THE NEURAL AND BEHAVIORAL PROFILE OF OLDER ADULTS AT RISK FOR DEVELOPING MILD COGNITIVE IMPAIRMENT

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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Abstract

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Improving the ability to detect Alzheimer’s disease (AD) at the earliest stages is essential to effectively treat afflicted individuals. Mild cognitive impairment (MCI) is thought to be an intermediary state between healthy aging and AD. The goal of the present dissertation was to examine older adults who are at heightened risk of developing AD – both patients with diagnosed MCI and a preclinical group of older adults at-risk for developing MCI. Our preclinical participants were undiagnosed and supposedly healthy members of the community, but were defined to be at-risk for MCI based on performance from a brief, standardized neuropsychological test. We administered a full neuropsychological battery after our screening and found that the preclinical group performed in the lowest quartile on measures that are conventionally impaired in MCI (Chapter 2). To establish a neural profile of this population, we investigated an ERP component associated with visual short-term memory (VSTM) capacity, the CDA (Chapter 2). We found that older adults at-risk for MCI had reduced VSTM and reduced differentiation of the CDA (Chapter 2). Additionally, we found that the P300, a well-characterized ERP component shown to be useful in determining conversion from MCI to AD, showed reduced amplitude in our at-risk group (Chapter 2). Electrophysiological signatures may
be especially sensitive markers of the very earliest stages of AD. To further characterize the preclinical group, we administered an object discrimination task to older adults at-risk for developing MCI and diagnosed MCI patients (Chapter 3). We based the task design on previous research showing that the medial temporal lobe (MTL), a region damaged early in MCI, is necessary to resolve visual interference in this object discrimination task. Critically, we manipulated the level of visual interference across conditions, and found that both memory-impaired groups, but not controls, benefited from reduced interference on the perceptual task. Indeed, by reducing the requirement to bind features of an object together, performance in the memory-impaired group rose to the level of healthy controls. In Chapter 4, we sought to extend these findings by investigating the role of interference in a task assessing VSTM. We reduced interference by presenting a retroactive spatial cue (retrocue, providing a cue for binding object to location), which again elevated performance in patients with MCI and MTL amnesia to the level of their age-matched controls. The results of these experiments suggest that one of the most critical determinants of behavior is interference in the environment, and that increased vulnerability to interference may be one of the first symptoms of pathological aging.
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Chapter 1

Introduction

Dementias including Alzheimer’s disease (AD) are one of the leading causes of disability in Canada and North America. Early detection is of paramount importance for effective treatment. Currently available treatments focus on preventing further spread of the disease rather than repairing existing brain damage. Advances in treatment are likely to focus on preventing further spread of disease. As such, early detection is critical for improved quality of life for these individuals. Mild cognitive impairment (MCI) is thought to be an intermediary state between healthy aging and dementia. By examining cognitive performance in healthy older adults who are at increased risk for developing MCI and AD, I have developed a neural and behavioral profile of preclinical MCI. This introductory chapter will focus on the earliest symptoms, early pathology, and putative preclinical changes associated with known MCI diagnosis, as well as theoretical implications of impaired cognitive performance in visual short-term memory (VSTM) and object recognition.

Defining Mild Cognitive Impairment

MCI is a disorder associated with increased risk for developing AD, and is generally considered to be an intermediate state between healthy aging and dementia (Petersen, 2004; Petersen et al., 2009; Petersen et al., 1999). MCI patients have normal activities of daily living, but they perform below age and education-adjusted norms on some neuropsychological assessments (Ferman et al., 2006). One recent meta-analysis found that between 29-33% of MCI patients convert to AD annually (A. Mitchell & Shiri-Feshki, 2009). MCI is also very heterogeneous: many MCI patients will not convert to AD or any dementia, but will either
remain with MCI status, or revert to healthy status (Nordlund et al., 2005). There are two subtypes of MCI: amnestic and non-amnestic. Amnestic MCI refers to a condition wherein one presents with a clinically significant memory impairment and is thought to be a precursor to Alzheimer’s disease (AD); whereas non-amnestic MCI is associated with impairments in other cognitive domains (i.e., language, executive function, attention) and is thought to lead to non-AD dementias (Ferman et al., 2006). Amnestic MCI is sometimes described as “MCI due to AD” to emphasize the underlying pathophysiology changes that occur (Albert et al., 2011). This dissertation will focus on the amnestic MCI subtype, or MCI due to AD.

According to recent recommendations by the National Institutes of Aging and the Alzheimer’s Association workgroup, there are four core clinical criteria for MCI diagnosis (Albert et al., 2011):

1. Concern regarding a change in cognition
2. Impairment in one or more cognitive domains
3. Preservation of independence in functional activity
4. Not demented

These four criteria, often called the Mayo Clinic Criteria, or the Petersen criteria (A. Mitchell & Shiri-Feshki, 2009) are the most common criteria used by clinicians without access to biomarker and other physiological measurements (Albert et al., 2011). Additional diagnostic criteria can include establishing evidence of longitudinal decline in cognition, genetic factors, and ruling out other causes of cognitive decline (i.e., vascular, traumatic, or other medical).

Of the four core clinical criteria described above, the most relevant to the present thesis are the first two, which I will simplify as subjective and objective memory decline, respectively.
**Subjective versus Objective Memory Decline**

A feeling of knowing that one has a memory problem may be the most informative measure of later AD diagnosis (Jessen et al., 2010; Jessen et al., 2014; Merrill et al., 2012). Subjective memory decline can be assessed by asking a single question, such as “Do you feel that you have memory impairments greater than those of your same aged-peers?” By using the aforementioned single question, most of the older adults we have tested do not report having memory impairments, (15 of 201, unpublished observation, Memory and Perception Laboratory Participant Database). Subjective memory as a core diagnostic criterion is a controversial issue (A. Mitchell & Shirifeshki, 2009), as one may present with clear objective cognitive impairments but not feel concerned about these impairments. Indeed, the heterogeneity of MCI may be related to the subjective criteria of diagnosis. Some people are more concerned about their health than others, and these individuals are more likely to seek out neurological assessment than their unworried peers, and are more likely to fall into the category of “worried well” – that is, someone with a subjective impairment with no consistent objective deficits (Ahmed et al., 2008). The converse is also possible: older adults who are unwell but unworried.

In contrast to subjective memory, objective memory deficits are relatively easy to establish using standard neuropsychological assessments. Objective impairments are defined as performance more than 1.5 standard deviations below age and education adjusted means (Marshall et al., 2011), and are well established in MCI (Nelson & O'Connor, 2008). There is no consensus on the exact neuropsychological battery to test for MCI, although most batteries include broad measures of memory, IQ, attention, executive function, and language (Nelson & O'Connor, 2008). Typically, aMCI patients perform in the impaired range on the Wechsler Memory Scale: Logical Memory I and II, the Rey-Osterreith Complex Figure task, and global
measures of cognitive function, such as the Mini Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA) (Strauss, Sherman, & Spreen, 2006).

**Diagnosing MCI**

If there are changes happening before an MCI diagnosis, how do we establish them? One way to do so is to assess objective cognitive changes. There are many brief cognitive screening tools available to psychologists, including the MMSE (Folstein, Folstein, & McHugh, 1975) and the MoCA (Nasreddine et al., 2005). The MMSE is the most widely administered of these tests, however, recent evidence suggests that the MoCA is more sensitive at detecting MCI than the MMSE (Larner, 2012; Markwick, Zamboni, & de Jager, 2012).

The MoCA is a ten-minute screening test and covers many different domains, including visuospatial attention and executive function, memory, attention, and orientation (Nasreddine et al., 2005). A passing score is defined as 26 or greater out of 30 points. Over the four-year time span preceding the writing of this thesis, the Memory and Perception Laboratory at the University of Toronto has tested 297 individual older adults. These participants are recruited through the Adult Volunteer Pool, a database of over 3000 volunteers in the City of Toronto. Of these 297 individuals, 95 have scored below 26 on the MoCA (unpublished observation, Memory and Perception Laboratory Participant Database). My initial goal was to further characterize these participants to determine whether this criterion of 26/30 was too strict. What I discovered over the course of the three empirical chapters that follow is that these participants may in fact have preclinical MCI. I will refer to participants categorized by MoCA performance below 26 as “at-risk” throughout this dissertation.
Pathology

One prominent model describing the pathophysiology of AD is described by Jack and colleagues (Jack et al., 2011; Jack et al., 2013). This model (Figure 1) suggests that the first changes are seen in amyloid-β plaque formation. Perhaps as a result of the amyloid changes, synaptic dysfunction is secondary (Palop & Mucke, 2010). Tau neurofibrillary changes occur next, with global brain atrophy prior to MCI diagnosis with cognitive change following diagnosis. Clinical status occurs before dementia diagnosis. The data presented in this thesis challenge the idea that the beginning of cognitive changes occurs immediately prior to MCI status. Our theoretically-guided understanding of the at-risk group suggests that this line (Figure 1, purple line) should shift to the left, reflecting subtle changes occurring in the preclinical phase.

![Figure 1](image.png)

*Figure 1. Modified from Jack et al., 2013. This model predicts cognitive change just prior to MCI diagnosis.*
The brain atrophy associated with AD pathology has been widely thought to begin in medial temporal lobe (MTL) structures (Braak & Braak, 1991). More specifically, the first blood flow changes happen in lateral entorhinal cortex, perirhinal cortex (PRC), and posterior parietal cortex (Khan et al., 2014). In our hypothesis that the preclinical group has early AD pathology, we assume that these regions are beginning to show structural change (Figure 2) in the at-risk. Collaborators are currently exploring this hypothesis using structural MRI scans from these participants.

![Figure 2](image.jpg)

**Figure 2.** Modified from Khan et al., 2014. A mouse model (a, EC-App/Tau) and preclinical Alzheimer’s disease patients (b) show converging damage in lateral entorhinal cortex (yellow), perirhinal cortex (PRC, red), and posterior parietal cortex (green).

These regions are thought to subserve performance on the experimental paradigms I will describe in the empirical chapters below. Specifically, the posterior parietal cortex (Figure 2, green) is vital for the VSTM tasks in Chapters 2 and 4, and the PRC (Figure 2, red) is critical for the object interference task in Chapter 3. The underlying assumption that the at-risk have structural changes consistent with early MCI and AD pathology forms the basis of the hypotheses in Chapters 2-4.
Developing a Profile

Neural Changes

One appealing tool for detecting early neural change associated with MCI is the use of electroencephalogram (EEG) measures. EEG is inexpensive, easy-to-use, and fast. Event-related potentials (ERPs) from EEG signal have been used in many clinical applications, including Alzheimer’s disease and MCI (Ally, Jones, Cole, & Budson, 2006; Lai, Lin, Liou, & Liu, 2010; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008; Polich, 2007; Polich & Kok, 1995; Polich, Ladish, & Bloom, 1990).

Figure 3. Modified from Ally et al., 2006. Alzheimer’s disease (AD) patients have a reduced amplitude and delayed latency of the P300 component, compared to older controls (OC).
The P300 (Figure 3) is a commonly studied ERP component thought to reflect working memory updating and the comparison of a target stimulus with a previously presented stimulus held in memory (Donchin, 1981). It is most commonly measured following the presentation of an infrequent stimulus (“oddball”). Many patient populations present with an aberrant P300, including patients with AD and MCI (Ally et al., 2006; Polich et al., 1990). For example, the P300 amplitude of MCI patients was shown to predict later conversion to AD (Lai et al., 2010), and an aberrant P300 was observed in the healthy children of AD patients who carried the presenelin-1 gene (“familial AD”) (Ally et al., 2006). These abnormal ERP signatures manifested as reduced amplitude and slower latency of the P300 than those of controls. The P300 often has a delayed latency and amplitude in healthy aging as well, however, the findings noted above are comparing healthy older adults to patients, and patients have the largest decrements in amplitude and latency (Polich & Kok, 1995). Taken together, these results suggest that the P300 is a promising detector of preclinical MCI. In Chapter 2, we tested at-risk participants on an auditory oddball task and found that they had an abnormal P300.

Cognitive Changes

Visual Short-Term Memory

Visual short-term memory (VSTM) is a critical cognitive ability, allowing for maintenance of visual information for a brief period of time after that information is no longer present in the environment. It is considered to be the visual storage element of working memory, and is limited in capacity to roughly three to four items for simple visual stimuli in healthy young adults (Cowan, 2001; Luck & Vogel, 1997; Todd & Marois, 2004; Vogel & Machizawa, 2004). VSTM performance declines in aging (Duarte et al., 2013; Vaughn & Hartman, 2009; Verhaeghen & Salthouse, 1997), MCI (Alescio-Lautier et al., 2007), and following MTL damage
The following section will provide a brief theoretical background of the current state of VSTM research generally, and will conclude with an overview of the existing literature in terms of MCI and VSTM.

VSTM is often assessed using a change detection task (Figure 4), in which participants see an array of simple visual stimuli during a memory array, and then must maintain a representation of those stimuli during a delay period. After the delay, a probe appears and the participant must decide if the probe array matches the previously presented memory array. In the case of the example stimulus in Figure 4, participants must indicate whether a single item is the same or different color as the item in that was in that location previously.

Figure 4. Example of a change detection task. Participants see a memory array containing a number of to-be remembered items. After a delay period, participants are shown a probe array containing a single item and are asked to determine if the item matches the item that was in that location previously. Here the correct answer would be the “same,” as the red circle is the same in both the memory array and probe array.
A change detection paradigm allows for the estimation of an individual’s VSTM capacity. As much as the ability to focus on relevant information in any working memory task is important, the need to inhibit irrelevant information is also critical. In a classic study, Conway and colleagues found that low working memory capacity individuals were more likely to hear their name in an auditory stream they were meant to ignore; whereas high capacity individuals were able to efficiently ignore their names (Conway, Cowan, & Bunting, 2001). Low working memory capacity participants were unable to effectively inhibit their task-irrelevant names, whereas high working memory capacity participants were able to inhibit this information.

