UNIVERSITY OF CALIFORNIA, SAN DIEGO

Pattern Separation in Healthy Aging and Dementia

A dissertation submitted in partial satisfaction of the requirements for the degree of

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in

Psychology

by

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The Dissertation of Katherine Mary Ingram is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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ABSTRACT OF THE DISSERTATION

Pattern Separation in Healthy Aging and Dementia

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The dissertation research described herein examined several facets of *pattern separation* (conceptualized as an encoding process whereby two very similar stimuli are stored as discrete representations). Previous research has conceptualized pattern separation as a discrete, high threshold process and has relied upon performance measures that are derived from that theory. More recently, it has been suggested that pattern separation may be better fit by a continuous, signal-detection-based model.

Should that be the case, it would mean that previous work examining pattern separation in aging and dementia has relied upon potentially misleading dependent measures.

The current project had three goals: 1) to determine the most appropriate cognitive modeling for pattern separation, 2) to examine whether or not pattern separation is selectively impaired in aging and dementia populations, and 3) to compare biomarkers of preclinical impairment with performance on behavioral recognition memory and pattern separation tasks. In Chapter 1, ROC and *d'* analyses showed that pattern separation is indeed best conceptualized as a continuous signal detection process. In Chapters 2 and 3, we took the framework for pattern separation identified in Chapter 1 and applied it to a population consisting of young adults, older adults, individuals with amnestic mild cognitive impairment (aMCI), and Alzheimer's disease. The general approach was to first try to equate performance across groups on a recognition memory task and then compare group performance on the pattern separation task. Taken together, Chapters 2 and 3 provided evidence that pattern separation is selectively impaired in aMCI and possibly in healthy older adults as well, and this deficit is not explained by a recognition deficit alone. In Chapter 4 we measured the relationship between behavioral performance measures (on both the recognition memory tasks and pattern separation tasks) and cerebrospinal fluid biomarkers (Aβ42 and tau levels) in healthy aging participants. We found a significant positive correlation between performance on both the recognition memory task and the pattern separation task, but only for pictures of everyday objects. Thus, these biomarkers are predictive of general memory performance for objects but do not selectively predict pattern separation performance.

INTRODUCTION

Memory complaints in an aging population are unsurprising and are even less so in dementia populations. Understanding the precise nature of the memory complaint in these different population groups, however, is vital to our understanding of the progression from healthy aging to mild cognitive impairment to Alzheimer's disease. To that end, there is a small but growing body of literature suggesting that *pattern separation* may be the core memory ability that is negatively impacted by aging. At its most basic level, pattern separation refers to an individual's ability to appreciate the difference between, and separately encode, one item and a similar (but not identical) study item. The existing research, however, is far from conclusive, and it primarily focuses on pattern separation in healthy aging populations, leaving mild cognitive impairment and Alzheimer's disease all but untested. The research discussed here aims to fill this gap in knowledge by examining pattern separation in healthy aging, mild cognitive impairment, and Alzheimer's disease using a procedure first refined and tested in the young adult population.

Pattern Separation and Pattern Completion

Pattern separation is conceptualized as an encoding process in which very similar stimulus inputs are stored as discrete, non-overlapping representations. In this way, at retrieval, one stimulus pattern can be retrieved and held to be distinct. The mechanism of pattern separation is thought to be important for its role in reducing potential interference between similar memory representations that would occur if they were represented by overlapping neurons (Holden, Hoebel, Loftis, & Gilbert, 2012). The counterpart to pattern separation is pattern completion, which is the process by which the presentation of a partial or degraded stimulus can reinstate the representation of a previously encoded

stimulus. Perhaps the most distinguishing feature of pattern separation versus pattern completion is that the mechanisms of the former are primarily present at encoding, while the mechanisms of the latter are in effect at retrieval.

Computational models of pattern separation and completion (see McClelland, McNaughton, & O'Reilly, 1995; Norman and O'Reilly, 2003; Treves & Rolls, 1994) place the two mechanisms in the realm of declarative memory, which refers to our conscious memory for facts and events. The medial temporal lobe is essential for declarative memory, and the hippocampus in particular has been identified for its role in forming new associative memories and for storing memories independently (for a review, see Squire, Stark, & Clark, 2004). The use of fMRI in young adult populations has provided evidence that the hippocampus plays an important role in pattern separation (Kirwan and Stark, 2007). Motley and Kirwan (2012) further found that the pattern of activation in the hippocampus was driven by the demands placed on the individual by the task. During an incidental encoding task where participants had to classify pictured objects as either a toy or not a toy, which required a focus on object identity and semantic classification, activation measured using fMRI was evident in the left hippocampus. Activation in the right hippocampus was evident when the task required participants to identify whether the presented item was new, old, or rotated, which required a focus on object orientation and spatial information (Motley and Kirwan, 2012). Additionally, there is a wide body of work from electrophysiological studies, lesion studies, animal model studies, and human functional neuroimaging studies examining the specific contributions of particular hippocampal subregions to pattern separation and completion (for a review see Yassa and Stark, 2011). The converging evidence suggests that while activity

pertaining to pattern separation is focused in CA3 and the dentate gyrus, activity pertaining to pattern completion is more broadly found in CA1, the subiculum, and the entorhinal and parahippocampal cortices (Bakker, Kirwan, Miller, & Stark, 2008).

Aging and Dementia

While a number of cognitive processes are negatively impacted by aging in humans, the most common complaint is of memory loss, a problem which is further exacerbated in individuals with dementia. Moreover, it has been suggested that the primary memory impairment associated with aging and dementia is in pattern separation abilities (Stark, Yassa, Lacy, & Stark, 2013; Yassa et al., 2010; Yassa, Mattfeld, Stark, & Stark, 2011; Yassa & Stark, 2011).

Two types of dementia are considered in the work described here: mild cognitive impairment (MCI) and Alzheimer's disease (AD). Mild cognitive impairment is most often categorized as a transitional state, or prodromal state, between healthy aging and Alzheimer's disease. As it is defined clinically, patients with MCI have a small impairment typically in one cognitive area (i.e., memory function) that is beyond what would be expected for age and education, but the patients are not otherwise cognitively impaired (Petersen et al., 1999; Petersen, et al., 2001). A large proportion of individuals with MCI eventually will be diagnosed with AD.

Those who typically go on to receive a diagnosis of AD have a specific type of MCI called amnestic mild cognitive impairment (aMCI). As the name implies, a slight impairment in memory functioning is what characterizes this clinical diagnosis. Of individuals presenting with aMCI, most will progress to AD at a rate of 10% to 15% per year, compared to a rate of 1% to 2% per year for healthy control subjects (Petersen et al.,

2001). Cumulatively, the conversion rate to AD from aMCI has been demonstrated to be up to 80% during a 6- year observation period (Petersen et al., 2001). Individuals with aMCI will be the focus of the work undertaken and discussed below in order to highlight the transition between healthy aging and AD.

Alzheimer's disease is characterized as a progressive dementia typically occurring in adults later in life. Pathologically, the hallmarks of AD include the degeneration of specific nerve cells, as well as the presence of neuritic amyloid plaques, and neurofibrillary tangles consisting of the protein tau (McKhann et al., 1984). While an unequivocal diagnosis of AD can only be given following an autopsy showing the characteristic brain pathology of the disease, these neuronal changes are thought to precede clinical symptoms by several years and as such are often present in older adults without dementia (Mattsson et al., 2009). For this reason, there has been a great deal of research investigating biological markers of AD such as cerebrospinal fluid (CSF) levels of amyloid β42 (Aβ42), tau, and phosphorylated tau (p-tau). The CSF levels of Aβ42 are typically found to be reduced in AD patients, which is thought to be a reflection of the aggregation and deposition of amyloid in the brain (Spies, Verbeek, van Groen, & Claassen, 2012). Work by Fagan and colleagues (2007) using positron emission tomographic imaging showed that CSF levels of Aβ42 correspond to the presence or absence of brain amyloid. The CSF levels of tau and p-tau are typically elevated in AD, understood to reflect the presence of neurofibrillary tangles and/or neurodegeneration (Fagan et al., 2009). These three biological markers can also be detected in preclinical populations, including both aMCI and cognitively normal older adults.

All of that being said, a diagnosis of probable AD can be made clinically if certain diagnostic criteria are met, and if there are no other physical or degenerative diseases that could account for the apparent cognitive and memory deficits. Diagnostic criteria for AD include: dementia established by clinical examination and documented by the Mini-Mental States Exam, deficits in two or more areas of cognition, progressive worsening of memory or other cognitive functions, and no disturbances of consciousness (McKhann et al., 1984).

The exact mechanisms leading to memory degradation vary based on population group, and in healthy aging those are a matter of some debate. Undoubtedly, changes in the medial temporal lobe in general, and the hippocampus specifically, are involved. In the case of dementia, the nature of the memory detriment is more obvious. In fMRI studies of aMCI patients, Dickerson et al. (2005) found greater hippocampal activation during memory encoding compared to controls, though there was no difference in hippocampal or entorhinal volumes. In AD, on the other hand, not only was there hippocampal and entorhinal atrophy, but compared with controls the AD group also showed hypoactivation in those same regions (Dickerson et al., 2005). This pattern of results seems to suggest that there is a stage of increased activation in the medial temporal lobe coinciding with aMCI. However, as the disease progresses, there is a decrease in both volume and activity in the region, and a decrease in performance accuracy. It has also been hypothesized that this pattern of increased activation in the medial temporal lobe could serve as a marker for impending cognitive decline, marking the transition from aMCI to Alzheimer's disease (Dickerson et al., 2004).

In healthy aging, there is a growing body of evidence that suggests that the dentate gyrus and CA3 in the hippocampus may be particularly vulnerable to age-related neurological changes (for a review, see Holden & Gilbert, 2012). Some evidence suggests that this neurological change is not based in degeneration, but is instead due to functional changes within the hippocampal system (Wilson, Gallagher, Eichenbaum, & Tanila, 2006; Wilson, Ikonen, Gallagher, Eichenbaum, & Tanila, 2005). These functional changes occurring during healthy aging may lead to an impaired ability to reduce similarity in the neural representation of new input patterns at encoding. In other words, the already stored information would interfere with the hippocampus' ability to store the new information as sufficiently dissimilar. In terms of pattern separation and completion, this could manifest as an over-reliance on pattern completion in aging populations, to the detriment of successful pattern separation.

Prior Research on Pattern Separating in Aging and Dementia

As the field stands now, there are eight experimental papers relevant to the question of whether or not pattern separation is impaired in healthy aging and dementia populations. Kirwan and colleagues (2012) had memory-impaired patients with hippocampal damage study face and object pictures, and then at test the patients saw either the exact same picture or a very similar picture intermixed with completely new items. They found that, while the hippocampal patients showed no difference from the matched controls on a baseline recognition test, they were much less likely to identify lures as being similar compared to the controls. This was taken as an indication that hippocampal damage produces a selective impairment in pattern separation. While not directly addressing aging and pattern separation, this study does provide evidence for the

importance of the hippocampus in pattern separation. The simple study/test design used here also highlights the paradigm present throughout the literature where, despite being consistently defined as an encoding phenomenon, pattern separation is always studied as a retrieval phenomenon with the assumption that the results generalize to encoding.

There are five papers that directly address pattern separation and aging, though their results and conclusions are mixed. Three of the papers used a continuous recognition memory task (Holden, Toner, Pirogovsky, Kirwan, & Gilbert, 2013; Toner, Pirogovsky, Kirwan, & Gilbert, 2009; Yassa et al., 2011). In these studies, participants were shown pictures of everyday items. Some of the items were repeated during the task, while some were very similar to but different from items previously shown. For each item, participants had to respond by indicating whether it was New (meaning they had never been shown this picture before), Old (meaning they had already seen this exact picture during the task), or Similar (meaning they had previously seen a picture very similar to but different from this one during the task). In this way, the very similar items were meant to increase interference and require pattern separation to successfully complete the task. Two of these papers found that young adults significantly outperformed the older adults in correctly identifying the similar lures as being Similar (Toner et al., 2009; Yassa et al., 2011). The older adults had more false alarms, that is, they were more likely to incorrectly identify Similar items as being Old. However, the performance of the older adults on the other trials (Old and New) did not significantly differ from the performance of the young adults. From these results, both Toner and colleagues (2009) and Yassa and colleagues (2011) concluded that pattern separation may be selectively impaired in otherwise healthy older adults. The third study, by Holden

et al. (2013), took the data previously reported by Toner et al. (2009), and further split the older adults into age-impaired and age-unimpaired groups based on their performance on the delayed recall subtest of the Hopkins Verbal Learning Test-Revised (HVLT-R). The age-impaired group scored within the normal range for young adults on the HVLT-R, while the age-impaired group scored more than one standard deviation below. Importantly, neither the age-unimpaired nor the age-impaired group was considered clinically impaired. Split into these groups, Holden and colleagues found that the age-unimpaired group and young adults significantly outperformed the age-impaired group at correctly identifying similar lures as Similar, but there was no difference between the three groups in correctly identifying either Old or New stimuli. This was taken as an indication that impaired object pattern separation is variable in the older adult population.

A fourth paper (Holden, Hoebel, Loftis, & Gilbert, 2012) used a delayed match-to-sample spatial location task. Participants were shown a circle on the screen and then, following a delay, they were presented with two circles and asked to pick which one was in the same place as the one they had seen previously. Of the two test circles, one was in the same location as the one studied earlier, while the second circle was to the left or right of the target circle at one of four spatial separations. The four spatial locations were meant to represent different degrees of pattern separation. Smaller separations create increased overlap among memory representations, creating a greater need for pattern separation. On average, they found that young adults outperformed the older adults at all spatial distances, and that both the young adults and the older adults showed decreasing performance accuracy as spatial separation decreased. While there was a significant main effect for both age group and spatial separation, the interaction between the two was not

significant. In other words, the performance of the older adults did not become more impaired as demands for pattern separation increased with decreasing spatial separation. They further broke the older adult group into age-impaired and age-unimpaired based on their performance on the delayed word recall measure from the HVLT-R. As in Holden et al. (2013), the age-unimpaired participants scored within the normal range for young adults on the HVLT-R, while the age-impaired group scored more than one standard deviation below those norms. Holden and colleagues found that while the age-impaired group's performance was significantly impaired compared to both the young adults and the age-unimpaired group, the age-unimpaired group did not significantly differ from the young adults across all distances of spatial separation. From these results they concluded that pattern separation may become less efficient with aging (in agreement with prior research), but these deficits may be rather variable in older adults. However, the absence of a significant interaction between performance and spatial separation across groups suggests that these data are more compatible with a general memory deficit associated with the age-impaired group, rather than a selective deficit in pattern separation.

The remaining paper examining pattern separation in the healthy aging population also used a spatial pattern separation task (Stark, Yassa, & Stark, 2010). Here they had participants study a pair of pictures, then, at test, one of the pictures may have been moved to a different location on the screen (by a small, medium, or large amount) and participants were asked to identify whether the pictures were in the same position as at study, or if one had been moved to a different location. Again, the different degrees of spatial separation were meant to represent different degrees of pattern separation. Performance was evaluated based on the probability that the participant responded

"different" for both the same and different distance conditions. Stark and colleagues found no difference in performance between groups, only an effect of picture distance across both groups (with the closest distance having the lowest probability of "different" responses). They further broke the older adults into age-impaired and age-unimpaired groups based on their scores on the delayed word learning test from the RAVLT. The age-unimpaired group scored within the normal range for young adults (ages 20 – 29) on the test of delayed word learning, while the age-impaired group scored within the normal range for their own age group (ages 60 – 80) on this measure. Stark et al. (2010) was the first group to use the partitioning strategy in the healthy aging population that the studies discussed previously relied upon. The rationale for doing so, and using the RAVLT delayed word learning task, came from animal models of pattern separation and aging where the rats were divided into impaired and unimpaired groups based on their performance on the Morris water maze. In the Stark et al. (2010) study, similar to what Holden and colleagues (2012) found, the age-impaired group performed much worse than both the age-unimpaired and the young adults on all the three spatial distance conditions (close, medium, and far), though the overall pattern of decreasing performance with decreasing spatial distance was similar across all three groups. However, comparing the young adults, the age-unimpaired adults, and the age-impaired adults there was no difference in performance in identifying pictures that were in the same spatial location. The performance of the age-unimpaired group did not look different from the young adults at any spatial distance. From these results they concluded that spatial pattern separation is selectively impaired in age-impaired older adults, though once again the

lack of significant interaction would seem to point toward a general memory deficit in the age-impaired older adults, rather than a specific deficit in pattern separation.

In addition to the healthy aging papers summarized above, there are two papers that have looked at pattern separation in a population with dementia. The first, from Yassa et al. (2010), had aMCI patients perform a continuous recognition memory task where they were shown pictures of everyday items. Their dependent measure consisted of the false alarm rate of the aMCI patients, as well as the separation bias scores (*P*("Similar" | Similar) – *P*("Similar" | New). Overall, they found that the aMCI patients had more false alarms on Similar items and showed a significant reduction in separation bias scores compared to the controls. Furthermore, as it was an fMRI task, Yassa and colleagues also demonstrated that the CA3 and dentate gyrus were hypoactive in aMCI patients on trials that taxed pattern separation ability. Their results suggested that changes to the CA3 and/or dentate gyrus region that occur in aMCI may lead to deficits in pattern separation.

The second paper used the Behavioral Pattern Separation task across the lifespan (using participants aged 20-89), and an aMCI population group (Stark et al., 2013). An assessment of "traditional recognition memory" was made by taking the number of Old items correctly identified as Old and subtracting out the New items mistakenly identified as being Old (essentially a measure of hit minus false alarms). Using this measure of traditional recognition, they found that performance on that measure remained the same across age groups, but the separation bias scores (*P*("Similar" | Similar) – *P*("Similar" | New) decreased with age. The aMCI group, however, showed impairment on both measures. As in previous papers, the older adult group (age 60+) was broken into age-

impaired and age-unimpaired groups based on RAVLT scores. In this case, both the aged groups performed the same on the measure of recognition memory, but the age-impaired group performed significantly worse on the pattern separation measure and their performance matched that of the aMCI group. Pattern separation, they concluded, not only shows an age-related decline in performance, but also a selective deficit in those older adults classified as age-impaired.

Unresolved Issues

Taken as a whole, the evidence thus far seems to indicate that the hippocampus, particularly the CA3 and dentate gyrus, is integral to pattern separation. Whether these regions are altered are a part of healthy aging, and then further as a part of aMCI and Alzheimer's disease, and whether these changes have consequences for an individual's ability to pattern separate is not clear. Only two papers have examined the behavioral effects in either of the dementias, though they both have found patients to be impaired on this function. In healthy aging, the story is further muddied by results splitting the aging population into "age-impaired" and "age-unimpaired." Essentially, of the four papers directly testing pattern separation in an aging population, two found impairment in pattern separation in their healthy aging populations, while the other two papers only found impairment when they further split the group based on performance on a delayed learning test. Additionally, the two that split the aged group and found preservation of pattern separation in some healthy aging individuals were also the two papers that used a spatial pattern separation task, while the other two papers used a continuous recognition task. Adding further confusion to the results, one set of authors originally found impairment in pattern separation in the older adult population with a continuous

recognition task (Toner et al., 2009), then reanalyzed their data by separating into age-impaired and age-unimpaired groups (Holder et al., 2013). Separated out this way, they only found impairment compared to young adult performance in the age-impaired group, seeming to indicate that their original finding of pattern separation impairment was driven by the age-impaired adults. At this point, it is difficult to say if there is impairment in pattern separation or not in healthy aging, and if this impairment is limited only to certain subsets of the population group.

Furthermore, there are a number of additional problems in the current literature, the most important of which are that the methodologies and framework of analysis used in the existing studies are all based on a threshold (all-or-none) model of pattern separation. Preliminary work using confidence ratings and ROC analysis in young adults has provided evidence for a continuous signal detection model of pattern separation, rather than a discontinuous high threshold process. If it is the case that a continuous model provides a better fit, then analyses looking at separation bias scores (Stark et al., 2013; Stark, Yassa, & Stark, 2010; Yassa et al., 2010; Yassa et al., 2011), difference scores (Holden, et al., 2013; Toner et al., 2009) and other corrections for bias or recognition memory (Kirwan et al., 2012; Yassa et al. 2011) are potentially misleading because they tend to interpret a conservative response bias as a deficit in discrimination ability. Indeed, recent work by Loiotile and Courtney (2015) using signal detection theory analyses showed that the previously used measures in pattern separation can actually lead to the wrong conclusion by failing to accurately characterize the reliability of the memory representation for the Old stimuli. A similar debate has also taken place in source memory (the ability to recall when or where or in what context a piece of

information had been learned) which shares many overlapping properties with pattern separation. Both pattern separation and source memory are concerned with distinguishing and accurately recalling the details from encoding. Success in both requires recollection of the conditions or features of a stimulus in more detail than is necessary for accurate recognition memory alone (e.g., based on familiarity). The accumulating evidence in the source memory literature points toward source memory being a continuous process (e.g. see Slotnick & Dodson, 2005; Slotnick, Klein, Dodson, & Shimamura, 2000; Wixted, 2007) which at the very least means that one should consider the possibility that the same might be true for pattern separation.

Current Investigation

The research described below investigates the theoretical assumptions that underlie the pattern separation paradigm, and further explores the nature of pattern separation in healthy aging and dementia populations. This research focuses on 3 distinct but related issues in the broad domain of pattern separation:

1. *Cognitive modeling of pattern separation* (Chapter 1). The participants in this research were young adults, and the question of interest was whether pattern separation is best conceptualized as a discrete (all-or-none) threshold process or as a continuous signal-detection process. To address that issue, we examined ROC curves and also examined accuracy for different levels of confidence in Old/New and Same/Different decisions in a task involving memory for everyday objects.
2. *The effect of aging, mild cognitive impairment, and Alzheimer's disease on pattern separation* (Chapters 2 and 3). In this research, the goal was to equate

performance between the healthy aging and aMCI groups on Old/New recognition to determine whether or not performance on the Same/Different (pattern separation) task was differentially impaired by dementia. In one study (Chapter 2), we used faces as stimuli as recent work suggested that face memory is unimpaired in patients with hippocampal lesions. This study investigated whether or not the same is true of aMCI patients and, if so, whether pattern separation abilities for Similar face stimuli might be impaired even if Old/New recognition for faces was not impaired. In a second study involving memory for objects (Chapter 3), a different approach to equating Old/New performance was used. In this study, aMCI patients and Alzheimer's patients were given extra study time in an effort to equate Old/New recognition performance. The question of interest was whether pattern separation would be impaired in the dementia populations even though Old/New recognition was equated.

3. *Biomarkers of preclinical impairment, and recognition and pattern separation abilities in older adults* (Chapter 4). For a subset of the older adults tested in Chapters 2 and 3 cerebrospinal fluid levels of Aβ42, tau, and p-tau were made available for analysis. Chapter 4 explores the correlation between behavioral performance on the memory tests of Chapters 2 and 3, and levels of these biomarkers.

CHAPTER 1

An experiment examining the possibility that pattern separation may be continuous (versus an all-or-none, threshold model of pattern separation) was first undertaken, as having a fundamental understanding of the nature of pattern separation will later be important for understanding any deficits (or lack thereof) in aging populations or patients with dementia. To test this possibility, a pattern separation and recognition memory test with participant confidence ratings was developed, which enabled us to evaluate an individual's ability to pattern separate at different levels of memory strength. According to the Complementary-Learning-Systems (CLS) model put forth by Norman and O'Reilly (2003), it should not be possible for pattern separation to occur at a memory strength that falls in a region of the memory strength scale that can often be achieved by lures as well. That is, if pattern separation is a threshold process that is selectively supported by the hippocampus, then, by definition, a threshold memory is of a memory strength that cannot be reached by lures. In a threshold model, only targets can exceed the threshold memory strength, and those that do will be recognized as Old with high confidence. Targets that do not exceed the threshold (as well as lures, none of which exceed the threshold), might also receive an "Old" decision, but such decisions would not be memory-based (i.e., they would merely be guesses) and would therefore be made with lower levels of confidence. Theoretically, we should not see evidence of pattern separation for targets declared to be "Old" at a confidence level that is also frequently assigned to lures. For example, it is not uncommon for lures to be mistakenly declared as "Old" with medium confidence. Therefore, targets declared as Old with medium confidence should not be associated with evidence of pattern separation on the subsequent Same/Different task.

Method

Participants

The participants were 90 undergraduate students (77 females, 13 males) who were recruited from the pool of undergraduate participants in the Psychology department at the University of California, San Diego (UCSD). They were young adults between the ages of 18 and 24, and received course credit for completing the experiment.

Materials and Design

The picture stimuli consisted of 300 color pictures of nameable, common objects (for examples see Figure 1A). These images were grouped in 150 similar picture pairs similar to those used by Kirwan and Stark (2007). For each participant, 100 single images from the pairs were randomly selected to serve as the study images. At test, 50 of those study images were randomly selected to be presented again (Old pictures), while for the other half of the study images the similar picture pair was instead presented (Similar pictures). An additional 50 never-studied pictures (New pictures) were added to the test bank. The experiment was run using an E-prime program (www.pstnet.com; Psychology Software Tools) to display the instructions and stimuli to participants, and to record their responses.

Procedure

Participants signed a consent form and were read instructions before they completed a short practice session to ensure that they understood the instructions. Following completion of the practice session, participants viewed 100 single images presented on a computer screen for 2 seconds at a time. In the test phase, the 50 Old pictures were randomly intermixed with 50 Similar pictures, and 50 New pictures. For

each presented image, participants were first asked to make a New versus Old decision, where New meant they had never seen this picture before, and Old meant they had seen this exact picture *or* something like it presented during the study phase. This New versus Old/Similar decision was made using a 6-point confidence rating scale (Figure 2). On this scale a rating of 1 indicated the participant had 100% confidence that the picture was New, while a rating of 2 or 3 would indicate lower levels of confidence that the picture was New. A rating of 6 indicated 100% confidence that the picture was Old, with 5 and 4 indicating lower levels of confidence.

Next, for any pictures participants identified as being Old (a rating of 4-6 on the scale), they were then asked to make a second rating indicating whether the presented image was identical to the one studied (Same), or if it had changed in any way (Different). Once again, they were asked to do so using a 6-point confidence rating scale (Figure 3), where a rating of 1 indicated 100% confidence that the picture was exactly the same as the one they saw earlier, with 2 and 3 indicating lower levels of confidence. At the other end of the scale, a rating of 6 indicated 100% confidence that the picture was different in some way than the one studied, with 5 and 4 indicating lower levels of confidence.

