MEMORY-BASED VIEWING: A POTENTIAL MARKER OF PATHOLOGICAL AGING

by

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ABSTRACT

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Markers of cognitive impairment are needed to distinguish normal from pathological aging prior to the onset of clinical symptomology to improve Alzheimer's disease (AD) treatment or prevention efforts. AD pathology is believed to develop years or even decades prior to diagnosis in medial temporal lobe subregions that provide input to the hippocampus (Braak & Braak, 1991), disrupting the ability of the hippocampus to bind individual elements of an experience to form cohesive memory representations. Eye movement behavior is a sensitive index of learning and effects of memory on eye movements have been shown to emerge rapidly (within 500-750ms of stimuli onset) in healthy, cognitively unimpaired individuals, regardless of task demands (Hannula, Ryan, Tranel, & Cohen, 2007). Importantly, memory-based viewing effects are completely absent from viewing patterns in patients with hippocampal amnesia (Hannula et al., 2007). Thus, eye movements measured during hippocampus-dependent tasks may detect subtle changes in cognition due to early pathology and may permit successful differentiation of normal from pathological aging prior to diagnosis. Fifty healthy, community-dwelling middle-aged (N = 22; age 40-55) and older adults (N = 28, age 65-80) were recruited. The Montreal Cognitive Assessment was used to identify individuals performing in the Mild Cognitive Impairment (MCI) range ("at risk"), MCI being a prodrome of dementia. Participants completed the Scene Face Pair Task (SFPT), where they were studied an arbitrary set of unique scene-face pairs. During the test phase, participants viewed 3-face displays superimposed on top

of previously studied scenes while eye movements were recorded. Participants were asked to indicate during the test phase whether the associate (i.e. the matching face of the previously studied scene) was present or absent in the 3-face display. All groups distinguished target-present from target-absent displays, although recognition performance was worse in the “at risk” group. While all three groups directed viewing disproportionately to the matching face within 500-750ms of 3-face display onset, memory-based viewing throughout the full time course of 3-face display in the “at risk” group was less robust. These results suggest that the SFPT, combined with explicit recognition and eye movement indices of performance, may be able to detect early deficits associated with pathological aging.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Introduction

By 2030, it is estimated that more than 20% of the American population will be 65 years of age or older (Colby & Ortman, 2014). While increased life expectancy is an impressive feat of modern medicine, age is the main risk factor for many late-life disorders, including dementia (Lindsay et al., 2002). Dementia is characterized by a loss of cognitive ability in multiple domains including memory, language, and problem-solving skills. Alzheimer's disease (AD), the most common form of dementia, is characterized by a progressive loss of cognitive function, particularly in the domain of learning and memory (Alzheimer's Association, 2017; Huang & Mucke, 2012). Ultimately, this progressive cognitive decline interferes with a person's ability to function independently and significantly impairs the quality of life of both patients and caregivers**.** By 2050, the prevalence of AD is projected to triple (Hebert, Weuve, Scherr, & Evans, 2013), resulting in financial, social, and public health burdens that may be unsustainable under the current health care system.

Therapeutic interventions currently available for treatment of AD are largely ineffective (Cummings, Morstorf, & Zhong, 2014; Huang & Mucke, 2012). It has been suggested that at the time of diagnosis, when available treatments are administered, the neurodegenerative changes associated with AD may be too substantial and irreversible (Jack et al., 2010; Selkoe, 2012; Waite, 2015). Therefore, early intervention, prior to significant degeneration and presentation of clinical symptoms, may be essential in improving treatment efforts and ultimately delaying the onset or progression of the disease. One major challenge associated with early intervention is distinguishing normal from pathological age-related cognitive changes. The boundary between healthy and pathological aging is unclear, at least during the prodromal stages of AD when cognitive abilities are declining yet functional independence is maintained. This is because some

degree of cognitive decline, particularly in the domain of learning and memory, is typically observed within the context of normal aging (Deary et al., 2009; Fjell et al., 2014; Harada, Love, & Triebel, 2013).

The primary objective of the current study was to identify potential markers of cognitive impairment that may be indicative of pathological decline prior to the onset of clinical symptomology. Here, I investigated the potential utility of hippocampus-dependent eye-movement-based relational memory effects as a marker of pathological impairment. The hippocampus is one of the earliest structures affected by AD pathogenesis and plays a critical role in learning and memory (Braak & Braak, 1991). Thus, hippocampal tasks may aid in differentiating normal from pathologically aging individuals, prior to the onset of more apparent decline that would warrant a diagnosis, given the subtle changes in cognitive functioning due to early pathology.

Neurobiological and Cognitive Changes in Pathological Aging

AD is characterized by the presence of two neuropathological hallmarks: amyloid plaques and neurofibrillary tangles (NFT) (Iqbal et al., 2005; Nelson, Braak, & Markesbery, 2009). Coagulations of amyloid-beta (Aβ) proteins form amyloid plaques, which are deposited inter-cellularly and disrupt cellular communication (Murphy & LeVine, 2010; Perl, 2010). NFTs, composed of phosphorylated tau proteins, lie within neuronal axons and disrupt nutrient transport (Braak, Thal, Ghebremedhin, & Del Tredici, 2011; Spires-Jones & Hyman, 2014). Pathological changes progress in a typical neuroanatomical pattern and correspond to specific stages of AD (Nelson et al., 2009). These changes begin in the medial temporal lobe (MTL), particularly the transentorhinal region of the perirhinal cortex (PRC) and hippocampus, and eventually spread to the neocortex (Braak & Braak, 1985; Braak & Braak, 1991). Importantly,

the topological progression of NFT pathology in AD correlates more closely with cognitive impairment and neuronal loss than Aβ plaques (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Fukutani et al., 1995; Guillozet, Weintraub, Mash, & Mesulam, 2003; Huang & Mucke, 2012; Mitchell et al., 2002; Nelson et al., 2012).

In the earliest stages of AD pathogenesis, prior to diagnosis, NFT pathology in the transentorhinal region of the PRC causes neuronal dysfunction and eventually cell loss, which effectively disrupts memory processing by disconnecting the hippocampus from neocortical association areas (Celone et al., 2006). These neuroanatomical changes ultimately lead to impairments in the ability to encode and retrieve new episodic memories, which is a behavioral hallmark of AD (Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Sexton et al., 2010; Yonelinas et al., 2007). As the disease progresses, individuals begin to show deficits in multiple cognitive domains, including decision making, visuospatial abilities, and executive functioning, which parallels NFT infiltration of the neocortex, particularly parietal and frontoparietal cortices (Braak & Braak, 1991; Giannakopoulos et al., 2003; Nelson et al., 2012; Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010). Critically, the neuropathological changes associated with AD are believed to begin decades prior to the onset of clinical symptoms (Jack et al., 2010). Therefore, identifying methods that can be used to detect subtle, early changes in MTL-dependent cognition may permit successful differentiation of normal from pathological aging prior to the expression of overt symptoms, guiding early interventions.

Mild cognitive impairment (MCI), often considered a prodromal stage of AD, is an intermediate state of cognitive functioning between normal aging and AD (Petersen, 2011; Walhovd et al., 2009). Individuals diagnosed with MCI are at higher risk of developing AD with

an annual conversion rate of 10-15% compared to 1-2% for the general population (Petersen, 2011). The Montreal Cognitive Assessment (MoCA), a brief test of global cognitive functioning, is particularly sensitive to early changes in cognition characteristic of MCI (Ismail, Rajji, & Shulman, 2010; Nasreddine et al., 2005). The MoCA is a brief but comprehensive assessment tool that tests cognitive function in AD-affected domains (Nasreddine et al., 2005), including memory, executive functioning, attention, language, and visuospatial skills. The MoCA can differentiate normal age-related cognitive impairment, from MCI and AD with high accuracy (Dong et al., 2012; Freitas, Simoes, Alves, Vicente, & Santana, 2012; Roalf et al., 2013; Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015) and can be used to track changes in cognitive abilities that are characteristic of disease progression (Freitas et al., 2012). Here, I used the MoCA to identify individuals who may be experiencing symptoms of MCI (Yeung, 2017), henceforth, referred to as "at risk" for pathological aging. Critically, "at risk" adults in the current study are healthy individuals who are living independently in the community without memory complaints. These individuals are categorized as "at risk" based strictly on MoCA performance in the lab. A comparison of patterns of viewing as a function of cognitive status, indexed by the MoCA, may result in the identification of markers in eye movement behavior that complement existing methods for identifying individuals on the path to pathological decline.