**Contralateral Delay Activity**

An electrophysiological measure of VSTM is the contralateral delay activity (CDA), an ERP correlate thought to represent an individuals’ VSTM capacity (Vogel & Machizawa, 2004). The CDA emerges during the maintenance period in the hemisphere contralateral to the attended stimulus display. This waveform is maximal at parietal electrode sites, and differentiates the number of items maintained by increasing negativity with increased load, up until an asymptote of individual capacity is reached (Figure 5).

![Figure 5](image.png)

*Figure 5. Modified from Vogel and Machizawa, 2004. The CDA becomes more negative with each item held in memory, until an individual’s visual short-term memory capacity is reached.*
Capacity and Processing-Related Limits

Researchers generally agree that VSTM is capacity limited, yet there is debate over whether the limit is due to the limited number of “slots”, or whether the limit is due to the amount and type of information in the visual environment. The first view, the slots view, suggests that VSTM contains a small amount of fixed-resolution slots. This view suggests that objects are the main storage unit of VSTM and, as described above, that individuals can maintain three to four objects (Luck & Vogel, 1997). Many of the studies initially supporting the idea of maintaining three to four items used simple colored stimuli, similar to what is shown in Figure 4. Luck and Vogel initially demonstrated that an individual can retain information about integrated objects rather than only simple features of objects (1997). For example, one can retain both four simple colored squares with the same accuracy as four colored squares, each with an individual colored square inside of the larger square (i.e., four objects of single features can be retained to the same degree as four objects with additional features). One study examined the features of objects by displaying their component parts in a change detection task (Xu, 2002). The results suggested that features were stored more efficiently when they were made into a cohesive object (e.g., a colored circle with a black bar through it to make a “Saturn”-like object), rather than when the features were presented as spatially separated objects (e.g., a colored circle or a black bar displayed separately).

In contrast, the second viewpoint proposes that capacity limits are due to the amount of information in the environment. This approach, called the resources view indicates that a fixed number of resources are distributed among items in the environment, and, with increasing items, resolution of representation decreases (Alvarez & Cavanagh, 2004; Wilken & Ma, 2004).
Alvarez and Cavanagh found that capacity estimates decreased with increasingly difficult items, suggesting that VSTM capacity is a function of information load (2004). One seminal study challenging the slots view used a modification of a change detection task, the color wheel (Wilken & Ma, 2004). The task is similar to a change detection task, however at probe, participants are asked to pick the color that was seen previously in that location, by clicking on the color wheel, using a mouse response (Figure 6). The elegance of this design lies in the ability to detect both precision and types of errors. As can be seen in the figure, responses can be distinguished between Target responses (i.e., correct responses), Guesses and Non-Target responses (i.e., incorrect responses). Additionally, one can estimate the precision of the mnemonic representation by determining how close the color of the target object was to the probe response, in color space (Wilken & Ma, 2004). The authors conclude that the capacity limits described previously do not include objects held in equally high-resolution representations.
Additional studies have suggested that more of a hybrid combination of these two theories may be appropriate. Xu and Chun examined the neural markers of the representational of different objects in space. They designed objects with simple or complex feature conjunctions that could change (i.e., a cylinder and a half-moon can be combined to form a mushroom cap). The authors found that activity in the inferior intraparietal sulcus tracked objects regardless of complexity, whereas activity in the superior intraparietal sulcus tracked a variable subset of the objects, dependent on complexity (Xu & Chun, 2006). The hybrid theory is consistent with a representational-hierarchical account of object processing described below – that is, that different neural regions hold representations of objects depending on their complexity (i.e., simple features in posterior visual regions, conjunctions of features in more anterior regions of the ventral visual stream).

**Figure 6.** Modified from Emrich and Ferber, 2012. Example of a colorwheel task and response type classification.
Aging, MCI, and the MTL

The inhibitory deficit hypothesis provides an explanation for the low working memory capacity in healthy aging as a function of reduced inhibition (Hasher, Lustig, & Zacks, 2007; Hasher & Zacks, 1988; Lustig, Hasher, & Zacks, 2007). This theory stresses the importance of efficiency of resources in memory, suggesting that inhibition requires the ability to limit information from activating working memory. This inhibition has two component functions that are related to the VSTM task described above: (1) to prevent irrelevant information from entering the focus of attention, and (2) to delete irrelevant information from the focus of attention. Both of these functions place key importance in keeping irrelevant information from current awareness.

Older adults have a reduced ability to filter irrelevant information, which leads to their reduced storage capacity (Sander, Werkle-Bergner, & Lindenberger, 2011). Additionally, the “leaky filter” older adults experience means that they are more susceptible to the effects of interference from irrelevant stimuli. Older adults show better memory for distractors than young adults (Rowe, Valderrama, Hasher, & Lenartowicz, 2006). Older adults’ inability to filter out distracting information in working memory leads to encoding distracting information into long-term memory. There have been three published studies examining the CDA in aging, and all have found impaired VSTM performance, both behaviorally and in terms of reduced differentiation of the CDA (Duarte et al., 2013; Jost, Bryck, Vogel, & Mayr, 2011; Sander et al., 2011). To date, there have been no published studies investigating the CDA in abnormal aging or MCI. In Chapter 2, we administered a VSTM task with concurrent EEG and found an abnormal CDA in the at-risk group, but intact CDA in the healthy older adults, suggesting that perhaps the
previously published studies did not use a strict enough neuropsychological criterion to evaluate healthy aging.

Older adults, MCI patients, and MTL amnesia cases have reduced inhibitory control, and are thus more susceptible to interference (Biss, Campbell, & Hasher, 2013; Cowan, Beschin, & Della Sala, 2004; Della Sala, Cowan, Beschin, & Perini, 2005; Dewar, Della Sala, Beschin, & Cowan, 2010; Dewar, Garcia, Cowan, & Della Sala, 2009; Ebert & Anderson, 2009). MCI and AD patients have greater impairments in VSTM than healthy older adults (Alescio-Lautier et al., 2007; Bublak et al., 2011; Della Sala, Parra, Luzzi, & Abrahams, 2012; Parra et al., 2009; Parra et al., 2010; Redel et al., 2010). Alescio-Lautier and colleagues examined VSTM in MCI and AD patients using a variation of a change-detection task (2007). To control for difficulty, the authors administered a span control task prior to the experimental task in order to assess individual memory capacity. Using this estimate, they ensured that the change detection task did not exceed each person’s individual memory capacity. Even though the task did not exceed their VSTM capacity, both MCI and AD patients were impaired at detecting change. Additionally, this memory impairment was greater when there was a distractor present in the one second delay between the studied image and probe image. With a distractor, participants were forced to shift their attention from the memory array (previous task) to the distractor (presently displayed). These results suggest that there may be a dysfunction in the attentional processes in these patients, and that reducing interference (i.e., the distractor), may be one way to ameliorate this difference.

Interestingly, another study assessing VSTM in MCI patients found that patients’ storage capacity estimates were not impaired compared to healthy controls, but patients had an elevated threshold viewing-time (Bublak et al., 2011). That is, MCI patients required a longer viewing at
encoding to report seeing any stimuli. The authors interpreted these results as owing to the fact that MCI patients may have deficits in pre-attentive processing (i.e., when objects in the visual field are first coded into neural representations). These ideas are consistent with the idea of MCI patients being particularly vulnerable to interference.

Together, these ideas suggest that changes in VSTM due to AD pathology are not necessarily due to storage impairments, per se, but rather to a specific problem in binding features of an object together. It is generally agreed that the hippocampus and medial temporal lobes play a critical role in the relational binding of components in a mnemonic representation (Olsen et al., 2015; Olsen, Moses, Riggs, & Ryan, 2012; Pertzov, Dong, Peich, & Husain, 2012; J. D. Ryan, Althoff, Whitlow, & Cohen, 2000; J. D. Ryan & Cohen, 2004). Parra and colleagues found that AD patients were impaired in a verbal short-term memory task at retaining both simple features (colored squares), and simple objects (e.g., banana, guitar), however they were more impaired when asked to bind the features (e.g., objects and colors bound together) (Parra et al., 2009). A series of studies from Neal Cohen’s lab have investigated binding and swap errors in hippocampal amnesia (Monti et al., 2015; P. D. Watson, Voss, Warren, Tranel, & Cohen, 2013). Using a spatial reconstruction task, participants are asked to study a series of novel objects, placed in specific locations on the screen. After a delay period, participants are asked to reconstruct the locations of the items, by dragging each object to its previous location. Patients make more “swap” errors, that is, they swap two objects for each other’s locations. This type of error suggests a problem with binding object to location. Such a binding error could lead to reductions in more typically measured capacity-limits.

Among the many mechanisms underlying VSTM performance (i.e., attention, visual perception, working memory, etc.), the MTL-driven item-location binding is critical to
performance. The impoverished MTL representations in MCI and MTL amnesia will lead to deficits in VSTM performance due to their increased susceptibility to interference and impairments in binding. These binding impairments could manifest as the higher-level binding of stimuli to their respective locations or as perceptual impairments in binding individual features within an object. It is the damaged representation that leads to impairments across a variety of task demands.

**Object Processing: The Representational-Hierarchical Model**

One model that predicts impaired perceptual object processing in MCI and MTL amnesia is the representational-hierarchical model. Traditionally, the MTL has been thought to exclusively support long-term declarative memory, our conscious memory for events (Eichenbaum & Cohen, 2001; Squire & Zola-Morgan, 1991). According to this theory, the primary function of the MTL is in long-term memory and not in other aspects of cognition, such as working memory and object perception (Clarke, Reinagel, Broadbent, Flister, & Squire, 2011; Kim et al., 2011; Squire & Wixted, 2011). However, recent reports have challenged this prevailing view that the mechanisms underlying memory and perception are anatomically segregated, suggesting that the MTL – in particular the perirhinal cortex (PRC) – is not only important for memory, but also essential for certain forms of perception (Barense et al., 2005; Bartko, Winters, Cowell, Saksida, & Bussey, 2007; Buckley, Booth, Rolls, & Gaffan, 2001; Bussey & Saksida, 2007; Bussey, Saksida, & Murray, 2003; Cowell, Bussey, & Saksida, 2010a, 2010b; Graham et al., 2006; Lee, Bussey, et al., 2005; McTighe, Cowell, Winters, Bussey, & Saksida, 2010; Murray & Bussey, 1999; Murray, Bussey, & Saksida, 2007; O'Neil, Cate, & Kohler, 2009; O'Neil et al., 2012; H. C. Watson & Lee, 2013). These findings have led to a representational-hierarchical account of PRC function (Figure 7), which holds that apparently
distinct mnemonic and perceptual functions may arise from common representations and
common mechanisms (Cowell et al., 2010a; Graham, Barense, & Lee, 2010; Murray & Bussey, 1999). More specifically, recent studies in humans (Barense et al., 2005; Barense, Henson, &
Graham, 2011; Barense, Henson, Lee, & Graham, 2010; Buckley et al., 2001; Bussey, Saksida, & Murray, 2002; Lee, Barense, & Graham, 2005; Lee & Rudebeck, 2010), monkeys (Burke et
al., 2011; Bussey et al., 2002, 2003), and rats (Bartko et al., 2007; Burke, Wallace, Nematollahi, Uprety, & Barnes, 2010; McTighe et al., 2010), suggest that the PRC is necessary for processing 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 (Desimone & Ungerleider, 1989; Martinovic, Gruber, & Muller, 2008; Riesenhuber & Poggio, 1999; Tanaka, 1996). According 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 (Bartko et al., 2007; Bussey et al., 2002; Cowell, Bussey, & Saksida, 2010c; Murray et al., 2007). 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, 2012; Lee, Yeung, &
Barense, 2012). These impoverished representations will lead to impairments on both mnemonic and perceptual tasks.

![Diagram](image)

**Figure 7.** 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 conjunctions of features, putatively at the level of an entire object. The PRC is thought to hold the bound representation of the many features comprising an object (for example, a soup can), whereas the hippocampus is thought to bind the object to a location (for example, the soup can at the top of the page).

Indeed, recent neuroimaging evidence in healthy young adults suggests that the PRC discriminates between novel object configurations of the same features comprising unique objects (Erez, Cusack, Kendall, & Barense, 2015). Under the representational-hierarchical framework, one would predict damaged PRC to reflect deficits in binding features of an object (e.g., shape, color) into a unitized percept. In Chapter 3, I administered an object discrimination task to MCI patients and older adults at-risk for developing MCI. I found that under conditions of high interference (visually similar features shown repeatedly across trials), MCI and at-risk cases were impaired in a perceptual task. In Chapter 4, I built on these findings by extending the interference manipulation to a task assessing VSTM. By presenting a retrocue during the delay period of a change detection task, we reduced interference and elevated VSTM performance in
MCI and MTL amnesia cases. These results are consistent with the idea that increased vulnerability to interference may be one of the first symptoms of AD pathology.

**Thesis Overview**

The three empirical chapters following have been previously published or submitted to peer-reviewed journals (see copyright acknowledgements). The original content has been preserved and modified for the format of the thesis. As each chapter was originally written to stand alone, there is some overlap in the material.

In Chapter 2 (Newsome, Pun, Smith, Ferber, & Barense, 2013), I describe the electrophysiological profile of the at-risk. I show that they had an aberrant P300 and argue that this is reflective of pathophysiology. I also show that they had reduced VSTM both in terms of behavioral capacity estimates and the CDA.

In Chapter 3 (Newsome, Duarte, & Barense, 2012), I further classify the at-risk group by examining interference reduction in object perception. I administered an object discrimination task with varying degrees of feature interference to at-risk and MCI patients, and find that reduced interference improved performance on this perceptual task.

In Chapter 4 (Newsome et al., submitted), I attempt to improve VSTM performance by reducing interference and administering a retrocue during the delay period of a change detection task. I show that MCI patients and MTL amnesia cases benefit from the reduced interference of the retrocue.

