 2000). It has four distinct features that can vary systematically, which could allow us to tease apart whether interference is part-specific or global in nature.
In conclusion, the findings of this study suggest that interference effects are driven by novel stimuli being mistakenly perceived as being familiar (as predicted by the representational-hierarchical model), rather than familiar stimuli being mistakenly perceived as being novel. This suggests that the forgetting is not driven by the loss of information (as would be suggested by a decay account of forgetting), but rather by insufficient binding into coherent representations, leading to an inability to later distinguish that information from other pieces of information. Future studies should further develop the anatomical specificity of this effect in humans, in particular how the perirhinal cortex and other medial temporal lobe regions play a role in causing the interference effects we see here.
References