Results

Response Proportions

The two rating scales provide two different measures of memory performance. The first is a measure of Old/New recognition memory performance, where the Similar items were treated as Old items. The average hit rate for participants on this task was 0.77, with a false alarm rate of 0.12 and a *d'* of 2.10. The second rating scale measured

performance on the Same/Different task where the average hit rate was 0.80, the false alarm rate was 0.48, with an average *d'* of 0.97 (see Table 1). In looking at overall response proportions, we can also use the two rating scales to ask where each stimulus type ultimately ends up being classified by the participants. For example, for New items, are they correctly identified as such on the first scale (in which case no Same/Different test occurs), or are they misidentified as being either Same (Old) or Different (Similar) on the second rating scale? Participants correctly identified New stimuli as being "New" 88% of the time, with incorrect responses evenly split between classifications of "Old" and "Similar". For Old stimuli, participants more often than not responded with "Old" (64%), but misses (i.e., "Similar" or "New" responses) tended slightly more toward "New" responses than "Similar" responses (20% vs. 16%). For Similar stimuli, on the other hand, participants were almost evenly split in responding with "Similar" (39%) and "Old" (35%), with "New" responses accounting for the remainder of the misses (26%) (Figure 4).

Old/New ROC Curves

Overall, participants were good at distinguishing New pictures from pictures that were the same or similar to what they had studied, showing a prototypically curvilinear ROC (Figure 5). This was the first decision and first confidence rating to which participants responded and was used as a measure of overall recognition memory. While the confidence rating scale could most accurately be referred to as New versus Old/Similar, for the sake of brevity it will hereafter be referred to as the Old/New decision. This ROC was constructed in standard fashion based on confidence ratings supplied by the participants. The most conservative (leftmost) point on the ROC

represents hit and false alarm rates computed using only old decisions made with high confidence (6). The next point up and to the right represents hit and false alarm rates computed using only old decisions made with high or medium confidence (5 or 6), and so on. The curvilinear nature of this ROC suggests a continuous underlying memory signal upon which the Old/New decision was based (Egan, 1958; Wixted, 2007).

Confidence and Accuracy

ROC data are cumulative, but another informative way to examine the data is to compute accuracy scores for each level of confidence separately. With regard to the New versus Old/Similar accuracy scores, the point of greatest interest is confidence rating of 5 on the Old vs. New rating scale. It is at this confidence rating level that participants often incorrectly identified lures (New items) as being Old/Similar, which is to say that they were well below 100% accurate when they give a confidence rating of 5 (Figure 6). Accuracy for confidence ratings of 6, by contrast, was close to 100% (so close that the number of lures incorrectly rated as 6 might be considered negligible). Because Old/New accuracy for items rated as 5 was only 80% correct, the number of lures that are incorrectly rated as 5 cannot be considered negligible. At the same time, Same/Different accuracy (the discrimination participants were asked to make for each test item after they had made the New vs Old/Similar decision) shows that for items receiving an Old/New confidence rating of 5 participants were still able to distinguish between Old and Similar items at a level significantly above chance ($t_{(75)} = 2.48$, $p = 0.02$) (Figure 7). That is, they were able to pattern separate at a lower confidence level (below threshold level). To be sure, they were not far above chance on the Same/Different task for items that received an Old/New confidence rating of 6 (57% correct). However, this accuracy score should

be considered in relation to the relatively low Same/Different accuracy score associated with items that received an Old/New confidence rating of 6 (68% correct). Given that the Same/Different task was hard even when Old/New recognition was very strong, it is not surprising that the Same/Different accuracy score was low when Old/New recognition was weaker. The key point is that although Same/Different performance was low for items recognized with an Old/New confidence rating of 5, it was clearly above chance. This finding suggests that a threshold model of pattern separation may need to give way to a signal-detection model of pattern separation.

Same/Different ROC Curves

To further investigate the threshold vs. continuous nature of pattern separation, a Same/Different ROC can be constructed in the same manner as the Old/New ROC was except using the confidence ratings from the Same/Different task. The set of items included in this analysis are the items that were declared to be Old (with a confidence rating of 4, 5 or 6) on the Old/New portion of the task. For example, the high-confidence hit rate for the ROC plot was calculated using Old items that were declared to be "Old" and computing the proportion of those items that received a confidence rating of 1 (100% sure Same) on the Same/Different task. The high-confidence false alarm rate for the ROC plot was calculated using Similar items that were declared to be "Old" and computing the proportion of those items that received a confidence rating of 1 on the Same/Different task.

This method of computing the Same/Different ROC ignores (i.e., collapses across) confidence in the New vs. Old/Similar decision. The Same/Different ROC computed in this manner has the appearance of being almost linear, which is the ROC

shape predicted by a threshold model (see Figure 8). However, the Same/Different ROCs can also be plotted separately for items that received "Old" decisions with ratings of 4, 5 or 6. This is important to do because Slotnick and Dodson (2005) showed that collapsing across Old/New confidence (as was done for the data in Figure 8) can create the false appearance of a linear source memory ROC. The same issue can affect the shape of a Same/Different ROC.

When broken down by Old/New confidence rating, the Same/Different ROC constructed from items that initially received an Old rating of 4 falls close to the chance diagonal, while the Same/Different ROC constructed items that received an Old rating of 5 falls somewhat above the chance diagonal and appears curvilinear. The Same/Different ROC is not linear for an Old/New confidence rating of 6, as a threshold model would clearly predict (Figure 9). For example, the data can be fit with a standard model known as the Dual-Process Signal detection (DPSD) model, which is a hybrid model that assumes a continuous signal detection process for decisions based on familiarity and an all-or-none threshold process for decisions based on recollection. A Same/Different decision theoretically cannot be based on familiarity (because both items should be familiar) but should instead be based on a recollection-like threshold pattern separation process (which, in turn, should yield a linear ROC). When the DPSD model is fit to the O/N 6 Same/Different ROC, its parameters (Familiarity *d'* = 0.69, Similar Recollection = 0.19) are difficult to interpret. Pattern separation is a recollection phenomenon, not a familiarity-based phenomenon, so a familiarity estimate that falls well above 0 is odd from this model's perspective. When we constrained the familiarity *d'* to be zero (as the DPSD model would assume), the fit of the model was significantly worse ($\chi^2_{(1)} = 50.7$, *p*

< 0.0001) indicating that the model needs a familiarity parameter. Nevertheless, the DPSD model interprets ROC curvilinearity as evidence of a continuous familiarity process. Because that interpretation is not easy to make sense of, a more parsimonious interpretation is that the curvilinearity reflects the fact that pattern separation is a continuous signal-detection recollection process. In other words, these findings indicate that pattern separation appears better supported by a continuous signal detection model than a discontinuous high threshold process. This is the same conclusion that has often been reached in studies of recognition memory that involve source recollection (Mickes, Wais, & Wixted, 2009; Slotnick & Dodson, 2005).

Discussion

This first experiment was designed to explore the cognitive modeling underlying pattern separation. Prior experiments behaviorally testing pattern separation have consistently conceptualized it as a discrete threshold process in that they have relied upon dependent measures that depend on the threshold account being correct. By introducing a methodology utilizing a confidence rating scale, we were able to directly test this assumption. An important component of a high threshold model is that successful pattern separation should only occur at the highest level of confidence, when participants are 100% confident that they have seen this item before. Looking at Old/New accuracy and confidence ratings it is clear that as accuracy increases so does confidence (Figure 6). For Old/New ratings of 6 participants responded with nearly 100% Old/New accuracy (which is how they were told to use a confidence rating of 6). Importantly, for an Old/New confidence rating of 5, Old/New accuracy was approximately 80% correct. Thus, this is a confidence rating that is commonly assigned not only to Old/Similar items, but also to

completely new items (Lures). The high threshold model predicts that pattern separation should only occur for items recognized as Old or Similar with the highest confidence rating. To test that prediction, we looked at how accurate participants were in making that Same/Different pattern separation decision for items that had received an Old/New confidence rating of 5. At this level of confidence participants were still significantly above chance in their ability to distinguish Old from Similar items (Figure 7), a result not accounted for in a high threshold model of pattern separation. This result *is* naturally predicted by a continuous signal-detection account.

Another test of a high threshold model is provided by an examination of the shape of the resultant ROC curves. A high threshold model of pattern separation predicts a linear Same/Different ROC curve. We did in fact see some evidence of an almost linear result in the ROC curve produced for the Same/Different decision when the data were collapsed across ratings of Old/New confidence (Figure 8). A better analysis, however, is to examine the ROC curves produced for the Same/Different decision broken down by Old/New confidence rating (Figure 9). Here the Old/New confidence rating of 6 shows not only well above chance performance in determining if the item was same or Different, but it is also clearly curvilinear in nature. The curvilinear nature of the O/N 6 Same/Different ROC in Figure 9 is apparent visually and is established statistically by the fact that the DPSD model had to assume a curvilinear familiarity component (which should not be necessary if pattern separation is a threshold process) in order to adequately fit the data.

Taken together, the results from both the confidence/accuracy analyses and the ROC curve analyses present clear evidence that pattern separation is not a high threshold

process, but one that is better represented by a continuous signal detection model. As such, pattern separation is not a discrete, all-or-none process that only occurs with the highest level of confidence rating, but rather a continuous process with degrees of successful pattern separation. Importantly, if pattern separation is a continuous process, then to effectively measure pattern separation deficits (such as in studies of healthy aging and dementia) it is essential to use signal-detection-based measures to quantify performance. To do otherwise, as in the current state of research, could yield misleading conclusions.

CHAPTER 2

Whereas Chapter 1 tested pattern separation in undergraduates using objects as stimuli, Chapter 2 tested pattern separation in undergraduates, older adults, and individuals with aMCI using faces as stimuli. The neuropathology of aMCI most consistently shows damage to the hippocampus and the entorhinal cortex (Petersen et al., 2001). Interestingly, patients with damage to the hippocampus show intact recognition memory for faces (Bird & Burgess, 2008; Smith et al., 2014). For aMCI patients, this could potentially present as a selective deficit in pattern separation related to face memory, but intact Old/New face recognition. Utilizing the same experimental design that was used in Chapter 1, this chapter examines both Old/New recognition memory and pattern separation for face stimuli in young adults, older adults, and individuals with aMCI.

Method

Participants

The young adult (YA) group consisted of 33 undergraduate participants (28 females, 5 males) who were recruited from the pool of undergraduate participants in the Psychology department at UCSD and received course credit for completing the experiment. The young adults were between the ages of 18 and 29, with a mean age of 21.

The older adult (OA) and aMCI participants were recruited from the pool of longitudinal study participants at the UCSD Shiley-Marcos Alzheimer's Disease Research Center. There were 50 older adult participants (32 females, 18 males) between the ages of 65 and 91 (mean age = 76±6), with a mean level education of 16.5 years (±2.5 years). There were 12 aMCI participants (5 females, 7 males) between the ages of 64 and

88 (mean age = 77±9), with a mean level of level education of 15 years (±4 years). The OA and aMCI groups were not significantly different from each other in either age or years of education ($t_{(13.87)} = 0.51$, $p = 0.62$ and $t_{(12.88)} = 1.09$, $p = 0.30$, respectively).

As part of the longitudinal study, each participant underwent a battery of cognitive and neuropsychological testing, including the California Verbal Learning Test (CVLT), the Mini-Mental Status Exam (MMSE), and the Dementia Rating Scale (DRS). For the older adults, the MMSE scores ranged from 27-30 ($M = 29.3$, $SE = 0.12$), and the DRS scores ranged from 133-144 ($M = 140.1$, $SE = 0.41$). For the aMCI group, the MMSE scores ranged from 21-30 ($M = 26.5$, $SE = 0.88$), and the DRS scores ranged from 123-142 ($M = 132$, $SE = 1.83$) (see Table 2 for demographic information).

Diagnosis of MCI was classified into 4 different types: memory only, memory and other domain, non-amnestic single domain, and non-amnestic multiple domains. For the purposes of this study, MCI participants were recruited from both the memory only ($n = 6$), and memory and other domain ($n = 6$) diagnostic groups to form the aMCI participant group.

Materials and Design

The picture stimuli consisted of 90 color portrait-style pictures of 45 different individuals obtained from the freely available database of the Psychological Image Collection at Stirling (http://pics.psych.stir.ac.uk). Each individual had two different portrait pictures, where the difference between the two pictures was anything from different facial expression, gaze direction, hairstyle, clothes, head rotation, or a combination of any of these (for examples see Figure 1B). For the study portion, 30 of the individual faces were randomly selected for each participant. During the test portion,

15 of those study images were randomly selected to be presented again (Old pictures), while for the other half of the study images the alternate picture portrait was instead presented (Similar pictures). The remaining 15 never-studied faces served as New items during the test portion of the experiment. For all participants, the experiment was run using an E-prime program (www.pstnet.com; Psychology Software Tools) to display the instructions and stimuli to participants, and to record their responses. For the young adult population, the experiment was run on a desktop computer in the Wixted Lab on the UCSD campus. The young adults entered all responses using the keyboard on their own. The older adult and aMCI groups were tested at the Shiley-Marcos Alzheimer's Disease Research Center using a laptop computer, most of whom required assistance in entering their responses with the keyboard and number pad.

Procedure

Though presented here as two different experiments, the young adults, older adults, and individuals with aMCI all completed the experiments in both Chapters 2 and 3 during the same session. The order in which the two conditions, faces versus objects, were presented was randomly assigned for each participant. After completing one condition, participants were offered a break before beginning the next condition. Otherwise, the procedure in this experiment was very similar to that used in Chapter 1. For the young adults, they first read and signed a consent form and were then read instructions before they completed a short practice session. For the older adults and aMCI participants they had already signed a consent form as part of the longitudinal study, so they were just read instructions and given the short practice portion. For all participants, after the practice portion they were then shown 30 pictures of faces presented on a

computer screen for 2 seconds at a time. The test phase then consisted of the 15 Old faces randomly intermixed with the 15 Similar faces and 15 New faces. Based on participant feedback during pilot testing, the rating scales were adjusted slightly from those used in Chapter 1 to make them as clear as possible for the aging and dementia groups. As each test item was presented on the screen, the rating scale would also appear and both would remain on the screen until the participant made a response. The first task remained a New versus Old recognition decision where they had to decide using a 6-point confidence rating scale if the face they were being shown was either completely new to them or a face they had seen in some way on the study list (see Figure 10). The second task was again a Same versus Different decision using a 6-point confidence rating scale they had to respond with whether the picture of the face looked similar but not the same or if it looked exactly the same (see Figure 11). The instructions on how to use the scales remained exactly the same as in Chapter 1.

Results

Response Proportions

As an initial measure of response performance, average hit rates, false alarm rates, and *d'* values were calculated for the three groups on both the Old/New portion and the Same/Different portion (see Table 3). While the hit rates for both portions of the experiment were similar for the young adults and older adults, both the Old/New and Same/Different false alarm rates were much higher for the older adults (0.31 and 0.65, respectively), which were very similar to the false alarm rates of the individuals with aMCI. As a result, the *d'* values for both the Old/New and Same/Different tasks were stratified based on population group with the young adults having the highest mean *d'*

(indicating the greatest amount of discriminability between the stimuli categories) and individuals with aMCI having the lowest. On the Old/New task the young adults had an average *d'* of 1.85, while the older adults had a *d'* of 1.45 and the individuals with aMCI had a *d'* of 1.06. Independent samples *t*-tests showed that the young adults had a significantly higher Old/New *d'* than the older adults ($t_{(81)} = 2.54$, $p = 0.01$), while the older adults *d'* was significantly higher than that of the aMCI group ($t_{(53.63)} = 2.84$, $p = 0.006$). In other words, this experiment did not equal Old/New face recognition across groups as had been hoped.

Discriminability was overall lower for the Same/Different task, but the pattern was the same. The young adults had an average *d'* of 0.94, the older adults had a *d'* of 0.48, and the individuals with aMCI had a *d'* of 0.20. Once again, independent samples *t*-tests showed the same pattern of results, with young adults having a significantly higher Same/Different *d'* than older adults ($t_{(81)} = 3.00$, $p = 0.004$), and the older adults significantly outperforming the aMCI group ($t_{(59.34)} = 2.72$, $p = 0.008$). As the three groups differed significantly on the Old/New *d'* measure we are unable to draw any conclusions from these values alone about selective impairment in pattern separation for either the older adult group or the aMCI group from this analysis alone.

As in Chapter 1, we once again examined how the different population groups ultimately classified the different test stimulus types (Old, New, or Similar) using the two rating scales. Performance was fairly equivalent across stimulus types when it came to classifying Old and New items, the majority of which were identified correctly (see Figure 12). Young adults, older adults, and individuals with aMCI all struggled to correctly identify the Similar faces (35%, 23%, and 23% correct, respectively). For young

adults, Similar faces were equally likely to be identified as being “Old” as they were “Similar”. The older adults and aMCI patients more often identified Similar faces as being “Old” (46% and 41%, respectively) but they both also identified the Similar faces as being “New” more often than correctly identifying them as being “Similar” (31% and 36%).

Old/New and Same/Different ROC Curves

Next, the data were examined in more detail by plotting the relevant ROCs. These ROC plots confirmed that all three groups performed well at distinguishing the completely new faces from those they had seen in some way before. ROC curves were plotted for the groups based on their hit rates and false alarm rates generated from the first confidence rating scale. What this means is that Old and Similar faces were grouped together and treated as the “target” items, while the New faces served as the “lure” items. A hit constituted correctly identifying Old and Similar faces on the “you saw this or something like it” end of the scale (a rating of 4-6), while a false alarm occurred for any New faces given the same confidence rating. As can be seen in Figure 13, young adults, older adults, and aMCI patients all performed above chance at distinguishing New faces from ones they had seen in some way. Looking at the ROC curves for the second rating scale (the pattern separation decision of “is this face exactly the same or is it different in some way?”) the three groups again fall on three different curves reflecting the same pattern of performance seen in the New versus Old/Similar portion of the task (see Figure 14). The Same versus Different ROC curves also highlight the difficulty of this portion of the task, where the curve for the aMCI patients is actually indistinguishable from chance performance, and the curve for the older adults is not much better. Aligning with what

was seen with the *d'* values for the three groups on the Old/New and Same/Different tasks, the ROC curves plotted in both Figures 13 and 14 all differ significantly from each other at the $p < 0.01$ level.

Confidence and Accuracy

Evidence for a selective pattern separation deficit. Looking at Old/New accuracy across confidence ratings, all three population groups showed the typical curve of meta memory (Figure 15). Higher confidence at each end of the scale was connected to higher levels of accuracy, that is, the confidence rating of 1 had higher accuracies than that of 2 and 3, while the confidence rating of 6 had higher accuracies than 5 and 4. Looking specifically at the confidence rating of 6 on the New versus Old scale, the accuracy of the aMCI group was not significantly different from both that of the older adults ($t_{(57)} = 0.14$, $p = 0.89$) and the young adults ($t_{(40)} = 1.57$, $p = 0.12$). Thus, while memory was impaired in the aMCI group, which resulted in fewer recognition decisions with a confidence rating of 6, when such decisions were made they were as accurate as the greater number of high-confidence recognition decisions made by the healthy aging and, perhaps, undergraduate groups. Thus, this second way of equating Old/New recognition performance across groups was more successful than the attempt to equate overall recognition memory accuracy.

In light of the fact that the Old/New accuracy of the aMCI patients did not significantly differ from the other two groups for the confidence rating of 6, their Same/Different accuracy associated with items that received a rating of 6 on the Old/New scale can be meaningfully compared. Remarkably, when the aMCI patients were 100% confident and more than 90% accurate that they had seen this face in some way before

(Old/New confidence = 6), they were no better than chance in identifying whether that same face was exactly the same as the one on the study list, or if it was different in some way. Indeed, the Same/Different accuracy for the aMCI patients was significantly worse than both the young adults ($t_{(40)} = 3.68$, $p < .001$) and the older adults ($t_{(57)} = 2.08$, $p < .05$). The older adults, however, were also significantly worse in their Same/Different accuracy than the young adults for the highest level of Old/New confidence ($t_{(79)} = 4.18$, $p < .001$) (Figure 16). This finding provides evidence that even older adults exhibit a selective pattern separation deficit relative to young adults under conditions where Old/New recognition is equated. In this case, their patterns separation deficit was not as severe as the deficit exhibited by aMCI participants.

High-threshold vs. continuous models of pattern separation. While the aMCI participants never performed above chance on the Same/Different task for Old/New confidence ratings of 4-6, the young adults were only above chance performance at the highest confidence rating. This result differs from what was observed in Chapter 1 and is consistent with predictions made by the high-threshold account. However, it seems likely that the key result (no better than chance performance on the Same/Different task for items that received an Old/New confidence rating of 5) may simply be a Type II error. For example, in the older adults there is once again clear evidence of continuous pattern separation as their Same/Different accuracy shows that at a confidence rating of 5 on the Old/New rating scale they were still able to distinguish between Old and Similar items at a level significantly above chance ($t_{(42)} = 3.24$, $p = 0.002$). This finding contradicts the high-threshold account and is again consistent with a continuous signal-detection account of pattern separation.

Age-impaired and Age-unimpaired Analyses

To compare our findings with findings from previous research, the older adult population was split into age-impaired and age-unimpaired groups. Previous work has made this distinction based on performance on either the delayed learning test on the RAVLT (Stark et al., 2010; Stark et al., 2013), or the delayed word recall test in the HVTL-R (Holden et al., 2012; Holden et al., 2013). As most participants had recently undergone the CVLT as part of their participation in the longitudinal study, their scores on the delayed recall test were used as the basis on which to classify them as either age-impaired or age-unimpaired.

The 39 older adults with relevant CVLT data were ranked by their CVLT scores and split into thirds. The top 1/3 of older adults recalled between 12 and 16 words out of a total 16 (M = 13.54, SE = 0.42) and were considered the age-unimpaired (AU) group. The bottom 1/3 of older adults recalled between 5 and 10 words (M = 7.54, SE = 0.35) and were considered the age-impaired (AI) group (similar to what was done in Stark et al., 2013). Comparing the age-unimpaired and age-impaired groups, the two groups did not differ significantly on either Old/New *d'* ($t_{(24)}$ = 1.47, p = 0.15) or Same/Different *d'* ($t_{(24)}$ = 0.13, p = 0.9). Thus, unlike in past work, our effort to identify distinct subgroups (age-unimpaired vs. age-impaired) was not successful based on *d'* comparisons.

To provide a more detailed look at the data, the ROC curves for the Old/New (Figure 17) and Same/Different (Figure 18) decisions can also be compared across the young adult, age-unimpaired, age-impaired, and aMCI groups. In dividing the older adult population in this way, we have an AU population that was not significantly different from the young adults on the Old/New task ($\chi^2_{(6)}$ = 0.13, p = 0.72), but performed

significantly worse on the Same/Different task ($\chi^2_{(6)} = 7.23$, $p = 0.007$). The AI group, on the other hand, did not perform significantly different from the aMCI group on either the Old/New ($\chi^2_{(6)} = 2.74$, $p = 0.10$) or the Same/Different task ($\chi^2_{(6)} = 1.60$, $p = 0.21$). Splitting the older adult group in this way provides additional evidence that, for face stimuli, when recognition memory for a group of older adults is equated with that of young adults, the older adults show a selective impairment in pattern separation. Conversely, when Old/New recognition memory in an older adult population is equated with that of individuals with aMCI, the aMCI group does not appear to show any further impairment in pattern separation. This result stands in contrast to what was found in the analysis presented earlier where Old/New recognition was equated between these two groups by examining pattern separation for items that received an Old/New confidence rating of 6. In that analysis, the aMCI group showed a significantly greater pattern separation deficit than the healthy aging group.

Discussion

One of the aims of Chapter 2 was to use a task with both a general recognition memory component and a pattern separation component in order to see if there were selective deficits in pattern separation in an aMCI population when recognition memory did not otherwise appear to be impacted. Based on past research showing that memory for faces remains intact in spite of damage to the hippocampus (Bird & Burgess, 2008; Smith et al., 2014) and that the pathology of aMCI appears to originate with damage to the hippocampus (Petersen et al., 2001) it was hypothesized that aMCI patients performing the same task as older normal controls might have equivalent performance on a general recognition task but perhaps show impairment in pattern separation. As it turns

out, the results from Chapter 2 suggest that the two groups were not evenly matched on Old/New recognition memory performance, making determinations of selective deficits in pattern separation difficult to decisively conclude. On the New versus Old/Similar ROC, the 3 groups all fall on 3 significantly different ROC curves with the young adults performing better than the older adults who in turn performed better than the aMCI participants (Figure 13). For the Same versus Different ROC, the pattern of results is the same. That is, all three groups fall on significantly different ROC curves, with young adults showing the greatest level of discriminability and individuals with aMCI showing the least amount of discriminability (Figure 14). Lacking an equivalent level of discriminability on the Old/New recognition memory task, it is difficult to determine from these results alone whether or not a selective pattern separation deficit exists in individuals with aMCI on the Same/Different task. However, other ways of equating Old/New performance across groups were more successful.

Although overall Old/New recognition for faces was not equated for the aMCI and healthy aging groups (as we had hoped), Old/New recognition accuracy *was* equated across groups for decisions made with high confidence. In fact, for New versus Old/Similar confidence ratings of 4 through 6 (identifying that they had seen this face in some manner on the study list), young adults, older adults and individuals with aMCI did not differ significantly in response accuracy (Figure 15). Interestingly, however, performance on the Same versus Different task for items that had received the highest rating of Old/New confidence (100% sure that they had seen this face in some manner before) the three population groups exhibited large differences in Same/Different accuracy, with young adults outperforming older adults, who in turn outperformed the

individuals with aMCI (Figure 16). Indeed, the individuals with aMCI never performed above chance in making the Same versus Different decision for any level of Old/New confidence rating, while the older adults were significantly above chance for confidence ratings of both 5 and 6. These results are consistent with the idea that there is a selective impairment in pattern separation both in healthy aging and in aMCI when recognition memory performance otherwise appears intact. However, the interpretation of a selective pattern separation deficit associated with healthy aging should be regarded with caution. Although high-confidence Old/New accuracy did not differ significantly between young adults and older adults, there is a trend towards higher Old/New accuracy for the younger adults. Thus, it could be argued that Old/New accuracy was not actually equated for these two groups (potentially accounting for the fact that Same/Different performance was not equated either).

With regard to high-threshold vs. continuous models of pattern separation, the results were somewhat equivocal but, on balance, still favored the continuous view. While in this experiment the young adults did not perform above chance with regard to pattern separation for lower Old/New confidence ratings (as expected by a threshold model), there were not nearly as many participants with only 33 in this experiment, versus 90 in Chapter 1 (Figure 16). The fact that older adults (n = 50) were above chance in Same/Different accuracy at an Old/New confidence rating commonly reached by lures (namely, an Old/New confidence rating of 5) still points to the likelihood that degrees of pattern separation exist, even in an older adult population that has overall worse memory performance on the pattern separation task. Reinforcing this conclusion is the fact that the

Same/Different ROC was clearly curvilinear for both young adults and older adults, contrary to what a threshold model of pattern separation predicts (Figure 14).