Hippocampus Supports Relational Memory Processing

As outlined above, the hippocampus, and adjacent input structures (e.g., transentorhinal region), are the earliest sites of pathological changes documented in AD (Braak & Braak, 1991; for review see Duyckaerts, Delatour, & Potier, 2009). Therefore, changes in the performance of tasks known to depend critically on the hippocampus may prove useful in the early detection of cognitive deficits that precede diagnoses of MCI or AD. It has been proposed that the hippocampus plays a critical role in relational memory binding and representation (Cohen &

Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Relational memory refers to the ability to bind information together in time and space to form cohesive representations of past experience (Konkel & Cohen, 2009). Bound representations of an experience can be spatial (e.g., memory for the relative location of objects in space), temporal (e.g., memory for the order in which events occurred), or associative (e.g., memory for intra- or inter-item associations, like a face-name pair).

The proposed role of the hippocampus in relational memory binding was informed by the anatomical organization of the MTL system. The MTL includes the hippocampus and the parahippocampal gyrus, which itself is comprised of the entorhinal (ERC), PRC, and parahippocampal (PHC) cortices (for review see Insausti et al., 2017; Squire, Stark, & Clark, 2004; Suzuki & Amaral, 1994). Information from the neocortex reaches the hippocampus by way of connections with structures in the parahippocampal gyrus, creating a hierarchical organization that supports memory functioning. The PRC and PHC serve as the gateway to the MTL memory system. The PHC receives polymodal input from cortical regions specialized for spatial or contextual processing, while the PRC receives input from high-level visual object processing sites in the ventral visual processing stream (for review see Eichenbaum & Lipton, 2008; Mishkin, Suzuki, Fadian, & Vargha-Khadem, 1997; Squire & Zola-Morgan, 1991). Information from PRC and PHC then projects to lateral and medial ERC, respectively, which provides the hippocampus with its input (for review see Suzuki & Amaral, 1994; Van Strien, Cappaert, & Witter, 2009). This means that the hippocampus is positioned at the apex of the MTL processing pathway and is in a position to bind the item-specific and contextual elements of an experience into complex associations, that make episodic memories distinctive (Konkel & Cohen, 2009; for review see Eichenbaum, Yonelias, & Ranganath, 2007).

Evidence consistent with the proposed role of the hippocampus in relational memory binding comes from non-human animal work (Bunsey & Eichenbaum, 1996; Dusek & Eichenbaum, 1997; for review see Wallenstein, Eichenbaum, & Hasselmo, 1998), neuropsychological experiments conducted with human amnesic patients (Hannula, Tranel & Cohen, 2006; Olsen et al., 2016; Ryan, Althoff, Whitlow, & Cohen, 2000; Konkel, Warren, Duff, Tranel, & Cohen, 2008; Yee, Hannula, Tranel, & Cohen, 2014) and neuroimaging experiments in healthy individuals (Davachi & Wagner, 2002; Hannula & Ranganath, 2008). For example, Konkel and colleagues (2008) compared the performance of amnesic patients to that of matched comparison participants on tests of item-specific and relational memory. In this study, participants saw sets of three abstract objects, presented one after another, in different spatial locations during encoding. At test, memory for the items, their spatial locations, their temporal sequence, or their associations (i.e., items that were part of a set) was examined. Results indicated that memory for relationships, regardless of the nature of those relationships, was compromised in amnesia, even in the subset of patients with damage limited to the hippocampus.

Consistent with the reported dependence of relational memory on the hippocampus, and the observed changes in hippocampal integrity that occur in MCI and AD, it seems reasonable to predict that tasks that require memory for relationships among items might be sensitive to early pathological alterations. Evidence consistent with this suggestion comes from a recent study conducted by Polcher and colleagues (2017) who reported that individuals with subjective cognitive complaints and those diagnosed with MCI, perform more poorly on a test of memory for arbitrary face-name pairs than age- and education-matched controls. This work highlights the potential sensitivity of relational memory tests to early cognitive changes that may distinguish healthy from pathological aging but critically, and in contrast to what was done here, individuals

in the Polcher et al. (2017) study were already showing overt signs and symptoms the disease process. The current study extends this work, as none of the participants in the present study had memory complaints or a diagnosis of MCI.

Eye-movement-based relational memory effect as a potential marker of incipient pathological aging

Eye tracking has been used to measure memory indirectly in a growing number of investigations and it has been proposed that this method may be an especially sensitive index of past experience. This is because eye tracking is non-invasive, does not require the use of potentially complicated instructions or response mappings, and is a continuous rather than discrete (i.e., button press) measure of processing that unfolds while stimulus materials are in view (for review see Hannula et al., 2010). The value of using eye movement behavior to index memory is evident in studies conducted with different populations, including infants (Richmond & Nelson, 2009; Richmond & Power, 2014), children with autism spectrum disorder (for review see Falck-Ytter, Bölte, & Gredebäck, 2013), amnesic patients (Hannula et al., 2015; Olsen et al., 2016), and individuals diagnosed with schizophrenia (Hannula, Ranganath, Ramsay, et al., 2010; Williams et al., 2010). Therefore, eye movement data may provide more information about potential differences in the integrity of memory as a function of age and MoCA performance than recognition responses alone - a possibility that is tested here.

To determine whether age and cognitive status affect memory-based viewing patterns and/or explicit recognition performance, we have adapted the scene face pair task (SFPT) that was originally used with amnesic patients (Hannula et al., 2007) and has since been vetted in several other studies (Mahoney, Kapur, Osmon, & Hannula, 2018; Nickel, Henke, & Hannula, 2015; Williams et al., 2010). Participants who complete this task are asked to commit several arbitrarily paired and pre-experimentally unfamiliar faces and scenes to memory. Subsequently,

memory is tested with displays that include three studied faces superimposed on a studied scene; sometimes the associate (i.e., the face that was paired with the scene during encoding) is present in the display. Critically, before the faces are presented, a preview of the scene itself is provided – this is meant to trigger pattern completion processes in the hippocampus (Hannula & Ranganath, 2009) and retrieval of the associated face. Across test phases, when the 3-face display is presented, participants may have been asked to identify the associate by making a button press to indicate whether the associate is present or not or given free-viewing instructions (Hannula et al., 2007; Mahoney et al., 2018). Eye movements are recorded whether explicit recognition responses are required or not. Critically, because all three faces presented in the test display are seen equally often during encoding, any preferential viewing cannot be a consequence of simple face-specific familiarity, but rather, requires representation and retrieval of learned scene-face relationships.

The SFPT has been used to investigate the time-course and potential automaticity of relational memory retrieval, following memory cues, in neurologically healthy individuals (Hannula et al., 2007; Mahoney et al., 2018; Nickel et al., 2015). In these experiments, preferential viewing of the associate (e.g., termed the *eye-movement-based relational memory effect*) was evident within 500-750ms of 3-face display onset and approximately one second prior to explicit recognition responses, even when participants attempted to conceal their knowledge (Mahoney et al., 2018). In addition, recent work has shown that eye-movement-based relational memory effects persist when scene cues are rendered invisible via visual masking (Nickel et al., 2016), though in this case, the effect occurred later in time. Collectively, these results indicate that eye movements provide important details about the temporal dynamics of memory processing and performance. Based on results like these, it has been proposed that the

expression of relational memory in eye movement behavior is obligatory or automatic. Furthermore, when eye movements are combined with explicit recognition responses, they may reveal dissociations in performance that would otherwise be overlooked (cf. Hannula, Baym, Warren, & Cohen, 2012).