In Chapter 5, I discuss the theoretical overlap between these very different experimental paradigms, and the underlying neural changes we believe are affecting the behavior in the preclinical group.
Chapter 2

Neural Correlates of Cognitive Decline in Older Adults At-risk for Developing MCI: Evidence from the CDA and P300

Abstract

Improving the ability to detect AD at the earliest stages is essential to effectively treat afflicted individuals. Electrophysiological signatures are a promising avenue for earlier diagnosis. In the present study, we investigated an ERP component associated with VSTM capacity, the CDA. Our participants were undiagnosed and supposedly healthy members of the community, but were defined to be at-risk for MCI based on performance from a brief, standardized neuropsychological test. We found that older adults at-risk for MCI had a reduced VSTM capacity and reduced differentiation of the CDA. In an additional experiment, we found that the P300, a well-characterized ERP component shown to be useful in determining conversion from MCI to AD, showed reduced amplitude in our at-risk group. Together, these findings suggest that electrophysiological signatures may be especially sensitive markers of the very earliest stages of AD.

Introduction

We investigated putatively healthy older adults from the community with no MCI diagnosis, but who fell below normative means on a standardized neuropsychological test developed to screen for MCI (Nasreddine et al., 2005). It is unknown whether these preclinical, but at-risk, participants would show a similar neural signature to that associated with MCI. In the
current study, we investigated two ERP correlates of behavior – the CDA and the P300 – in a group of fully-functioning older adults from the community who had no MCI diagnosis, but who are at-risk for MCI based on their MoCA performance. The P300 is a well-established component known to be associated with diagnosis of MCI/AD (Lai et al., 2010), whereas to our knowledge, the CDA has never been investigated in an MCI/AD population.

The CDA has been characterized as an online signature of VSTM involvement (Vogel & Machizawa, 2004; Vogel, McCollough, & Machizawa, 2005). This component emerges around 300 ms into the task as a sustained, negative-going activity over posterior electrode sites. It is typically assessed with a visual change detection task, in which a limited number of simple visual stimuli must be maintained in working memory over a brief delay. CDA amplitude during this delay predicts VSTM capacity. That is, the amplitude of the CDA waveform increases with each additional item held in VSTM, until one’s individual VSTM capacity is reached. Once capacity has been reached, the CDA no longer differentiates between higher loads. The CDA likely originates from several coordinated frontal and parietal sources, which are considered to be two nodes in the neural networks regulating working memory, selective attention, and executive functions (Constantinidis & Procyk, 2004). Specifically, the prefrontal cortex is thought to play a role in both top-down attentional control as well as VSTM maintenance and consolidation and patients with prefrontal lesions have demonstrated an abnormal CDA for the contralesional visual field (Voytek & Knight, 2010). The posterior parietal cortex, however, is involved in the temporary storage of visual information and subserves shifts of attention to stimuli in the environment (Posner & Dehaene, 1994; Todd & Marois, 2004; Vogel & Machizawa, 2004). It is well-established that both brain areas are affected in MCI/AD (Khan et al., 2014; Mitolo et al., 2013; Nho et al., 2012), with corresponding deficits in VSTM (Alescio-
Lautier et al., 2007; Ko & Ally, 2011; Parra et al., 2009; Parra et al., 2010) and top down control (Redel et al., 2010). Although it has been shown that older adults have reduced differentiation of the CDA relative to younger adults (Duarte et al., 2013; Jost et al., 2011; Sander et al., 2011), it is not known whether the CDA is affected in MCI. In the present study, we predicted that our at-risk group would show reduced differentiation of the CDA, reflecting a smaller VSTM capacity.

In contrast to the recently discovered CDA, the P300 is one of the most commonly studied ERP components. It is characterized by a positive deflection with a latency between 250 and 500 ms and is most pronounced after infrequent (odd) auditory stimuli. P300 amplitude is thought to reflect the amount of attentional resources required to match the current stimulus with the representation of an earlier stimulus held in working memory (Donchin, 1981). The P300 has a broad range of clinical implications, and is known to be associated with the clinical diagnosis of MCI/AD (Ally et al., 2006; Lai et al., 2010; Polich, 2007; Polich & Kok, 1995; Polich et al., 1990). Although the P300 reflects some aspects of working memory engagement, its precise role remains elusive (Donchin, 1981; Polich & Kok, 1995). One putative neural generator of the P300 is the temporal parietal cortex (Barry & Rushby, 2006), a region known to be affected by AD (Braak & Braak, 1991).

A recent study utilized a simple, auditory oddball paradigm in AD and MCI patients found that the P300 amplitude was reduced and latency was delayed in both patient groups at both original test and at a one-year follow-up, suggesting that this physiological marker occurs before diagnosis of AD (Lai et al., 2010). Interestingly, Ally and colleagues found that the healthy and cognitive intact biological children of AD patients also had a reduced P300 amplitude and delayed latency (Ally et al., 2006). Importantly, these relatives of AD patients were healthy and cognitive intact, but their P300 was still abnormal. Together, these findings
suggest that the P300 may serve as a robust measure of AD risk, and here, we predicted that in our at-risk group, P300 amplitude would be reduced and latency would be delayed.

In summary, the existing literature suggests that two ERP components, the CDA and the P300, might be sensitive to preclinical MCI. To test this, we investigated a group of fully functioning older adults recruited from the community who did not meet MCI diagnostic criteria, but in whom neuropsychological screening indicated risk for developing MCI. We administered two ERP tasks: (1) a VSTM task during which we measured the CDA and (2) an auditory oddball task during which we measured the P300. We predicted that relative to older and younger adult controls, the at-risk group would have less differentiation of the CDA and an aberrant P300.

Methods

Participants

We recruited 13 younger adults from the Toronto community. Of these, one was excluded from data analysis due to EEG technical failure, leaving 12 remaining participants (nine female, $M_{age} = 24.33$ years, SD = 3.47, $M_{education} = 15.97$ years, SD = 1.44, all right-handed). We also recruited 27 older adults from the Adult Volunteer Pool at the University of Toronto, a database of over 3000 older adult participants. Of these, two were excluded for excessive EEG noise (more than 34% of trials rejected). Based on their MoCA scores, we classified the remaining 25 participants as either “healthy” ($n = 13$, passing MoCA score: $\geq 26$, eight female, $M_{age} = 69.54$ years, SD = 6.30, $M_{education} = 16.23$ years, SD = 3.81, all right-handed), or “at-risk” ($n = 12$, failing MoCa score: $\leq 25$, seven female, $M_{age} = 73$ years, SD =...
5.86, $M_{education} = 16.45$ years, SD = 4.36, two left-handed). The older adult groups were matched for age, $t(23) = 1.42, p = .17$, and all groups were matched for educations, $ts < .27, ps > .79$.

To create groups of equal numbers, we recruited older adults who had previously been randomly selected from the Adult Volunteer Pool and whose MoCA score was known, but importantly, the experimenter was blinded to those scores. At the conclusion of the experimental task, a new version of the MoCA was administered, which is reported here (Table 1). All participants reported normal or corrected-to-normal vision, no psychiatric/neurological disorders (e.g., Parkinson’s disease, AD, epilepsy, stroke, multiple sclerosis), no current psychoactive drug use, no past cerebrovascular incident, and no CNS-active medications. Participants in the present study did not express a subjective memory complaint. All participants lived independently and arrived at the lab on their own. All participants provided informed consent and were compensated for their time. The study was approved by the University of Toronto Ethics Review Board.

**Neuropsychological Battery**

To further assess the cognitive profile of the at-risk group, 11 of the 12 at-risk participants returned for a thorough neuropsychological assessment within one year of original experimental testing. The battery consisted of the Logical Memory subtest from the Wechsler Memory Scale (Wechsler, 2009), Trails A & B (Reitan & Wolfson, 1985), the Digit Span subtest of the Wechsler Adult Intelligence Scale (Wechsler, 2008), and the Visual Object and Space Perception Battery (Warrington & James, 1991).

Results are shown in Table 1. Relative to established norms, the at-risk group was not significantly impaired on any of these measures. However, consistent with the well-established episodic memory impairments in early MCI/AD (Ferman et al., 2006; Hodges, 2000; Petersen,
2004; Petersen et al., 2009; Petersen et al., 1999) and impaired executive function (Ashendorf et al., 2008), the at-risk participants were in the lowest quartile on some measures of episodic recall and Trails B. Thus, although they did not meet diagnostic criteria for MCI – they had neither subjective nor objective memory impairments (Petersen et al., 1999) – available neuropsychological evidence indicates that their memory is in the low average range and they may be on the trajectory to MCI.
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<th>Measure</th>
<th>At-risk ($n = 12*$)</th>
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<th>Younger Adults ($n = 12$)</th>
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<td>24.33 (3.47)</td>
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<td>Education</td>
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**Notes:** *for the neuropsychological battery, n = 11. Maximum and cut-off scores are listed in parentheses. Standard deviations (SDs) are indicated in parentheses next to the average raw scores. Percentile scores for the group average relative to established norms are shown when available.*

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Design and Procedure

Memory Capacity Estimate

Prior to the CDA task, VSTM capacity was estimated using a change detection task (Vogel, Woodman, & Luck, 2001). Participants were asked to maintain one to six uniquely colored squares over a 1200 ms delay period, and to indicate whether any changes occurred between the sample and test arrays. Thirty trials were presented per set size (180 trials total). EEG was not recorded during this task. Memory capacity ($K$) was estimated by applying the following formula (Cowan, 2001; Pashler, 1988):

$$K = \text{set size} \times (\text{hits} - \text{false alarms})$$

A participant’s highest score of all set sizes reflected the memory capacity estimate. This task took approximately 10 minutes.

CDA

Each trial began with a centrally presented left- or right-facing arrow appearing 2° above the fixation cross (Figure 8). Participants focused their attention in the direction of the arrow, while maintaining central fixation. Following a 300-400 ms delay, a memory array consisting of between one and four colored squares on each side of the visual field was presented for 200 ms. Following a 900 ms fixation cross, the probe display containing only one square in each hemifield appeared until participants indicated if the probed object on the cued side had changed color. Trials were self-paced and participants were able to take a break to blink after every trial. Participants were allowed to practice until they felt comfortable with the task. The CDA task took approximately 30 minutes.
Figure 8. Schematic of a single trial from the change detection task. Participants were instructed to shift their attention to the arrow-cued side for the remainder of the trial while fixating on the central cross. Participants pressed a button to indicate whether the object shown on the cued side of the probe display had changed color. This is an example of a “same” trial, because the probed square is orange in both the memory array and the probe array. ERP analyses were time-locked to the onset of the memory array.

**P300**

We administered an auditory oddball task with procedures identical to Lai and colleagues (Lai et al., 2010). Participants indicated whether each 20 ms pure tone burst (0 ms rise/fall time) was a low tone (1000 Hz, standard trials), or a high tone (2000 Hz, oddball trials) with one of two keyboard responses. There were 600 trials in total (500 standard, 100 oddball). The bursts were presented at a variable interstimulus interval of 1-2 seconds. Trials were placed in blocks of five, after which the participants took a self-paced blink break. Stimuli were presented through
Sennheisers headphones at 80dB SPL. All participants exhibited normal hearing sensitivity at audiometric frequencies between 1000-2000 Hz. There was a short practice of 20 trials with feedback. There was no further feedback for the experimental task. The P300 task took approximately 30 minutes.

**EEG Processing and ERP Analysis**

Scalp-recorded EEG data were collected from 64 Ag-AgCl electrodes using an ActiveTwo amplifier system (BioSemi, Netherlands). Electrodes were placed according to the 10-20 standard system, and all were referenced offline to two additional electrodes placed on bilateral mastoid processes. Two supplementary electrodes were placed on the outer canthi of the left and right eyes in order to record the horizontal electrooculogram, and two more leads were placed below the left and right eyes to record the vertical electrooculogram. EEG was recorded with 24-bit resolution and a sampling rate of 512 Hz. Offline data were downsampled to 256 Hz and digitally filtered between 0.1 Hz and 30 Hz.

All ERP processing was conducted in Matlab (Version R2011) using the EEGLAB toolbox (Delorme & Makeig, 2004) and the ERPLAB toolbox (Lopez-Calderon & Luck, 2014). Epochs containing any eyeblink artifacts (more than 80 µV of peak-to-peak amplitude) and horizontal eye movements (more than 35 µV of step-like artifacts) were automatically removed. Trial rejection numbers did not differ for any of the groups (at-risk, M_{rejection} = 13.34, SD = 12.12, vs. healthy older adult, M_{rejection} = 7.83, SD = 10.44: t(23) = 1.22, p = .23; healthy older adult vs. young adult, M_{rejection} = 4.89, SD = 3.66: t(23) = 0.93, p = .36). EEG segments of 1100 ms including 200 ms of pre-stimulus baseline, time-locked to stimulus onset, were created and averaged separately for each participant, electrode, and condition. All epochs were baseline corrected and amplitudes were measured relative to the 200 ms baseline.
**CDA**

We assessed the CDA from 300-800 ms following onset of the memory array. We calculated the mean amplitude for each participant in each set size (1,3,4) of the CDA component for correct trials only. ERPs were analyzed from three sites (CP3/CP4, PO7/PO8, P5/P6) (Jost et al., 2011; Sander et al., 2011). Based on previous research, we predicted young adults would have greater CDA differentiation and a higher VSTM capacity than healthy older adults (Duarte et al., 2013; Jost et al., 2011; Sander et al., 2011). Most importantly, we predicted that healthy older adults would have more CDA differentiation and a higher $K$-estimate than the at-risk older adults.

**P300**

We assessed the P300 as the latency window between 300-500 ms after stimulus onset and calculated the peak amplitude and latency for each participant. Consistent with previous experiments using similar paradigms, ERPs were analyzed from three electrode sites (Fz, Cz, Pz) (Ally et al., 2006). We predicted that the at-risk group would have reduced P300 amplitude and delayed latency relative to healthy older adults.

**Data Analysis**

Analyses were performed with the ANOVAs described below. Because we were interested in effects of aging and effects of preclinical MCI, we restricted follow-up tests to comparisons between young adults vs. healthy older adults, and healthy older adults vs. at-risk older adults. For all analyses, $p$-values and degrees of freedom reflect the Greenhouse-Geisser correction where appropriate.
Results

Behavioral Results: Memory Capacity Estimate

Maximum $K$-estimates from the memory capacity estimate task are shown in Table 1. The healthy older adult group had a significantly larger $K$-estimate than the at-risk group, $t(23) = 2.36, p = .03$. Although numerically the younger adults had a larger capacity than the healthy older adults, this difference was not significant, $t(23) = -1.69, p = .11$.