Following other research, the healthy older adult population was separated into age-unimpaired and age-impaired groups. Now with four groups of comparison, the ROC curves show equivalent discrimination on the New versus Old/Similar task for the young adults and the age-unimpaired adults, but worse discrimination for the Same versus Different task for the age-unimpaired adults (Figures 17 and 18). This result would seem to indicate a selective deficit in pattern separation for healthy aging older adults (who also perform well on a task of delayed recall). The age-impaired group, on the other hand, appears the same as the aMCI participants on both Old/New recognition and Same/Different pattern separation, indicating perhaps when the aMCI group is matched with a healthy aging group on Old/New recognition there is not a selective pattern separation deficit (at least not specific to aMCI, as aging alone does seem to present a pattern separation-based deficit based on this analysis).

As a further check on whether the Old/New recognition task and the Same/Different pattern separation task were measuring the same component of memory, the *d'* values for each individual participant on both tasks were plotted. Had it been the case that the recognition task and pattern separation task were merely different measures of the same memory process, the *d'* values from the two tasks should show a significant positive correlation. As measures of the same memory process, displaying a high level of discrimination performance on one of the tasks should result in the same high level of discrimination on the second task. When *d'* performance on the two tasks was correlated within young adults, older adults, and individuals with aMCI, none of the groups showed

a significant correlation between *d'* as a measure of discriminability on the Old/New task and *d'* on the Same/Different task ($r_{(31)} = 0.160$, $p = 0.375$; $r_{(48)} = 0.213$, $p = 0.138$; $r_{(10)} = 0.056$, $p = 0.862$, respectively) (see Figure 19). This result is surprising and could potentially indicate that Old/New recognition for faces is largely based on a non-pattern-separation process (such as familiarity), though it could also be the result of a Type II error.

CHAPTER 3

Thus far, the results suggest that older adults and individuals with aMCI reliably exhibit Same/Different discrimination deficits relative to young adults. However, for some tests, Old/New recognition performance was not equated across groups, making it hard to definitively attribute those Same/Different discrimination deficits to a selective impairment in pattern separation. However, even for tests in which Old/New performance was equated, both the older adults and individuals with aMCI still exhibited Same/Different discrimination deficits relative to young adults. Thus, the results are suggestive of a selective pattern separation deficit in both groups (one that may be more severe for individuals with aMCI).

The reason for using a stimulus set made up of pictures of faces in Chapter 2 was that prior research with amnesic patients suggested that it might serve to equate Old/New recognition performance across groups (Bird & Burgess, 2008; Smith et al., 2014). However, Old/New recognition differed in the way it might be expected to differ for any stimulus set, with young adults outperforming older adults who, in turn, outperformed aMCI patients. Therefore, in Chapter 3, study time was varied across groups in an effort to equate Old/New recognition performance between groups. The stimulus set for this study consisted of pictures of objects.

The methodology used in Chapter 3 is much like that used in the previous chapters. Prior work on pattern separation in healthy aging relied on methodologies that assumed a threshold model, yielding mixed results. However, based on the results reported in Chapter 1, the first step in better understanding pattern separation in healthy aging and dementia is to use a study/test paradigm that utilizes confidence ratings, which allows for the possibility that pattern separation is a continuous process and also allows

ROC analyses to be performed. For the aMCI and AD populations, two groups that almost definitely will show memory impairment, a primary aim in this chapter will be to manipulate study time in such a way as to raise the Old/New recognition memory performance of the dementia groups to the level of the older adult population before comparing performance on a pattern separation task. Although the older adults were not given more study time compared to the young adults, the Old/New recognition performance of those two groups turned out to be unexpectedly similar (a desirable outcome for detecting a pattern separation deficit that might exist). The specific aims of Chapter 3 are as follows: (1) equate Old/New recognition memory performance across all groups, (2) use confidence rating scales and ROC analyses to measure performance across all groups, and (3) compare pattern separation performance across the lifespan of aging and dementia including young adults, older adults, individuals with aMCI, and individuals with AD.

Method

Participants

The participants in Chapter 3 were the same as those who participated in the experiment of Chapter 2 with a few exceptions: some early participants were used for pilot data for the experiment in Chapter 3 which was then changed, and a few individuals were only able to successfully complete one of the two tasks due to computer issues. This experiment also called for the additional recruitment of individuals with probably Alzheimer's disease who only completed the experiment in Chapter 3. For those completing both experiments (the young adults, older adults, and individuals with aMCI) the order of experiments was randomized, with half performing the faces task first, and

half performing the objects task first. Following the completion of one task they were offered a break before completing the second task.

The young adult group consisted of 30 undergraduate participants (25 females, 5 males) who had been recruited from the pool of undergraduate participants in the Psychology department at UCSD, and received course credit for completing the experiment. The young adults were between the ages of 18 and 29, with a mean age of 21 (*SD* = 2.12).

Once again, the older adults, individuals with aMCI, and individuals with probable AD were recruited from the pool of longitudinal study participants at the UCSD Shiley-Marcos Alzheimer's Disease Research Center and were largely the same individuals from Chapter 2 (excluding the AD participants). There were 45 older adult participants (29 females, 16 males) between the ages of 65 and 88 (mean age = 75±6), with a mean level education of 16.5 years (±2.5 years). There were 12 aMCI participants (5 females, 7 males) between the ages of 64 and 88 (mean age = 77±9), with a mean level of level education of 15 years (±4 years). The aMCI group was identical to that of Chapter 2, and, as such, was made up of six individuals with only memory impairment, and six individuals with impairments in memory and another domain. There were 17 participants with probable AD (4 females, 13 males) between the ages of 64 and 89 (mean age = 77±7), with a mean level of education of 15 years (±2.5 years). In a one-way between subjects ANOVA, none of the three groups differed significantly in terms of either age or years of education ($F_{(2, 70)} = 0.52$, $p = 0.60$ and $F_{(2, 69)} = 1.99$, $p = 0.15$, respectively).

As in Chapter 2, all participants from the Shiley-Marcos Alzheimer's Disease Research Center underwent a yearly cognitive battery of cognitive and neuropsychological testing including the California Verbal Learning Test (CVLT), the Mini-Mental Status Exam (MMSE), and the Dementia Rating Scale (DRS). For the older adults, the MMSE scores ranged from 27-30 (M = 29.3, SE = 0.12), and the DRS scores ranged from 133-144 (M = 140.1, SE = 0.41). For the aMCI group, the MMSE scores ranged from 21-30 (M = 26.5, SE = 0.88), and the DRS scores ranged from 123-142 (M = 132, SE = 1.83). For the AD group, the MMSE scores ranged from 17-28 (M = 22.4, SE = 0.80), and the DRS scores ranged from 84-136 (M = 117.6, SE = 3.15) (see Table 4 for demographic information).

Materials and Design

The picture stimuli were pulled from the object image pool used in Chapter 1. In order to avoid floor effects in the aMCI and AD groups the number of items on the study list was limited to 30 pictures. For the test, participants were shown 15 Old, 15 Similar, and 30 New items (for examples see Figure 1A). For all participants, the experiment was run using an E-prime program (www.pstnet.com; Psychology Software Tools) to display the instructions and stimuli to participants, and to record their responses. For the young adult population, the experiment was run on a desktop computer in the Wixted Lab on the UCSD campus. The young adults entered all responses using the keyboard on their own. The older adult and aMCI groups were tested at the Shiley-Marcos Alzheimer's Disease Research Center using a laptop computer, most of whom required assistance in entering their responses with the keyboard and number pad.

Procedure

The overall structure of this experiments was very similar to what occurred in Chapters 1 and 2. For the young adults tested in the Wixted Lab, they first read and signed a consent form, before being read instructions and given a short practice session on the computer. Once again, for the participant pool from the Shiley-Marcos Alzheimer's Disease Research Center, they had already signed a consent form as part of the longitudinal study, so after verbally agreeing to participate in this experiment they were read the instructions and given the short practice session.

The study phase was varied across participants groups as a means of boosting memory performance to the level of young adults and older adults on the Old/New recognition memory task for the aMCI and AD participants groups. For the young adults and older adults, after the practice portion, they were shown 30 randomized pictures of every-day objects presented on a computer screen for 1 second at a time. The aMCI group was shown 30 randomized pictures presented on a computer screen for 2 seconds at a time. Additionally, the study list repeated a second time, in another randomized order, for the aMCI group. For the AD participants, the 30 randomized pictures were presented on the computer screen for 2 seconds at a time and the study list was presented three times.

For all participants the test phase proceeded in exactly the same manner. The test stimuli consisted of 15 Old object pictures randomly intermixed with 15 Similar object pictures and 15 New object pictures. The same testing procedure as Chapter 2 was used where the test item was displayed on the screen at the same time as the rating scale and remained there until the participant made a response. The first task, again, was a New

versus Old recognition task with a 6-point confidence rating scale (see Figure 20). The second task was again a Same versus Different decision using a 6-point confidence rating scale identical to the one used in Chapter 2 (see Figure 11). The instructions on how to use the scales remained exactly the same as in Chapters 1 and 2.

Results

Response Proportions

Beginning with performance on the Old/New task, the average hit rate and false alarm rates were nearly equivalent across the young adult, older adult and aMCI groups, while the AD group had both a lower average hit rate and higher average false alarm rate (see Table 5). For the Same/Different task the hit rates were much the same as they were for the Old/New task for the young adults, older adults, and individuals with aMCI. The false alarm rates, however, went up across all three groups, though to a greater degree for both the older adults and individuals with aMCI compared to the young adults. While the AD group performed below all of the other groups in terms of Old/New discriminability, the *d'* values of the young adults did not differ significantly from either the older adults ($t_{(73)} = 1.45$, $p = 0.15$), or the individuals with aMCI ($t_{(40)} = 1.01$, $p = 0.32$). For the Same versus Different measure of discriminability, however, the average *d'* of the young adult group was significantly better than that of both the older adults ($t_{(73)} = 2.80$, $p = 0.006$) and the aMCI group ($t_{(40)} = 2.59$, $p = 0.013$). The older adults and individuals with aMCI did not differ significantly on either the Old/New or Same/Different measures of *d'* ($t_{(55)} = 0.020$, $p = 0.98$; $t_{(55)} = 0.77$, $p = 0.44$, respectively).

The fact that Old/New performance was numerically higher for the young adult group, even if not significantly so, makes it hard to fully rule out the possibility that

Old/New performance was not equated across groups. That caveat notwithstanding, given the similar Old/New performance across groups, as measured by *d'*, the observed differences in the Same/Different *d'* are again suggestive of a selective deficit in pattern separation for both older adult and aMCI participants.

Examining how the different stimulus types were ultimately classified according to population group, we see nearly equivalent performance for young adults, older adults, and individuals with aMCI in correctly identifying Old items and New items, while the AD patients overall made more errors (see Figure 21). All groups were far less accurate in identifying the Similar items. The young adults were the only group to label Similar items as "Similar" more often than incorrectly labeling them as "New" or "Old" by correctly labeling Similar items 46% of the time, with most errors falling under the "Old" label. The older adult and aMCI groups showed a very comparable pattern of performance, correctly identifying Similar items around 33% of the time with most of the errors identified as "Old" (and most of the Similar items in general identified as "Old"). The AD patients rarely correctly identified Similar items as being "Similar" (12%), rather they largely identified those items as being "Old" (52%).

Confidence and Accuracy

Plotting the Old/New accuracy of participants by New versus Old/Similar confidence rating again produces a meta memory curve akin to what was found in Chapter 2 (see Figure 22). While the AD group consistently performed below the other groups, all groups showed the highest level of accuracy for the highest confidence ratings (1 and 6), and chance performance for the confidence ratings used to reflect guessing (3 and 4). The only exception to this pattern was the accuracy of the aMCI group at the

Old/New confidence rating of 3. Here, the aMCI group was on average 92% accurate in identifying New items (*SE* = .08). This result was largely driven by the fact that only four of the twelve participants used the confidence rating of 3 at all, and three of those four only used it one time with 100% accuracy. The lone participant to use the confidence rating more than once used it six times with 66% accuracy (a result more fitting with the traditional curve of meta memory). Thus, this high score appears to be an anomaly.

The young adults, older adults, and individuals with aMCI all showed equivalent performance across confidence ratings, in particular those ratings indicating that they had seen this picture in some manner before (4-6). Looking at the Same versus Different accuracy for Old/New confidence ratings of 4-6 there was again a scaling of accuracy by confidence rating and generally equivalent performance across population groups (see Figure 23). Once again, the aMCI group appeared to break the pattern of decreasing Same/Different accuracy at the Old/New confidence rating of 4 with an average accuracy of 71% (*SE* = .16). This result was again driven by only three participants using this confidence rating, one of whom was 100% accurate with three responses. Additionally, the Same/Different accuracy for aMCI participants at the confidence rating of 4 did not significantly differ from that of either the young adults ($t_{(4.12)} = 1.15$, $p = 0.31$) or the older adults ($t_{(17)} = 0.63$, $p = 0.54$), and was not significantly above chance performance ($t_{(2)} = 1.36$, $p = 0.31$).

Given the equivalent performance of the young adults, older adults, and individuals with aMCI at the Old/New confidence rating of 6, we can once again compare the Same/Different accuracy at that level of confidence. The Same/Different accuracy of the young adults was significantly better than both the older adults ($t_{(71)} = 2.2$,

$p = 0.03$) and the individuals with aMCI ($t_{(39)} = 2.37$, $p = 0.02$). The older adults and individuals with aMCI did not differ significantly from each other in Same/Different accuracy ($t_{(54)} = 0.87$, $p = 0.39$). The accuracy of the aMCI group also did not differ significantly from that of the AD group ($t_{(24)} = 0.51$, $p = 0.62$). Thus, yet again, with Old/New performance equated, the older adults appeared to show a selective impairment in pattern separation when compared with the young adults. The aMCI group also shows impairment in pattern separation compared to the young adults. Although this impairment appears to be greater than that of the older adults, the difference was not significant. These results match what was found comparing the *d'* values between the groups, where older adults and individuals with aMCI show selective impairment in pattern separation compared to the young adults.

With regard to evidence of continuous pattern separation, none of the groups were significantly above chance for Same versus Different accuracy at the Old/New confidence rating of 5, though all groups had fewer participants than those in Chapters 1 and 2. Above chance performance for Same/Different accuracy only occurred at the Old/New confidence rating of 6 for the young adults ($t_{(28)} = 10.04$, $p < 0.001$), older adults ($t_{(43)} = 9.35$, $p < 0.001$), and individuals with aMCI ($t_{(11)} = 4.61$, $p = 0.001$). Although these data correspond to predictions made by the threshold account, power to detect above-chance Same/Different accuracy for Old/New confidence ratings of 5 was low.

Old/New and Same/Different ROC Curves

Using the same hit rate and false alarm rate calculations as in Chapter 2, the New versus Old/Similar ROC curves for the four population groups were plotted. All groups

performed well on the Old/New task with curves falling well above chance performance (see Figure 24). In contrast to the *d'* results, the ROC curve of the young adults was significantly different from the curve of the older adults ($\chi^2_{(6)} = 7.55$, $p = 0.006$). However, the *d'* results did show a non-significant trend favoring the young adults over the older adults, so perhaps that difference is real after all. In that case, the fact that Same/Different performance of young adults exceeded that of older adults might not be indicative of a selective pattern separation deficit in older adults. According to the ROC analysis, the Old/New performance of the older adults did not differ significantly from that of the individuals with aMCI ($\chi^2_{(6)} = 1.83$, $p = 0.18$), matching what was found comparing *d'* values (recall that the aMCI group received extra study time, so this result is not as surprising as it might seem at first glance). Performance on the Same versus Different task was much closer to chance for all four groups, with the AD group performing below all other groups (see Figure 25). Once again, the performance of the young adults was significantly better than that of both the older adults ($\chi^2_{(6)} = 11.95$, $p < 0.001$) and the individuals with aMCI ($\chi^2_{(6)} = 11.23$, $p < 0.001$). The performance of the aMCI group, however, was not significantly different from that of either the older adults ($\chi^2_{(6)} = 0.75$, $p = 0.39$) or the AD group ($\chi^2_{(6)} = 2.26$, $p = 0.13$).

These results clearly suggest a selective pattern separation deficit for individuals with aMCI because, whether measured by *d'* or by ROC analysis, their Old/New performance was similar to that of younger adults. Even so, the aMCI group exhibited noticeably worse performance on the Same/Different task compared to young adults. The results for older adults were more equivocal. Their Same/Different performance was clearly worse than that of younger adults, which is consistent with a pattern separation

deficit, but their Old/New performance may have been worse as well (at least according to ROC analysis). Thus, standing alone, these results do not strongly point to a selective pattern separation deficit in older adults. However, when combined with the confidence analysis (Figures 22 and 23), there are trends in the data that are suggestive of a selective pattern separation deficit not only in individuals with aMCI but also in older adults.

These results differ from the *d'* analysis, particularly with regard to the comparison of the young adults and the older adults on the Old/New task. The ROC analysis was used as its measurement properties are superior to that of *d'*, however, this can only be said to be true if the signal detection model provided a good fit for these data. For unknown reasons, the fits were noticeably poor for the Old/New ROC in this experiment. Based on the combined degrees of freedom, we would expect, given a perfect fit, a χ^2 of 6 when comparing two curves. For the Old/New task the average produced χ^2 was 36.8, while for the Same/Different task the average was 6.7. This poorness of fit for Old/New recognition was unanticipated and we can find no obvious reason for why it occurred. In fitting the signal detection model to the data from Chapter 2 the resultant χ^2 values averaged 8.7 on the Old/New task, and 5.3 on the Same/Different task, so it does not appear to be a problem related to the Old/New ROC curves, but rather very specifically to the Old/New ROC curves in Chapter 3. Given the poorness of fit, it is hard to know how much weight to assign to these ROC analyses.

Age-impaired and Age-unimpaired Analyses

Once again, in keeping with previous research, the older adult population was split into age-impaired and age-unimpaired groups based on their performance on the delayed recall test in the CVLT. Though the results are reported here for the sake of

completeness, this analysis did not prove to be informative. The 39 older adults with relevant CVLT data were the same as those in Chapter 2. As such, the same older adults made up the age-unimpaired group, recalling between 12 and 16 words out of a total 16 (M = 13.54, SD = 0.41), while the age-impaired group recalled between 5 and 10 words (M = 7.54, SE = 0.35). Comparing *d'* values for the AU and AI groups showed that they were significantly different on the Old/New task ($t_{(24)} = 2.88$, $p = 0.008$) but not on the Same/Different task ($t_{(24)} = 1.66$, $p = 0.11$), providing initial indication that the two groups are at least quantitatively different in recognition memory.

The ROC curves for the New versus Old/Similar decision were re-plotted with the age-impaired and age-unimpaired groups (see Figure 26). Comparing the ROC curves of the age-unimpaired and age-impaired groups again showed that the two groups performed significantly different on this task ($\chi^2_{(6)} = 27.27$, $p < 0.0001$). The performance of the age-unimpaired group did not differ significantly from that of the young adults ($\chi^2_{(6)} = 2.69$, $p = 0.10$), or the individuals with aMCI ($\chi^2_{(6)} = 3.56$, $p = 0.06$), while the AD patients still performed significantly below all other groups. A similar pattern of results is found looking at the ROC curves for the Same/Different decision (see Figure 27). The performance of the age-unimpaired adults and the young adults remained matched ($\chi^2_{(6)} = 0.598$, $p = 0.44$), only now the performance of the individuals with aMCI did not differ from that of the age-impaired groups ($\chi^2_{(6)} = 0.082$, $p = 0.78$). The performance of the age-unimpaired and age-impaired groups also remained significantly different ($\chi^2_{(6)} = 5.23$, $p = 0.02$). The results suggest that when there is an older adult group that is equated with the young adults in terms of recognition memory, we do not see selective deficits in pattern separation (the age-unimpaired group). On the other hand, the age-impaired group

performed significantly worse than both young adults and individuals with aMCI on the Old/New recognition task, and then showed impairment similar to the aMCI group on the Same/Different task. A simple interpretation suggests that the AI adults were merely overall worse memory performers. Indeed, one caution against giving this analysis any real weight is that, for older adults, Old/New *d'* values were significantly correlated with Same/Different *d'* values ($r_{(43)} = 0.452$, $p = 0.002$) (see Figure 28). This finding is in contrast to the lack of significant correlation found in Chapter 2. Given the correlation between Old/New and Same/Different performance for the older adults it seems likely that separating the older adult group into age-unimpaired and age-impaired groups merely sorted out better memory performers from weaker memory performers.

Discussion

This study investigated the Old/New recognition and pattern separation abilities of young adults, older adults, and two dementia populations. In order to observe evidence of selective deficits in pattern separation, an effort was made to equate Old/New performance across the groups by varying study time. Comparing average *d'* values, the older adults did not differ significantly from the young adults in terms of New versus Old/Similar *d'*, but their ability to discriminate Old from Similar items was significantly worse. The aMCI patients looked nearly identical to the older adult group, and did not differ from them significantly in terms of average *d'* measures for either the Old/New or Same/Different decisions (see Table 5). An identical pattern of results was found comparing the Same/Different accuracy between groups at the highest level of Old/New confidence. For those objects that participants were 100% sure they had seen in some way before, the young adults, older adults, and individuals with aMCI were all equally

accurate (Figure 22). When it came to making a Same versus Different decision for those objects, however, the young adults were significantly more accurate than both the older adults and the individuals with aMCI (Figure 23). Taken together, these results indicate that pattern separation is selectively impaired in a healthy aging population, but not specifically further impaired in an aMCI population. That is, with performance equated on the Old/New recognition task, individuals with aMCI did not perform any differently from age and education matched controls, but, as a whole, this aged population was less able to discriminate between similar items than a young adult population.

Although the data are consistent with the idea that a pattern separation deficit is evident in older adults (even when Old/New recognition is equated), the one caution is that the ROC analysis suggested that younger adults and older adults were not equated with respect to Old/New recognition after all. In that case, the results would not demand an interpretation in terms of a selective pattern separation deficit. The overall pattern of results does seem to more unequivocally establish a selective pattern separation deficit in aMCI patients.

The finding that older adults were significantly worse than young adults at a pattern separation task is in line with the bulk of the previous research (Holden et al., 2012; Toner et al., 2009; Yassa et al., 2011 versus Stark et al., 2010), but (the above caveat notwithstanding) the results of Chapter 3 additionally provide evidence that this is the case even when performance was otherwise matched on an Old/New recognition task. The evidence indicating that individuals with aMCI performed similarly to older adults on the pattern separation task when recognition memory was equated does, however, differ from the previous findings from Stark et al. (2013) and Yassa et al. (2010), both of

whom found a selective pattern separation impairment in their aMCI group compared to a healthy older adult group. It is worth noting that the finding of impaired pattern separation in aMCI by Yassa et al. (2010) was based on comparing false alarm rates across groups and separation bias scores (essentially a measure of hits minus false alarms), a method prone to interpreting a conservative response bias as a deficit in discrimination ability. The work by Stark et al. (2013) attempted to equate recognition memory across groups based on a hits minus false alarms calculation. Importantly, the aMCI group was found to perform worse than the older adult population on both their measure of "traditional" recognition memory and pattern separation. First, this would seem to highlight the importance of matching Old/New recognition performance between older adults and individuals with aMCI before drawing conclusions about impairment in pattern separation and reinforce the findings of Chapter 3. Second, the conclusions of Yassa et al. (2010) and Stark et al. (2013) may not align with those found here as their analyses were based on high-threshold measures of memory performance. Given the evidence that pattern separation is better fit by a continuous signal detection-based model rather than a high threshold model, it would make more sense to equate Old/New performance using *d'* scores or ROC analysis.

Using individuals' performance on the delayed word recall on the CVLT to generate age-impaired and age-unimpaired groups produced two different older adult groups, one that matched the young adult and aMCI groups on Old/New performance, and one that performed significantly below all groups but the AD participants. The age-unimpaired group appeared to be even better able to discriminate than the young adult group on the New versus Old/Similar decision, and, when equivalently matched on the

basic recognition task, the age-unimpaired older adults did not appear distinguishably worse than the young adults on the pattern separation task (Figures 26 and 27). Thus, there is no evidence of a selective pattern separation deficit for the age-unimpaired group.

For the age-impaired older adults, on both the Old/New recognition measure and the Same/Different pattern separation measure their level of discrimination was overall worse than both the young adults and age-unimpaired older adults, only matching the aMCI group on the Same/Different task. In short, the age-unimpaired group looked like the young adult group, while the age-impaired group merely looked like an overall memory-impaired group. These findings go against prior research that has split the older adult population and found selective impairment in pattern separation in the age-impaired group, and not the age-unimpaired group, when compared with young adults (Holden et al., 2012, Holden et al., 2013; Stark et al., 2010). While the age-impaired group in our study did show impairment in pattern separation, it was in no way selective as the group was also significantly impaired on the test of recognition memory. Our results also go against the findings from Stark et al. (2013). In their study they found the AU and AI groups matched on their measure of recognition memory, but the AI group was significantly worse at pattern separation, matching that of the aMCI group. In our study, the AU and AI groups were significantly different on both measures, most likely a reflection of the two groups representing high memory performers and low memory performers. The novelty of our results are obviously tempered by the significant correlation between Old/New *d'* values and Same/Different *d'* values for the older adults (Figure 28). As sorting the older adults based on their CVLT delayed recall scores produced two groups that were significantly different in terms of performance on the

Old/New task it is perhaps unsurprising that these two groups were again significantly different in performance on the Same/Different task. Whether sorting participants based on data from the CVLT (or HVLT-R or RAVLT) merely sorts the generally strong memory performers from the generally weak memory performers is certainly an important question to consider, though noticeably absent from any of the prior research employing this methodology.

As mentioned earlier, the discriminability performance on the Old/New recognition task and the Same/Different pattern separation task was plotted by individual performance and a correlation coefficient between the two measures was computed. Unlike in Chapter 2, which found no significant correlations within the respective population groups, the older adults showed a significant positive correlation ($r_{(43)}$ = 0.452, p = 0.002) between Old/New *d'* and Same/Different *d'*. It is perhaps worth noting the young adults also showed a trend toward positive correlation ($r_{(28)}$ = 0.321, p = 0.08) (Figure 28). In the case of pictures of objects, more so than pictures of faces, it would seem that performance on the Old/New recognition task might be a good predictor of performance on the Same/Different pattern separation task, at least for the young adult and older adult populations.

Similarly, as almost all of the young adult, older adult, and aMCI participants had completed the experiments in both Chapters 2 and 3, individual discriminability performance on one test with one set of stimuli could be compared with discriminability performance on the other. That is, if an individual does well at discriminating between pictures of objects on the Old/New recognition task, does that individual also do well at discriminating between pictures of faces on the same task? And if a person did well at the

Same versus Different pattern separation task with objects is that person also likely to do well making the same decision with pictures of faces? Across all three participant groups there was a striking absence of any significant correlations in performance on the two tasks (see Figures 29 and 30). As a whole, this provides some measure of evidence that memory for faces is indeed a different kind of memory than that for objects. Performing well on a task that requires successfully distinguishing completely new pictures of everyday objects from ones that had been seen previously in some way does not necessarily mean that same person will do well at an identical task involving pictures of faces, and vice versa. This also appears to be the case for distinguishing between very similar stimuli, where success with pictures of objects does not necessarily result in success with pictures of faces.