The SFPT has also been used to examine the integrity of relational memory in amnesic patients (Hannula et al., 2007) and individuals diagnosed with schizophrenia in whom there is suspected hippocampal dysfunction (Williams et al., 2010). Critical for the purpose of the proposed study, memory-based viewing effects are completely absent from the viewing patterns of hippocampal amnesic patients, even when they happen to have gotten the explicit recognition response correct (Hannula et al., 2007), and are delayed and reduced in magnitude when schizophrenia patients were tested (Williams et al., 2010). Furthermore, and consistent with the proposed dependence of these eye-movement-based relational memory effects on hippocampal integrity, preferential viewing of the associate is predicted by hippocampal activity during presentation of a scene cue in healthy college-aged participants (Hannula & Ranganath, 2009). Here, for the first time, it is examined whether and how age and cognitive status affect explicit recognition and viewing patterns in the SFPT.

Current Study

The goal of the current study was to examine the integrity of relational memory in the context of normal and potentially pathological aging using both standard explicit recognition responses and eye movement data. Middle-aged adults, older adults and healthy individuals categorized as “at risk” based on MoCA performance were tested on the SFPT while eye movements were recorded. Use of the middle-aged group was informative because this age group is most-often neglected in studies of aging and memory and allowed me to more comprehensively

characterize differences in hippocampus-dependent cognition as a function of age. The first aim of the study was to characterize relational memory performance using explicit measures of recognition in cognitively normal and "at risk" adults. Consistent with the proposed role of the hippocampus in relational memory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001), and the sensitivity of the MoCA to symptoms characteristic of MCI (Ismail et al., 2010; Nasreddine et al., 2005), it was predicted that explicit recognition would be poorer among individuals categorized as "at risk", and to a lesser extent in healthy older adults. The second aim was to determine whether or not there were changes in the patterns of memory-based viewing effects in older and "at risk" participants that have been reliably documented in the viewing patterns of healthy young adults (Hannula et al., 2007; Mahoney et al., 2018). It was hypothesized that cognitively unimpaired middle-aged and older adults would show early memory-based viewing within 500-750ms of stimulus onset, as has been reported in healthy young adults and comparison participants age-matched to amnesic patients (Hannula et al., 2007). The same effects might be delayed among "at-risk" participants, much as they were in data from schizophrenia patients (Williams et al., 2010). Importantly, even if the onset of memory-based viewing is matched across groups, differences in the magnitude of this viewing effect across time might distinguish them. Time-course analyses were expected to be especially useful in this regard, as they permit evaluation of viewing changes that occur early and late in a test trial.

Method

Participants

Twenty-two middle-aged (age 40-55 years, M_{age} = 48.55, *SD* = 4.42, 13 females) and 28 older (age 65-80 years, M_{age} = 71.93, *SD* = 4.05, 13 females) healthy, non-demented adults participated. Adults were recruited from the community and through two centers at the University of Wisconsin-Milwaukee: The Center of Aging and Translational Research (CATR) and Osher, a

lifelong learning institute. All of the participants had normal or corrected to normal vision, reported no history of neurological conditions, psychiatric disorders, substance abuse, or subjective memory complaints. Participants were ultimately separated into three groups based on their age and MoCA performance. The MoCA is a brief assessment of global cognitive function designed to detect MCI. The maximum score on the exam is 30 points, with scores of 26 or higher indicating "normal" performance, and scores below 26 are indicative of mild cognitive impairment. Here, individuals performing within the normal range were labeled as "healthy" whereas adults who performed below the normal threshold were labeled "at risk" regardless of age. Overall, there were 18 middle-aged (age 40-55), 18 older (age 65-80), and 14 "at risk" (age 40-80) adults. All participants gave informed consent prior to participation and the study was conducted in accordance with guidelines of the UWM Institutional Review Board.

G*Power (version 3.1; Faul, Erdfelder, Lang, & Buchner, 2007) was used to estimate the sample size needed for sufficient power to detect early viewing time differences (i.e., within 500-750ms of display onset) based on the data from previously published work that was best matched to the current study (i.e. Experiment 4, Hannula et al., 2007). With a reported effect size (Cohen's d) equal to 1.69, a minimum sample size of 11 participants per group was required to achieve power equal to .95 (with alpha set to .05, two-tailed). The sample size was increased to 18 for counterbalancing purposes.

Neuropsychological Assessment

A battery of neuropsychological tests was selected to assess performance in three cognitive domains: memory, attention, and executive function. Tests of long-term memory were the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Thompkins, 1987) and the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). The CVLT is a test of verbal episodic memory task. In five learning trials,

participants hear and then recall a list of 16 words that can be separated into four semantic categories. The CVLT measures free and cued recall immediately (short-delay) and following a 20 minute interval (long-delay). The BVMT-R is a test of visuospatial memory. In three learning trials, participants view a stimulus display featuring six simple line figure drawings for 10s and then attempt to reproduce as many of the drawings in the correct location on their response page. Participants attempt to reproduce the display following a 25 minute delay. Tests of attention included the Digits Forward (Wechsler, 1981) and the Trail Making Test A (Reitan, 1992). The Digits Forward exam requires individuals to listen to and repeat a sequence of digits. The number of digits in a set increases until two consecutive mistakes are made and the task is terminated. The Trail Making Test A participants must connect a set of circled numbers or letters in ascending order. Executive Function was assessed using Digits Backward (Wechsler, 1981), Trail Making Test B (Reitan, 1992), and Color Word Interference Task (Delis, Kaplan, & Kramer, 2001). In the Digits Backward exam, a string of digits read by the experimenter is repeated in the backward order by the participant. The number of elements in a set increase until two consecutive mistakes are made and the task is terminated. This is a test of working memory abilities, as it requires both active maintenance and manipulation. The Trail Making Test B requires participants to connect circles, each filled with a letter or number, alternating categories and progressing in ascending order. Successful performance depends on the ability to flexibly switch between mental sets. Finally, in the Color Word Interference (CWI) task (Delis, Kaplan, & Kramer, 2001), participants complete a set of trials including color-naming, word reading, color-word interference, and switching trials where they alternate between reporting the color of ink that the word is printed in or reading the word itself. Successful performance requires inhibitory control (i.e., when reading is to be avoided) and set shifting abilities.

Materials and Apparatus

The materials consisted of 162 full-color scenes (81 indoor; 81 outdoor) and 162 full-color face images (81 females; 81 males). Each face was 250 x 250 pixels and superimposed on a 300 x 300 pixel grey background; scenes were 800 x 600 pixels.

Eye position was recorded at a rate of 60 Hz (i.e., approximately every 17ms) using an Applied Science Laboratories (ASL, Bedford, MA) D6 Remote Eye Tracking System. Fixations were calculated offline using the Eyenal Software Package (ASL, Bedford, MA) by averaging subsequent viewing samples into a single fixation if changes in gaze point were less than 1 degree of visual angle and had a minimum duration of 100ms.

Design and Procedure

After providing informed consent, participants completed the MoCA and then the battery of neuropsychological tests previously described (CVLT, BVMT-R, Trail Making Test A and B, Digit Span Forward and Backward, CWI). Following neuropsychological assessment, participants completed the SFPT while eye movements were recorded. Distance from the screen was between 18 and 31 inches and a calibration procedure was performed using a 3 x 3 spatial array prior to testing. As in past studies (Hannula et al., 2007), elements in the array (i.e., letters A-I) were positioned in three equally spaced rows and columns across the screen, covering the bounds of the stimulus display. Participants were asked to fixate on each letter as eye position was recorded. Alignment of the fixations was checked following calibration and if the result was suboptimal, the process was repeated. Calibration was then checked prior to each experimental block and if drift was evident, the process was repeated.

The experiment consisted of three interleaved blocks of encoding and test. During the encoding phase, participants were presented with 42 unique scene-face pairings and were asked to commit each pair to memory. Each trial began following fixation on a centrally-located crosshair.

The scene appeared on the screen for 2s and then a face was superimposed on top of the scene. The scene-face pair remained on the screen for 4s. Each scene-face pair was presented three times, with the pairs presented in a different randomized order in three runs, prior to the test phase.

Participants completed 12 trials per test block. Six of these trials were target-present and six were target-absent. Across blocks, there were 36 test trials (18 target-present, 18 target-absent). Following central fixation, the test trial began with the presentation of a studied scene for 2s to encourage retrieval of the associate (i.e, the face that had been paired with that scene during encoding). After scene presentation, three studied faces were superimposed on top the scene and this 3-face display remained in view for 6s. All of the faces presented in the test display were seen during encoding, which meant that identification of the associate could not be due to face familiarity. There were two experimental conditions: target-present and target-absent. Target-present displays included the face that had been paired with the scene during encoding (i.e., the associate), while target-absent displays did not contain the associate. Instead, all three of the faces in target-absent displays had been encoded with different scenes. After the 3-face display was removed from view, a prompt appeared indicating that participants should make a recognition response. The response screen instructed participants to press button number "1" on the keypad if the associate was present in the display and press number "2" button if the associate was missing from the set of alternatives.