Behavioral Results: CDA Task

We conducted a $3 \times 3$ mixed-design ANOVA on the behavioral $K$-estimates from the CDA task. This revealed a main effect of set size, $F(1.14, 38.61) = 126.50, p < .001, \eta_p^2 = .79$, a main effect of group, $F(2, 34) = 4.52, p = .02, \eta_p^2 = .21$, and a marginal set size $\times$ group interaction, $F(2.27, 38.61) = 2.82, p = .06, \eta_p^2 = .14$. To investigate what was driving the set size $\times$ group marginal interaction, we conducted two separate $2 \times 3$ ANOVAs, in which our group factor was either at-risk older adults vs. healthy older adults, or healthy older adults vs. young adults. The ANOVA comparing at-risk older adults vs. healthy older adults showed significant main effects of set size, $F(1.17, 27.01) = 64.22, p < .001, \eta_p^2 = .74$, and group, $F(1, 23) = 4.18, p = .05, \eta_p^2 = 15$, with no significant interaction, $F(1.17, 27.01) = 1.75, p = .20, \eta_p^2 = .07$, indicating that, overall, performance in the at-risk group was lower than in the healthy older adults. However, the ANOVA comparing healthy older vs. young adults showed only a significant main effect of set size, $F(1.04, 23.94) = 142.36, p < .001, \eta_p^2 = .86$, but not other significant effects or interactions, $F's < 1.69, ps > .21, \eta_p^2's < .07$, suggesting performance between the young and older adult groups was not significantly different.
ERP Results: CDA Task

We conducted a 3 (group) × 3 (electrode) × 3 (set size) mixed-design ANOVA on the CDA data (Figure 9). This revealed a main effect of set size $F(2, 68) = 25.09, p < .001, \eta_p^2 = .43$, an electrode × group interaction, $F(4, 68) = 3.41, p = .01, \eta_p^2 = .17$. There were no other significant effects or interactions, $Fs < 1.31, ps > .27, \eta_p^2s < .07$, which importantly included no three-way interaction of set size × electrode × group, $F(4.69, 79.73) = 1.31, p = .27, \eta_p^2 = .07$, thus justifying collapsing across electrode site in subsequent analyses. To investigate the nature of the set size × group interaction, we conducted two separate 2 (group) × 3 (set size) ANOVAs, in which our group factor was either at-risk older adults vs. healthy older adults or healthy older adults vs. young adults, so that we could directly investigate effects of preclinical MCI and effects of aging. Critically, the comparison of at-risk older adults vs. healthy older adults showed a significant set size × group interaction, $F(1.70, 39.09) = 4.05, p = .02, \eta_p^2 = .15$, indicating that the degree of differentiation across set size differed between at-risk adults and their controls. However, the healthy older adults vs. young adult comparison showed no set size × group interaction, $F(1.91, 43.89) = 1.11, p = .34, \eta_p^2 = .05$, suggesting there was no variance in differentiation between the young and healthy older adult groups. These findings correspond to the behavioral findings described above: There were no behavioral or physiological differences between the young and older adults, yet the at-risk older adults showed lower behavioral performance as well as reduced electrophysiological differentiation, compared to healthy older adults. There were no effects or interactions with electrode in the at-risk older adult vs. healthy older adult ANOVA, $Fs < 1.30, ps > .28, \eta_p^2s < .05$. The healthy older adult vs. young adult ANOVA revealed a main effect of electrode, $F(1.46, 33.66) = 4.01, p = .04, \eta_p^2 = .15$ and a
marginal electrode × group interaction, \( F(1.46, 33.66) = 2.73, p = .09, \eta^2_p = .11 \). There were no other significant interactions, \( Fs < 1.61, ps > .21, \eta^2_p s < .07 \).
Figure 9. CDA: Event-related potentials from the CDA in the younger adults (N = 12), healthy older adults (N = 13) and the at-risk older adults (N = 12). We calculated the CDA by subtracting ipsilateral from contralateral activity, time-locked to the onset of the memory array. We analyzed activity from six electrode sites: CP3/CP4, P5/P6, PO7/PO8 during the 300-800 ms latency window indicated by the gray box. We found that the at-risk participants showed reduced differentiation of the CDA. By contrast, both healthy younger and older adult control groups showed differentiation at all set sizes.
To further investigate differentiation within each group, we then performed individual 3 (set size) × 3 (electrode) repeated-measures ANOVAs within each group. For young adults, this revealed a significant main effect of set size, $F(2, 22) = 11.95, p < .001, \eta^2_p = .52$, and pairwise comparisons between each set size were significant for 1 vs. 4 ($p < .001$), 3 vs. 4 ($p = .02$), and marginal for 1 vs. 3 ($p = .06$). The ANOVA also revealed a marginal main effect of electrode for the younger adult group, $F(1.30, 14.27) = 3.82, p = .06, \eta^2_p = .26$. For healthy older adults, the ANOVA revealed a main effect of set size, $F(2, 24) = 21.69, p < .001, \eta^2_p = .64$, and pairwise comparisons between each set size were all significant, $ps < .02$. There were no main effects or interactions with electrode in the healthy older adult group, $Fs < 2.0, ps > .12, \eta^2_p s < .14$. In contrast to young and healthy older adults, there was no effect of set size in the at-risk group, $F(2, 22) = 1.61, p = .23, \eta^2_p = .13$, indicating that the at-risk participants did not show differentiation of the CDA as set size increased. There were no main effects or interactions with electrode in the at-risk group, $Fs < .79, ps > .42, \eta^2_p s < .07$.

**Behavioral Results: P300 Oddball Task**

Behavioral results of the P300 oddball task are shown in Table 1. There was no difference in accuracy between the at-risk group and healthy older adults, $t(23) = -0.67, p = .51$, or between healthy older adults and younger adults, $t(23) = 1.08, p = .29$.

**ERP Results: P300 Amplitude**

A 3 (group) × 3 (electrode) mixed-design ANOVA was performed on the P300 peak amplitude data (Figure 10). This revealed a marginally significant main effect of group, $F(2, 34) = 3.14, p = .056, \eta^2_p = .156$, a significant effect of electrode, $F(1.48, 50.27) = 5.08, p = .02, \eta^2_p = .13$, and a significant group × electrode interaction. We performed follow-up independent
samples $t$-tests at each electrode to compare the at-risk group vs. healthy older adults, and healthy older adults vs. younger adults. These revealed reduced P300 amplitude in the at-risk group at Fz, $t(23) = -2.09, p = .05$, and marginally reduced amplitude at Cz, $t(23) = -1.94, p = .065$, but no significant reduction at Pz, $t(23) = -1.31, p = .20$. Younger adults showed a larger amplitude than older adults at Pz, $t(23) = -2.76, p = .01$, but not at Fz, $t(23) = 1.46, p = .16$, or Cz, $t(23) = -0.91, p = .37$.

**ERP Results: P300 Latency**

The ANOVA described above was also conducted on the latency data. This revealed a main effect of electrode, $F(1.66, 56.44) = 8.02, p = .002, \eta^2_p = .19$. However, in contrast to our predictions and to previous studies (Lai et al., 2010; Papaliagkas et al., 2008; Polich et al., 1990), we found no other significant effects or interactions, $F_s < 2.04, ps > .15$, $\eta^2_p$s < .11.
Figure 10. P300: Event-related potentials from the P300 oddball condition in the younger adults (N = 12), healthy older adults (N = 13), and at-risk older adults (N = 12). We analyzed activity from three electrode sites (Fz, Cz, and Pz) during the 300-500 ms latency window indicated by the gray box. We found that the P300 amplitude was significantly reduced in at-risk participants compared to healthy older adult controls at Fz, marginally reduced amplitude at Cz, and not significantly different at Pz.
Discussion

To our knowledge, this study provides the first evidence of reduced differentiation of the CDA in a preclinical population who had no MCI diagnosis, but whose neuropsychological screening indicated risk for developing MCI. We found that, consistent with their VSTM impairment, the at-risk group displayed an abnormal CDA, with no significant differentiation between set sizes. In a profile similar to that observed in cases with diagnosed MCI/AD (Lai et al., 2010), we found that these at-risk individuals also demonstrated some evidence for a reduced P300 amplitude.

The CDA is an ERP component thought to reflect the number of items currently being held in VSTM, is reflective of individual capacity limit (Vogel & Machizawa, 2004), and originates from several coordinated sources with a major hub in the parietal cortex (Todd & Marois, 2004). Both parietal and frontal brain regions are thought to underlie top-down attentional control, and in fact, patients with prefrontal cortex damage have both behavioral impairments and an abnormal CDA pattern when stimuli are presented contralateral to the lesioned hemisphere (Voytek & Knight, 2010). Thus, it is likely that the CDA amplitude is also influenced by top-down control, and may reflect the complexity of processing or an increase in complexity of representations of the stimuli (Alvarez & Cavanagh, 2004; Gao et al., 2009). One recent study found that the CDA amplitude at P1/P2 was sensitive to number of objects, whereas amplitude at another site, P7/P8 was sensitive to number of features (Wilson, Adamo, Barense, & Ferber, 2012).

Although no published studies have investigated the effect of MCI/AD pathology on the CDA, there have been a few published studies investigating age-related effects on the CDA. Older adults have a reduced CDA amplitude relative to younger adults (Duarte et al., 2013), as...
well as a reduced differentiation of the CDA (Jost et al., 2011). Notably, however, in the current study, we did not find a behavioral or physiological effect of healthy aging on VSTM in terms of the CDA. That is, healthy older adults were not impaired relative to young adults in terms of their CDA differentiation. These results are in contrast to three previous studies examining aging in the CDA, which have all shown a reduced CDA amplitude for older adults (Duarte et al., 2013; Jost et al., 2011; Sander et al., 2011). In these past studies, older adults were, however, not split according to level of cognitive decline. If we had not split our groups according to MoCA performance in the present study, we would likely have found deficits which we would have attributed to normal, cognitive aging rather than to pathological decline. This highlights the importance of using sensitive cognitive screening measures in studies of healthy aging to ensure that the sample of healthy older adults is uncontaminated with preclinical MCI.

By the same token, the fact that these at-risk participants were putatively healthy members of the community, who were randomly selected from a large volunteer participant panel and did not meet MCI diagnostic criteria, indicates that these electrophysiological signatures may be particularly sensitive to the earliest stages of the disease process. The true predictive power of these measures must be established in longitudinal studies that assess whether a given individuals’ electrophysiological profile is a better predictor of conversion to MCI/AD than a failing MoCA score. Such experiments are currently underway. EEGs are easily performed, inexpensive, and noninvasive, making this a promising and accessible method for preclinical screening. Identification of robust preclinical markers will hasten diagnosis, allowing for earlier treatment, future planning, and maximization of quality of life. In conclusion, the present finding provide evidence that electrophysiological markers of short-term memory and attention are altered in a preclinical group of older adults with no MCI diagnosis, but in whom
neuropsychological screening indicated risk for developing MCI. Our results from these putatively healthy community-dwelling volunteers indicate that the CDA and P300 may be particularly sensitive to the earliest stage of the disease process.

These results indicate that there are early neural changes occurring in the at-risk group, possibly as a result of MTL and posterior parietal cortex changes associated with AD pathology (Khan et al., 2014). Impoverished representations in the MTL may have caused the impaired performance the item-location binding required in the CDA task. In the following chapter, I investigated whether impoverished MTL representations in the at-risk group and a group of MCI patients affects the binding of features within an object.
Chapter 3

Reducing perceptual interference improves visual discrimination in mild cognitive impairment: Implications for a model of perirhinal cortex function

Abstract

Memory loss resulting from damage to the 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 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 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 and the requirement to bind features into a cohesive object, 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.

**Introduction**

MCI patients have incipient damage to key brain structures known to be vital for memory: namely, the MTL (Loewenstein et al., 2009; Schmidt-Wilcke, Poljansky, Hierlmeir, Hausner, & Ibach, 2009). As described in the introduction, a representational-hierarchical model of object processing suggests that a region of the MTL, the PRC, is vital for not only mnemonic demands, but also certain forms of perception. This account holds that common representations of the environment arise from common mechanisms rather than distinct mnemonic and perceptual functions (Cowell et al., 2010a; Graham et al., 2010; Murray & Bussey, 1999). 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 (Figure 7). 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 years ago that amnesia may be related to an increased vulnerability to interference (Warrington & Weiskrantz, 1970). Although this theory was later rejected (Warrington & Weiskrantz, 1978), there has been a recent resurgence in
the idea (Bartko, Cowell, Winters, Bussey, & Saksida, 2010; Cowan et al., 2004; Della Sala et al., 2005; Dewar, Alber, Cowan, & Della Sala, 2014; Dewar et al., 2010; Dewar et al., 2009; 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 the 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., 2011; Burke et al., 2010), 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, Groen, 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. Healthy controls, who presumably had an intact PRC, performed as well under conditions of high interferences 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 (Baxter, 2012; Peterson, Cacciamani, Barense, & Scalf, 2012; L. 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 AD, with the PRC demonstrating significant atrophy (Du et al., 2001; Guillozet, Weintraub, Mash, & Mesulam, 2003; Juottonen et al., 1998; Loewenstein et al., 2009; Pennanen et al., 2004; Schmidt-Wilcke et al., 2009; Taylor & Probst, 2008). MCI patients who later convert to AD show damage to the MTL (Bell-McGinty et al., 2005), including to the PRC (T. W. Mitchell et al., 2002). Evidence suggests that MCI and AD patients have visuoperceptual deficits that may be more subtle than standardized visuoperceptual tests can pick up (Alegret et al., 2009; Alegret et al., 2010), 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 and colleagues (2012) to MCI patients. 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 (Du et al., 2001; Loewenstein et al., 2009). 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.