CHAPTER 4

A definitive diagnosis of Alzheimer's disease can only officially be made post-mortem based on brain biopsy or autopsy that shows the requisite neuropathological features of Alzheimer's. While a clinical diagnosis of either probable or possible AD can be made it typically requires a patient history from both the patient and an informant, cognitive testing, physical exams, and neurological exams, culminating in lab panels and neuroimaging in order to rule out any other possible cause of dementia (Galasko et al., 1998). Given the complexities of clinically diagnosing Alzheimer's, considerable focus has been placed on finding a clinically valid biomarker that could not only indicate the presence of AD, but also serve as an indicator of preclinical AD. Several biomarkers have been studied for this purpose, but the focus of Chapter 4 will be on cerebrospinal fluid (CSF) levels of amyloid β42 (Aβ42), total tau, and phosphorylated tau (p-tau) (for a review of preclinical biomarkers see Shim & Morris, 2011).

Cerebrospinal fluid levels of Aβ42 are the primary constituents of amyloid plaques in the brain, while levels of CSF tau and phosphorylated tau are indicators of neurofibrillary tangles. In general, patients with AD have lower levels of CSF Aβ42 compared to controls, but higher levels of tau and p-tau (Engelborghs et al., 2006; Fagan et al., 2007; Fagan et al., 2009; Galsako et al., 1998). Additionally, low levels of Aβ42 are also associated with brain atrophy in preclinical Alzheimer's, which is to say in individuals who will eventually develop Alzheimer's disease but who are currently presenting as non-demented (Fagan et al., 2009; Schott, Bartlett, Fox, & Barnes, 2010). In both studies they found that non-demented individuals with low levels of CSF Aβ42 had smaller brain volumes than those with higher measured levels. Schott and colleagues followed participants for a year and found that the normal control group that started with

lower levels of CSF Aβ42 had significantly more whole brain loss, ventricular expansion, and hippocampal atrophy than the normal control group with higher levels of Aβ42. Both papers concluded that this was likely reflecting the aggregation of Aβ42 in the brain, and that these structural changes were occurring prior to a detectable cognitive impairment. It has also been shown that levels of CSF tau and p-tau are inversely correlated with whole brain volume in very mild and mild AD, and that the observed increases in CSF tau and p-tau are later events that seem to follow the reduction in CSF Aβ42 and correlate with further structural damage and clinical onset and progression (Fagan et al., 2007).

While it is clear that a lowered level of CSF Aβ42 is a good marker of preclinical brain amyloid and brain atrophy, less has been done to examine correlations with cognitive behavior. Engelborghs et al. (2006) found that CSF Aβ42 levels positively correlated with MMSE scores for AD patients but did not cognitively test the normal controls. Schott et al. (2010) divided the normal control group based on Aβ42 levels and found no difference between the two groups on MMSE, Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog), category fluency, or AVLT-delayed recall. Only on Trails B, a task with a timed component, did they find that the lower Aβ42 level group performed significantly slower. Another study found no correlation with baseline CSF Aβ42 level and cognitive function, but decreased Aβ42 levels (sampled 4 years apart) were associated with decreased delayed word recall scores on the ADAS-Cog subscale, and slower results on A Quick Test of Cognitive Speed (Stomrud et al., 2010). Similarly, they found that an increase overtime in CSF p-tau significantly correlated with slower results on A Quick Test of Cognitive Speed (Stomrud et al., 2010). A final study correlated performance on a pattern separation task in an AD population with Aβ42

levels (Wesnes, Annas, Basun, Edgar, & Blennow, 2014). Here they showed AD patients 14 pictures of everyday scenes and objects, then after a short delay they presented the same 14 pictures along with 14 novel but similar pictures and participants had to decide for each picture whether they had seen it before or not. They found that the percentage of correctly rejected novel stimuli (Similar pictures) was significantly correlated with Aβ42 levels, but only for the "difficult" separations (Wesnes et al., 2014).

The purpose of Chapter 4 was to use the healthy older adults tested in Chapters 2 and 3, some of whom may have CSF profiles consistent with AD but are otherwise asymptomatic, and determine whether CSF levels of Aβ42, total tau, or p-tau were correlated with either Old/New recognition memory or pattern separation performance.

Method

Participants

Sixteen of the older adult participants (11 females, 5 males) from Chapters 2 and 3 had previously consented and volunteered to undergo a spinal tap in conjunction with the longitudinal study at the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). The average age of this older adult subset was 73.4 years (±4.6 years), with a mean level of education of 17.3 years (±1.5 years). In this older adult subset the MMSE scores ranged from 28-30 (M = 29.5, SE = 0.18), and the DRS scores ranged from 136-144 (M = 141.1, SE = 0.63). As of their most recent yearly exam (the same date behavioral testing occurred), all of the older adult participants were placed within the normal control cohort at the ADRC.

Procedure

As part of the longitudinal study at the ADRC, participants were asked if they would consent to a spinal tap procedure for the collection of cerebrospinal fluid. Participation in the spinal tap procedure was not a requirement for being in the longitudinal study. Participants agreeing to the spinal tap scheduled a separate appointment to come in to the ADRC in the early morning to have the lumbar puncture performed by the neurologist. Quantification of Aβ42 was accomplished using the xMAP assay according to manufacturer instructions. The resulting CSF Aβ42, tau, and p-tau data for the overlapping participants tested in Chapters 2 and 3 were made available for the purposes of comparing the individual's behavioral data with neurobiological data.

Results

The first comparison of interest in Chapter 4 was whether the level of Aβ42 measured in a participant's cerebrospinal fluid was correlated with performance on a behavioral test of memory. The second comparison of interest was whether the level of either CSF tau or p-tau was correlated with behavioral performance. To this end, both the New versus Old/Similar *d'* values, a measure of recognition memory, and Same versus Different *d'* values, a measure of the ability to pattern separate, were plotted against the three biomarker levels for the sixteen older adults participants. This was done separately for both the everyday objects picture stimuli from Chapter 3 and the pictures of faces stimuli from Chapter 2.

Correlation Between Object Stimuli and Aβ42

Beginning with the object-based stimuli, for the test of recognition memory there was a significant positive correlation between Aβ42 levels and the *d'* values for the

Old/New decision ($r_{(14)}$ = 0.61, p = 0.01) (Figure 31). Comparing the Aβ42 levels and the Same versus Different *d'* values, there was a trend to a positive correlation, but it was not significant at the $p < .05$ level ($r_{(14)}$ = 0.44, p = 0.09) (Figure 32). Three of the sixteen participants had CSF collected 3-4 years before the behavioral testing of Chapters 2 and 3 was conducted. Prior work has shown that CSF Aβ42 levels remained stable over short-term studies of less than three years (Andreasen et al., 1999; Blennow et al., 2007; Le Bastard, et al., 2013), but the levels decreased in long-term studies of three years or more (Huey et al., 2006; Tapiola et al., 2000). As such, it is possible that the collected Aβ42 levels do not accurately reflect present day conditions for the three participants with CSF drawn in 2011. The correlations reported above were therefore recalculated using the 13 older adult participants with CSF collected since 2012. Plotting the correlation between Aβ42 level and Old/New *d'* values once again yielded a significant positive correlation ($r_{(11)}$ = 0.67, p = 0.01) (Figure 33). Comparing the levels of Aβ42 and the Same/Different *d'* values resulted in evidence of a significant positive correlation ($r_{(11)}$ = 0.64, p = 0.02) (Figure 34).

Correlations Between Object Stimuli and Tau

The levels of CSF tau and p-tau were also plotted with behavioral performance for the object-based stimuli. The results did not differ if all 16 older adults were included, or only the 13 with spinal taps in the last three years, so the data from all 16 participants will be considered here. Both total tau (Figure 35) and p-tau (Figure 36) show a significant negative correlation with Old/New *d'* ($r_{(14)}$ = -0.61, p = 0.01, $r_{(14)}$ = -0.66, p = 0.006, respectively). For the Same/Different decision, however, there was no correlation with the CSF levels of total tau (Figure 37) or p-tau (Figure 38) ($r_{(14)}$ = -0.12, p = 0.66,

$r_{(14)}$ = -0.11, p = 0.69, respectively). Thus, unlike for CSF Aβ42 which was significantly correlated with both behavioral measures of memory, CSF tau only showed a significant correlation on the test of Old/New recognition memory.

Correlations Between Face Stimuli and Aβ42 and Tau

For the experiment conducted in Chapter 2 testing participants' ability to remember and discriminate between pictures of faces there was no difference in the results whether the data was analyzed with all 16 participants or the 13 with the most recent spinal taps, so only the data from all 16 will be presented here. In terms of Old/New discrimination and level of Aβ42, there was no compelling evidence of a significant correlation between the two variables ($r_{(14)}$ = 0.26, p = 0.33) (Figure 39). There also was no evidence of a significant correlation between level of CSF Aβ42 and Same/Different discrimination ($r_{(14)}$ = 0.006, p = 0.98) (Figure 40). The same lack of significant correlation with Old/New *d'* values was found for both total tau (Figure 41) and p-tau (Figure 42) ($r_{(14)}$ = -0.29, p = 0.28, $r_{(14)}$ = 0.05, p = 0.85, respectively). The same lack of significance was also found for the Same/Different test for both total tau (Figure 43) and p-tau (Figure 44) ($r_{(14)}$ = 0.02, p = 0.94, $r_{(14)}$ = 0.02, p = 0.94, respectively). Combined with the significant correlations found with the object stimuli, once again these results point to the likelihood that memory for faces is of a different type than memory for objects.

Discussion

The older adult participants considered in this chapter were otherwise classified as being cognitively normal, but worse performance for both Old/New recognition memory and pattern separation was correlated with lower levels of Aβ42 for the object-based

stimuli. Combined with previous findings that indicate that lower levels of Aβ42 are associated with preclinical impairment (Engelborghs et al., 2006; Fagan et al., 2007; Fagan et al., 2009; Galsako et al., 1998), it is possible that relative impairment on an Old/New or a Same/Different task, as measured by *d'*, may also be correlated with preclinical impairment. This pattern of positive correlation also fits with prior research from Wesnes et al. (2014), which found a significant positive correlation between Aβ42 levels and participants correctly rejecting similar stimuli. Their correlation between CSF Aβ42 and performance on a pattern separation task, however, was found in an Alzheimer's population, while the correlations presented in this chapter were in cognitively normal older adults indicating that this positive correlation precedes an Alzheimer's diagnosis.

There was also a significant negative correlation for both total tau and p-tau, but only for the test of Old/New recognition memory. There is limited prior research comparing levels of tau with behavioral performance. Stomrud and colleagues (2010) did find that in cognitively normal older adults, an increase overtime in CSF p-tau was significantly correlated with slower results on A Quick Test of Cognitive Speed. Thus it seems likely that higher measured levels of CSF tau and p-tau are related to decreases in cognitive performance. As CSF levels of total tau and p-tau are indicators of neurofibrillary tangles, rather than the amyloid plaques associated with Aβ42, it is possible something about the neuropathology of neurofibrillary tangles differentially impacts recognition memory and not pattern separation. This possibility, however, is hard to reckon with the significant negative correlation between levels Aβ42 and p-tau ($r_{(14)} = -0.67$, $p = .005$) which would seem to indicate that participants were likely showing

evidence of both neurofibrillary tangles and amyloid plaques. Levels of total tau, on the other hand, only showed a significant positive correlation with p-tau ($r_{(14)} = 0.63$, $p = 0.01$). Age was not significantly correlated with any of the three biomarkers.

Importantly, the average *d'* values of the 16 older adults with CSF data did not differ significantly from the older adult cohort as a whole from Chapter 3 on either the Old/New task ($t_{(59)} = 0.67$, $p = 0.51$) or the Same/Different task ($t_{(59)} = 0.73$, $p = 0.47$); neither did the subset of 13 older adults with CSF data from the last three years ($t_{(56)} = 0.75$, $p = 0.46$, $t_{(56)} = 1.54$, $p = 0.13$, respectively). This offers another indicator (in addition to the MMSE and DRS scores) that this subset of older adults with CSF draws did not noticeably stand out from the cognitively normal older adults.

Interestingly, the significant correlations between biomarkers and behavioral performance were only present when the stimuli under consideration consisted of pictures of everyday objects, and not when pictures of faces were tested. Once again, the average *d'* values for the CSF cohort did not differ significantly from the overall older adult group from Chapter 2 on either the Old/New task ($t_{(64)} = 1.30$, $p = 0.20$) or the Same/Different task ($t_{(64)} = 0.63$, $p = 0.53$). The apparent lack of Aβ42, tau, and p-tau correlation with performance on face stimuli for both the recognition memory and pattern separation tasks again provides evidence (albeit negative evidence) that memory for faces is different than that for objects. The original motivation for using face stimuli was based on previous research showing that patients with hippocampal lesions showed intact recognition memory specifically for faces (Bird & Burgess, 2008; Smith et al., 2014). Previous research has shown that lowered levels of Aβ42 were also correlated with increased hippocampal atrophy (Schott et al., 2010). The implication here is that the older adults

with lower levels of CSF Aβ42 in our study could potentially also show hippocampal atrophy, while they also did not show any greater difficulty in recognizing faces than the older adults with higher levels of Aβ42 (akin to patients with hippocampal lesions showing no facial recognition deficits). This evidence suggests that memory for faces is not a hippocampal-dependent process, and is in fact separate from memory for pictures of objects.

GENERAL DISCUSSION

The research discussed here was undertaken with three goals in mind with regard to pattern separation. The first was to examine whether pattern separation is best conceptualized as a discrete high threshold process, or a continuous signal-detection process. To that end, the experiment presented in Chapter 1 used confidence-based ROC analysis to distinguish between the two theoretical perspectives. Using this approach enabled us not only to investigate the possibility that pattern separation may be a continuous process, but also enabled us to measure performance with greater precision relative to previous investigations. The results of Chapter 1 provided compelling evidence that pattern separation is better fit by a continuous signal detection model. For example, the Same/Different ROC curve produced for the highest Old/New confidence rating was clearly curvilinear (Figure 9) as only a signal-detection-based model would predict. In addition, after establishing that the Old/New confidence rating of 5 was often given to lures (New objects) (Figure 6), we found that the Same/Different accuracy associated with Old and Similar items receiving an Old/New confidence rating of 5 was significantly above chance (Figure 7). This is a result that cannot be explained by high threshold models of pattern separation, but is easily accounted for if pattern separation is a continuous, signal-detection process.

Additional support for a continuous model of pattern separation can be found in Chapters 2 and 3. Although in Chapter 2, the young adult group no longer showed Same versus Different performance above chance at the Old/New confidence rating of 5, the older adult population did (Figure 16). This finding suggests that pattern separation occurs in degrees and raises the possibility that the same finding was not observed in the young adults due to a lack of statistical power. Furthermore, the Old/New and

Same/Different ROCs produced by the older adults, young adults, and individuals with aMCI are all beautifully curvilinear when performance levels are above chance (Figures 13 and 14). A threshold model of pattern separation predicts a linear ROC. In Chapter 3, the only above-chance performance for the Same/Different decision occurred at the Old/New confidence rating of 6 (Figure 23), in agreement with the predictions of a threshold model. However, the Same/Different ROCs produced by the population groups performing above chance were still clearly curvilinear (Figure 25), which is hard for a threshold model to accommodate. Taken as a whole, the evidence suggests that a continuous, signal-detection model provides a better account of pattern separation.

The second purpose of this research was to examine the effect of aging, mild cognitive impairment, and Alzheimer's disease on pattern separation. In particular, we wanted to equate performance across groups on an Old/New recognition task to determine whether or not pattern separation is differentially impaired in aging, dementia or both. In Chapter 2, we used stimuli consisting of pictures of faces based on recent work showing that patients with bilateral hippocampal lesions were unimpaired at memory for faces (Bird & Burgess, 2008; Smith et al., 2014). We hypothesized that aMCI patients, whose pathology includes hippocampal atrophy, might also show equivalent Old/New recognition memory for faces compared to an older adult control group. However, the results comparing the *d'* values and ROC curves of the three groups showed that performance was not equated on the Old/New recognition task (Figure 13), which prevented us from interpreting the similarly staggered performance on the Same/Different task in terms of a selective pattern separation deficit (Figure 14). Performance on the Old/New task *was* equated across groups at the highest Old/New

confidence rating (100%), which allowed us to use the corresponding Same/Different accuracy to more meaningfully test for the existence of a selective pattern separation deficit. In fact, when participants were 100% confident that they had seen this face in some way before, young adults, older adults, and individuals with aMCI all performed significantly different from each other at determining whether the face was exactly the same or different in some way. That is, not only did the older adults perform worse than the young adults, the individuals with aMCI performed even worse than the older adults. This result points to a selective impairment in pattern separation for faces not only in aging but in dementia as well.

In Chapter 3, we used pictures of everyday objects and altered the timing and number of presentations during the study session in order to equate the performance of young adults, older adults, individuals with aMCI, and Alzheimer's patients on the Old/New recognition task. While the signal-detection theory parameters produced for the Old/New ROC fit inexplicably poorly, the *d'* values for the young adults, older adults, and individuals with aMCI did not differ significantly from each other. In this case, comparing the *d'* values on the Same/Different task we only found a selective deficit for the older adults compared to the young adults. While the individuals with aMCI were significantly worse at the pattern separation task than the young adults, they were not significantly worse than the older adults. Identical results were found comparing the Same/Different accuracies of the three groups at the highest level of Old/New confidence (Figure 23). Then again, one caution in interpreting the results for the older adults is that, according to the ROC analysis, Old/New performance was not equated across groups (with the young adults outperforming the older adults). Although the ROC fit from this

condition was poor for reasons unknown, an argument could be made that Old/New performance was not actually equated for older adults and young adults (which may in turn explain why performance was also not equated on the Same/Different pattern separation task). These concerns do not apply to the aMCI group. Both the *d'* and ROC analysis suggested that Old/New performance was equated for young adults and individuals with aMCI, yet the aMCI group still showed a significant pattern separation deficit.

Overall, the evidence in Chapters 2 and 3 indicates that older adults likely show an impairment in pattern separation compared to young adults, and that individuals with aMCI almost certainly do. Importantly, at least for the individuals with aMCI (and also for the older adults in some analyses), this pattern separation deficit is not one that can be explained by a general recognition memory deficit. While it is possible that individuals with aMCI may show a pattern separation deficit even compared to older adults, in agreement with previous work (Stark et al., 2013; Yassa et al., 2010), our results do not provide convincing evidence one way or the other on this point.

The third goal of this research was to compare biological markers of preclinical impairment with behavioral tests of recognition memory and pattern separation in an older adult population. For a subset of the older adult population tested in Chapters 2 and 3 cerebrospinal fluid levels of Aβ42, tau, and p-tau had been voluntarily collected as part of a separate study at the ADRC. As a result, we were able to compare the performance of 16 individuals on both Old/New and Same/Different tasks for faces and objects with their level of CSF Aβ42, total tau, and p-tau. While prior research has shown that lower levels of CSFAβ42 are a good indicator of preclinical impairment, and that pattern

separation is positively correlated with Aβ42 level in AD, there is not yet any research comparing Aβ42 levels with the performance of cognitively normal older adults. We found a significant positive correlation between both Old/New *d'* and Same/Different *d'* for object stimuli (Figures 33 and 34), but not face stimuli (Figures 35 and 36). Critically, we observed this correlation in individuals who are otherwise identified as cognitively normal.

While not one of the explicit purposes of this research, the data collected across these four chapters also yielded two additional interesting pieces of information about the nature of memory. The first is that object memory appears to be qualitatively different than face memory. Evidence for this already exists in the literature from the findings that memory for faces is preserved in patients with bilateral hippocampal lesions (Bird & Burgess, 2008; Smith et al., 2014). The clearest support for this concept here can be seen in Chapter 4, where CSF Aβ42 levels are not at all correlated with either Old/New *d'* or Same/Different *d'* for faces (Figures 35 and 36), but there was a significant correlation for both measures when objects were used. Lower levels of CSF Aβ42 are correlated with hippocampal atrophy (Schott et al., 2010), so it follows that individuals potentially showing a decrease in hippocampal volume (namely, healthy aging participants with low levels of CSF Aβ42) do not perform any differently when it comes to memory for faces, only objects. Some additional support for the idea that memory for faces and objects may be different can be found in the correlations comparing Old/New and Same/Different *d'* values across Chapters 2 and 3. For the young adults, older adults, and individuals with aMCI who completed both experiments we were able to correlate performance on the Old/New task for faces with their performance on the Old/New task with objects and we

found no significant correlation for each of the three groups (Figure 29). We similarly tested the correlations on the Same/Different task and again found no evidence of a significant correlation in any of the groups (Figure 30). These results demonstrate that better recognition or better pattern separation with one stimulus set does not predict better performance in the other. These are null correlational results, so they do not themselves provide strong evidence for a difference in face memory and object memory, but they are least consistent with that possibility.

The second interesting result is that our Old/New and Same/Different tasks also appear to be measuring different memory processes. To be sure, that was the assumption underlying our methodological setup, but it was not clear that we would see evidence of it. In the experiment in Chapter 2 we found no significant correlation between Old/New and Same/Different *d'* values for young adults, older adults, and individuals with aMCI (Figure 19). In Chapter 3, there was only a significant correlation between the two measures for the older adults, though there was a trend in that direction for the young adults (Figure 28). If both tasks were measuring the same memory process, then performance on one would support performance on the other and we would expect to see evidence of significant correlations. Again, these null results cannot support any strong conclusions, but they do point to the interesting possibility that old/new recognition and pattern separation abilities are largely independent.

There are a few limitations in the current research which point to some clear directions for future exploration. The first is the relatively low number of aMCI participants. Recruiting aMCI participants proved to be challenging, at least in part because it exists as a transitional diagnosis between healthy aging and dementia. Indeed,

many of the potential aMCI participants for this study were found to have converted to Alzheimer's before they could be tested. Certainly, an obvious first point for future research would be to have aMCI participants in numbers closer to those of the controls. A second limitation to the current research was the failure to equate Old/New *d'* values and ROC curves for the three participant groups in Chapter 2. Based on research with hippocampal lesion patients it was thought that recognition memory performance might be the same for all three groups without alterations in the study phase methodology. As this turned out not to be true, the next iteration of this experiment should adjust study time and/or list repetition for both the older adult and aMCI groups to equate Old/New performance. Finally, the poorly generated fits for the Old/New ROC curves only in Chapter 3 remain difficult to explain. The signal-detection model fit all other parts of the data well, and the poor fit in this one circumstance was unexpected. Overall, signal detection theory and ROC analysis still provide a more sophisticated measurement tool with which to examine pattern separation.

TABLES

Table 1. Average hit rate (HR), false alarm rate (FA), and *d'* values for the young adult participants on both the Old/New decision and the Same/Different decision.

Old/New		Same/Different	
HR	0.77	HR	0.80
FA	0.12	FA	0.48
d'	2.10	*d'*	0.97

Table 2. Demographics table of averages (standard error) for young adults (YA), older adults (OA), and individuals with amnestic mild cognitive impairment (aMCI).

	YA	OA	aMCI
Gender (M/F)	5/28	18/32	7/5
Age (yr)	21.318 (0.36)	75.86 (0.92)	77.25 (2.59)
Education (yr)	N/A	16.49 (0.36)	15.08 (1.24)
MMSE score	N/A	29.3 (0.12)	26.5 (0.88)
DRS score	N/A	140.1 (0.41)	132 (1.83)

Table 3. Average hit rate (HR), false alarm rate (FA), and *d'* values for young adults (YA), older adults (OA), and individuals with amnestic mild cognitive impairment (aMCI) on both the Old/New decision (O/N) and the Same/Different decision (S/D).

Group	O/N HR	O/N FA	O/N *d'*	S/D HR	S/D FA	S/D *d'*
YA	0.75	0.16	1.85	0.78	0.49	0.94
OA	0.77	0.31	1.45	0.79	0.65	0.48
aMCI	0.69	0.35	1.06	0.70	0.65	0.20

Table 4. Demographics table of averages (standard error) for young adults (YA), older adults (OA), individuals with amnestic mild cognitive impairment (aMCI), and individuals with Alzheimer's disease (AD).

	YA	OA	aMCI	AD
Gender (M/F)	5/25	16/29	7/5	13/4
Age (yr)	21.30 (0.39)	75.86 (0.92)	77.25 (2.59)	76.82 (1.65)
Education (yr)	N/A	16.61 (0.37)	15.08 (1.24)	15.38 (0.62)
MMSE score	N/A	29.3 (0.13)	26.5 (0.88)	22.4 (0.80)
DRS score	N/A	140.2 (0.42)	132 (1.83)	117.6 (3.15)

Table 5. Average hit rate (HR), false alarm rate (FA), and *d'* values for young adults (YA), older adults (OA), individuals with amnestic mild cognitive impairment (aMCI), and individuals with Alzheimer's disease (AD) on both the Old/New decision (O/N) and the Same/Different decision (S/D).

Group	O/N HR	O/N FA	O/N *d'*	S/D HR	S/D FA	S/D *d'*
YA	0.87	0.07	2.96	0.84	0.46	1.29
OA	0.82	0.07	2.70	0.87	0.63	0.87
aMCI	0.81	0.05	2.71	0.79	0.59	0.72
AD	0.74	0.27	1.44	0.65	0.59	0.23

FIGURES

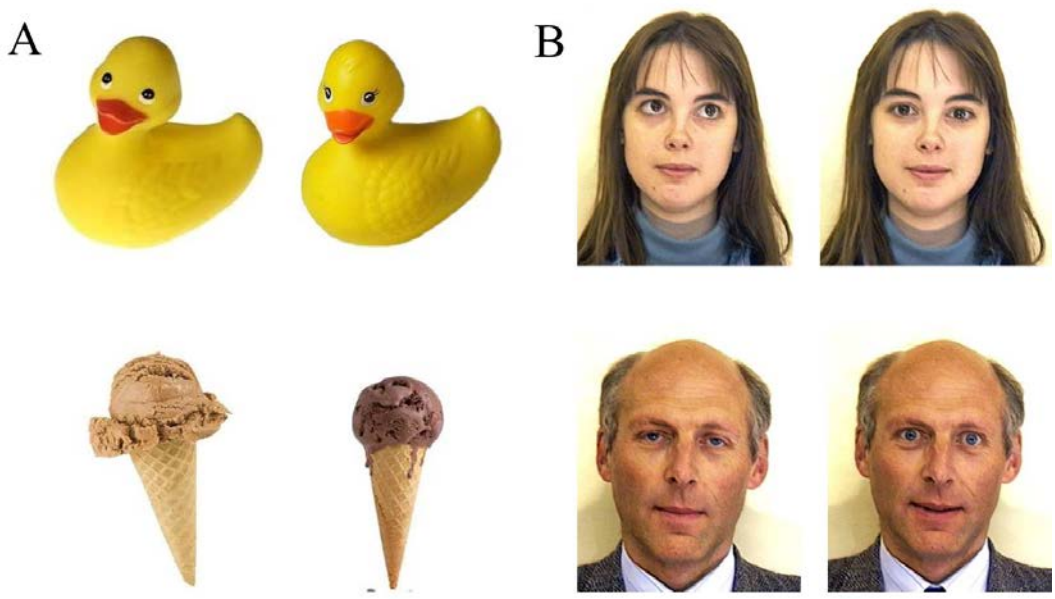

Figure 1. Example of stimuli pairs. For the object pictures (A), the similar pictures were visually similar and from the same object category. For the face pictures (B), the similar pictures varied on aspects such as gaze, facial expression, and hair style.