Counterbalancing was conducted as previously described by Mahoney et al. (2018). Briefly, individual faces and scenes were each assigned to one of nine lists (i.e., 18 faces or scenes per list), with each list containing an equal number of male and female face exemplars or indoor and outdoor scene exemplars. Individual participants encoded scenes and faces from seven of nine lists (i.e., 126 scene-face pairs). From the set of nine, different lists were assigned,

for a given participant, to the target-present and target-absent conditions. Exemplars from corresponding scene and face lists were randomly assigned to pairs for encoding. Faces from six of the seven encoded lists were used in the 3-face test displays, faces from the seventh list were not. Scenes that were paired with faces from one of the encoded lists were used to create target-present test displays (i.e., an encoded scene presented with its studied associate and two additional encoded faces). Scenes that were paired with faces from the seventh list during encoding were used to create target-absent test displays (i.e., an encoded scene along with three encoded faces, none presented with the scene during encoding).

Individual participants within a group were yoked so that pairs of participants were tested using identical 3-face test displays. Differences in encoding history meant that the same display was target-present (i.e. contained the studied associate) for one participant and target-absent (i.e. did not contain the studied associate) for another. Use of this yoking procedure meant the same face (i.e., the associate for one yoked participant), presented in the context of the same test display, could be used for viewing time analyses whether displays were target-present or target-absent (see Figure 1). Participants were also yoked across groups so that corresponding middle-aged, older, and "at risk" adults experienced the exact same encoding and test events. Finally, counterbalancing also ensured that across test trials, the critical face (i.e., the associate in target-present trials; the matched comparison face in target-absent trials) appeared equally often in all three spatial locations for each experimental condition.

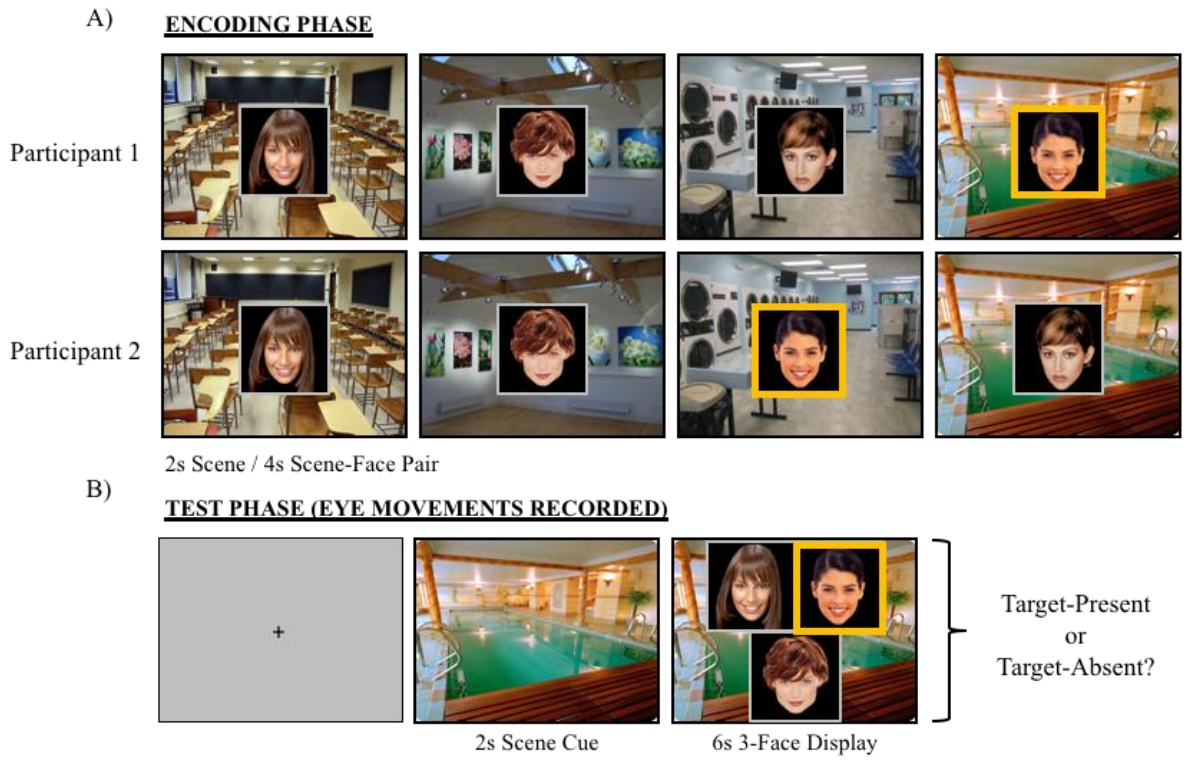

Figure 1. The Scene-Face Pair Task. (**A**) Representative example of scene-face pairs presented during the encoding phase for two participants. Each scene was presented for 2s then a face was superimposed on top of the scene. The scene-face pair remained on screen for 4s. Each scene-face pair was presented three times prior to testing. (**B**) Representative example of a test trial. The experimental trial began once participants fixated on a centrally located crosshair. The scene was presented for 2s to prompt retrieval of the matching face, then a three-face display was superimposed on top of the scene and remained on screen for 6s. Critically, because of the counterbalancing procedure, pairs of participants within the same group (ex. participants 1 and 2 here) were tested with the same displays. Due to differences in encoding history, the test display contained the associate for one participant (i.e., target-present trial) and did not contain the associate for another participant (i.e., target-absent trial). Across groups, participants were yoked so that encoding and test were identical for a given middle-aged, older, and "at risk" set. Following the scene-face display, a prompt screen appeared asking for a recognition response. Individuals were told to press button number "1" if the associate was present or button number "2" if the associate was absent. Yellow boxes surrounding the critical face are for illustration only. *Figure adapted from Mahoney et al. (2018).*

Eye Movement Analyses

Individual trials from the test phase were removed from the analyses if the total viewing time was less than 65% of the 3-face display duration (cf. Hannula et al., 2012; Mahoney et al., 2018). A total of 22.48% of the trials were eliminated from the analyses (middle-aged *M* =

18.21%, *SD* = 22.51%; older adults *M* = 17.14%, *SD* = 13.94% ; "at risk" *M* = 34.72%, *SD* = 19.60%). All of the participants had at least four trials in target-present or target-absent conditions for analysis, similar to past procedures (Hannula et al., 2007; Mahoney et al., 2018).

Eye movement analyses were based on viewing time directed to two faces of interest: (1) *associates* of scene cues from target-present trials and (2) *matched comparison faces* from target-absent trials. As previously indicated, matched comparison faces were associates for other participants in the counterbalanced design. Evidence for effects of memory on eye movement behavior was examined using three measures: (1) global viewing (2) time course of viewing and (3) first and final gaze durations.

Global Viewing Time

The proportion of total viewing time directed to critical faces (i.e. associates in target-present displays and matched comparison faces in target-absent displays) was calculated for each trial collapsed across the entire six second three-face display presentation period. The denominator was the total viewing time directed to the 3-face display (Hannula et al., 2007), rather than total 3-face display duration. Rationale for this choice can be found in Box 1 of Hannula et al. (2010). Next, the magnitude of the memory-based viewing effect was calculated by computing a difference score for each participant by subtracting the mean proportion of viewing time directed to matched comparison faces from the mean proportion of viewing time directed to associates. Difference scores greater than zero would indicate that memory for scene-face relationships affected viewing behavior, with higher values indicating that more time was spent viewing associates.