**Methods**

**Participants**

Ten patients with clinically diagnosed amnestic MCI participated in this study. These participants were recruited through the Emory Alzheimer’s Disease Research Center, Atlanta, Georgia. Of these ten, three were excluded on the basis of their near perfect scores on the MoCA (Nasreddine et al., 2005) and 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 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 (three female, \( M_{\text{age}} = 68.43 \) years, SD = 8.69) completed a detailed neuropsychological battery (Table 2). 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 Pool to participate in the study. Of these, ten individuals (seven female, \( M_{\text{age}} = 71.11 \) years, SD = 6.22) scored below 26 on the MoCA (\( M_{\text{MoCA}} = 24.3, \) SD = 1.05) and were considered to be at-risk for MCI (Damian et al.,
The remaining nineteen individuals (fourteen female, $M_{\text{age}} = 71.05$ years, $SD = 5.33$) scored above 25 on the MoCA ($M_{\text{MoCA}} = 27.78$, $SD = 1.47$) and were included as control participants. Participants gave informed consent, and they were compensated for their time. These participated were tested in the Memory and Perception 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, 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, $t(27) = 6.61$, $p < .001$, and from those of MCI patients, $t(14) = 4.21$, $p < .001$. MCI patients’ performance on the MoCA was lower than the at-risk group, $t(15) = 2.08$, $p = .05$. Due to scheduling constraints, two of the MCI patients were not administered the MoCA. Importantly, the MoCA was administered after the experimental task for all remaining subjects, so the experimenter could not be biased by a participants’ MoCA performance on the administration of the task. Age did not differ between controls, MCI patients, or those at-risk for MCI, $t$s $< 0.21$, $ps > .49$. 
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All MCI participants were diagnosed with amnestic subtypes. Patients with multidomain amnestic diagnoses are described in the following manner: “Lang” – amnestic + language, “Exec fx” – amnestic + executive function. Individual cells for each MCI patient represent raw data scores, parentheses reflect Z-scores.
**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 (~9° x 9°) 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 15s 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 (Figure 11abc).

The task was administered under two conditions (High Interference, 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 (Figure 11abc). 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, an 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 ABC; letters represent individual feautres). 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 (Barense, Groen, et al., 2012).
The high interference condition contained 88 consecutive trials of high ambiguity object
discriminations (44 match, 44 nonmatch, intermixed in a pseudorandom sequence; Figure 11b).
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 nonmatch) that were each
interspersed with two trials containing photographs of easily discriminable everyday objects (58
trials, 29 match, 29 nonmatch, Figure 11a,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 low
interference, 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.
Figure 11. 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). The high interference condition was a 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, although 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).
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 Barense 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 in size (match) or different (nonmatch) (Figure 11d). For nonmatch trials, the length of each side of the square randomly varied from 67 to 247 pixels. The difference between 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 were designated as hits, and incorrect responses of “different” to images that were the same were designated as false alarms (MacMillan & 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 trails were 88 trials in the high interference condition, and 30 trials in each low interference condition. These data were subjected 3 (group: healthy controls, at-risk, MCI patients) $\times$ 3 (condition: Low Interference 1, High Interference, Low Interference 2) mixed-design ANOVA. 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 otherwise stated.

**Planned Analysis: Control Task**

We calculated $d'$ for the difficult size task in the same manner as described above. We then performed independent samples $t$-tests to compare performance of MCI patients and at-risk participants to healthy controls. We predicted no significant differences in performance across groups.

**Results**

**Interference Task**

Data from the interference task are shown in **Figure 12**. The results of our 3 (group) × 3 (condition) ANOVA revealed main effects of interference, $F(2, 66) = 15.79, p < .001$, and group, $F(2, 33) = 3.07, p = .03$, and an interference × group interaction, $F(4, 66) = 1.99, p = .05$. Follow up $t$-tests indicated that, as predicted, both the MCI patients and the at-risk group were impaired on the high interference condition, compared with healthy controls, $t$s > 2.20, $ps < .02$, with no differences between the MCI patients and the at-risk group, $t(15) = 0.73, p = .48$ (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, $t$s > 0.81, $ps > .21$, nor were the MCI patients impaired on the second low interference condition, $t(24) = .80, p = .22$. Unexpectedly, the at-risk group was impaired, relative to controls, on the second low interference condition, $t(27) = 1.99, p = .03$. Since 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 fully recover from the interference in the previous high interference condition. Reaction data and proportion correct split according to match and nonmatch trials are shown in Table 3.

![Graph showing 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 SEM. *p < .05 (comparisons of MCI patient group and at-risk group to healthy controls).](image)

**Figure 12.** 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 SEM. *p < .05 (comparisons of MCI patient group and at-risk group to healthy controls).

**Control Task**

We compared performance of the at-risk group and MCI patients to healthy controls using independent samples t-tests and found that neither group was impaired, t < 0.94, p > .18 (Figure 12). A paired t-test showed no evidence that control participants found the difficult size condition as difficult as the high interference condition, t(18) = 1.40, p = .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 3 shows the reaction time and proportion correct for match and nonmatch trials.

Table 3. Reaction time and accuracy (proportion correct) for each participant group for match and nonmatch trials, respectively.

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**Discussion**

In this study, we tested amnestic 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, Groen, 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 damage included the PRC (see Figure 13 for a direct comparison), and suggests that memory disorders involving the MTL may reflect a heightened vulnerability to visual interference.

**Figure 13.** Supplemental comparison of performance between MCI patients, at-risk participants, and the hippocampal (HC) cases and medial temporal lobe (MTL) cases presented previously in Barense et al., 2012.
These findings, when considered together with research in humans with focal MTL damage (Barense, Groen, 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 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 Figure 11). 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 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; 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 hour delay filled with psychometric tests) (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 AD-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.

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 (Devanand, Bansal, Liu, Hao, & Pradhaban, 2012; Harris et al., 2010; Khan et al., 2014; Wakabayashi, Honer, & Masliah, 1994). The PRC is heavily connected to these structures and is part of the neural circuit affected early in MCI (Bell-McGinty et al., 2005; T. W. Mitchell et al., 2002; Schuff & 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; McTighe et al., 2010), and (2) functional neuroimaging revealing PRC activity in healthy participants during the discrimination
task performed here (Barense, Groen, et al., 2012), and other tasks taxing complex object perception (Barense et al., 2010; Devlin & Price, 2007; Erez et al., 2015; Lee, Seahill, & Graham, 2008; O'Neil et al., 2009). In addition, based on the intact performance of amnesic patients with focal hippocampal damage (Figure 13), 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 they might go on to develop MCI. 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 Petersen criteria (Petersen 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 (Markwick et al., 2012; Nasreddine et al., 2005). Additionally, the present study indicates that 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 condition, \( r(33) = .54, p < .01 \) (Bonferroni-corrected), but not the other three conditions, \( r(33)s < .29, p > .09 \) (Bonferroni-corrected). We are currently following up the at-risk participants on additional cognitive and physiological longitudinal assessments.

Although we prefer to consider these results in terms of impoverished object representations impairing perception, it is worth noting that there is a visual 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
(Hannula, Tranel, & Cohen, 2006; Olson et al., 2006), with evidence suggesting that the MTL is
important in online processing of highly similar visual objects (Warren, Duff, Jensen, Tranel, &
Cohen, 2012; Warren, Duff, Tranel, & Cohen, 2011). We are certainly not opposed to the notion
that MTL structures are important for working memory, and indeed, this will be addressed
further in Chapter 4. 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 another (Barense, Groen, et al., 2012; Erez et al., 2015; Erez, Lee, & Barense, 2013). 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 (Barense, Ngo, Hung, & Peterson, 2012;
Lee & Rudebeck, 2010).

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. In Chapter 4, I further
investigate the role of interference in MCI pathology by administering a VSTM task in which we manipulated the presence of a cue that provided location information and reduced interference.

**Chapter 4**

**A retroactive spatial cue improved VSTM capacity in mild cognitive impairment and medial temporal lobe amnesia but not in healthy older adults**

**Abstract**

Visual short-term memory (VSTM) is a vital cognitive ability, connecting visual input with conscious awareness. VSTM performance declines with mild cognitive impairment (MCI) and medial temporal lobe (MTL) amnesia. I demonstrated that VSTM capacity is also impaired in older adults at-risk for MCI in Chapter 2. Many studies have shown that providing a retrospective cue (“retrocue”) improves VSTM capacity estimates for healthy young adults. However, one study has demonstrated that older adults are unable to use a retrocue to inhibit irrelevant items from memory. It is unknown whether patients with MCI and MTL amnesia will be able to use a retrocue to benefit their memory. We administered a retrocue and a baseline (simultaneous cue, “simucue”) task to young adults, older adults, MCI patients, and MTL cases. Consistent with previous findings, young adults showed a retrocue benefit, whereas healthy older adults did not. In contrast, both MCI patients and MTL cases showed a retrocue benefit – the use of a retrocue brought patient performance up to the level of age-matched controls. We speculate that the patients were able to use the spatial information from the retrocue to reduce interference and facilitate binding items to their locations.
Introduction

Visual short-term memory (VSTM) is a critical cognitive ability, allowing for maintenance of visual information for a brief period of time after that information is no longer present in the environment. It is considered to be the visual storage element of working memory, and is limited in capacity to roughly three to four items for simple visual stimuli in healthy young adults (Cowan, 2001; Luck & Vogel, 1997; Todd & Marois, 2004; Vogel & Machizawa, 2004). VSTM performance declines in both healthy aging (Vaughn & Hartman, 2009; Verhaeghen & Salthouse, 1997), mild cognitive impairment (MCI, (Alescio-Lautier et al., 2007), and following medial temporal lobe (MTL) damage (Ezzyat & Olson, 2008; Olson et al., 2006; Pertzov et al., 2013).

VSTM capacity is typically measured using a change detection task, where participants view an array of simple visual items to be remembered (memory array) (Figure 14). Following a short delay, participants view a second array (probe array) and indicate whether the probe is identical to the memory array. A large body of evidence suggests that the use of a retroactive cue (retrocue) presented after viewing the memory array, but before the probe array, improves VSTM performance in younger adults (Duarte et al., 2013; Kuo, Stokes, Murray, & Nobre, 2014; Landman, Spekreijse, & Lamme, 2003; Lepsien, Griffin, Devlin, & Nobre, 2005; Lepsien & Nobre, 2007; Makovski & Jiang, 2007). The retrocue signals the to-be-probed item and location and thus indicates that all other uncued items and locations are irrelevant. In a typical retrocue paradigm, performance on the retrocue condition is compared to a baseline condition in which there is either no cue, or a cue appears simultaneously with the probe array (simucue).
Figure 14. Schematic of the experimental design, with example stimuli from each condition. In both retrocue and simucue trials, a memory array appeared on screen for 1000 ms. This memory array contained between one and six colored circles (i.e., there were six set sizes in total). This was followed in both conditions by a delay period of 1000 ms. In retrocue trials, an arrow pointing to the to-be probed location was displayed for 100 ms. Here, the arrow is directing attention to the location which previously contained a red circle. After a 400 ms delay, a probe is displayed, and participants decide whether the color of the object is the same or different than the color of the object in that location previously. In contrast, in simucue trials, the probe and cue appeared simultaneously. Both of the above are examples of “same” trials.

Why is the retrocue beneficial? Since the initial retrocue work was published over ten years ago, there has been debate in the literature as to the precise mechanisms at play (Gazzaley & Nobre, 2012; Gozenman, Tanoue, Metoyer, & Berryhill, 2014; Griffin & Nobre, 2003; Kuo et al., 2014; Lepsien et al., 2005; Makovski & Jiang, 2007, 2008; Makovski, Sussman, & Jiang, 2008; Pinto, Sligte, Shapiro, & Lamme, 2013; Sligte, Scholte, & Lamme, 2008; Souza, Rerko, &
One suggestion is that the retrocue works by reducing inter-item interference – focusing attention on one critical item during the delay period enhances memory for that critical item by releasing memory interference from other items (Souza et al., 2014). That is, following the retrocue, uncued items from the initial memory representation can be deemed irrelevant and be deleted. An additional explanation is that the retrocue works by reducing probe interference – specifically, focusing attention on a critical item during the maintenance period helps to solidify memory for that item, which makes it more resistant to interference from the probe array (Makovski et al., 2008).

Although these two explanations differ in terms of the origin of interference (i.e., interference from all items vs. interference specific to the probe), both are in agreement that at the heart of the retrocue benefit lies a reduction in interference. Given this, it may be theoretically informative to consider how the retrocue affects VSTM in cases with increased vulnerability to interference. Here we investigated the retrocue benefit in three participant groups with diminished VSTM capacity and heightened susceptibility to interference: older adults, patients with MCI and cases with MTL amnesia. Each of these populations will be discussed in turn below.

One prominent theory, inhibitory deficit theory, proposes a mechanism for reduced VSTM capacity in older adults: According to this theory, older adults have difficulties deleting task-irrelevant information from working memory and are thus susceptible to interference (Hasher et al., 2007; Hasher & Zacks, 1988; Lustig et al., 2007). Indeed, many studies have shown that older adults are more affected by irrelevant information than young adults because they are unable to inhibit it (Amer & Hasher, 2014; Biss, Campbell, et al., 2013; Biss, Ngo, Hasher, Campbell, & Rowe, 2013; Healey, Hasher, & Campbell, 2013; Lustig et al., 2007;
Weeks & Hasher, 2014). Under this view, one might expect that older adults will not benefit from the retrocue because they are unable to use the cue to resolve inter-item interference from the memory array. That is, even though the retrocue signals items that can be removed from memory, older adults will be unable to benefit from this information because they have problems deleting irrelevant items from memory. Consistent with this notion, the one study that has examined the effects of a retrocue in aging found that older adults did not show an increase in VSTM capacity with the retrocue, in contrast to the well-documented retrocue benefits observed in younger adults (Duarte et al., 2013). That said, on other measures, there was evidence that the retrocue did benefit older adults to some extent: older adults had faster reaction times (RT) on retrocue than non-cue trials and also showed modulated electrophysiological responses on retrocue trials (contralateral delay activity, CDA, a measure typically associated with VSTM capacity). Specifically, the CDA observed in older adults was attenuated after the retrocue, suggesting that the retrocue reduced memory load.