Figure 2. New versus Old confidence ratings used in Chapter 1, where “Old” was used to indicate pictures they had seen in some way before.

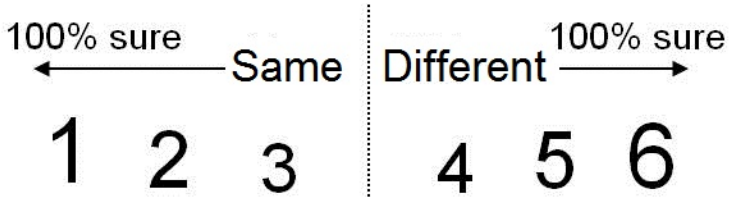

Figure 3. Same versus Different confidence ratings used in Chapter 1.

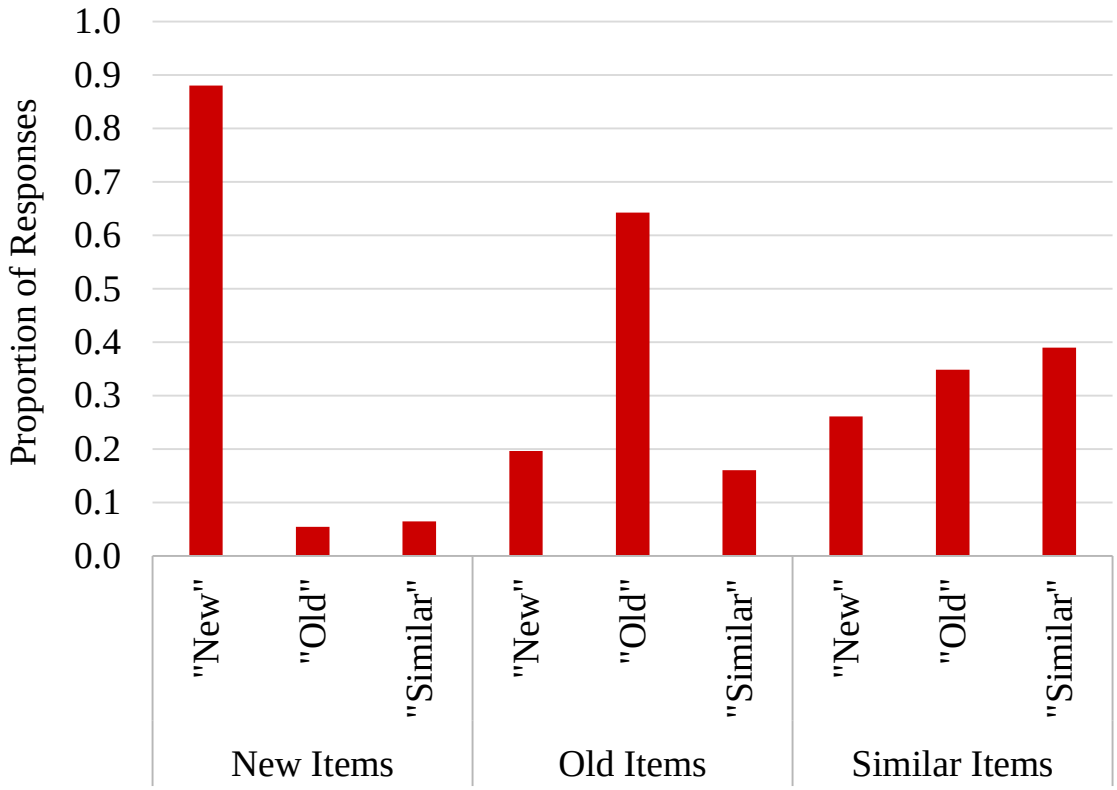

Figure 4. Response proportions for New, Old, and Similar objects.

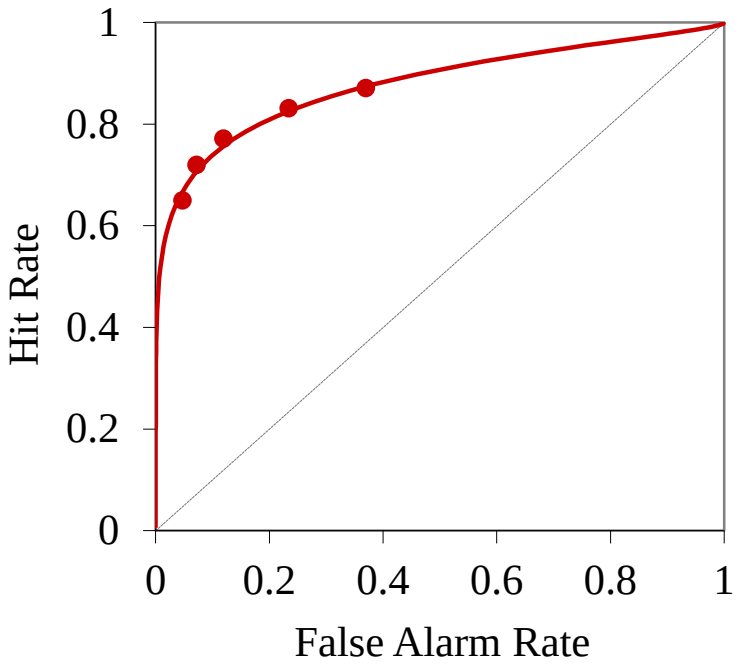

Figure 5. ROC curve for distinguishing Old/Similar objects from New objects.

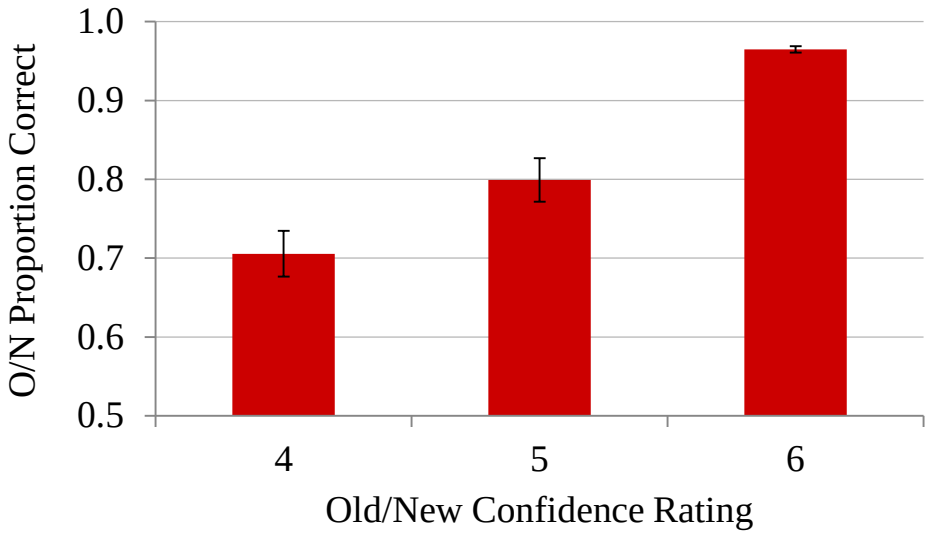

Figure 6. Proportion correct in distinguishing whether an object was New or had been seen in some way before based on Old/New confidence ratings.

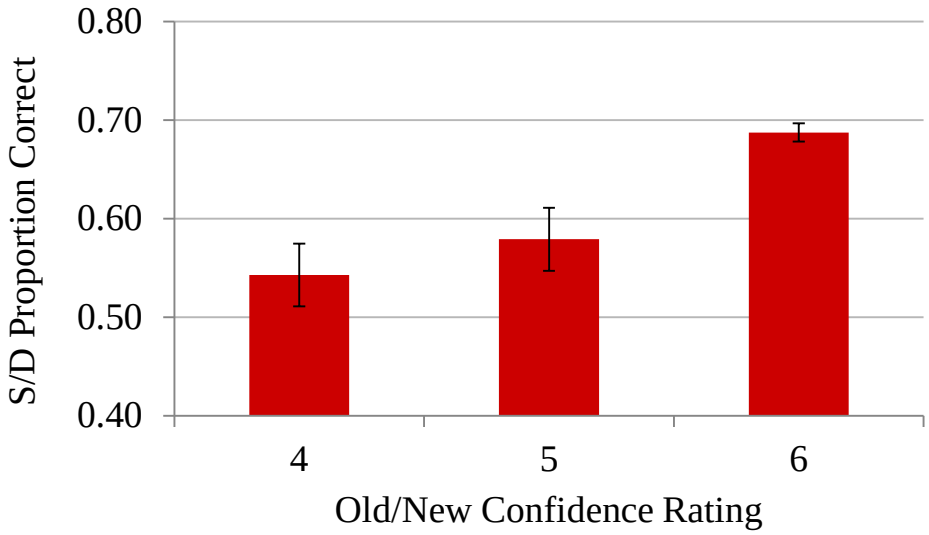

Figure 7. Proportion correct in determining whether an object was exactly the Same or Different in some way based on Old/New confidence ratings.

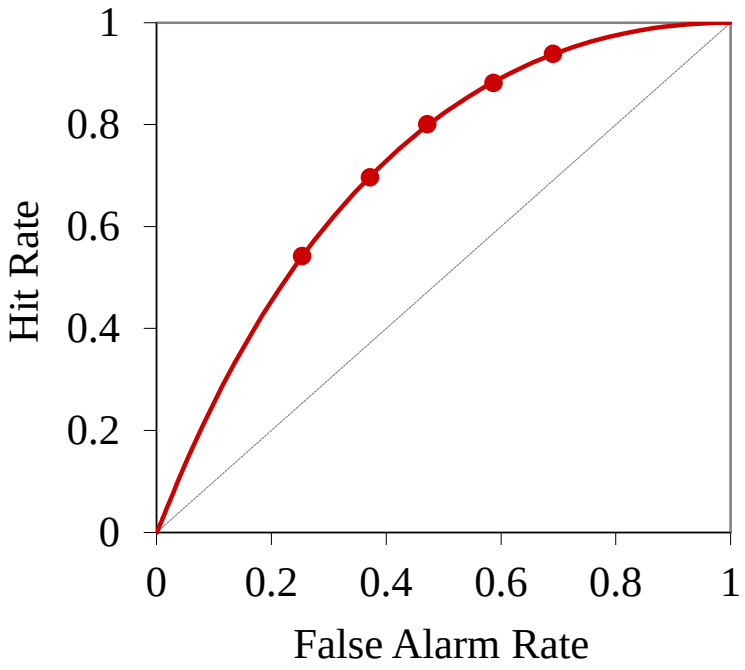

Figure 8. ROC curve for the Same/Different decision collapsed across Old/New confidence ratings.

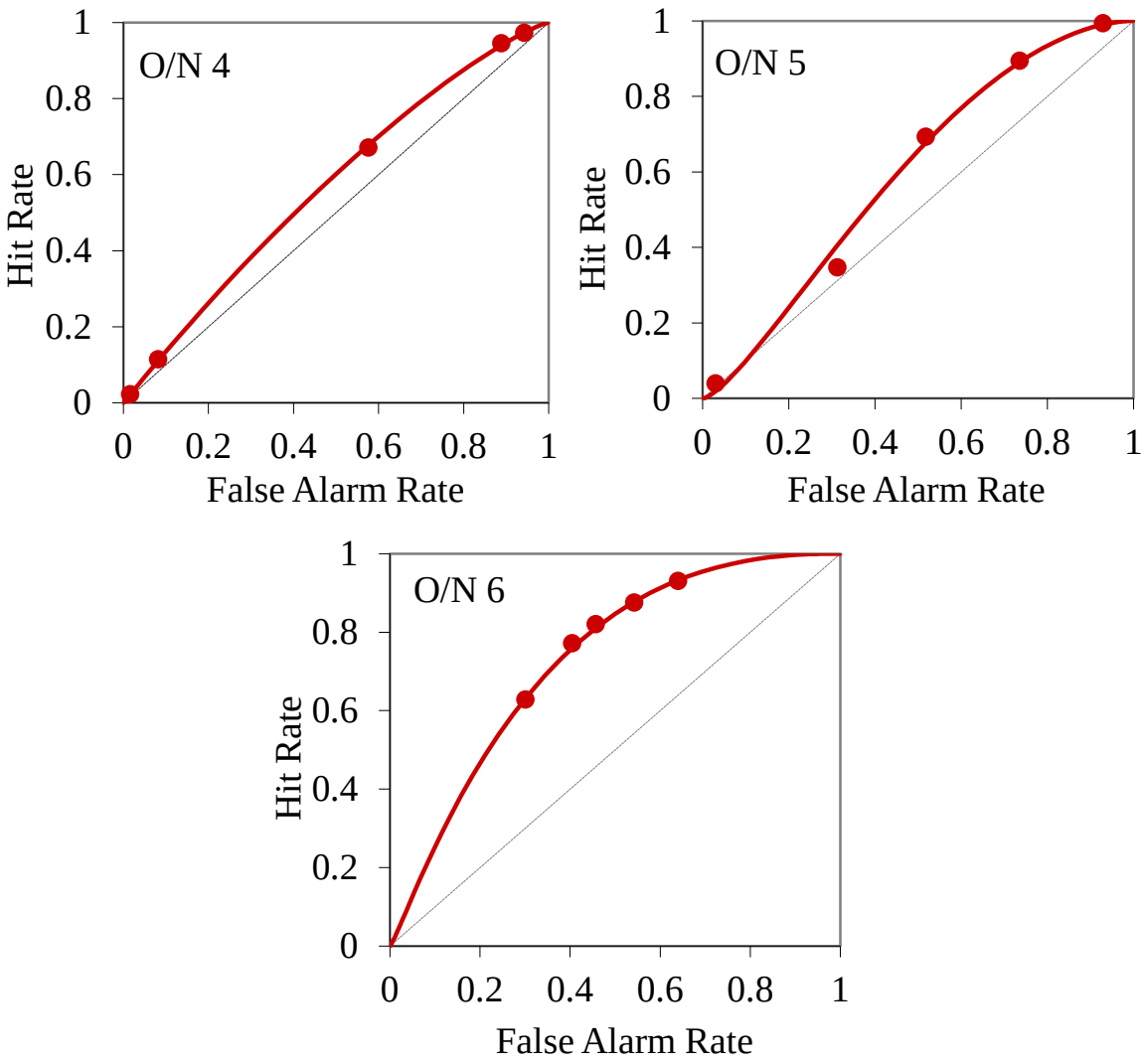

Figure 9. ROC curves for the Same versus Different decision broken down by increasing level of Old/New confidence rating (O/N 4 through 6).

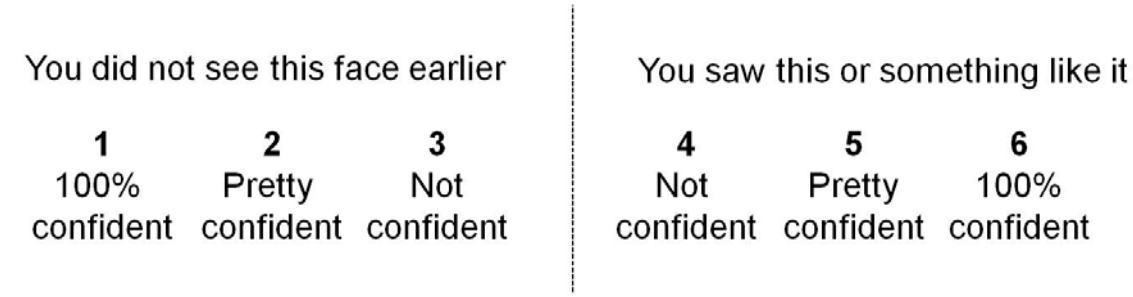

Figure 10. Confidence ratings used in Chapter 2 for the test of New versus Old recognition ("You did not see this face earlier" versus "You saw this or something like it").

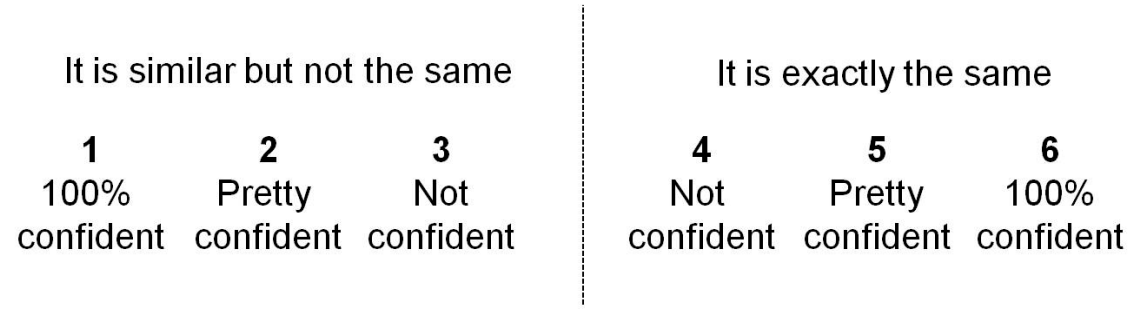

Figure 11. Confidence ratings used in Chapters 2 and 3 for the pattern separation test of Different versus Same.

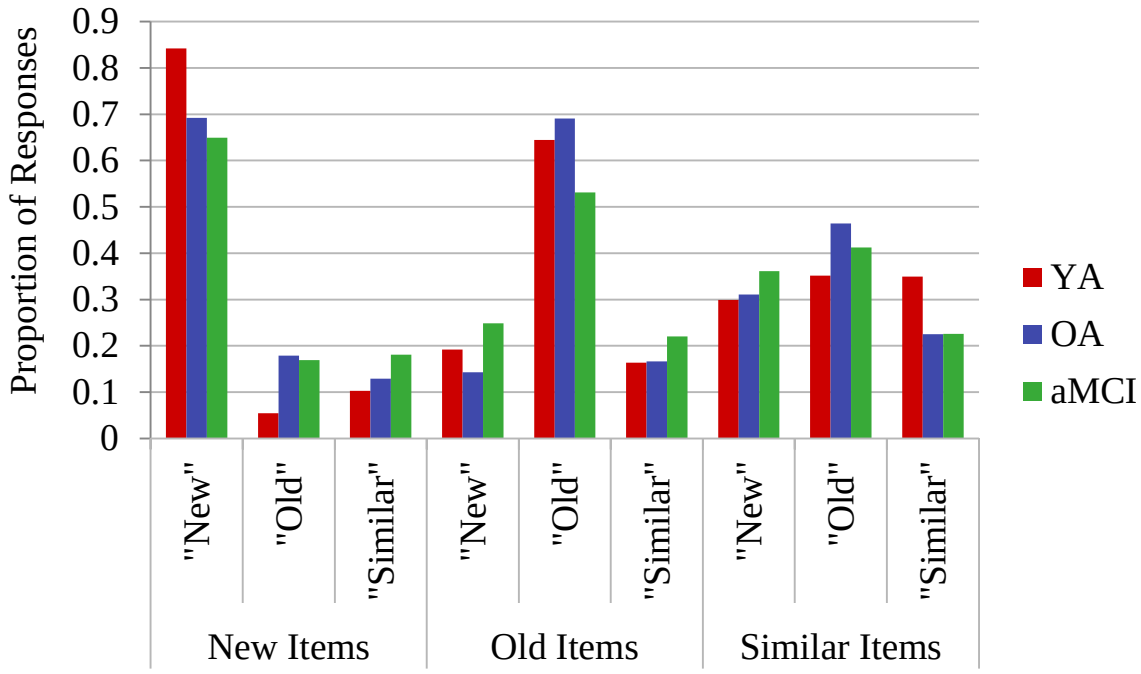

Figure 12. Response proportions for New, Old, and Similar faces for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

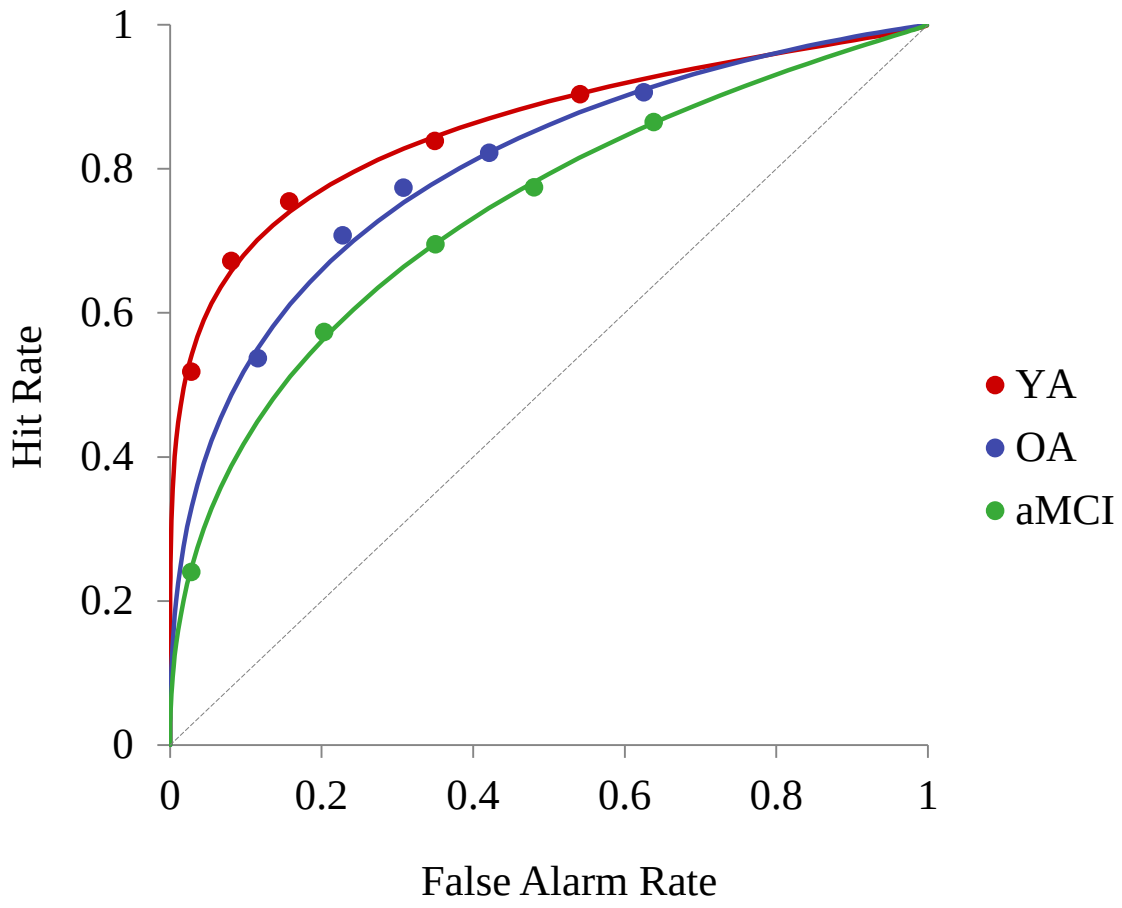

Figure 13. New versus Old/Similar ROC curves for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

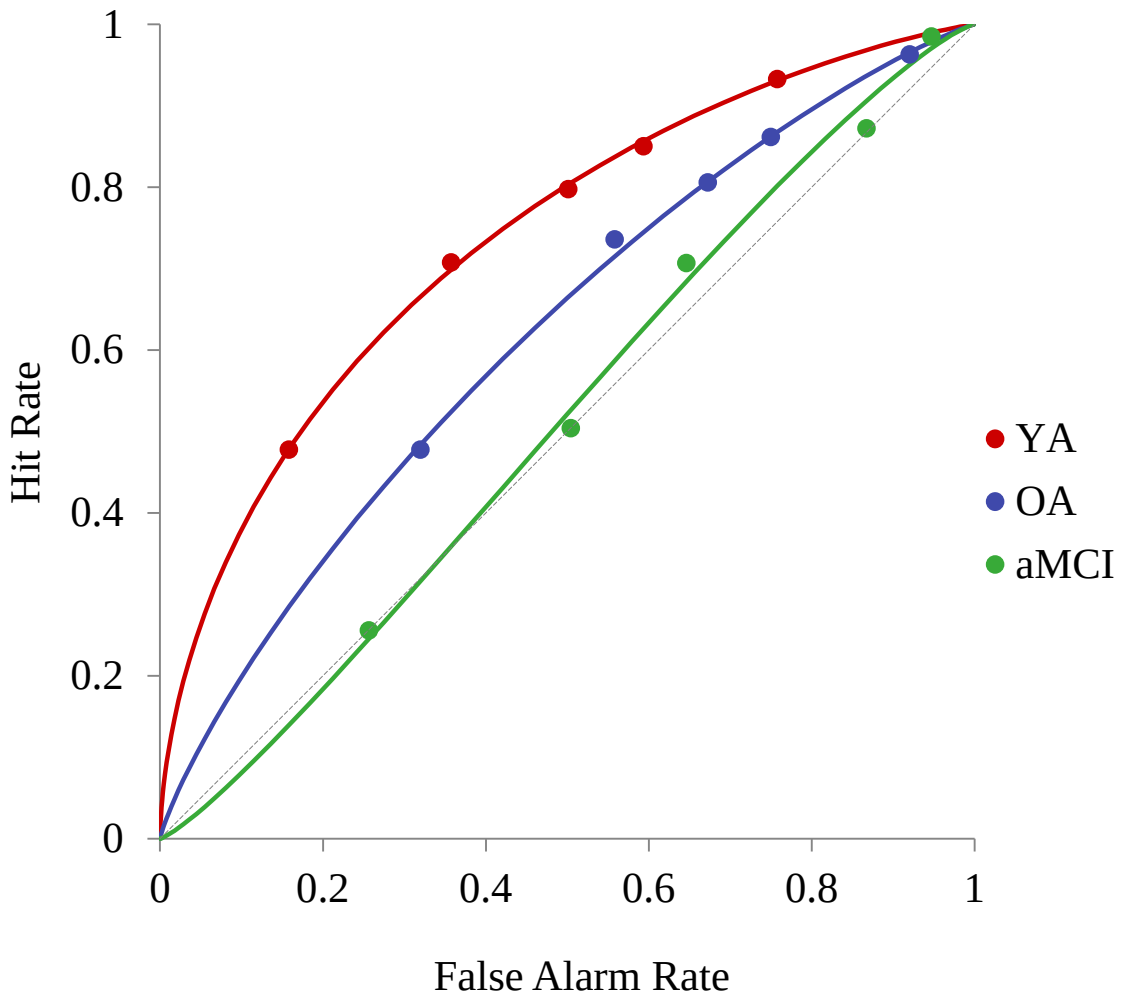

Figure 14. Same versus Different ROC curves for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