Time Course of Viewing

Time course analyses were conducted to examine viewing as it unfolded over the course of 3-face display during the test trial. In initial analyses, consistent with observations of early memory-based viewing in previous work (Hannula et al., 2007; Mahoney et al., 2018), analyses

were limited to data from the first second of the test trial following 3-face display onset. In this case, data from individual trials were subdivided into consecutive 250ms time bins beginning with 3-face display onset (i.e. 0-250ms, 250-500ms, 500-750ms, 750-1000ms). Of interest here was whether memory-based viewing effects had the same rapid onset, evident within 500-750ms of 3-face display appearance, as has previously been reported in healthy college-aged participants (Hannula et al., 2007; Mahoney et al., 2018; Nickel et al., 2015). Subsequently, data were subdivided into 1000 ms time bins (i.e., 0-1000, 1000-2000, …, 5000-6000) beginning with the onset of 3-face display. This approach permitted us to examine whether there were any differences in viewing patterns across groups over the course of the full test trial. In each of these analyses, the proportion of total viewing time directed to associates or matched comparison faces was calculated separately for each time bin. As was done for global viewing measures, difference scores were then calculated for each subject to index the magnitude of memory-based viewing in each time bin.

First and Final Gaze

The final measure used here was based on analyses of gaze duration. Gaze duration was calculated by summing the durations of consecutive fixations directed to the critical face (i.e. associate or matched comparison face) in each 3-face display following the first entry and the final entry into the critical region of interest (i.e. the location occupied by the associate in target-present displays and the location occupied by matched comparison faces in target-absent displays). The duration of each consecutive fixation were summed until an eye movement was made away from the region occupied by the critical face. Difference scores were then calculated to measure the magnitude of memory-based viewing in the first and final gaze and comparisons were made across groups.

Results

Mauchly's test of sphericity was calculated for each ANOVA. Greenhouse-Geisser adjusted degrees of freedom and p-values were reported if sphericity was violated. Post hoc tests were Benjamini-Hochberg corrected for multiple comparisons.

Sample Characteristics and Neuropsychological Performance

Demographic characteristics of the sample can be found in Table 1. Middle-aged, older, and "at risk" groups were well-matched for years of education *(F* (2,47) = 0.59, p = .55, η^2 = 0.02) and sex (X^2 (4, $N = 50$) = 3.65, p = .45). There were significant differences in age between the groups *(F* (2,47) = 62.81, p < .01, η^2 = 0.73). The middle-aged group was significantly younger than older and "at risk" groups (t's (30) ≥ 6.83, p's < .01, d's ≥ 0.43), while older and "at risk" groups were well-matched in age (t (30) = 1.67 , p = .10, d = 0.10). Additionally, there were differences in MoCA performance between the groups (F (2,47) = 66.26, p < .01, η^2 = 0.74). Middle-aged and older adults performed significantly better on the MoCA than "at risk" adults (t's (30) ≥ 10.19, p's < .01, d's ≥ 3.63). No differences were evident in MoCA performance between middle-aged and older adults (t (34) > 0.79, p = .43, d = 0.26). Despite differences in MoCA performance, middle-aged, older, and "at risk" groups performed within the normal range on all neuropsychological test examinations (see Table 2).

Table 1. Sample demographic characteristics.

	Middle-aged	Older	"At Risk"
N	18	18	14
Age Range	40-55	65-80	40-80
Age (years)*	47.83 (4.44)	71.39 (3.71)	66.86 (10.74)
Sex (M:F)	7:11	10:8	7:7
Education (years)	16.22 (2.78)	16.39 (2.52)	15.43 (2.41)
MoCA (/30)*	28.06 (1.35)	27.72 (1.18)	23.35 (1.22)

Note. MoCA = Montreal Cognitive Assessment. *Demographic characteristics that were different between the groups: Middle-aged adults were significantly younger than older and "at risk" groups, while there were no differences in age between older and "at risk" participants. Middle-aged and older adults had significantly higher MoCA scores than "at risk" group. There were no differences in MoCA performance between middle-aged and older adults.

Table 2. Neuropsychological Performance

	Middle-aged	Older	"At Risk"
CVLT (Norm = -1 – 1)			
SD Free	-0.39 (0.88)	0.17 (1.12)	-0.07 (1.14)
LD Free	-0.11 (1.02)	0.08 (0.79)	-0.18 (1.22)
BVMT-R (Norm = 40 – 60)			
Delayed Recall	59.72 (5.69)	55.94 (11.58)	47.36 (12.83)
Trails (Norm = 7 – 13)			
Numbers	11.41 (2.06)	13.55 (1.50)*	12.14 (3.18)
Switching	11.17 (1.79)	12.39 (2.73)	10.71 (3.05)
Digits (Norm = 7 – 13)			
Forward	11.06 (1.92)	10.94 (2.36)	9.43 (3.74)
Backward	8.00 (1.81)	9.22 (3.08)	7.79 (3.70)
CWI (Norm = 7 – 13)			
Color Naming	9.82 (3.35)	10.50 (2.59)	9.78 (2.91)
Word Reading	10.70 (2.36)	11.77 (2.41)	10.14 (2.74)
Inhibition	11.17 (2.82)	11.61 (2.70)	9.57 (2.68)
Switching	11.76 (1.52)	12.05 (2.75)	10.42 (2.70)

Note. CVLT = California Verbal Learning Test; SD = Short Delay; LD = Long Delay; BVMT-R = Brief Visuospatial Memory Test-Revised; CWI = Color Word Interference. CVLT performance was normalized for each individual according to age and sex. Performance within the range of -1 to +1 for the CVLT was considered normal. BVMT performance was normalized for each individual according to age and performance within the range of 40-60 was considered normal. Trails B and Digits Forward/Backward performance were normalized for each individual according to age and performance within the range of 7-13 was considered normal. Middle-aged, older, and "at risk" groups all performed within the normal range on each neuropsychological test, with the exception that older adults performed better than the normal age range for Trails A (*).

Explicit Recognition Performance

It was hypothesized that participants from all three groups would be able to differentiate target-present from target-absent displays because all of the participants were healthy, non-demented independently functioning adults. Additionally, it was predicted that explicit recognition would be poorer among individuals categorized as "at risk", and that age-related decrements might also be evident between middle-aged and older adults, although to a lesser extent. Recognition responses were categorized for each participant as *hits* (target-present display – report associate was present), *misses* (target-present display – report associate was absent), *false alarms* (target-absent display – report associate was present) and *correct rejections* (target-absent display – report associate was absent). Differences in recognition accuracy were examined using corrected recognition scores, calculated as the percentage of hits plus the percentage of correct rejections divided by 2 (i.e., (% hits + % correct rejections) / 2). As predicted, participants from all three groups successfully distinguished target-present from target-absent trials more often than would be expected by chance (t's ≥ 5.08, p's $\leq .001$; see Figure 2) and a one-way ANOVA revealed that there were differences in performance across groups ($F(2, 47) = 3.34$, $p < .04$, $\eta^2 = 0.12$). Results of post-hoc comparisons indicated that recognition performance was marginally better for the middle-aged group than the "at risk" adults (t (30) = 2.46, p = .07, d = 0.87) but that the performance of older adults was not statistically different from middle-aged or "at-risk" adults (t's (34) ≥ 1.38, p's $\leq .18$, d's ≥ 0.49). Collectively, these results suggest that while participants from all three groups were able to perform the task, performance was marginally down among individuals characterized as "at risk" group compared to the middle-aged sample.

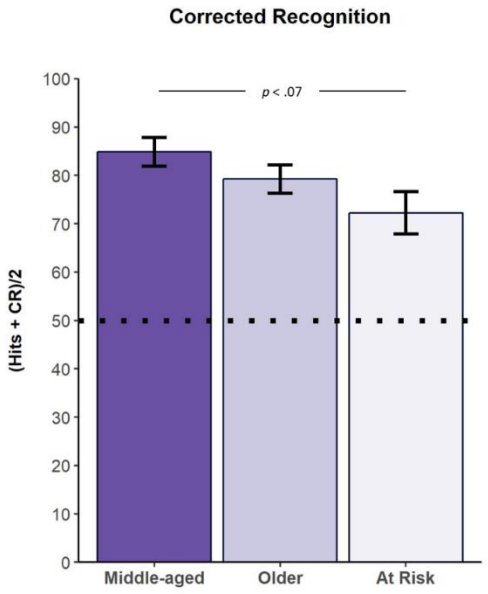

Figure 2. *Explicit recognition performance.* CR = correct rejections. Corrected recognition performance (Mean ± SEM) during the test phase of the SFPT. The dashed black line represents chance performance. While all groups differentiated target-present from target-absent displays better than what would be expected by chance, "at risk" adults explicit recognition performance was significantly lower than middle-aged adults. Older adults performance was numerically lower than middle-aged adults, however, this difference was not statistically significant.