Turning to MCI and MTL amnesia, accumulating evidence suggests that patients with MCI and MTL amnesia have compromised VSTM (Alescio-Lautier et al., 2007; Ezzyat & Olson, 2008; Jiang, Olson, & Chun, 2000; Olson et al., 2006; Parra et al., 2009; Parra et al., 2010; Pertzov et al., 2013; Redel et al., 2010). One study suggested that patients with MTL damage showed intact VSTM for individual items, but were impaired at binding the item’s identity with its location (Pertzov et al., 2013). Similar binding deficits occur in Alzheimer’s disease patients and cognitively intact persons with the E280A presenilin-1 mutation, commonly termed “familial Alzheimer’s disease” (Della Sala et al., 2012; Parra et al., 2009; Parra et al., 2010). It is possible that the spatial information provided by the retrocue may help to ameliorate these deficits by facilitating access to the location information. In addition, recent evidence
suggests that both MCI patients and MTL amnesics may be disproportionately vulnerable to interference relative to their age-matched counterparts. Indeed, recent work has shown that removing irrelevant visual information altogether improves performance on memory tasks (Dewar et al., 2014; Dewar et al., 2010; Dewar et al., 2009; Dewar, Hoeveijzers, Zeman, Butler, & Della Sala, 2015), as well as perceptual discrimination tasks (Chapter 2, Newsome, Duarte & Barense, 2012). Thus, to the extent that MCI patients and MTL amnesia cases can use spatial information from the retrocue to reduce interference from irrelevant items, it may disproportionately benefit their performance relative to that observed in age-matched controls. That is, although the patients’ overall capacity may be lower than controls, their retrocue performance may exceed their own baseline simucue performance because they can use the spatial cue to counteract their binding deficits and vulnerability to interference.

To our knowledge, there have been no investigations of retrospective attention in MCI or MTL amnesia, and it remains an open question as to whether the retrocue could confer a VSTM benefit to these patients. Here we tested these ideas by assessing retrospective attention in VSTM to four participant groups: young adults, healthy older adults, older adults with amnestic MCI, and older adults with MTL amnesia. We investigated the effect of the retrocue in two ways: performance (in terms of capacity estimates and RT) and the percent benefit conferred by the retrocue relative to the baseline simucue condition (for both capacity and RT). In short, we confirmed previous results that healthy old adults did not benefit from the retrocue and we report the novel finding that memory-impaired cases showed a disproportionate retrocue benefit, which brought their capacity estimates up to that of healthy older adults. These results are consistent with inhibitory deficit theory of aging, and suggest that there may be different mechanisms by which these distinct groups use the retrocue.
Methods

Participants

We recruited four groups of participants: younger adults, older adults, MCI patients, and MTL amnesia cases. Fourteen younger adults (M_{\text{age}} = 21.50 \text{ years}, SD = 1.99, M_{\text{education}} = 15.29 \text{ years}, SD = 1.26) were recruited from undergraduate courses at the University of Toronto and nineteen healthy older adults (M_{\text{age}} = 65.68 \text{ years}, SD = 4.79, M_{\text{education}} = 16.47 \text{ years}, SD = 3.67, M_{\text{MoCA}} = 27.78, SD = 1.55) were recruited from the University of Toronto Adult Volunteer Pool. The young and older adult groups did not differ in education, \( t(31) = 1.16, p = .26, d = 0.40 \).

In addition to these healthy participants, nine patients with clinically diagnosed amnestic MCI were recruited through the Emory University Alzheimer’s Disease Research Center. All patients had a full neuropsychological workup and consensus diagnosis from a group of neuropsychologists (see Table 2 for neuropsychological test results). Of these nine patients, one was excluded for having both a perfect score on the Montreal Cognitive Assessment, MoCA (Nasreddine et al., 2005) and a score well within the normal range on the Mini Mental Status Exam, MMSE, (Folstein et al., 1975). This patient has not attended or sought services from the memory clinic for the entire five year period following experimental testing, leading us to believe he was “worried well” (Ahmed et al., 2008). Of the remaining eight patients (four female, M_{\text{age}} = 64.63 \text{ years}, SD = 9.56), all presented with an amnestic diagnosis (see Table 2 for subtype breakdown). The MCI patients and healthy older adults did not differ in age or education, \( t(25)s < 0.41, ps > .68 \).

Two amnesic cases, DA and LD, with documented MTL damage participated in the study. These patients were recruited through Baycrest Hospital’s MemoryLink Program. Both DA and LD have been described previously (Kwan et al., 2015; Rosenbaum et al., 2008). Both
patients had severe deficits in memory performance as evidenced by standard
europsychological tests and circumscribed lesions to the MTL (Figure 15). DA was 61 years
old at the time of experimental testing and has 17 years of education. Following herpes
encephalitis, DA incurred bilateral MTL damage, with more pronounced damage on the right
hemisphere. LD was 62 years old at the time of testing, with 19 years of education. LD had a
surgical resection of his left temporal lobes secondary to a history of seizures. DA and LD did
not differ from the healthy older adult group in terms of age or education, Crawford’s $t(19) <
1.21, ps > .12$.

All participants provided informed consent and were compensated for their time and
travel expenses. The study was approved by the Ethics Review Boards of Georgia Institute of
Technology, Emory University, Baycrest Hospital and the University of Toronto.

Figure 15. Figure modified from Kwan et al., 2015 and Rosenbaum et al., 2008. (A) MRI slice of
damage for LD. (B) MRI slice of damage for DA. Images are presented according to
radiological convention (right hemisphere displayed on left side of image).
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All MCI participants were diagnosed with amnestic subtypes. Patients with multidomain amnestic diagnoses are described in the following manner: “Lang” = amnestic + language, “Exec fx” = amnestic + executive function, “Vis-spatial” = amnestic + visuospatial

Individual cells for each MCI patient represent raw data scores, parentheses reflect Z-scores. Individual cells for each MTL patient represent scaled scores rather than raw (see Kwan et al., 2015).

Note: For LD, the Hopkins Verbal Learning Test was administered rather than the CVLT.
Experimental Design

This paradigm was modeled from Experiment 3 of Makovski, Sussman, and Jiang (2008). Participants were presented with a memory array followed by a probe array after a brief delay and were asked to indicate whether the stimulus in the probe array was the same color as the stimulus that had occupied that location previously seen in the memory array (Figure 14). There were two conditions: retrocue and a simultaneous cue (simucue) that served as a baseline. In both conditions, a memory array appeared on screen for 1000 ms, and contained between one and six colored circles. The circles were 1.31° in diameter, and their colors were chosen from a library of nine colors: brown (RGB = 115, 69, 56), red (RGB = 218, 37, 29), orange (RGB = 231, 120, 23), yellow (RGB = 248, 195, 0), green (RGB = 0, 146, 63), light blue (RGB = 0, 124, 195), dark blue (RGB = 40, 22, 111), purple (RGB = 144, 30, 120), and pale gray (RGB = 220, 220, 220). These stimuli were displayed equidistant from the center, on an imaginary circle with a diameter of 5°. After the memory array, a blank delay screen appeared for 1000 ms. In retrocue trials, after the blank screen, a white arrow appeared in the center of the screen, which directed attention to the to-be-probed location. This arrow always pointed to the location that would later be probed (100% valid). After a 400 ms delay, the single probed item was displayed. In contrast, in simucue trials, the probed item was displayed simultaneously with the white arrow pointing to the probe. The white arrow served as the cue in both conditions. Participants indicated whether the probed item matched the item from that location in the memory array. Equal numbers of simucue and retrocue trials were presented for each of the six set sizes, with 50% of the probed items matching the stimulus from the memory display (i.e., “same” trials). There were 25 trials for each combination of cue type (i.e., retrocue or simucue), set size (i.e., 1-6), and response type (i.e., “same” or “different” trials), making a total of 600 trials. The experiment was divided into
10 blocks of 60 trials each. Participants could take a break between each block of trials, and all trial types were randomized.

In retrocue trials, the cue appeared *retroactively* after the memory array but before the probe, whereas in simucue trials, the cue appeared *simultaneously* with the probe. As such, in simucue trials the cue did not serve to enhance performance but simply to equate perceptual input across the two conditions. Thus, the simucue condition allowed for an assessment of baseline VSTM performance, to which we could compare any enhancements due to the retrocue. Participants were instructed to remember all of the items presented in the memory array, and that the cue would indicate with 100% accuracy which item would be tested. Participants were encouraged to respond as quickly and as accurately as possible, but were told that speed was not as important as accuracy. The task was programmed using Presentation (Version 14.5, www.neuro-bs.com).

**Planned Statistical Analysis**

We report two primary performance measures: absolute performance (for both capacity estimates and RT) and retrocue benefit (for both capacity estimates and RT). Thus, there were four primary dependent variables that were each subjected to the analyses described below: (1) Absolute capacity in terms of $K$-estimates, (2) Capacity retrocue benefit, (3) Absolute speed in terms of RT, (4) RT retrocue benefit. We were interested in effects of aging, MCI, and MTL amnesia. As such, we restricted our comparisons to young vs. older adults (Aging), older adults vs. MCI (MCI), and older adults vs. MTL amnesics (MTL Amnesia). We planned to perform mixed-design ANOVAs comparing group, set size, and cue (if applicable) for each of these dependent variables and we planned to perform independent samples t-tests to follow up any significant interactions. We predicted retrocue benefits to be greatest once capacity had been
reached. We defined capacity as maximum $K$-estimate of the simucue. As such, we split our follow-up t-tests into low set sizes that did not exceed capacity for any group (1-2), and high set sizes (3-6) that exceeded capacity. For all analyses, we report Greenhouse-Geisser corrections where appropriate.

**Absolute Performance Analysis**

To examine VSTM performance, we calculated memory capacity estimates ($K$), where $K$ is defined by the formula provided by Cowan (2001):

$$K = \text{set size} \times (\text{hits} - \text{false alarms})$$

Separate $K$-estimates were computed for each participant, cue type (i.e., retrocue or simucue), and set size (i.e., 1-6). Additionally, RTs were collected for each participant, cue type, and set size. These $K$-estimates and RT data were submitted to the analyses described below.

**Retrocue Percent Benefit Analysis**

For both $K$-estimates and RTs we calculated a measure of the benefit from the use of a retrocue relative to the simucue baseline, using the following formulas:

$$\text{Capacity benefit} = \frac{K_{\text{retrocue}} - K_{\text{simucue}}}{K_{\text{retrocue}} + K_{\text{simucue}}} \times 100$$

$$\text{Reaction time benefit} = -\frac{RT_{\text{retrocue}} - RT_{\text{simucue}}}{RT_{\text{retrocue}} + RT_{\text{simucue}}} \times 100$$

These calculations normalized each participant’s retrocue benefit to his or her overall capacity, thus allowing the comparison of increases across groups. For both formulas, a positive percent benefit score reflects improved performance – either in terms of increased $K$-estimates or faster RTs – from the use of a retrocue. These data were submitted to ANOVAs to investigate MCI patients and controls as described below.
Note: This benefit calculation could also be described as a “normalized” percent benefit, since the denominator includes both conditions, rather than just the simucue performance. We used this normalized calculation since some patients had low (<1) or negative K-estimates, which would have distorted the raw capacity benefit analysis.

**MTL Patient Analysis**

Given that there were only two MTL cases, these data were not suitable for parametric statistical tests. Instead we used Crawford’s modified \( t \)-tests to compare each patient to the older adult control group on each of the four dependent variables described above (Crawford & Garthwaite, 2007).

**Results**

**Absolute Capacity (K-estimates)**

**Aging**

We conducted a 2 (group: young adults, older adults) × 2 (cue: retrocue, simucue) × 6 (set size: 1-6) mixed-design ANOVA on the \( K \)-estimates shown in **Figure 16** and **Table 5**. All main effects and interactions were significant: main effects of cue, \( F(1, 31) = 34.77, p < .001, \eta_p^2 = .53 \), set size, \( F(2.23, 69.09) = 154.39, p < .001, \eta_p^2 = .83 \), and group, \( F(1, 31) = 7.58, p = .01, \eta_p^2 = .20 \), and interactions of cue × group, \( F(1, 31) = 11.61, p = .002, \eta_p^2 = .27 \), set size × group, \( F(2.23, 69.09) = 11.57, p < .001, \eta_p^2 = .27 \), cue × set size, \( F(2.49, 77.06) = 8.92, p < .001, \eta_p^2 = .22 \). The critical three-way cue × set size × group interaction was also significant, \( F(2.49, 77.06) = 4.71, p = .007, \eta_p^2 = .13 \).

To follow up this interaction, we conducted independent samples \( t \)-tests across groups at low (1-2) and high (3-6) set sizes for both cue types. These showed that young adults simucue
performance was higher than older adults simucue performance only at higher set sizes of the retrocue condition, \( t(31) = 3.80, p = .001, d = 1.34 \), and marginally at higher set sizes of the simucue condition, \( t(31) = 1.79, p = .08, d = 0.63 \), but not at lower set sizes of either condition, \( t(31) < 1.18, ps > .25, ds < 0.41 \).

![Figure 16](image)

**Figure 16.** Absolute capacity in terms of K-estimates in younger adults (YA, \( N = 14 \)), older adults (OA, \( N = 19 \)), and mild cognitive impairment patients (MCI, \( N = 8 \)). Our primary finding was that the retro-cue raised MCI VSTM capacity to the level of their age-matched counterparts.

**MCI**

We conducted a 2 (group: older adults, MCI) \( \times 2 \) (cue) \( \times 6 \) (set size) mixed-design ANOVA on the K-estimates shown in Figure 16 and Table 5. This revealed main effects of cue, \( F(1,25) = 29.41, p < .001, \eta^2 = .54 \), set size, \( F(2.05, 51.32) = 53.58, p < .001, \eta^2 = .68 \), a cue \( \times \) set size interaction, \( F(2.97, 74.33) = 4.99, p = .003, \eta^2 = .17 \), and a cue \( \times \) group interaction, \( F(1, 25) = 13.74, p = .001, \eta^2 = .36 \). Additionally, there was a marginally significant three-way
interaction of cue × set size × group, $F(2.97, 74.33) = 2.39, p = .08, \eta_p^2 = .09$. There were no other significant effects or interactions, $Fs < 1.31, ps > .28, \eta_p^2 s < .05$.