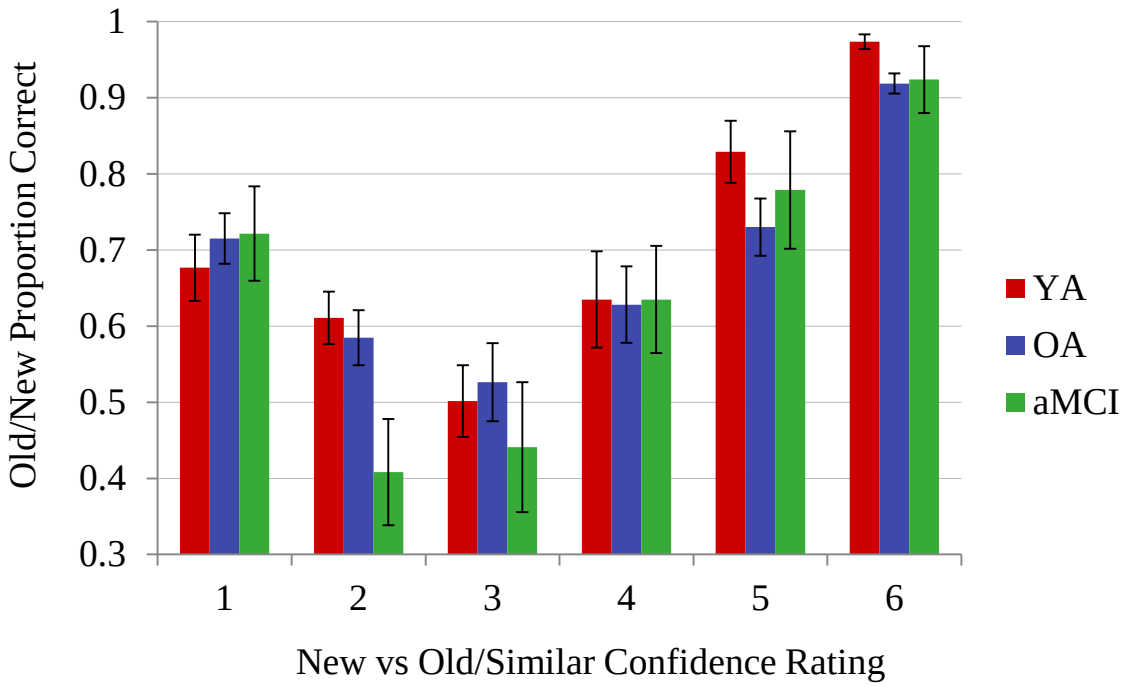

Figure 15. Proportion correct for New versus Old/Similar confidence ratings for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

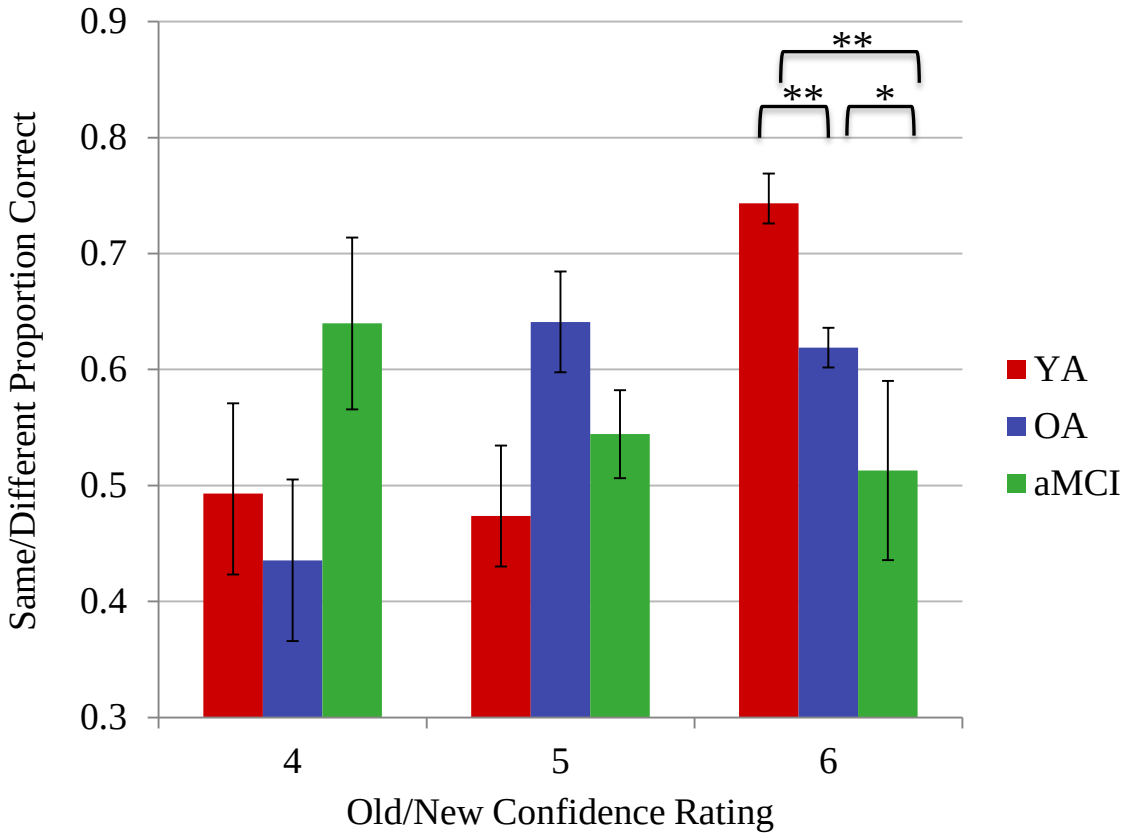

Figure 16. Proportion correct in determining whether an item was exactly the Same or Different in some way based on Old/New confidence ratings for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

* $p < .05$, ** $p < .001$

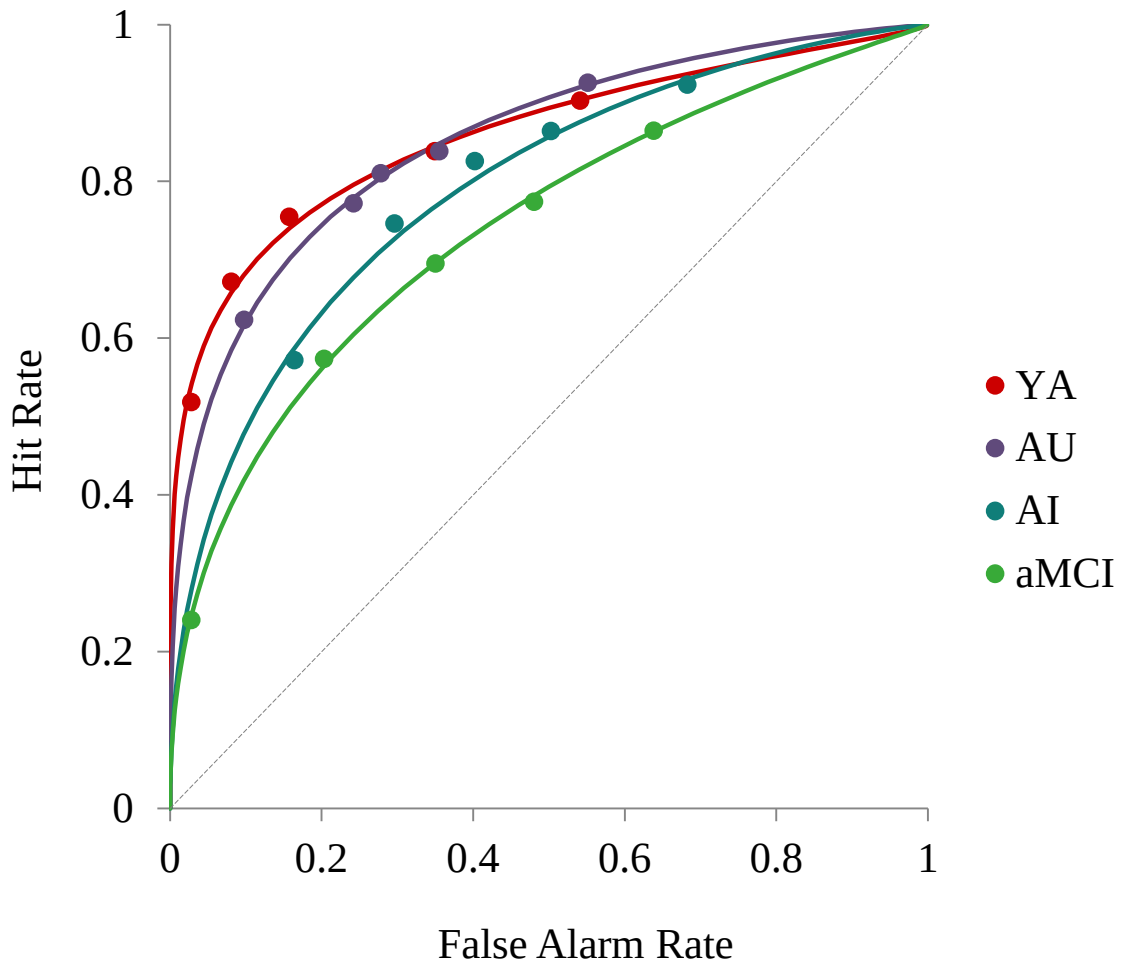

Figure 17. New versus Old/Similar ROC curves for young adults (YA), age-unimpaired adults (AU), age-impaired adults (AI), and participants with amnestic mild cognitive impairment (aMCI).

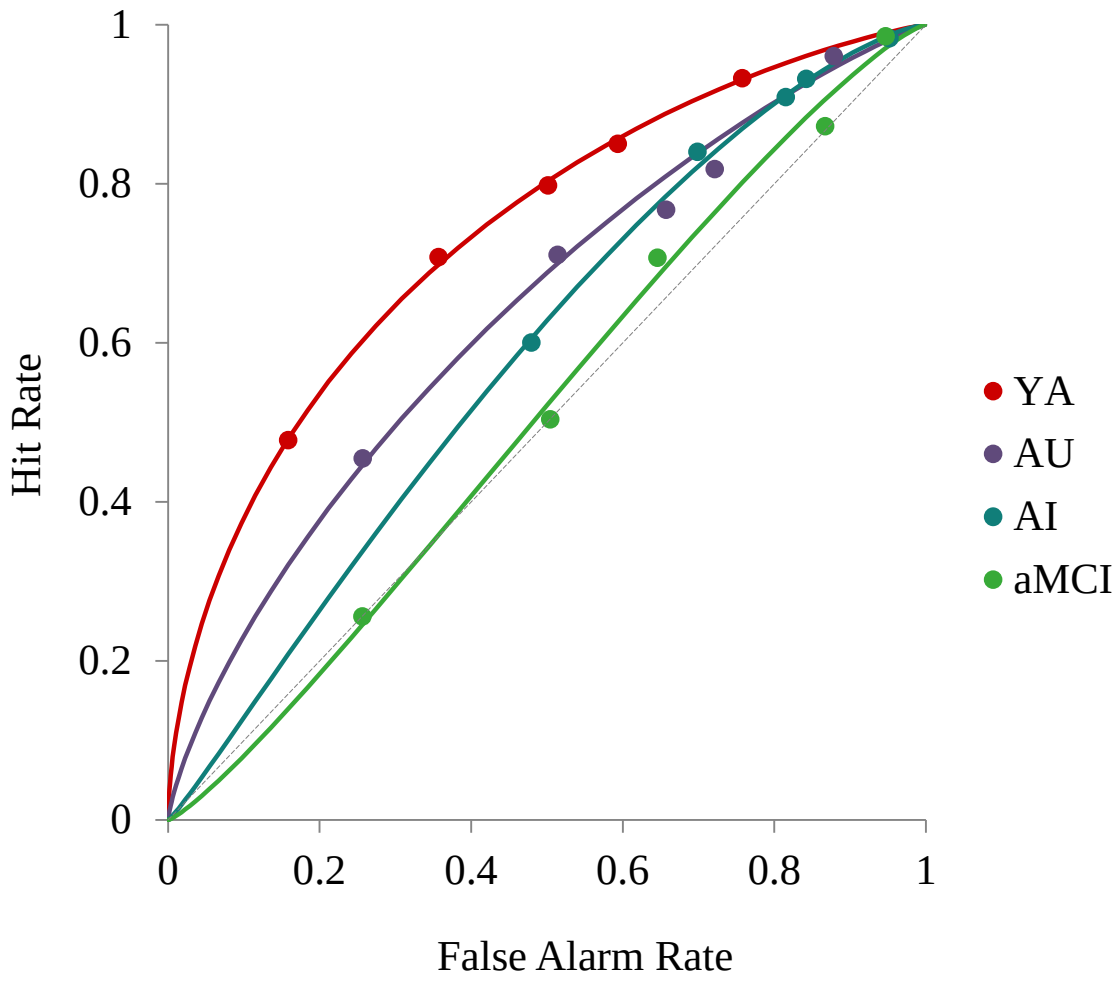

Figure 18. Same versus Different ROC curves for young adults (YA), age-unimpaired adults (AU), age-impaired adults (AI), and participants with amnestic mild cognitive impairment (aMCI).

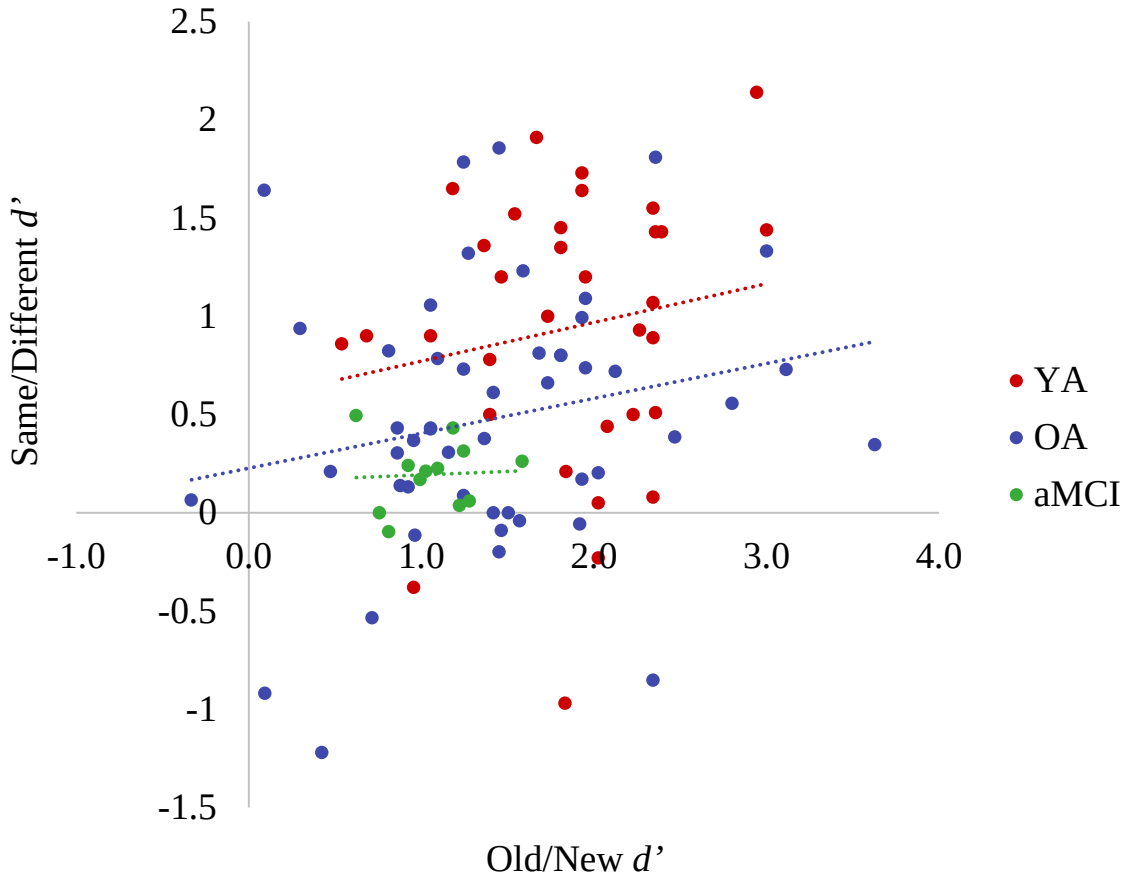

Figure 19. Correlation plot of individual participants' Old/New *d'* values and Same/Different *d'* values for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

YA $r_{(31)} = 0.160$, $p = 0.375$
OA $r_{(48)} = 0.213$, $p = 0.138$
aMCI $r_{(10)} = 0.056$, $p = 0.862$

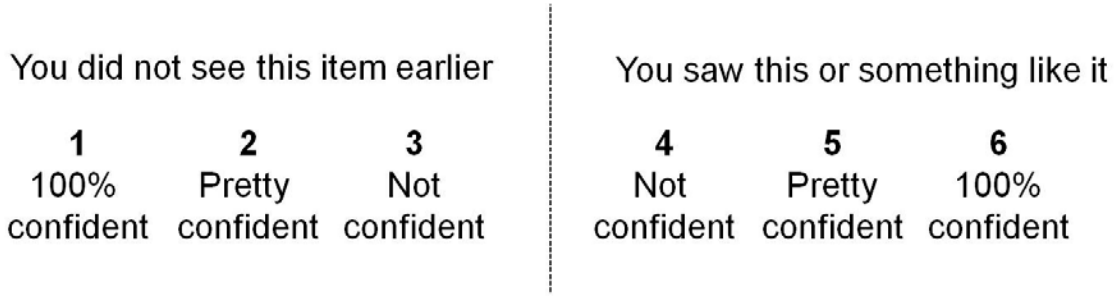

Figure 20. Confidence ratings used in Chapter 3 for the test of New versus Old recognition ("You did not see this item earlier" versus "You saw this or something like it").

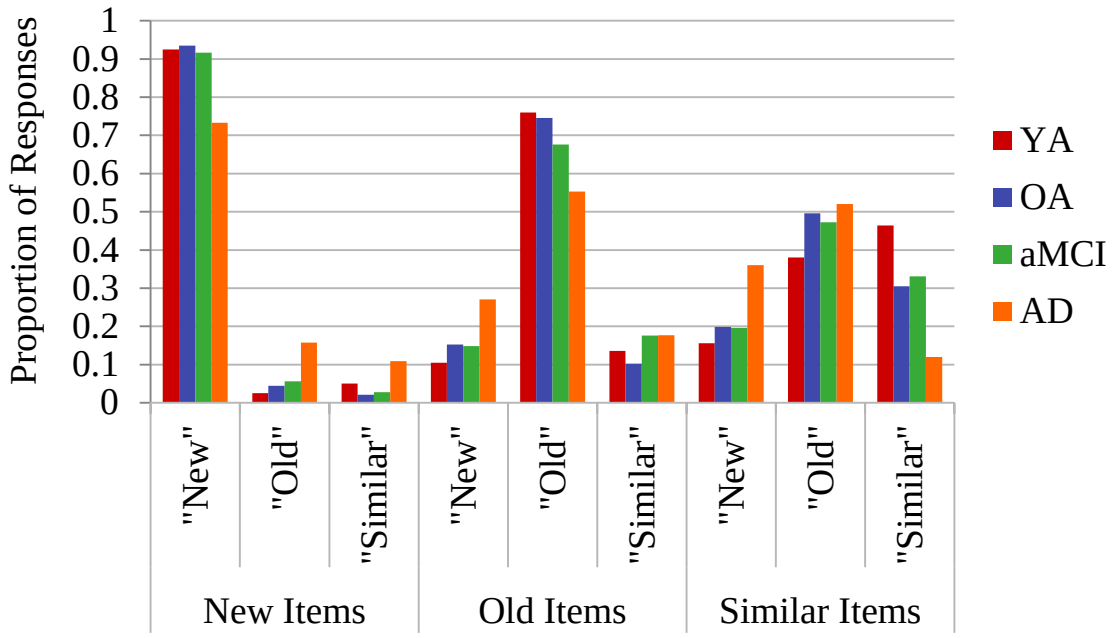

Figure 21. Response proportions for New, Old, and Similar faces for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

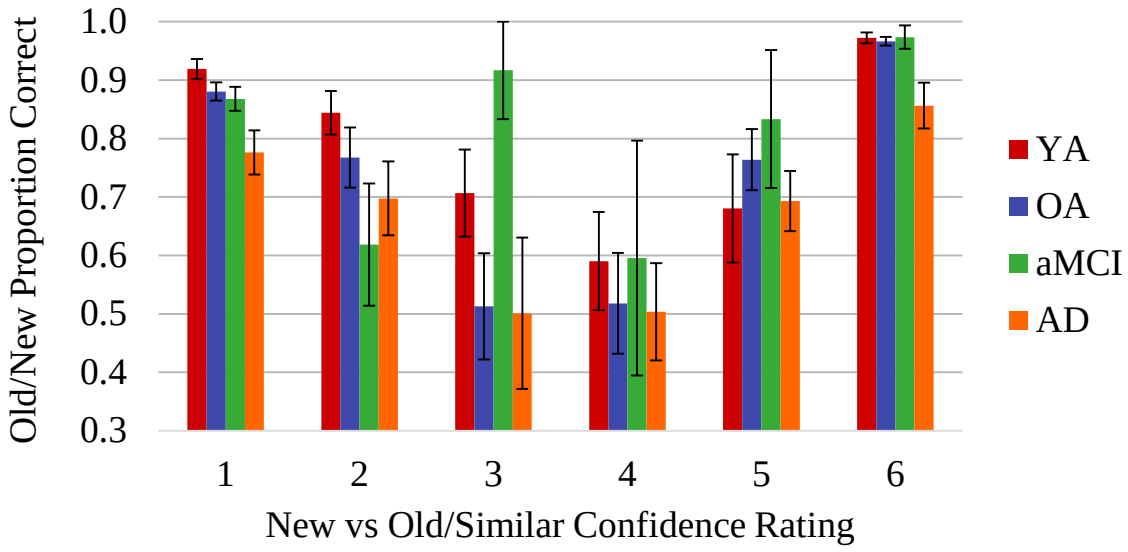

Figure 22. Proportion correct for New versus Old/Similar confidence ratings for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

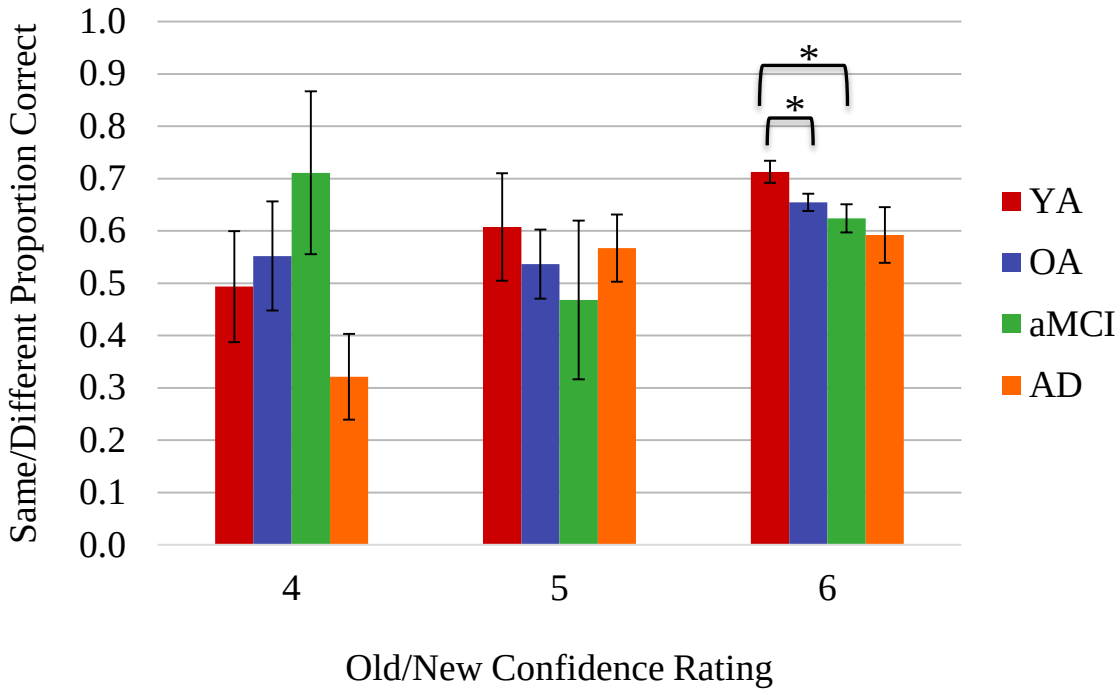

Figure 23. Proportion correct for whether an object was exactly the Same or Different based on Old/New confidence rating for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

* $p < .05$

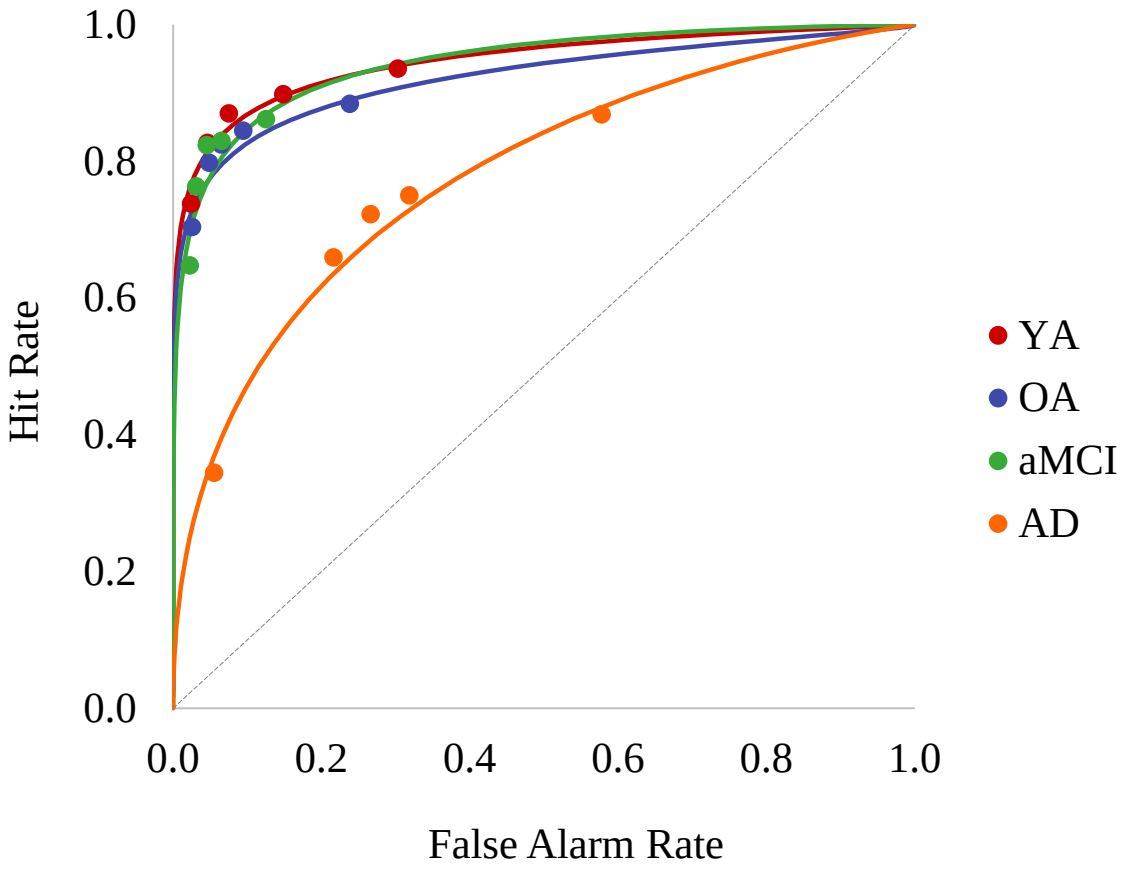

Figure 24. New versus Old/Similar ROC curves for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