Global Viewing Time

It was predicted that significant memory-based viewing effects would be evident in the data from participants in each group. In other words, more time would be spent looking at the associates of scene cues than at matched comparison faces. However, it was also possible that age and cognitive status would affect the magnitude of this eye-movement-based relational memory effect. One-sample t-tests calculated separately for each group indicated that eye movements were directed preferentially to faces that were associates of scene cues (t's ≥ 4.22, p's $\leq .001$), indicating that memory was evident in the global viewing patterns of all three groups.

Results of a one-way ANOVA revealed differences in global viewing patterns across groups ($F(2, 47) = 5.52$, $p < .007$, $\eta^2 = 0.19$; see Figure 3a). The post-hoc comparisons indicated

that the memory-based viewing effect was greater in middle-aged adults than "at risk" (t (30) = 2.87, $p < .01$, $d = 1.02$) and marginally greater than in healthy older adults (t (34) = 2.07, $p = .06$, $d = 0.69$). The numerical difference in memory-based viewing time was not statistically significant when healthy older adults were compared with those "at risk" for cognitive impairment based on MoCA scores (t (30) = 1.55, $p = .13$, $d = 0.54$). In sum, individuals "at risk" and older adults spent less time viewing the associate than healthy middle-aged adults.

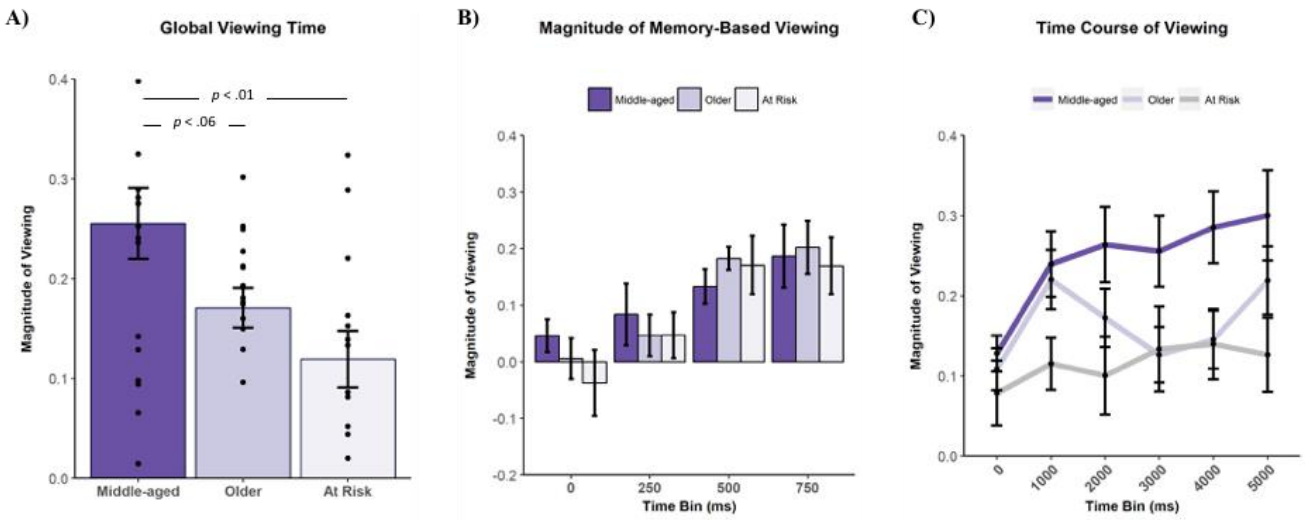

Figure 3. *Memory-based viewing during the test phase.* (A) Global magnitude of memory-based viewing (target present – target absent) during the 3-face display (Mean ± SEM) collapsed across the six second viewing session. Global viewing was significantly lower in "at risk" adults and marginally lower in healthy older adults compared to middle-aged participants. (B) First second of memory-based viewing (Mean ± SEM) broken down into 250ms time bins. All three groups showed onset of the eye-movement-based relational memory effect within 500 – 750ms time bin, as has previously been reported in healthy college-aged participants (Hannula et al., 2007). (C) Time course of viewing (Mean ± SEM) broken down into 1000ms time bins. While there was not a significant group by time bin interaction effect, inspection of panel C shows a unique pattern of viewing throughout the time course of 3-face display for each group. Middle-aged adults exhibited the highest magnitude of memory-based viewing of the associate that persisted throughout the time course. Older adults early viewing (i.e., the first two seconds of 3-face display) resembled viewing patterns in middle-aged participants. However, later viewing in older adults resembled that of "at risk" adults. Finally, "at risk" adults showed the lowest magnitude of associated viewing throughout the 3-face display period.

Time course of Viewing

Time course analyses may be more sensitive to between-group differences in memory-based viewing patterns that might otherwise be obscured by collapsing data from the full duration of the test trial. It was hypothesized that cognitively unimpaired middle-aged and older adults would exhibit memory-based viewing effects within 500-750ms of 3-face display onset, on par with what has been reported in young adults (Hannula et al., 2007). However, the magnitude of memory-based viewing effects might be lower in older adults than in middle-aged adults. In other words, while the early time course might be preserved with age, the strength of the viewing effect might not be, as relational memory impairments have been documented when older adults were tested (Grady & Ryan, 2017, pp. 167-208). Furthermore, and as has been reported in individuals diagnosed with schizophrenia (Williams et al., 2010), memory-based viewing effects in the group "at risk" for cognitive impairment might be delayed in onset, lower in magnitude or less consistent overall compared to non-impaired middle-aged and older adults. To determine when in time the eye-movement-based relational memory effect emerged, one sample t-tests were computed using data from the first second of the test trial, subdivided into 250ms time bins. In contrast to predictions, participants from all three groups displayed disproportionate viewing of the matching face beginning at 500-750ms (t's $\geq$ 3.32, p's $\leq$ .01). To determine whether there were any differences in early viewing patterns across groups a 3 x 4 repeated measures ANOVA with the factors group (middle-aged, older, "at risk") and time bin (0-250ms, 250-500ms, 500-750ms, 750-1000ms) was computed (see Figure 3b). Results indicated that the magnitude of the memory-based viewing effect increased with the passage of time (main effect of time bin: $F(2.10, 98.70) = 13.83$, $p < .001$, $\eta^2 = 0.15$), but the main effect of group ($F(2, 47) = 0.23$, $p = .79$, $\eta^2 = 0.003$) and the group by time bin interactions ($F(4.20, 98.7)$

= 0.52, p = .79, η^2 = 0.01) were not significant. These results are consistent with the proposed automaticity of early memory-based viewing and suggest that the early time-course is preserved in older adults and those who perform below the threshold for normal performance on the MoCA.

To examine how memory-based viewing unfolded across the full time course of the 3-face displays, a 3 x 6 repeated measures ANOVA with group and time bin as factors was computed (see Figure 3c). Results revealed a significant main effect of group (F(2, 47) = 5.31, p < .01, η^2 = 0.09) and a main effect of time bin (F(4.22, 198.63) = 4.14, p < .01, η^2 = 0.05) but the group by time bin interaction was not significant (F(8.45, 198.63) = 1.04, p = .41, η^2 = 0.02). Additional exploratory analyses were calculated in each time bin to see whether there were any group differences in patterns of viewing with progression of the test trial. Visual inspection of Figure 3c suggests a clear difference between healthy middle-aged adults and those categorized as "at-risk" throughout the duration of the trial. The viewing patterns of healthy older adults appear more closely matched to middle-aged participants early in the test trial, but better matched to "at-risk" participants late in the test trial. Differences between "at risk" and middle-aged viewing time courses were evident beginning at the 1000-2000ms time bin and persisted throughout the 3-face display (t's (30) ≥ 1.78, p ≤ .08, d's ≥ 0.63). Older adults and middle-aged adults viewing differed late in the viewing session beginning at the 3000-4000ms time bin and persisting until the 4000-5000ms time bin (t's (34) ≥ 2.29, p ≤ .02, d's ≥ 0.76). Older adults viewing differed from "at risk" adults at the 1000-2000ms time bin (t(30) = 2.06, p = .04, d = 0.73). However, these effects were not significant after Benjamini-Hochberg corrections for multiple comparisons. It is possible, and this is considered in the discussion section, that the

study is currently underpowered and that differences might be evident with increased sample size.