To follow up this interaction, we conducted independent samples $t$-tests across groups at low (1-2) and high (3-6) set sizes for both cue types. These revealed that MCI patients had lower simucue K-estimates than older adults at higher set sizes, $t(25) = 2.09, p = .047, d = 0.88$ but MCI patients did not differ from older adults at any other set size or condition, $t(25)s < .91, ps > .37, ds < 0.38$. 
MTL Amnesia

To compare each MTL case to older adult controls, we used Crawford’s modified $t$-tests that compared each patient relative to older adult controls for low (1-2) and high (3-6) set sizes at each cue type (Figure 17, Table 5). DA showed marginally smaller $K$-estimates on small set sizes of the simucue condition, $t(18) = 1.36, p = .09$, but performance did not significantly differ from controls at any other set size or condition, $t(18)s < 1.05, ps > .15$. LD did not perform significantly different from controls at any size or condition, $t(18)s < 0.99, ps > .17$.

Figure 17. Absolute capacity in terms of $K$-estimates in older adults (OA, $N = 19$) and medial temporal lobe amnesic cases ($N = 2$: LD and DA). The only differences observed between patients and controls were that LD showed lower simucue performance than controls at set size 5 and DA showed lower simucue performance than controls at set size 6.
Retrocue Capacity Benefit

To further investigate performance on the retrocue relative to performance on the simucue, we created a percent benefit score that reflected improvements from the retrocue. These data were subjected to the analyses described below.

**Aging**

We performed a 2 (group: young adults, older adults) x 6 (set size) mixed-design ANOVA with dependent variable of percent benefit (Figure 18). This revealed main effects of set size, $F(2.60, 80.44) = 4.91, p = .005, \eta^2_p = .14$, group, $F(1, 31) = 6.31, p = .02, \eta^2_p = .17$, and a set size $\times$ group interaction, $F(2.60, 80.44) = 3.16, p = .04, \eta^2_p = .09$. To investigate this interaction, we performed independent samples $t$-tests across groups at low (1-2) and high (3-6) set sizes. These revealed that young adults had a greater retrocue benefit than older adults at higher set sizes, $t(31) = 2.90, p = .007, d = 1.02$. There was no difference between the groups at low set sizes, $t(31) = 1.30, p = .20, d = 0.46$. These results suggest that young adults showed a greater retrocue benefit as set size increased, whereas older adults did not.

We investigated the retrocue benefit relative to zero benefit by performing one sample $t$-tests for each group. Younger adults showed a retrocue benefit greater than zero at higher set sizes, $t(13) = 4.95, p < .001, d = 1.32$, but not at low set sizes, $t(13) = 1.33, p = .21, d = 0.35$. Older adults did not show a retrocue benefit greater than zero at either low or high set sizes, $t(18)s < 1.62, ps > .12, ds < 0.37$. 
Figure 18. Percent benefit from use of a retrocue in younger adults (N = 14), older adults (OA, N = 19) and mild cognitive impairment patients (MCI, N = 8). We found that the MCI patients and younger adults showed a retrocue benefit at higher set sizes, whereas older adults did not show a retrocue benefit. Error bars reflect SEM.

**MCI**

We performed a 2 (group: older adults, MCI) x 6 (set size) mixed-design ANOVA with dependent variable of percent benefit (Figure 18). This revealed main effects of group, $F(1, 25) = 12.36, p = .002, \eta^2_p = .33$, set size, $F(2.36, 59.14) = 6.34, p = .002, \eta^2_p = .20$, and a set size $\times$ group interaction, $F(2.36, 59.14) = 4.89, p = .008, \eta^2_p = .16$. To investigate this interaction, we conducted independent samples t-tests across groups at low and high set sizes. MCI patients showed a greater retrocue benefit than older adults at set sizes higher set sizes, $t(25) = 3.63, p = .001, d = 1.53$, but not at lower set sizes, $t(25) = 0.62, p = .54, d = 0.26$.

We investigated the retrocue benefit relative to zero benefit by performing one sample t-tests for each group, as described above. MCI patients showed a retrocue benefit greater than
zero at higher set sizes, \( t(7) = 2.67, p = 0.03, d = 0.94 \), but not at low set sizes, \( t(7) = 0.60, p = 0.57, d = 0.21 \).

When considered with the absolute capacity analysis above, these results indicate that MCI patients had a reduced baseline simucue performance compared to their age-matched controls, and that the retrocue brought their performance up to the level of their healthy counterparts on the same condition.

**MTL Amnesia**

We compared the retrocue benefit scores of each MTL case to healthy older adult controls using Crawford’s modified \( t \)-tests (Figure 19) and found that LD showed a retrocue benefit greater than controls at higher set sizes, \( t(19) = 2.15, p = .02 \), but not at low set sizes, \( t(19) = 1.13, p = .14 \). DA showed a retrocue benefit greater than controls at both high and low set sizes, \( t(19) 's > 2.45, ps < 0.01 \).
Figure 19. Percent benefit of retrocue capacity in older adults (OA, N = 19) and medial temporal lobe amnesic cases (N = 2: LD and DA). LD showed a retrocue benefit compared to controls at set sizes 4-5, and DA had a retrocue benefit compared to controls at set size 6. Error bars reflect SEM.
Table 5. K-estimates for retrocue and simucue performance for each set size and group.

**Retrocue**

<table>
<thead>
<tr>
<th></th>
<th>Set Size 1</th>
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<th>Set Size 3</th>
<th>Set Size 4</th>
<th>Set Size 5</th>
<th>Set Size 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger Adults</td>
<td>0.92 (0.08)</td>
<td>1.79 (0.26)</td>
<td>2.66 (0.41)</td>
<td>3.25 (0.72)</td>
<td>3.65 (0.73)</td>
<td>4.23 (0.99)</td>
</tr>
<tr>
<td>Healthy Older Adults</td>
<td>0.94 (0.06)</td>
<td>1.75 (0.29)</td>
<td>2.50 (0.37)</td>
<td>2.70 (0.52)</td>
<td>2.72 (0.96)</td>
<td>2.54 (0.97)</td>
</tr>
<tr>
<td>MCI</td>
<td>0.87 (2.38)</td>
<td>1.68 (2.14)</td>
<td>2.46 (2.00)</td>
<td>2.88 (1.78)</td>
<td>2.53 (2.12)</td>
<td>2.77 (2.06)</td>
</tr>
<tr>
<td>LD</td>
<td>0.96</td>
<td>2.00</td>
<td>2.52</td>
<td>3.20</td>
<td>2.94</td>
<td>0.96</td>
</tr>
<tr>
<td>DA</td>
<td>0.96</td>
<td>1.76</td>
<td>2.50</td>
<td>3.52</td>
<td>3.73</td>
<td>3.36</td>
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**Simucue**

<table>
<thead>
<tr>
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<th>Set Size 4</th>
<th>Set Size 5</th>
<th>Set Size 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger Adults</td>
<td>0.96 (0.04)</td>
<td>1.82 (0.22)</td>
<td>2.50 (0.45)</td>
<td>2.84 (0.77)</td>
<td>3.04 (0.94)</td>
<td>2.96 (1.08)</td>
</tr>
<tr>
<td>Healthy Older Adults</td>
<td>0.93 (0.07)</td>
<td>1.75 (0.21)</td>
<td>2.33 (0.50)</td>
<td>2.65 (0.58)</td>
<td>2.56 (0.75)</td>
<td>2.29 (0.73)</td>
</tr>
<tr>
<td>MCI</td>
<td>0.89 (2.38)</td>
<td>1.63 (2.17)</td>
<td>1.80 (2.22)</td>
<td>2.09 (2.14)</td>
<td>1.59 (2.48)</td>
<td>1.82 (2.50)</td>
</tr>
<tr>
<td>LD</td>
<td>0.95</td>
<td>1.76</td>
<td>1.80</td>
<td>2.03</td>
<td>1.00</td>
<td>2.88</td>
</tr>
<tr>
<td>DA</td>
<td>0.85</td>
<td>1.50</td>
<td>2.50</td>
<td>2.72</td>
<td>3.18</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*K-estimates for each set size, condition, and group. Standard deviations are shown in parentheses.*
Absolute Speed (RT estimates)

RTs were collected for each participant, cue type, and set size. To ensure our effects were not artifacts due to multiplicative slowing (Faust, Balota, Spieler, & Ferraro, 1999), we performed the same analyses on long-transformed RTs. This did not meaningfully change the results.

Aging

We conducted a 2 (group: young adults, older adults) x 2 (cue) x 6 (set size) mixed-design ANOVA with dependent variable of RT (see Table 6). This revealed main effects of cue, \( F(1, 31) = 422.88, p < .001, \eta^2_p = .93 \), set size, \( F(2.36, 73.05) = 106.83, p < .001, \eta^2_p = .78 \), and group, \( F(1, 31) = 71.44, p < .001, \eta^2_p = .70 \) The following interactions were significant: set size x group, \( F(2.36, 73.05) = 28.71, p < .001, \eta^2_p = .48 \), cue x set size, \( F(3.59, 111.29) = 11.45, p < .001, \eta^2_p = .27 \), and cue x set size x group, \( F(3.59, 111.29) = 4.04, p = .006, \eta^2_p = .12 \). Finally, we observed a marginal cue x group interaction, \( F(1, 31) = 3.64, p = .06, \eta^2_p = .11 \).

Independent samples t-tests comparing young and older adults showed that younger adults had faster RT than older adults at all set sizes and conditions, \( t(31) > 5.73, ps < .001, dz > 2.02 \).

MCI

We conducted a 2 (group: older adults, MCI) x 2 (cue) x 6 (set size) mixed-design ANOVA with dependent variable of RT (Table 6). This revealed main effects of cue, \( F(1, 25) = 316.41, p < .001, \eta^2_p = .93 \), set size, \( F(2.20, 55.06) = 71.95, p < .001, \eta^2_p = .74 \), a cue x set size interaction, \( F(3.66, 91.50) = 7.63, p < .001, \eta^2_p = .23 \), and a set size x group interaction, \( F(2.20,
55.06) = 6.42, \( p = .002, \eta_p^2 = .20 \). There were no other significant effects or interactions, \( Fs < 1.17, ps > .29, \eta_p^2s < .05 \).

Independent samples \( t \)-tests older adults and MCI patients showed that older adult controls responded faster than MCI patients at smaller set sizes of both conditions, \( t(25)s > 2.20, ps < 0.04, ds > 0.93 \). There was no difference in reaction times at higher set sizes of both conditions, \( t(25)s < .65, ps > .52, ds > .28 \).

**MTL Amnesia**

We compared individual RT of the MTL cases to controls using Crawford’s modified \( t \)-tests and found DA was slower than controls only at lower set sizes of the simucue condition, \( t(19) = 1.95, p = .03 \), but not at any other set sizes or conditions, \( t(19)s < 1.09, ps > .15 \). LD’s RTs were not different from controls at any condition or set size, \( t(19)s < .54, ps > .30 \).
Table 6. RTs for retrocue and simucue performance for each set size and group.

### Retrocue

<table>
<thead>
<tr>
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<th>Set Size 1</th>
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<th>Set Size 4</th>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RTs</td>
<td>578.99</td>
<td>584.57</td>
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<td></td>
<td>(89.47)</td>
<td>(94.26)</td>
<td>(114.55)</td>
<td>(100.09)</td>
<td>(119.28)</td>
<td>(120.95)</td>
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<td><strong>Healthy Older Adults</strong></td>
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<tr>
<td>RTs</td>
<td>789.63</td>
<td>854.78</td>
<td>932.69</td>
<td>1062.37</td>
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<td>1189.90</td>
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<tr>
<td></td>
<td>(121.16)</td>
<td>(161.55)</td>
<td>(175.59)</td>
<td>(182.14)</td>
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<td>964.41</td>
<td>1026.83</td>
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<td></td>
<td>(216.13)*</td>
<td>(284.73)</td>
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<td><strong>DA</strong></td>
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RTs for each set size, condition, and group. Standard deviations are shown in parentheses. Bold values depict significantly slower reaction times as revealed by independent t-tests comparing healthy older adults vs. MCI patients, or by Crawford’s modified t-tests comparing LD and DA to controls. * = p < .05, ¥ = p < .1

### Simucue

<table>
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<tr>
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<td>(278.59)¥</td>
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<td>(260.02)</td>
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<td>1330.92*</td>
<td>1144.67</td>
<td>1074.98</td>
<td>1155.41</td>
<td>1152.01</td>
<td>1279.75</td>
</tr>
</tbody>
</table>

RTs for each set size, condition, and group. Standard deviations are shown in parentheses. Bold values depict significantly slower reaction times as revealed by independent t-tests comparing healthy older adults vs. MCI patients, or by Crawford’s modified t-tests comparing LD and DA to controls. * = p < .05, ¥ = p < .1
Retrocue RT Benefit

**Aging**

The retrocue RT benefit data were subjected to a 2 (group: young adults, older adults) × 6 (set size) mixed-design ANOVA with dependent variable of RT percent benefit. This revealed a main effect of set size, $F(3.51, 108.81) = 10.12, p < .001, \eta^2_p = .25$, a marginal main effect of group, $F(1, 31) = 3.83, p = .06, \eta^2_p = .11$, and a set size × group interaction, $F(3.51, 108.81) = 6.81, p < .001, \eta^2_p = .18$. To investigate the interaction, we conducted independent samples $t$-tests across groups at high and low set sizes. These revealed that young adults had a greater retrocue RT percent benefit than older adults at higher set sizes, $t(31) = 2.61, p = .01, d = .92$, but not at lower set sizes, $t(31) = .37, p = .71, d = .13$.

**MCI**

The RT percent benefit data were subjected to a 2 (group: older adults, MCI) × 6 (set size) mixed-design ANOVA with dependent variable of retrocue RT percent benefit. This revealed a main effect of set size, $F(3.47, 86.74) = 6.96, p < .001, \eta^2_p = .22$, with no other significant effects or interactions, $F$s < 1.14, $p$s > .34, $\eta^2$s > .04. These analyses suggest that retrocue benefit RT slowed as set size increased for both groups. In other words, as set size increased, relative RT speed gains from the retrocue diminished.