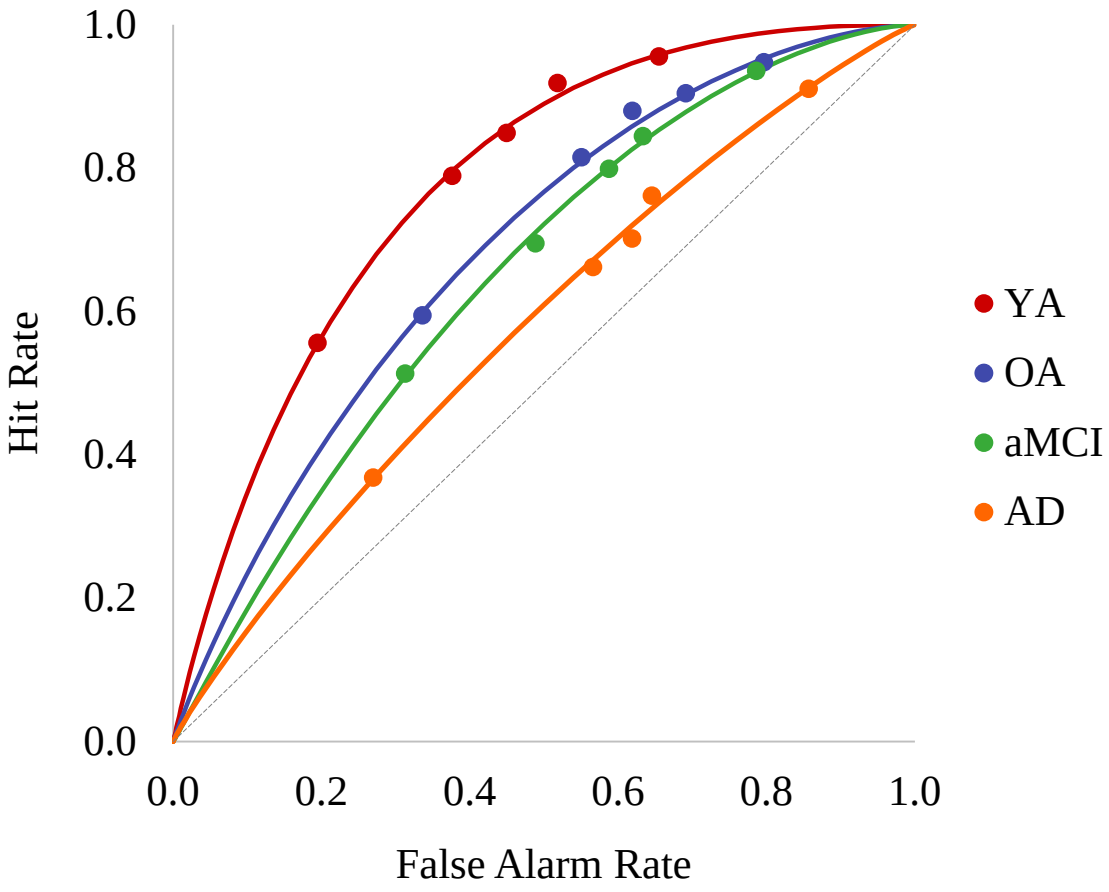

Figure 25. Same versus Different ROC curves for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

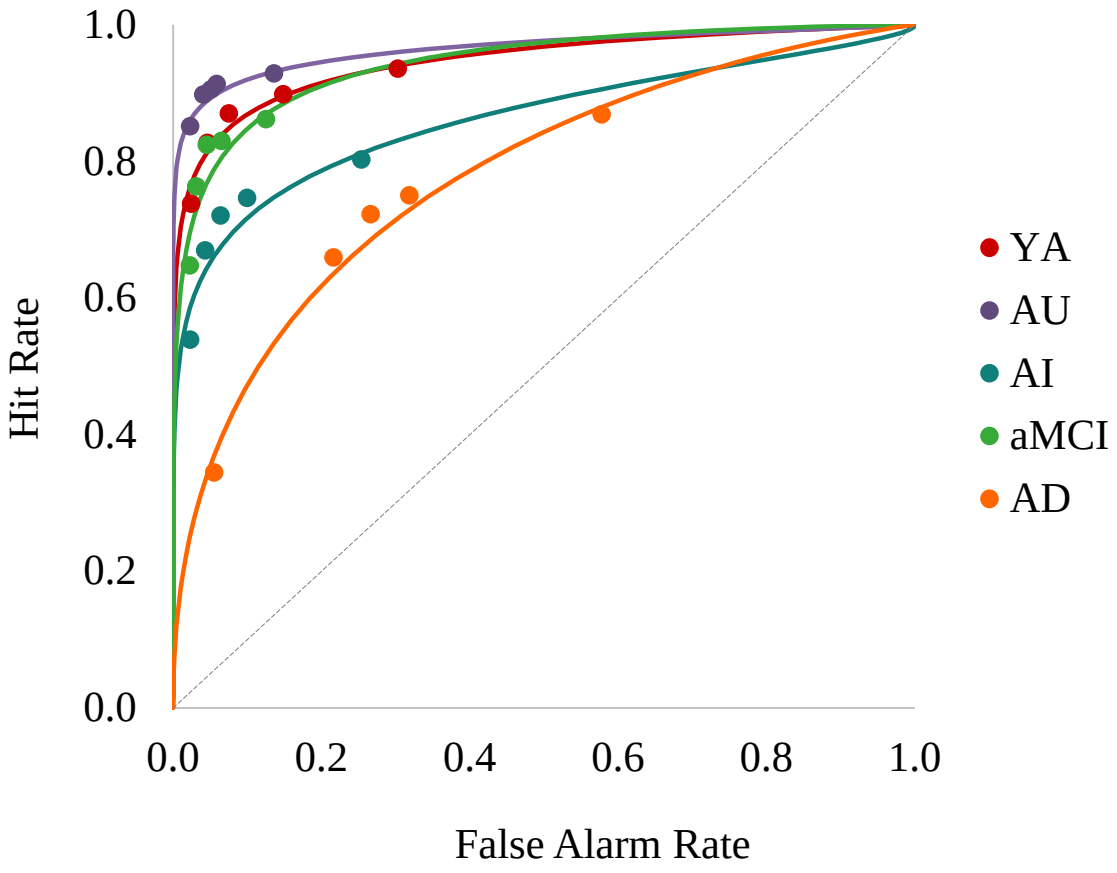

Figure 26. New versus Old/Similar ROC curves for young adults (YA), age-unimpaired adults (AU), age-impaired adults (AI), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

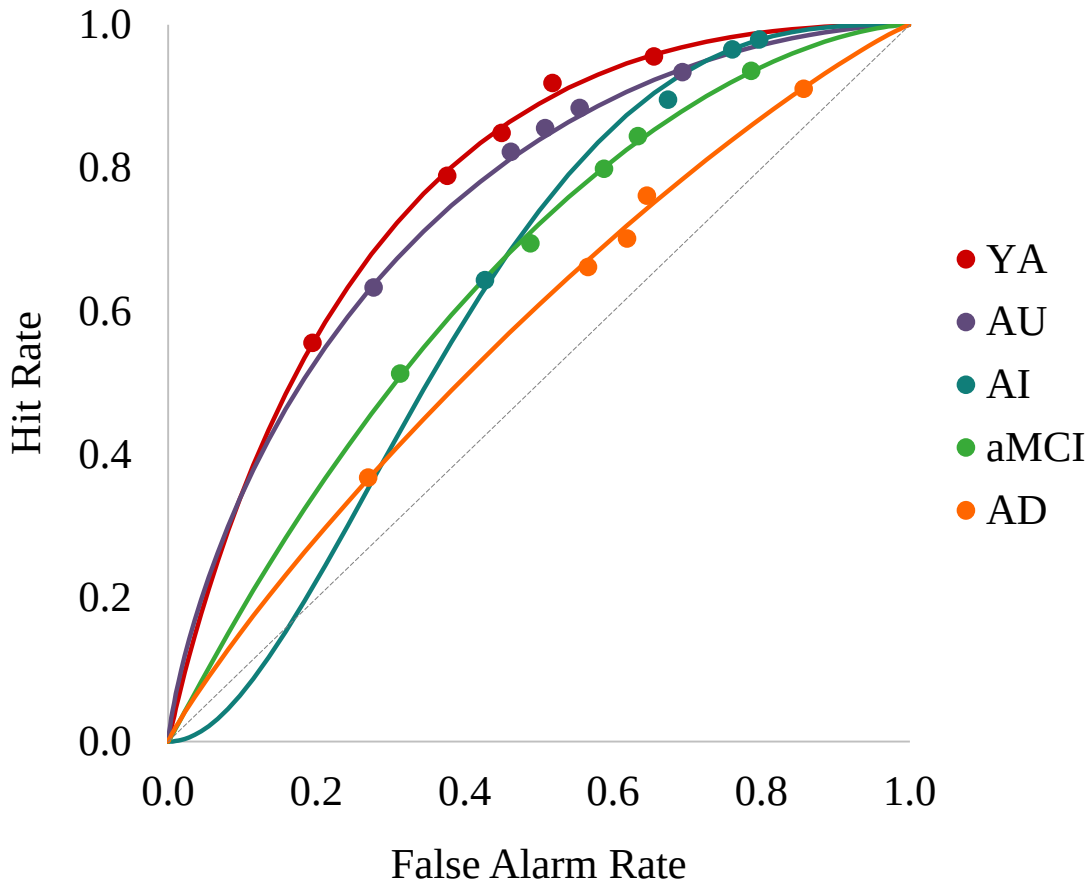

Figure 27. Same versus Different ROC curves for young adults (YA), age-unimpaired adults (AU), age-impaired adults (AI), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

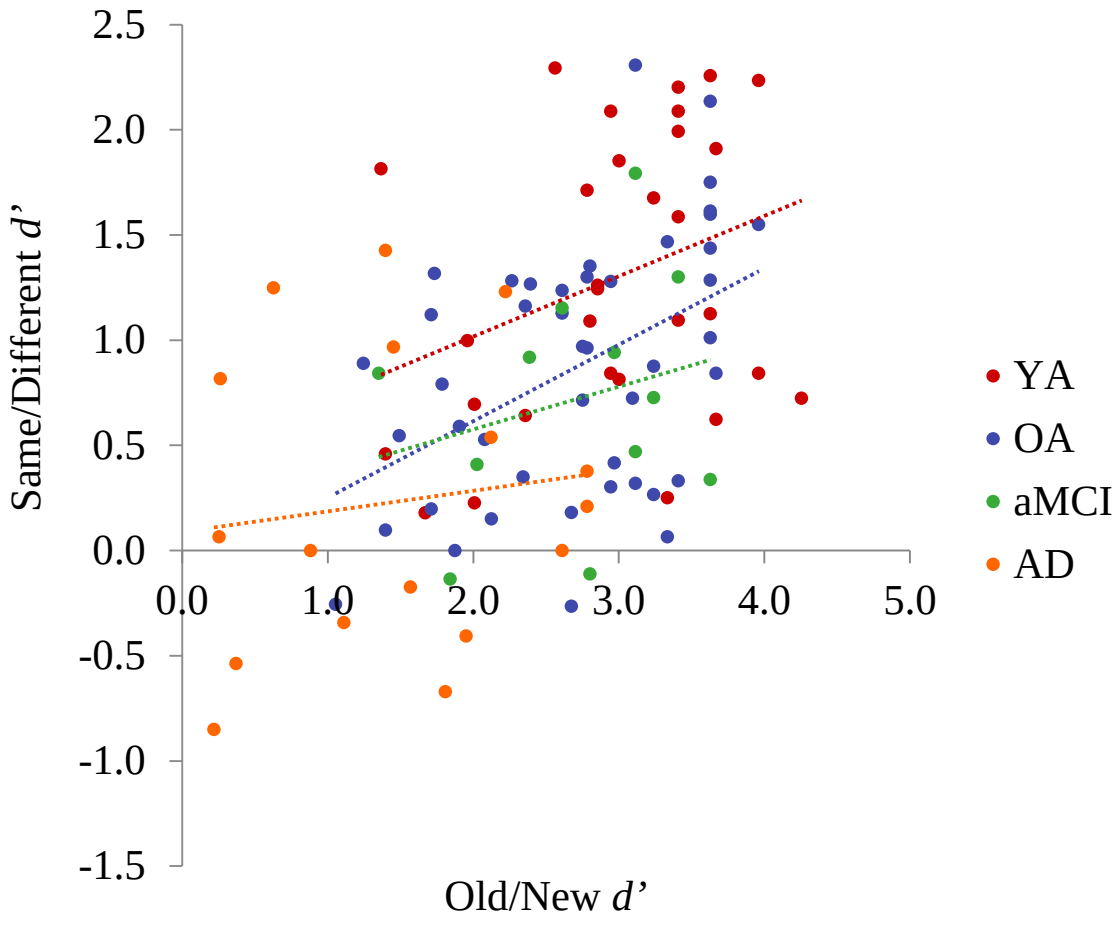

Figure 28. Correlation plot of individual participants' Old/New *d'* values and Same/Different *d'* values for young adults (YA), older adults (OA), participants with amnestic mild cognitive impairment (aMCI), and participants with probable Alzheimer's disease (AD).

YA $r_{(28)} = 0.321$, $p = 0.084$
*OA $r_{(43)} = 0.452$, $p = 0.002$
aMCI $r_{(10)} = 0.250$, $p = 0.433$
AD $r_{(15)} = 0.124$, $p = 0.635$

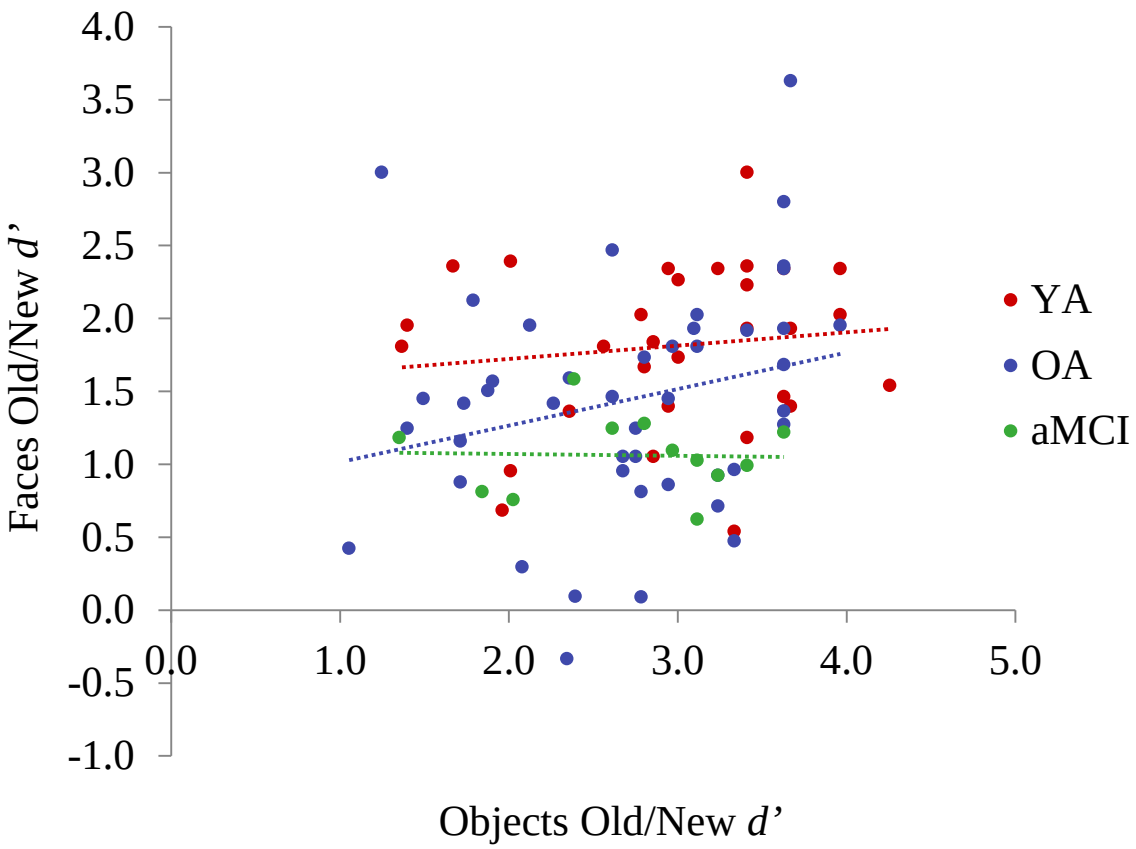

Figure 29. Correlation plot of individual participants' Old/New *d'* values for pictures of objects versus pictures of faces for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

YA $r_{(28)} = 0.121$, $p = 0.635$
OA $r_{(43)} = 0.243$, $p = 0.108$
aMCI $r_{(10)} = -0.032$, $p = 0.923$

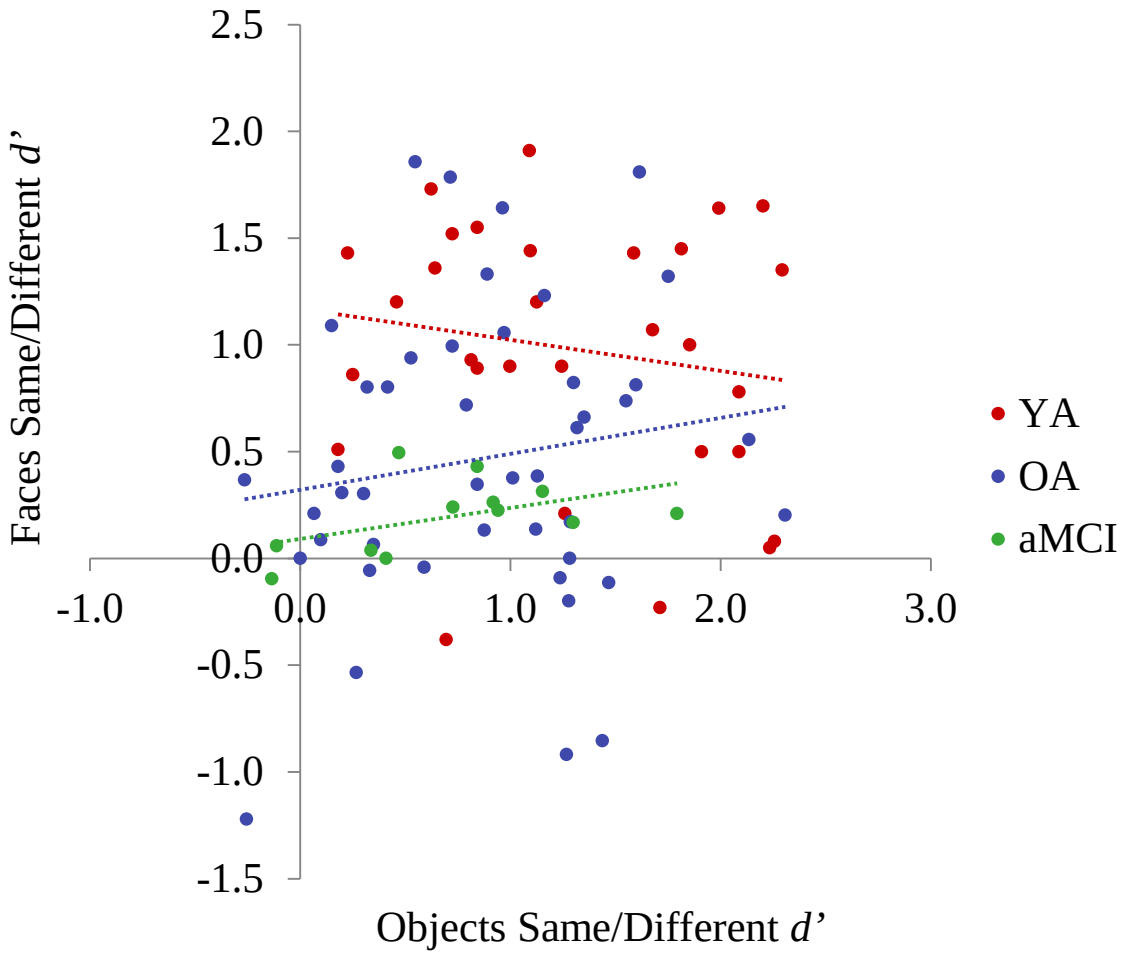

Figure 30. Correlation plot of individual participants' Same/Different *d'* values for pictures of objects versus pictures of faces for young adults (YA), older adults (OA), and participants with amnestic mild cognitive impairment (aMCI).

YA $r_{(28)} = 0.121$, $p = 0.635$
OA $r_{(43)} = 0.243$, $p = 0.108$
aMCI $r_{(10)} = -0.032$, $p = 0.923$

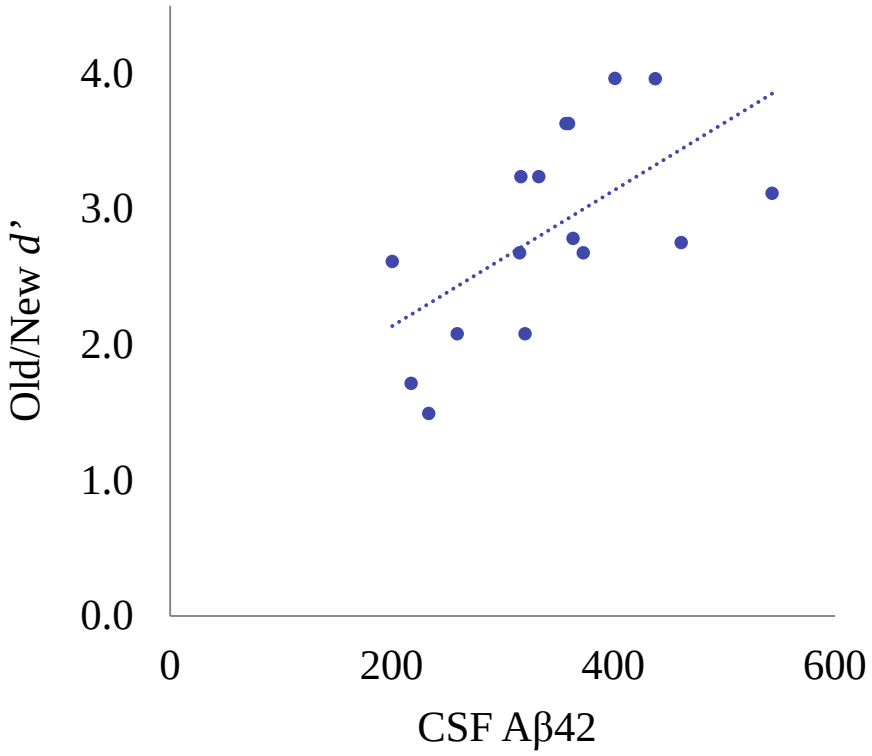

Figure 31. Old/New *d'* values for object stimuli plotted with CSF Aβ42 level for all 16 older adult participants.

*$r_{(14)} = 0.61$, $p = 0.01$

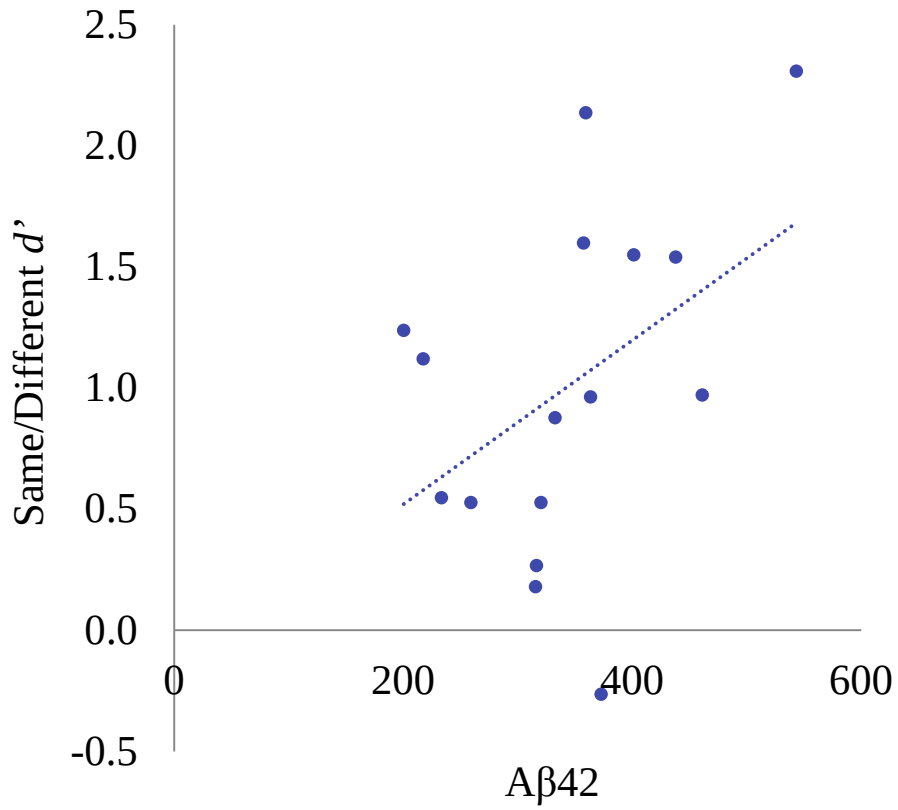

Figure 32. Same/Different *d'* values for object stimuli plotted with CSF Aβ42 level for all 16 older adult participants.