First and Final Gaze

Differences in the persistence of memory-based viewing were examined through first and final gaze. One-way ANOVAs were used to examine the effect of group on first and final gaze duration magnitudes. Results revealed marginal differences in first gaze duration across groups ($F(2, 46) = 2.94$, $p = .06$, $\eta^2 = 0.11$; see Figure 4a). The post-hoc comparisons indicated that middle-aged adults had a marginally greater first gaze durations to the associate than the "at risk" participants (t (29) = 1.86, $p = .11$, $d = 0.68$). Similarly, results indicated marginal differences in final gaze duration across groups ($F(2, 46) = 2.79$, $p = .07$, $\eta^2 = 0.10$). The post-hoc comparisons indicated that middle-aged adults had a marginally greater final gaze durations to the associate than the "at risk" participants (t (29) = 2.00, $p = .15$, $d = 0.72$). These results suggest that the tendency to stay fixated on associates following the first and final eye movement to its location may be impaired in "at risk" adults compared to healthy middle-aged counterparts.

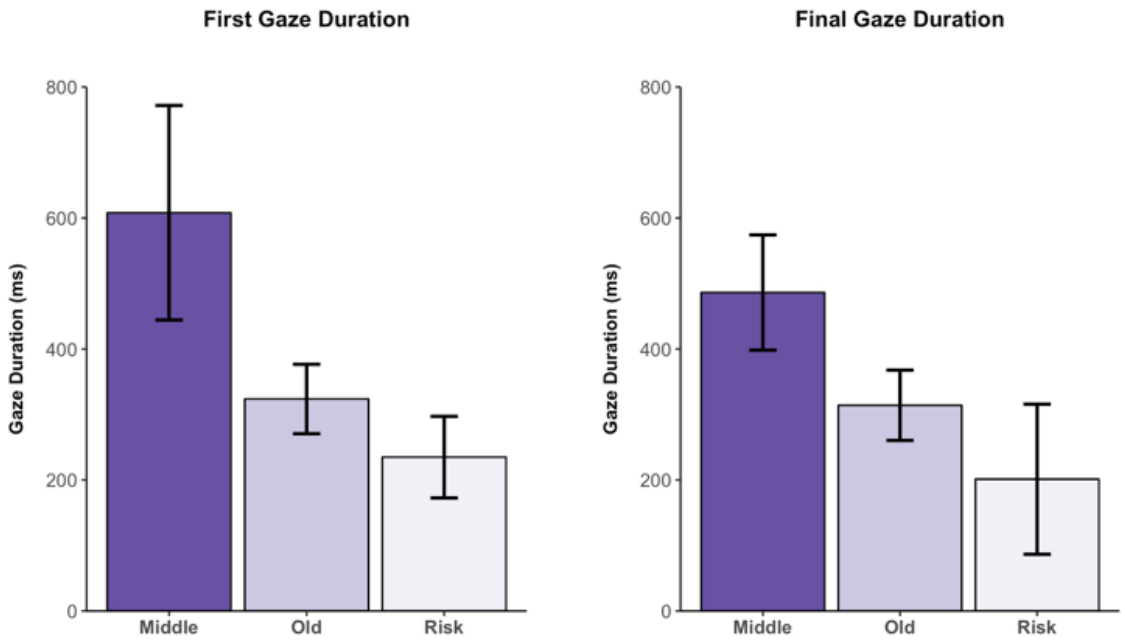

Figure 4. *First and final gaze.* Difference in gaze duration (total time viewing target present face – target absent foil) upon (A) first (Mean ± SEM) and (B) final entry into the target ROI. There was a marginally significant effect of group on first gaze duration, such that "at risk" adults spent less time viewing the associate upon first fixation than middle-aged adults. No group differences were evident in final gaze duration.

Discussion

The general aim of the current study was to examine age-related changes in relational memory and to explore the potential utility of using eye movement behavior as an index of memory performance to differentiate normal from pathological aging. Hippocampus-dependent relational memory was assessed using the SFPT in combination with eye tracking procedures in healthy middle-aged and older adults, as well as adults whose MoCA score fell below the cutoff for normal performance, suggesting they might be at risk for cognitive impairment. Participants from each group studied several scene-face pairs and memory for those pairs were tested with 3-face displays superimposed on studied scenes. Differences in performance associated with age (i.e., based on comparisons between middle-aged and older adults) were only evident in eye movement behavior, not explicit recognition performance, an outcome that suggests that changes

in relational memory with age may be subtle. In contrast, participants in the group categorized here as "at risk" for pathological aging were impaired, relative to healthy middle-aged participants, on measures of explicit recognition and eye movement behavior. These findings indicate that, while the integrity of relational memory may change to some extent with age, additional deficits can be detected in individuals at risk for pathological aging.

It is important to note that participants in the "at-risk" group did not have a formal diagnosis of MCI or AD and had not expressed concerns about memory function – instead, their "at-risk" status was based solely on MoCA performance assessed in the lab. Consistent with the absence of any formal diagnosis or complaints about memory, the performance of participants from all three groups was in the normal range on all of the tests that were part of our cognitive assessment, even the subset sensitive to changes in long-term memory. Research indicates that pathological changes in MTL structures occur years prior to the onset of clinically detectable symptoms (Braak & Braak, 1991; Jack et al., 2010). Results reported here suggest that tests of relational memory, combined with direct and indirect measures of performance, may be better able to detect early deficits that are missed by standardized neuropsychological assessments.

Subtle decrements in relational memory are observed in normal aging

Numerically, relational memory performance, examined directly through recognition responses and indirectly in eye movement behavior, was worse in the healthy older compared to middle-aged adult. However, these differences were only statistically significant for the global viewing time measure. The magnitude of memory-based viewing (i.e., the difference in proportion of total viewing time directed to associates and matched comparison faces) was lower in the healthy older adult sample than the middle-aged sample. This pattern of results suggests that eye movement behavior may be more sensitive to changes in the integrity of memory

associated with age or perhaps choice-certainty than explicit recognition responses. The lack of differences in explicit recognition between middle-aged and older adults is rather surprising as age-related decrements in relational memory performance are well documented (Naveh-Benjamin, 2000; Rhodes, Castel, & Jacoby, 2008; Ryan, Leung, Turk-Browne, & Hasher, 2007). This discrepancy could be because we examined age-related changes by comparing healthy older adults performance to healthy middle-aged adults, while most past work used healthy young adults as a reference group (Grady & Ryan, 2017, pp. 167-208). This suggests that changes in relational memory from middle age to older adulthood are rather subtle, compared to the amount of change observed from young adulthood. It will be important, however, in future studies to compare performance between middle-aged and young adults, to ascertain if and to what magnitude relational memory deficits are detectable beginning in middle age.

Additional analyses were performed to determine whether and how viewing patterns changed over the course of the test trial. While there was not a significant time bin by group interaction when data were separated into 1000ms time bins, there is a notable pattern in the data. Viewing patterns of older adults look very similar to the middle-aged sample early in the trial – a result consistent with the observation that the eye-movement-based relational memory effect emerged 500-750ms following 3-face display onset. This could indicate that the integrity or quality of the retrieved memory representation may be as good in healthy older adults as the middle-aged sample. The time-course of this viewing effect, significant by the 500-750ms, is consistent with what has been reported in several studies conducted with healthy college-aged participants (e.g., Hannula et al., 2007; Mahoney et al., 2018). Following the first two seconds of viewing, the pattern of memory-based viewing in older adults changed, resembling that of the “at risk” group. The change in older adult viewing behavior later in the session could be due to issues in

confidence in the retrieved memory representation. Past work demonstrates that recollection processes, or retrieval of contextual aspects associated with the encoding episode, are disrupted in older adults (for review see Schoemaker, Gauthier, & Pruessner, 2014) due to age-related changes in the structure and function of the hippocampus (Driscoll et al., 2003; Raz et al., 2005). To compensate for disrupted recollection abilities, older adults rely on familiarity, or recognition devoid of contextual information associated with the encoding episode, to guide recognition performance (for review see Schoemaker et al., 2014; Yonelinas, 2002). In the current study, all three faces in the test display were studied equally often suggesting that the indication of the associate could not be due to familiarity. Impaired recollection may have lead to indecision and reevaluation of the other faces within the display later in the viewing session to better inform the upcoming recognition response. However, more work is needed to clarify the disrupted time course of associate viewing in healthy older adults and how relational memory decrements are associated with hippocampal structural integrity in the context of normal aging.