**MTL Amnesia**

As above, we compared retrocue benefit RT scores for individual amnesic cases using Crawford’s modified $t$-tests. These statistics showed that both LD’s and DA’s retrocue RT percent benefit was not different from controls at any set size, $t(19)s < 1.07, p$s > .14.
Discussion

In the present study, we administered a VSTM task and manipulated the presence of a spatial retroactive cue (retrocue) versus a baseline cue that was presented simultaneously with the probe array (simucue). To our knowledge, we provide the first evidence that patients with MCI and MTL amnesia benefited from a spatial retroactive cue. The use of a retrocue brought patient performance up to the level of healthy older adult controls, effectively eliminating their deficit on the simucue condition. This pattern of performance manifested as a larger retrocue benefit for patients than healthy older participants. These results provide novel evidence that retroactively cueing spatial attention improved VSTM performance in MCI and MTL amnesia. Consistent with previous research, healthy young adults showed a retrocue benefit, and healthy older adults did not show a retrocue benefit. These effects emerged at higher, but not lower set sizes. All groups showed faster RTs for retrocue than simucue trials.

Why is it that healthy older adults do not benefit from the retrocue, whereas the MCI and MTL patients, who are also older adults, do benefit? Firstly, it is important to emphasize that patients almost never outperformed their aged-matched counterparts, but they were able to derive a greater benefit from the use of the retrocue. We speculate that the patients and healthy older adults responded to the retrocue in different ways. Consistent with inhibition deficit theory described above (Hasher et al., 2007; Hasher & Zacks, 1988; Lustig et al., 2007), older adults do not benefit from a retrocue because they are unable to use it to inhibit irrelevant items from the memory representation, which makes them susceptible to interference from extraneous items in the memory array and/or interference caused by the probe. In fact, our results replicate the only known published study on the retrocue effect in aging (Duarte et al., 2013). More specifically, older adults showed no retrocue benefit in terms of capacity, but did show a faster reaction time.
for retrocue trials. It was speculated that older adults used the retrocues to facilitate priming of
perceptual and/or motor networks associated with target detection but that the cue itself
interfered with maintenance of array items, limiting potential benefits to performance.

Why did the patients’ accuracy estimates benefit from the retrocue? The present task
requires a participant to identify whether a specific item occurred in a specific location. Previous
research has suggested that such item-location binding is particularly impaired in MCI and MTL
amnesia (Pertzov et al., 2013). We hypothesize that the retrocue may help to overcome these
item-location binding deficits by providing a critical piece of information: the location. In
contrast to the simucue which also provides location information after the memory array, the
retrocue provides location information retroactively to the memory array – when there are no
other concurrent task demands or exogenously presented stimuli. This task was rife with
proactive interference: the same colored circles repeated over multiple trials and participants
were required to remember items within this limited stimulus set (Nobre et al., 2004). Within a
single trial participants were required to maintain as many as six items in memory, creating high
levels of inter-item interference. Further interference happens at the probe display, when both a
probe item was displayed and a decision was made. As described in the introduction, one
description for how the retrocue works is by reducing probe interference by focusing attention on
the critical item during the delay period. The retrocue helps protect the existing memory
representation for the critical item, and by doing so, reduces overall interference (Makovski et
al., 2008).

We speculate that having no competing mental operations or visual representations is
critical to the retrocue being effective. In young adults, for example, Makovski (2008) notes that
performance is worse on a partial report VSTM task where a single probe is presented at the test
phase than the whole report, suggesting that interference is apparent even during the seemingly minimal probe phase.

Our previous work has suggested that the same patients may be particularly vulnerable to a barrage of visual information. Specifically, patients with MCI were vulnerable to interference from irrelevant features of objects processed on previous trials (Chapter 3, Newsome, Duarte, & Barense, 2012). We attributed this increased vulnerability to interference to damage to perirhinal cortex and interpreted the results within the context of a recent representational-hierarchical theory (Cowell et al., 2010a). This view proposes that simple, low-level features of objects are represented within posterior regions of the ventral visual stream, and more complex feature conjunctions are represented in more anterior regions. The perirhinal cortex is proposed to sit at the apex of the stream and represent the complex conjunctions of features that compose objects (Graham et al., 2010). In explaining our previous findings, we suggested that the perirhinal cortex may protect from visual interference by suppressing the representations of lower level features represented in earlier regions of the visual stream (Barense, Ngo, et al., 2012; Peterson et al., 2012).

This suppression mechanism is similar to what has been argued in regard to inhibition-deficit theory, which suggests that older adults are unable to inhibit irrelevant information from entering VSTM, and thus have reduced memory capacity (Hasher & Zacks, 1988; Verhaeghen & Salthouse, 1997). Representing stimuli at their feature- and object-levels is likely accomplished by different brain regions (i.e., complex objects in perirhinal cortex (Cowell, 2012) and simple features in posterior visual regions (Desimone & Ungerleider, 1989)). In the present study, we are not taxing object representation, but rather putting an object in space, which is thought to be represented in the hippocampus, the next level of representational complexity (Lee et al., 2012).
Both the perirhinal and hippocampal cortices are damaged in the patient groups in the present study, with similar vulnerabilities to interference across vastly diverse tasks (i.e., VSTM with simple color circles versus perceptual discrimination with complex novel objects).

At first glance, the simple colored circle stimuli in our present study seem less complex than the multicomponent novel objects in Chapter 2 and other previous studies (Erez et al., 2015; Newsome et al., 2012; Wilson et al., 2012). However, the level of representation required to solve the current VSTM task is more complex than it may seem – in addition to maintaining item identity (i.e., color), participants must also bind that identity to one of six possible locations. MCI and MTL patients are known to be impaired in binding an object’s identity with its location (Pertzov et al., 2013), whereas healthy older adults’ reduced VSTM capacity is not thought to be affected by binding (Pertzov, Heider, Liang, & Husain, 2015). In this sense, the retrocue provides a cue to one of the critical features: location. We speculate that facilitating access to this spatial information, and thus reducing spatial interference, is fundamental to the improved patient performance. That is, MCI and MTL patients have impaired spatial binding abilities, and may be able to use the additional spatial information from the retrocue to facilitate binding items to their locations to counteract their binding deficits. However, the MCI and MTL patients are also older adults and experience the same inhibitory control deficits associated with aging (Hasher & Zacks, 1988). As such, whereas their performance on the retrocue condition improved relative to their performance on the simucue condition, it did not exceed that of their older adult controls.

In conclusion, we found novel evidence that MCI patients and MTL amnesic cases were able to use a retrocue to improve their VSTM capacity estimates to the level of healthy controls. Consistent with previous findings, we also found that young adults had a retrocue benefit, but
older adults did not. We postulate that the spatial information provided by the retrocue reduced interference and facilitated binding in the memory-impaired cases, which brought their performance to the level of their healthy older adult counterparts.
Chapter 5

General Discussion

Summary

In Chapter 2, I investigated putatively healthy older adults recruited from the community with no MCI diagnosis, but who fell below normative means on a standardized neuropsychological test designed to screen for MCI. We hypothesized that these older adults at a higher risk for developing MCI would show reduced VSTM capacity in terms of behavior and CDA amplitude. Consistent with our hypotheses, we found that the at-risk group showed a reduced VSTM capacity and an abnormal CDA. In an additional experiment, we found that the same group showed a reduced P300 amplitude similar to that observed in cases with diagnosed MCI/AD. These results suggest that electrophysiological markers may be particularly sensitive to the earliest stages of the disease process.

Chapter 3 examined feature interference in MCI and older adults at-risk for developing MCI. We demonstrated that memory impaired cases were vulnerable to interference from irrelevant features of objects processed on previous trials (Newsome et al., 2012). We attributed this increased vulnerability to interference to the damaged perirhinal cortex in these patients (Barense et al., 2012). According to the representational-hierarchical framework, simple, low-level features of objects are thought to be represented within posterior regions of the ventral visual stream, and more complex features are thought to be represented in more anterior regions, with the perirhinal cortex sitting at the apex of the stream and representing bound conjunctions of features comprising complex objects (Cowell, Bussey, & Saksida, 2010). In explaining these findings, we suggested that the perirhinal cortex may protect from visual interference by
suppressing the representations of lower level features represented in earlier regions of the visual stream (Peterson, Cacciamani, Barense, & Scalf, 2012, Barense, Ngo, Hung, & Peterson, 2012). This suppression mechanism is similar to what has been argued in regard to inhibition-deficit theory, which suggests that older adults are unable to inhibit irrelevant information from VSTM, and thus have reduced memory capacity (Hasher & Zacks, 1988; Verhaeghen & Salthouse, 1997). They are unable to inhibit representations of irrelevant stimuli, which leads to problems in both perception AND memory.

In Chapter 4, we further investigated reduced VSTM capacity in MCI patients and cases with MTL amnesia by using a manipulation that reduced interference – the retrocue. The retrocue brought patient performance up to the level of healthy controls, effectively eliminating their deficit on a baseline condition. This pattern of performance manifested as a larger retrocue benefit for patients than controls. We attributed this performance increase to the fact that the retrocue provides a spatial location cue, helping to bind item and location information. The item-location binding occurring in this VSTM task may be a hippocampally-driven process (Pertzov et al., 2013), whereas the feature binding in the perceptual discrimination task administered in Chapter 3 is thought to be affected by PRC representations (Barense, Groen, et al., 2012).

Admittedly, the stimuli in Chapters 2 and 4 (simple circles) were far less complex than the multicomponent novel blob-like objects in Chapter 3. Processing of these multicomponent objects may happen in different regions, depending on their complexity. That is, simple features are processed in posterior VVS regions, whereas conjunctions of features are processed in more anterior regions of VVS, with the PRC representing the bound features comprising a whole object, and the hippocampus representing bound item-location pairs. Healthy young adults show a clear differentiation in the amplitude of the contralateral delay activity (CDA) component, a
measure thought to reflect the number of items being maintained in memory (Vogel & Machizawa, 2004), for single-feature blobs versus more complex, multi-feature blobs (Wilson, Adamo, Barense, & Ferber, 2012). Importantly, this distinction was found at separate electrode sites: the CDA at sites P7/P8 was related to binding of features, but the CDA at sites P1/P2 was related to the individual objects themselves. This work suggests that the CDA may reflect both the number of discrete objects held in VSTM as well as the more flexible, feature-feature binding of complex objects. These results suggest that a deficit in filtering irrelevant information may be operating at multiple levels of representation. In addition to these filtering deficits, older adults with pathological development may have impoverished representations of complex stimuli, which may be reflected in the vulnerabilities to interference seen in the present data.

Our hypotheses were that in line with the early neural changes described in the introduction (Khan et al., 2014), namely PRC and posterior parietal cortex, patients with MCI and older adults at-risk for MCI would be impaired on tasks that placed high demand on these regions. Consistent with these hypotheses, MCI patients were impaired on the object discrimination task taxing PRC (Chapter 3), and both patients and older adults at-risk for MCI were impaired on VSTM tasks which taxed posterior parietal cortex (Chapter 2,4). In addition, the ERP signature stemming from the posterior parietal cortex, the CDA, suggest neural abnormalities (Chapter 2). Together, these findings provide evidence for diagnostic measures of early decline.

**Caveats**

Although the electrophysiological results of Chapter 2 and behavioral results of Chapter 3 are consistent with our hypotheses that the at-risk group may have preclinical MCI, or similar pathology involving MTL structures, we are unable to conclusively make any statements about
their diagnostic status. The true power of this research will come with longitudinal assessment, beyond the temporal scope of a doctoral dissertation. The MoCA was designed to screen for cognitive decline in aging populations (Nasreddine et al., 2005), however, poor performance on the MoCA may also reflect a number of other cognitive disorders unrelated to MCI/AD, including Parkinson’s disease (Zadikoff et al., 2008), stroke (Godefoy et al., 2011), and vascular cognitive impairment (Ihara, Okamato, & Takahashi, 2013). The variability in MoCA scores across these empirical chapters suggests there is an overall heterogeneity in the at-risk group. Longitudinal follow-ups in these participants will give us a better estimate of the long-term predictive diagnostic power of these various potential screening measures.

**Future Directions**

This work has large implications for real world experiences in older adults. The perceptual interference findings suggest that memory-impaired populations have an initial deficit in encoding stimuli – that is, they are unable to resolve visual interference build-up from previous experiences in order to solve the current task. Similarly, the VSTM findings suggest that types of mistakes patients make are related to problems with binding an item to its location. By reducing interference in terms of cueing location, as in the retrocue, we can improve mnemonic performance. One can easily imagine this translating to confusion navigating the real world. In one arm of my research program, I plan to investigate real world effects of visual interference. As one example, I will design a virtual navigation paradigm in which we can implement my previous findings in terms of reducing interference for older adults. In addition to manipulations of visual interference (i.e., similar objects within a room), I will explore the use of spatial cues to enhance memory performance for older adults. Combining this paradigm with EEG, I will investigate the error-related negativity (ERN) component to elucidate neural markers.
for these errors. Recent evidence also suggests that the CDA, thought to be the
electrophysiological marker for VSTM capacity, also reflects evidence of visual search (Emrich,
Al-Aidroos, Pratt, & Ferber, 2009). To this end, I will also investigate the role of the CDA in
visual search of the navigable environment. These data will improve our understanding of the
mechanisms of forgetting in older adults.

Conclusions

In the present dissertation, I presented evidence that older adults at-risk for developing
AD – both patients with MCI and a preclinical group of older adults at-risk for MCI have
behavioral impairments consistent with an increased vulnerability to interference. By reducing
interference in two very distinct tasks (object discrimination and VSTM), we were able to
improve performance up to the level of healthy controls. I additionally provided evidence of
abnormal electrophysiological signatures in the at-risk group, consistent with the idea that they
have an underlying neural pathology. The results of these experiments suggest that one of the
most critical determinants of behavior is interference in the environment, and that increased
vulnerability to interference may be one of the first symptoms of AD.
References


O'Neil, E. B., Protzner, A. B., McCormick, C., McLean, D. A., Poppenk, J., Cate, A. D., et al. (2012). Distinct patterns of functional and effective connectivity between perirhinal cortex and other...
cortical regions in recognition memory and perceptual discrimination. *Cerebral Cortex, 22*, 74-85.