$r_{(14)} = 0.44$, $p = 0.09$

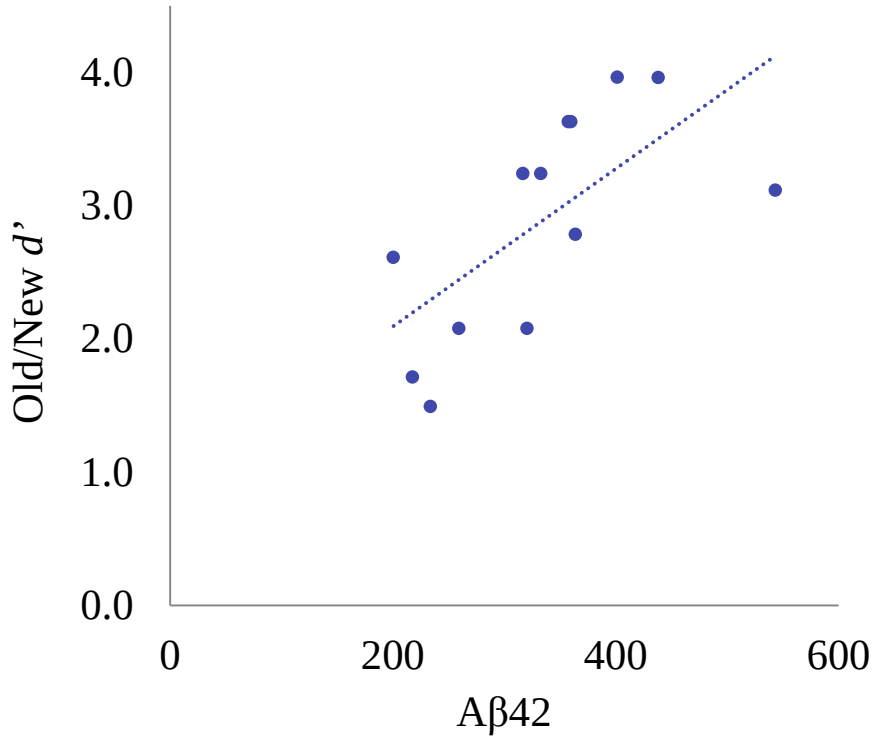

Figure 33. Old/New *d'* values for object stimuli plotted with Aβ42 level for 13 older adult participants with CSF collected since 2012.

*$r_{(11)} = 0.67$, $p = 0.01$

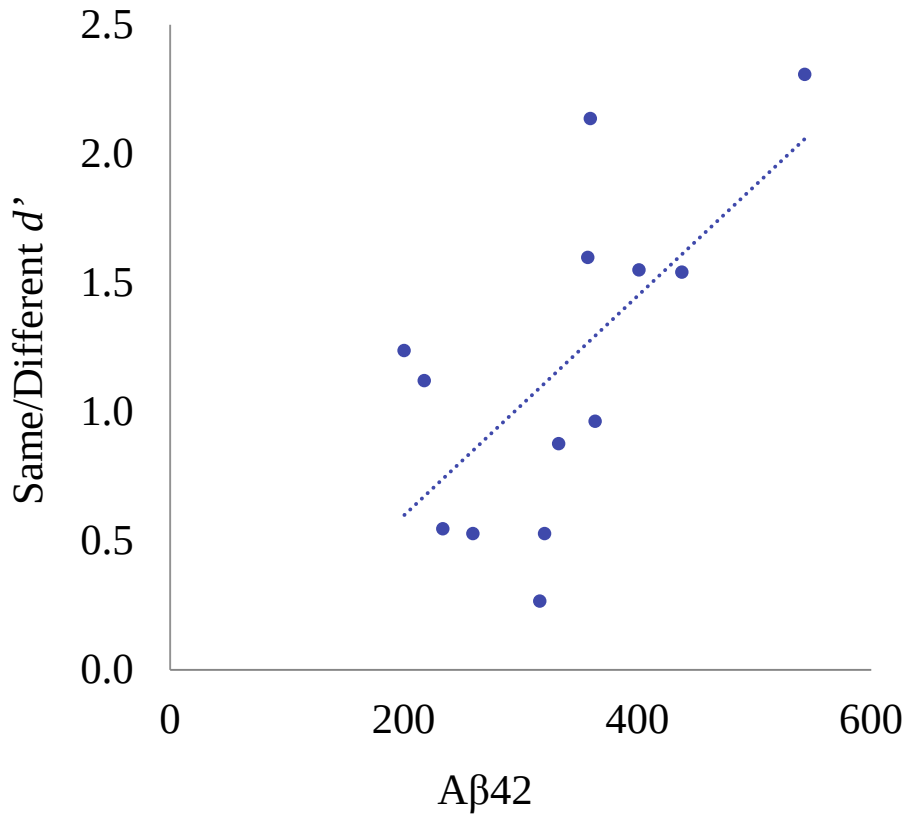

Figure 34. Same/Different *d'* values for object stimuli plotted with Aβ42 level for 13 older adult participants with CSF collected since 2012.

*$r_{(11)} = 0.64$, $p = 0.02$

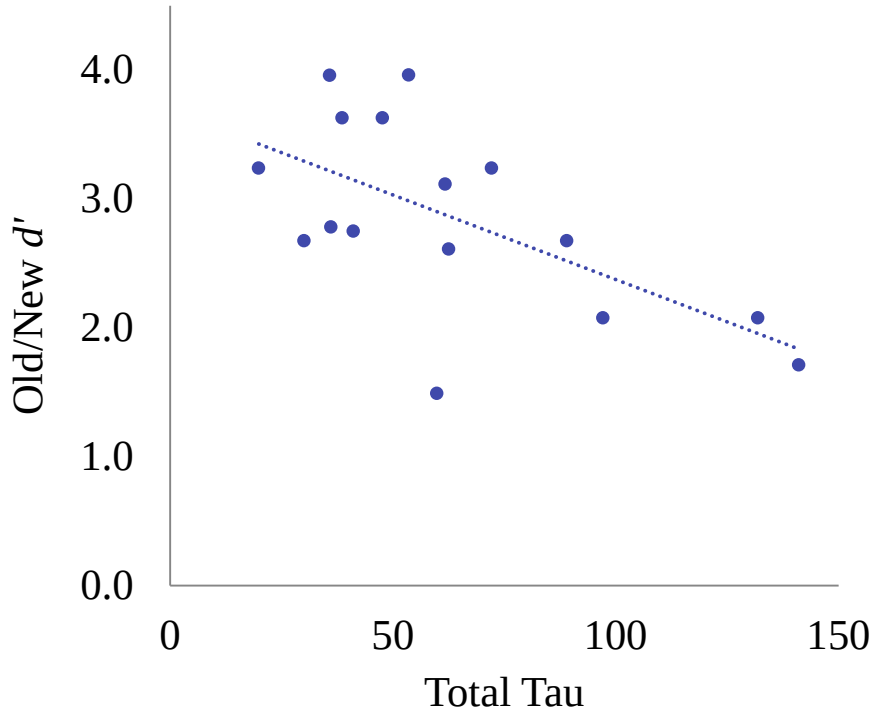

Figure 35. Old/New *d'* values for object stimuli plotted with CSF total tau level for all 16 older adult participants.

*$r_{(14)}$ = -0.61, p = 0.01

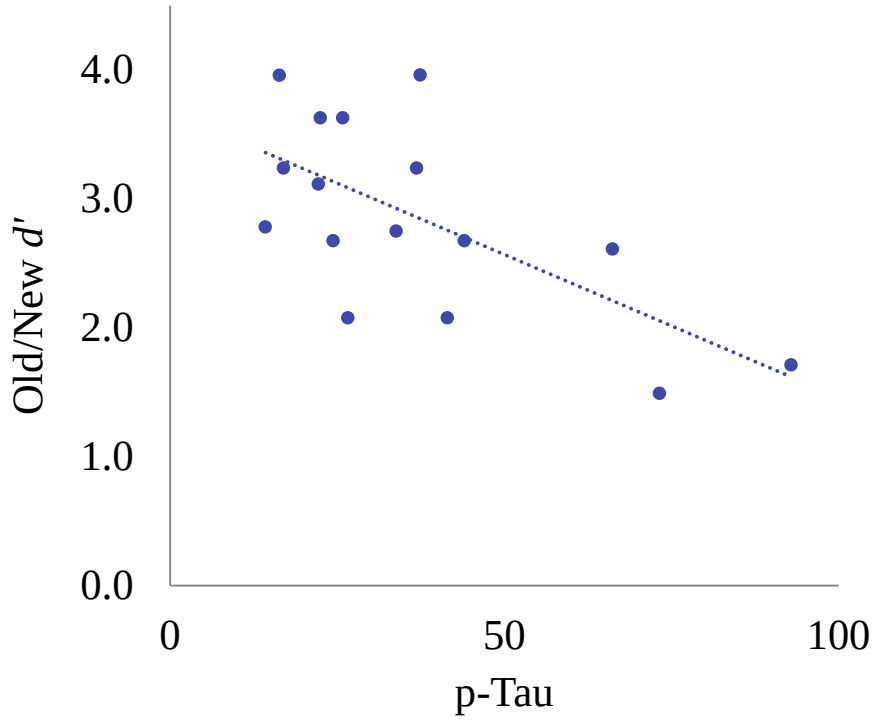

Figure 36. Old/New *d'* values for object stimuli plotted with CSF p-tau level for all 16 older adult participants.

*$r_{(14)}$ = -0.66, p = 0.006

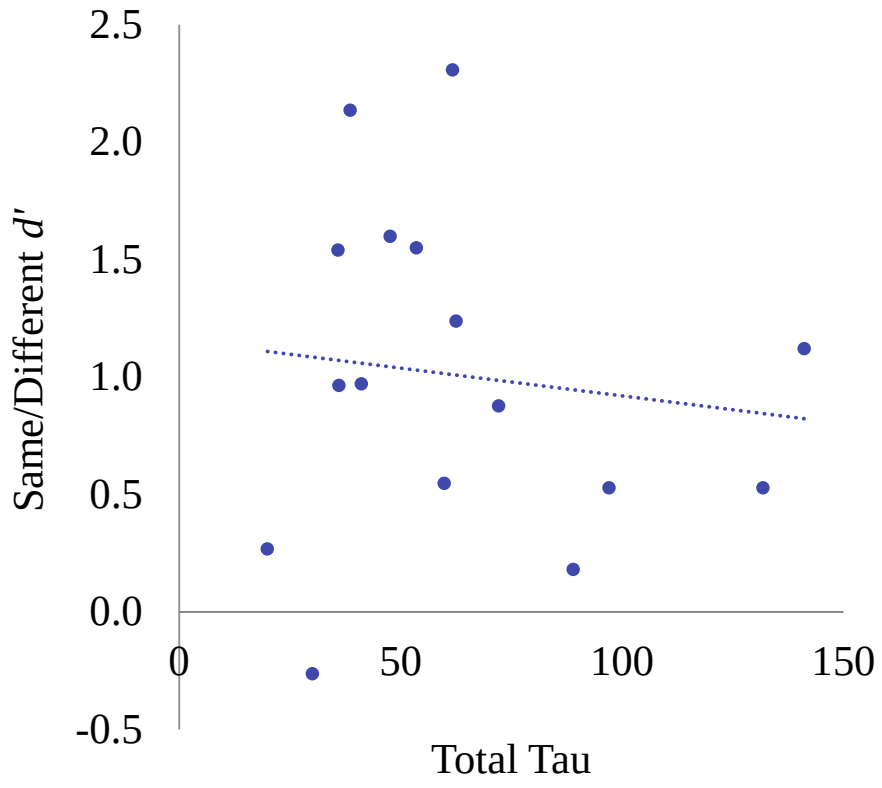

Figure 37. Same/Different *d'* values for object stimuli plotted with CSF total tau level for all 16 older adult participants.

$r_{(14)} = -0.12$, $p = 0.66$

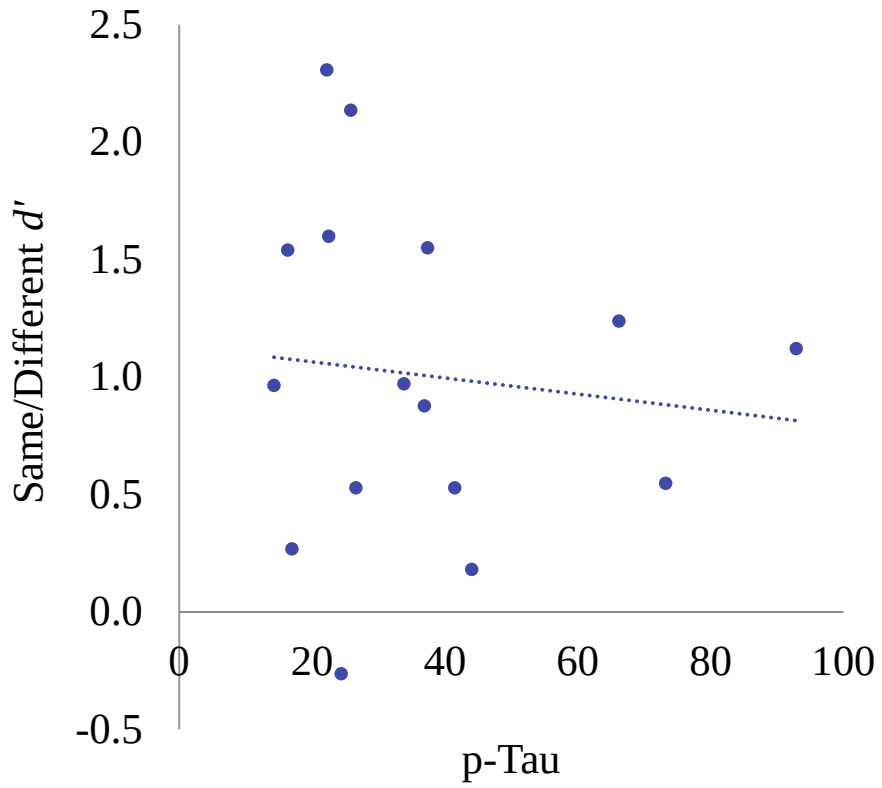

Figure 38. Same/Different *d'* values for object stimuli plotted with CSF p-tau level for all 16 older adult participants.

$r_{(14)} = -0.12$, $p = 0.69$

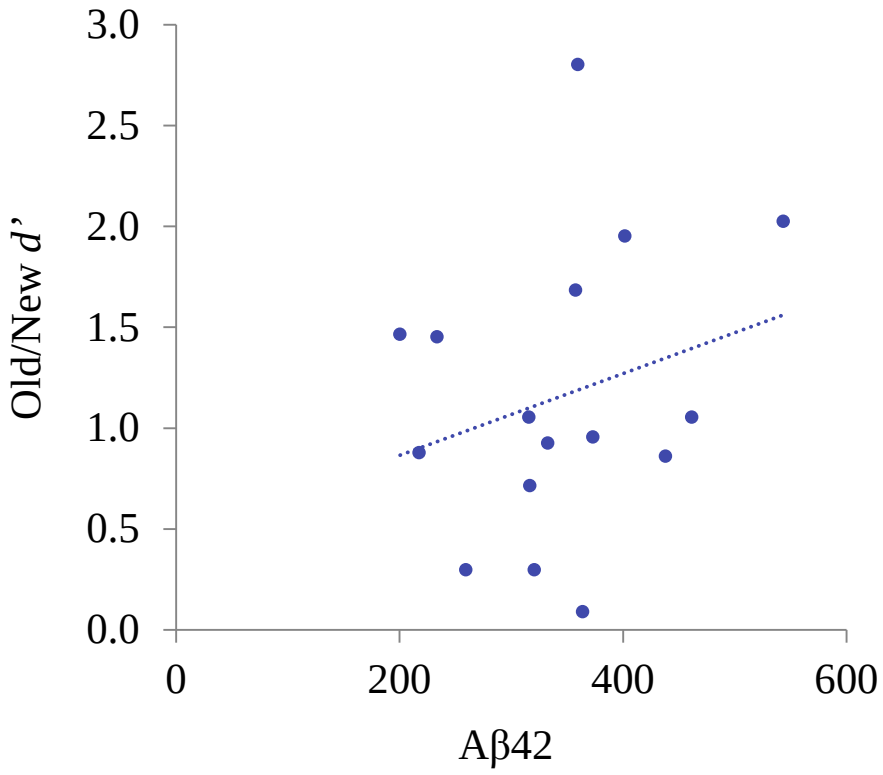

Figure 39. Old/New *d'* values for face stimuli plotted with CSF Aβ42 level for all 16 older adult participants.

$r_{(14)} = 0.26$, $p = 0.33$

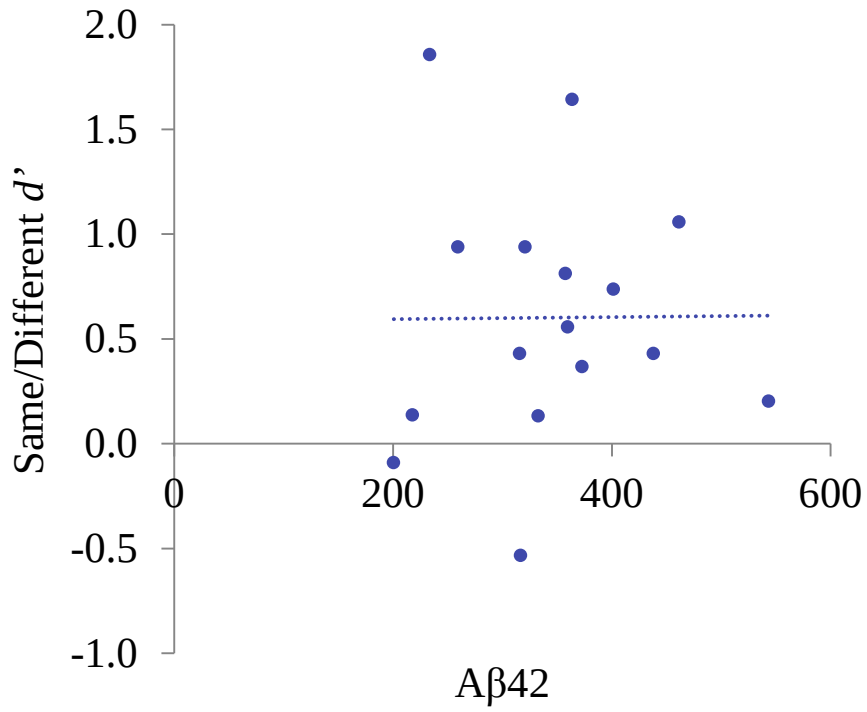

Figure 40. Same/Different *d'* values for face stimuli plotted with CSF Aβ42 level for all 16 older adult participants.

$r_{(14)} = 0.006$, $p = 0.98$

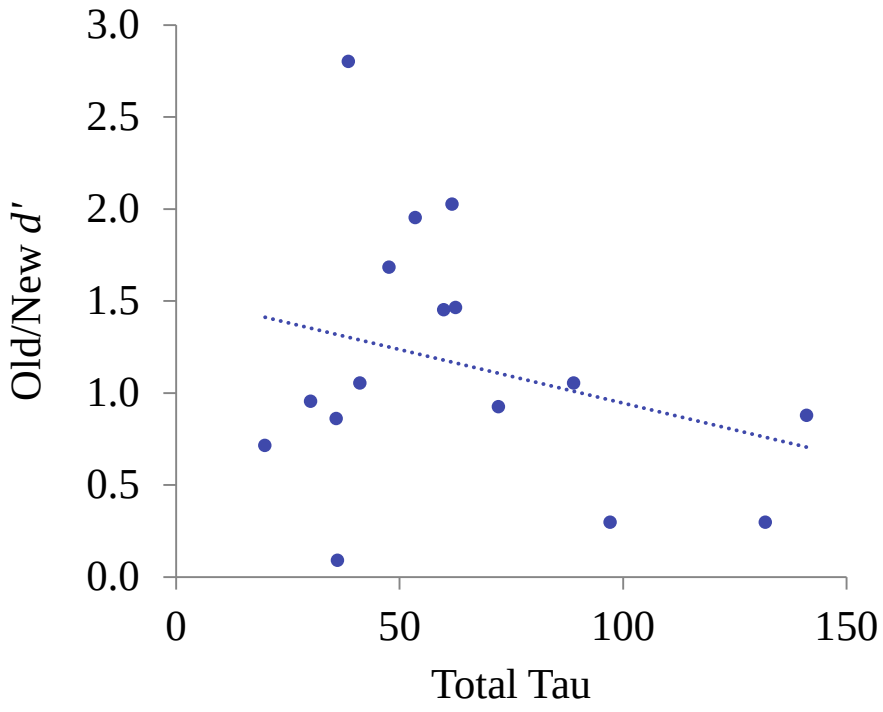

Figure 41. Old/New *d'* values for face stimuli plotted with CSF total tau level for all 16 older adult participants.

$r_{(14)} = -0.29$, $p = 0.28$

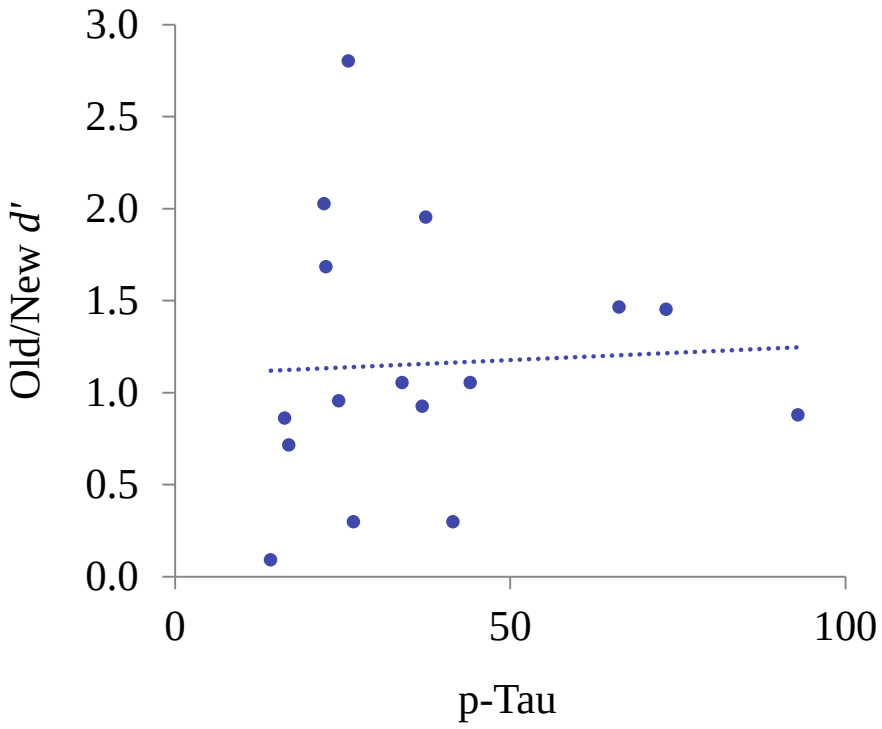

Figure 42. Old/New *d'* values for face stimuli plotted with CSF p-tau level for all 16 older adult participants.

$r_{(14)} = 0.05$, $p = 0.85$

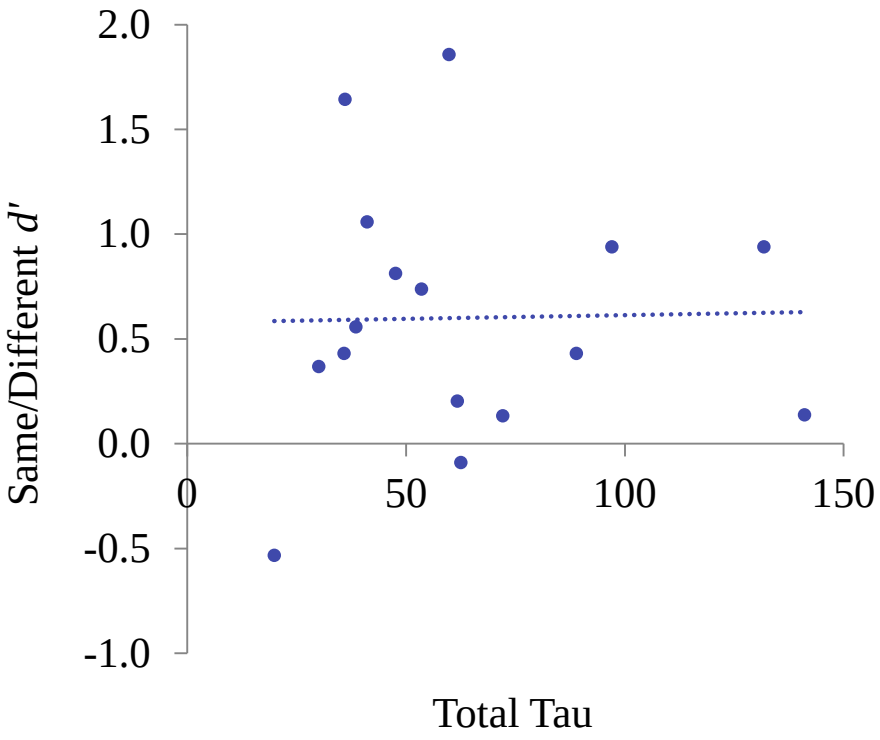

Figure 43. Same/Different *d'* values for face stimuli plotted with CSF total tau level for all 16 older adult participants.

$r_{(14)} = 0.02$, $p = 0.94$

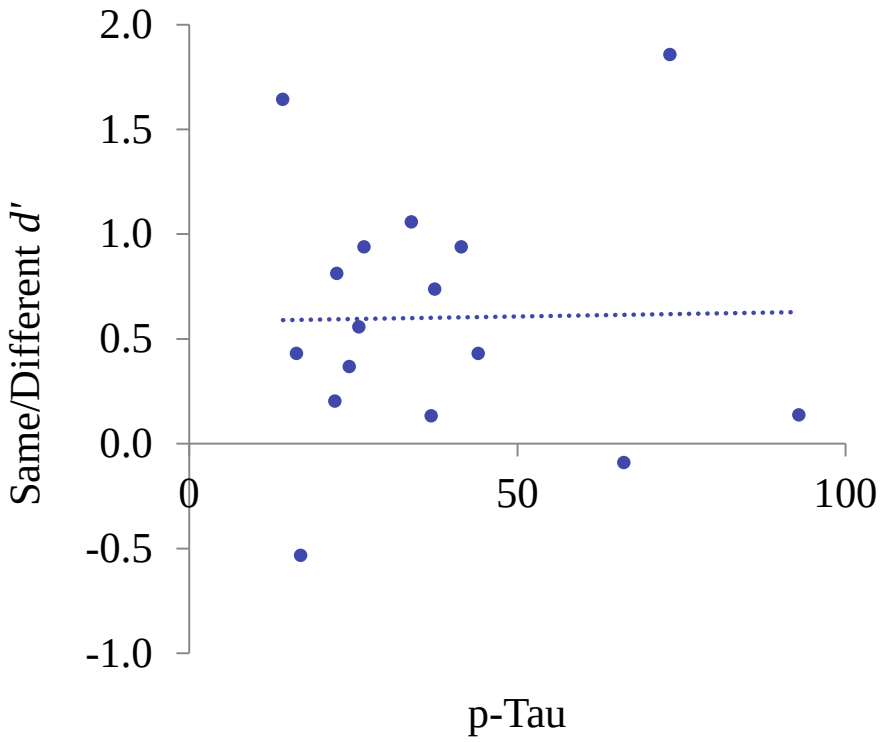

Figure 44. Same/Different *d'* values for face stimuli plotted with CSF p-tau level for all 16 older adult participants.

$r_{(14)} = 0.02$, $p = 0.94$

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