Relational memory impairments in those "at risk" for pathological aging are more pronounced than with normal aging

Changes in relational memory performance, relative to the middle-aged sample, were also evident in individuals categorized as "at risk" for pathological cognitive impairment using the MoCA. Differences in "at risk" performance were evident not only in eye movement but also in explicit recognition responses. In addition, explicit recognition and viewing behavior were also lower in this group than in the group of older adults that performed above threshold on the MoCA, although these differences were not statistically significant. This suggests a differential course of relational memory impairments in individuals who are "at risk" for pathological aging compared to healthy middle-aged adults. Relational memory recognition performance impairments in individuals at increased risk for AD (i.e., individuals with subjective cognitive

complaints and MCI) have previously been reported (Polcher et al., 2017). As SFPT performance is dependent on hippocampal integrity (Hannula et al., 2007; Williams et al., 2007), this finding of impaired performance in healthy adults deemed "at risk" for pathological cognitive impairment is consistent with the idea that the integrity of input to the hippocampus and/or the functional integrity of this structure itself may be compromised, disrupting hippocampal relational processing.

It was predicted that, much like schizophrenia patients with suspected abnormalities in hippocampal function, participants categorized here as "at risk" for cognitive impairment might show delayed or lower magnitude eye-movement-based relational memory effects. Preferential viewing of the associates didn't emerge in patients with schizophrenia until 1250ms after 3-face display onset, and even then, were much reduced related to a healthy matched comparison group. In contrast, and consistent with what was described for our healthy older adults sample, "at-risk" participants showed significant memory-based viewing within 500-750ms of 3-face display onset. This is the same onset time that has been reported consistently when younger adults were tested with the SFPT (Hannula et al., 2007; Mahoney et al., 2018). Notably though, there were significant reductions in global viewing time relative to the middle-aged sample and numerical reductions relative to the older-adults sample. More generally, evaluation of Figure 3c shows that the magnitude of memory-based viewing effect was lower in "at risk" adults over the course of the entire time course of 3-face display relative to middle-aged adults. Additionally, the gaze data show that compared to healthy middle-aged adults, "at risk" individuals spent less time viewing the association upon their first eye movement to its location. It is possible that disrupted viewing patterns in "at risk" adults represent very early stages of hippocampal pathology or disruption of processing by virtue of early pathological changes in structures that provide the

hippocampus with its input (i.e., transentorhinal area). This is because the deficits observed in "at risk" adults aren't as pronounced as they are in schizophrenia, but are more robust than what was observed in the healthy older adult sample tested here. Future work is needed to better elucidate the association between direct and indirect indices of SFPT performance, hippocampal integrity, and clinical progression of AD.

Study Limitations

This study is not without its limitations. First, the sample was predominantly Caucasian and highly educated. It will be important to diversify the sample in the future to gain a better understanding of age-related cognitive decline in a more representative sample. In addition, to make our middle-aged and older adults groups more distinct, we arbitrarily separated the groups by a span of 10 years (middle-aged 40-55 years; older adults 65-80) and are missing adults aged 56-64. This age range may be a critical period in the onset of cognitive impairments and may be important to include in future investigations. It may also be important to add a young adult reference group in order to examine relational memory changes that may become apparent as early as middle age.

Next, our sample size estimation was based upon the reported effect size from the early viewing contrast of hippocampal amnesic patients and healthy matched comparison participants (Hannula et al., 2007). With an effect size of 1.69, it was indicated that 11 participants per group would be sufficient to detect differences in memory-based viewing. However, it was inappropriate to assume that the impairments in relational memory performance in older and "at risk" adults would be comparable to the impairments documented in amnesic patients with substantial volume reductions in the hippocampus that are visible in anatomical scans. I have therefore conducted a new sample size estimate – assuming an effect size of 0.80 (which is the

cutoff for a large effect size, but well below 1.69), a cutoff for significance equal to .05, and having set power to .85, a sample of 72 participants (24 per group) is needed. Additional participants will, therefore, be recruited to ensure that marginal effects reported in the results section here are not due to insufficient power.

While the current study revealed informative results about age-related impairments in the relational memory system in normal and potentially pathological aging, longitudinal studies are needed to more accurately determine the pattern and magnitude of decline in hippocampus-dependent memory associated with age. Although "at risk" participants in this study were identified using the MoCA, this doesn't guarantee that the neurobiological changes underlying the cognitive impairments are homogenous. Longitudinal assessments will be necessary to determine which adults will age normally or develop AD and to elucidate how these changes in cognitive status relate to SFPT performance and eye movement behavior. Longitudinal studies are required to determine whether the apparent sensitivity of relational memory tasks to changes in cognitive status has any predictive value – i.e., whether these tests might be used to differentiate normal from pathological aging during preclinical stages of AD.

Future Directions

It is critical to gain a better understanding of the association between MTL-integrity, SFPT performance, and eye tracking to determine its utility as a tool to identify risk populations during preclinical stages of AD. Past work has demonstrated an association between hippocampal integrity and memory-based viewing (Hannula et al., 2007; Hannula et al., 2009; Williams et al., 2010). The activity of the hippocampus during scene presentation of the testing trials predicted the magnitude of memory-based viewing during three-face display viewing (Hannula et al., 2009). Moreover, eye-movement-based relation memory effects are altered or completely absent

in populations with hippocampal abnormalities (Hannula et al., 2007; Williams et al., 2010). However, no studies have examined the association between MTL structural volume and relational memory performance in aging.

I plan to fill this gap by employing the SFPT in combination with eye tracking and ultra high-resolution 7 Tesla MRI to examine the association between MTL subregion volume (anterolateral ERC, posteromedial ERC, perirhinal cortex, parahippocampal cortex, hippocampus (subiculum, CA1, CA2, CA3, DG)), memory-based viewing, and explicit recognition performance. This project is expected to provide novel insights into whether and how the structural integrity of the hippocampus changes with age and cognitive status. More generally, I will be able to examine whether measures of relational memory predict differences in hippocampal subfield and/or MTL cortex volume estimates, which may be a marker of pathological aging processes. One possibility is that measures of memory-based viewing could be used as a cost-effective proxy for hippocampal health.

Conclusion

In conclusion, currently available treatments for AD are thought to be ineffective because by the time of diagnosis when they are typically administered, the neurodegenerative changes associated with AD are potentially too advanced to be reversed or halted. It is necessary to identify markers that may predict incipient pathological decline before the onset of clinical symptomology. AD pathology is believed to begin years or even decades prior to diagnosis in the transentorhinal region of the PRC, which essentially disrupts the ability of the hippocampus to bind the item-specific and contextual elements of an experience into complex associations. I investigated whether explicit recognition and eye movement behaviors during the hippocampus-dependent SFPT would be sensitive to detect subtle deficits associated with normal aging (i.e.,

from middle-aged to older adulthood) and early pathology in adults who performed in the MCI range on the MoCA (i.e., “at risk”). Differences in performance associated with age were only evident in eye movement behavior, not explicit recognition performance, which suggests that non-pathological changes in relational memory from middle age to older adulthood may be subtle and that eye movement measures may be more sensitive in detecting subtle deficits than explicit recognition. In contrast, participants “at risk” for pathological aging were impaired, relative to healthy middle-aged participants, on measures of explicit recognition and eye movement behavior. These findings indicate that the SFPT in combination with eye tracking may be sensitive in detecting impairments indicative of pathological decline, although, further work is needed to assess the utility of recognition and eye movement measures as markers of incipient decline.

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